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Nasal versus oronasal raised volume forced expirations in infants – A real physiologic challenge

Mohy G. Morris, M.D., M.Sc., Ph.D.

Department of Pediatrics, Pulmonary Medicine Section, College of Medicine, University of Arkansas for Medical Sciences, Arkansas Children's Hospital, Little Rock, Arkansas 72202, USA

Summary

Raised volume rapid thoracoabdominal compression (RTC) generates forced expiration (FE) in infants typically from an airway opening pressure of 30 cm H₂O (V₃₀). We hypothesized that the higher nasal than pulmonary airway resistance limits forced expiratory flows (FEF%) during (nasal) FE_n, which an opened mouth, (oral) FE_o, would resolve. Measurements were performed during a brief post-hyperventilation apnea on twelve healthy infants aged 6.9–104 weeks. In two infants, forced expiratory (FEFV) flow volume (FV) curves were generated using a facemask that covered the nose and a closed mouth, then again with a larger mask with the mouth opened. In other infants (n=10), the mouth closed spontaneously during FE. Oronasal passive expiration from V₃₀ generated either the inspiratory capacity (IC) or by activating RTC before end-expiration, the slow vital capacity (jSVC). Peak flow (PF), FEF₂₅, FEF₅₀, FEF_{25–75}, FEV_{0.4} and FEV_{0.5} were lower via FE_n than FE_o (p<0.05), but the ratio of expired volume at PF and forced vital capacity (FVC) as percent was higher (p<0.05). FEF₇₅, FEF₈₅, FEF₉₀, FVC as well as the applied jacket pressures were not different (p>0.05). FEFV curves generated via FE_o exhibited higher PF than FV curves of IC (p<0.05); PF of those produced via FE_n were not different from FV curves of IC (p>0.05) but lower than those of jSVC (p<0.05). In conclusion, the higher nasal than pulmonary airways resistance unequivocally affects the FEFV curves by consistently reducing PF and decreases mid-expiratory flows. A monitored slightly opened mouth and a gentle anterior jaw thrust are physiologically integral for raised volume RTC in order to maximize the oral and minimize nasal airways contribution to FE so that flow limitation would be in the pulmonary not nasal airways.

Keywords

raised volume rapid thoracoabdominal compression; infant lung function; expiratory flow limitation; nasal airway resistance; vital capacity; jaw thrust; bronchodilator response

INTRODUCTION

Airway inflammation and hyperresponsiveness are important in the pathogenesis of pediatric respiratory diseases such as asthma, bronchopulmonary dysplasia and cystic fibrosis (CF). In infants, the raised volume rapid thoracoabdominal compression (RTC) technique is more reliable than the tidal volume RTC because flow limitation is more often achieved. Flow limitation can provide direct useful information about airway function.

Mohy G. Morris, M.D., M.Sc., Ph.D., Associate Professor of Pediatrics, University of Arkansas for Medical Sciences, Arkansas Children's Hospital, 1 Children's Way, Slot 512-17, Little Rock, Arkansas 72202-3591, USA, Phone: (501) 364-1006, Fax: (501) 364-3930, morrismohyg@uams.edu.

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Whereas in cooperative older children and adults a mouth piece and a nose-clip are used during forced expiration in order to bypass the nasal resistance, raised volume RTC requires an infant sleeping supine, sedated with chloral hydrate and the use of a facemask which covers the mouth and nose. Hence, both nasal and oral airways contribute to the forced expiratory airflow in infants.^{1–12} Infants are obligatory or preferential nose breathers, yet their average nasal resistance is 13 cm H₂O/L/sec, which is nearly 50% of the total airway resistance as in adults.¹³ Thus, any compromise in the dimensions of the nasal airways results in significant respiratory distress especially with the combined immaturity of neuromuscular responses which impedes the conversion to mouth breathing in early infancy.^{7,13–18} The nasal cycle which is under autonomic control consists of spontaneous and often reciprocal changes in unilateral nasal airflow associated with congestion and decongestion of the nasal mucosa that could alter airflow in one nostril by up to 80%. Superimposed on the nasal cycle, nasal mucosal swelling and nasal airflow resistance could increase due to the following: (1) the infant's supine position during testing which could increase the central venous pressure; and (2) the hyperventilation which decreases blood carbon dioxide.^{14,15,19–22} Cold ambient temperature and rhinitis could swell the nasal turbinates which increases nasal expiratory resistance.^{21,23} Hence, testing has been recommended three weeks after an upper respiratory tract infection.^{5,6,7,24,25} Consequently, changes in lower airway resistance with disease or therapeutic interventions may be masked unless the sensitivity of the infant lung function test employed is increased by dissociating the upper from the lower airways.^{6,7,26} Taken together, we thought that maintaining an opened mouth during raised volume RTC from an airway opening pressure (Pao) of 30 cm H₂O (V₃₀) was crucial.⁶ We hypothesized that the known higher nasal than pulmonary airway resistance would decrease the forced expiratory flows (FEF_%) during a nasal (FE_n) forced expiration, even in an infant who was an obligatory or preferential nose breather, which an opened mouth, that is (oronasal) FE_o, would resolve.

MATERIALS AND METHODS

Subjects

Measurements were performed on twelve healthy infants, seven Caucasians (2 boys) and five blacks (2 boys) participating in a respiratory study (Table 1). Median (range) age was 28.4 (6.9–104.0) weeks, weight was 8.00 (4.21–10.90) kg and body length was 69.2 (53.7–87.0) cm. The infants were sedated with chloral hydrate (60–100 mg/kg) orally or rectally. Clearing the nose of the sleeping infant of inspissated mucus before initiating the tests was important.^{5,6,14} Their oxygen saturation and heart rate were monitored with a pulse oximeter during testing and until they were fully awake after.^{5,6,24} The ethics committee of the institution approved the testing protocol and informed written parental consent was obtained prior to each infant test. Parents were present during testing.

Testing Protocol

Details of the custom made computer controlled apparatus and measurement techniques were described elsewhere.^{5,6,24} The appropriate size clear facemask (Rendell-Baker Soucek pediatric facemask; Gary Hull Anesthesia, California, USA) was embedded in a thick roll of firm silicone putty applied around the nose and a slightly opened mouth and an airtight seal was achieved (Fig. 1). Visual checks were necessary to ensure that the facemask did not distort the nose especially in black infants because of their short nasal bridge.^{6,14,16} Putty could often be pushed away from an airway opening using a stick inserted through the facemask port without having to remove the mask.⁶ Using a shoulder roll, the infant's head was adjusted with the neck slightly extended. The investigator then exerted a gentle anterior mandibular thrust during forced expiration while ensuring the mouth remained open.⁶ For older toddlers and very small infants, the assistant who also sat with the author by the

infant's head, applied both hands against the body and ramus of the mandibles, adjusted the head and neck and performed the anterior jaw thrust.^{6,24,27,28} The assistant then supported the valve assembly with the fingers once the author had connected it to the facemask port. Sometimes, the assistant had to exert gentle pressure on the small infant's cheeks in order to keep the mouth open. The amount of pressure applied on the small infant's cheeks which opened the mouth was predetermined by visualizing the latter through the facemask port before inserting the T-valve prior to each raised volume RTC. The investigator then began performing manual hyperventilation and initiated the maneuver via the keyboard (see below). The mouth was immediately re-inspected after completing each maneuver.

Signals (flow, Pao, jacket pressure (Pj) and flow-volume loops) were displayed in real time on two computer monitor screens. Close monitoring of the rising Pao during lung inflations was helpful in minimizing aerophagia and triggering automated raised volume RTC in a timely fashion.⁶

Automated raised volume RTC

Using intermittent thumb occlusions of the expiratory limb of the Y adapter, the infant was manually hyperventilated by diverting a constant bias airflow (5–15 L/min) circulating in the adapter through the balloon valve and pneumotachometer into the facemask to induce a brief post-hyperventilation apnea (PHA). Automated raised volume RTC was then triggered via a computer keyboard stroke as follows:^{5,6} the pneumatic circuit's airflow, which was pre-adjusted according to the infant's age and size, delivered a lung inflation to the pre-determined (pPao) Pao of 30 cm H₂O. Lung inflation was then automatically halted. The airway was occluded for 0.20 s before activating jacket inflation. Automatic jacket inflation was triggered at the end of the 0.20 sec airway occlusion. However, the expiratory valve opened after a fixed preset time delay of 0.05 s after activating jacket inflation. Forced expiration then proceeded from V₃₀ to residual volume. A minimal jacket driving pressure (range, 0–3 cm H₂O) was maintained. Raised volume RTC was repeated until flow limitation was achieved with no further increase in FEF_{25–75} and FVC despite increasing the applied jacket pressure.^{5,6,11} The mouth and nares were routinely visualized through the facemask port before and immediately after each raised volume RTC maneuver. If the mouth was found closed or obstructed by putty during a maneuver, it was consistently noted down (Fig. 1).

In each subject, at least two FVC measurements within 10% of each other were obtained. The actual Pao (aPao), which is the average Pao during the 0.20 sec airway occlusion period, the average Pj plateau and the forced expiratory time (fFVC) were obtained from recorded signals.⁶ The best intrasubject FEFV curve via FE_o and FE_n that had the highest sum of FVC and FEF_{25–75} were compared.^{5,6,11}

Nasal ventilation and forced expiration

Unexpectedly, an opened mouth often closed or became obstructed by putty during testing (Fig. 1). A lightly sedated infant often actively closed his/her mouth towards the end of testing when oral sucking movements became more active. Therefore, the mask and putty were removed and replaced after re-opening the mouth (Fig. 1) when the sedated infant relaxed back into sleep, often after inserting a pacifier in his/her mouth for a brief period. During manual hyperventilation, a startled infant indicated that the mouth had closed. Consequently, the entire inflating airflow to the lungs was diverted to the nasal airways likely causing a true inspiratory flow limitation with oscillations.^{20,29} During manual hyperventilation, the disappearance in real-time on the computer monitor screen of the prominent peak of maximum flow in the passive flow-volume loops was a critical clue that the mouth had closed and/or was obstructed by putty. Unless the hyperventilation was then

aborted and the valve assembly disconnected from the facemask port to re-inspect the mouth, the decreased PF would subsequently be revealed in the generated FEFV curve indicating a FE_n (personal observations).

In infants no. 1 and 2, raised volume RTC was performed with a size 0 clear facemask embedded in putty which completely covered the nose and a closed mouth, then again with a larger mask with the mouth opened. In other infants ($n=10$), the mouth closed spontaneously or became obstructed by the putty or the mandible was supported without exerting pressure on the cheeks of a lightly sedated young infant who then kept his/her mouth closed during forced expiration (personal observations).

Measuring the inspiratory capacity (IC) and slow vital capacity ($jSVC$)

For comparisons with the peak flow of FEFV curves, we attempted to generate at least one oronasal passive and one passive-forced expiratory flow volume curve from V_{30} which produced the IC and $jSVC$, respectively, as follows:^{5,6}

If the squeeze jacket had been applied to perform RTC, it was unfastened. After inducing the PHA, the last manual lung inflation was maintained until an airway opening pressure (P_{ao}) plateau was observed at V_{30} and the inspiratory flow signal ceased to rise in real-time on the computer monitor screen. The occlusion of the Y adapter's expiratory limb was then terminated. Passive expiration from V_{30} was allowed to be completed by watching the flow signal and the flow-volume loop in real-time on the computer monitor screen (Figs. 2–4). Flow was integrated to produce volume which is the IC.

With the squeeze jacket (j) fastened around the infant, the investigator observed the flow signal in real time and triggered RTC before end-passive expiration from V_{30} during the PHA. Flow was integrated to produce volume which is the $jSVC$.

Statistical analysis

Median, interquartile range (IQR) and range of PF, $FEF_{\%}$, $FEV_{0.4}$, $FEV_{0.5}$, $fFVC$, FVC, and the ratio of the expired volume at peak expiratory flow and forced vital capacity (FVC) as percent ($V_{PEF}/\%FVC$) were calculated (Table 2). Statistical analysis included the Wilcoxon paired-sample test (signed rank test) to compare measured variables from the best FEFV curve via FE_o and FE_n from each infant. p values of less than 0.05 for a one-tailed test were regarded as significant.³⁰ The raw data of $FEF_{\%}$ from the best intrasubject FEFV curve via FE_o and FE_n were plotted against the flow rate (ml/sec) (Fig. 5).³¹ The percent difference (median, IQR, range) for $FEF_{\%}$, FVC and timed-volumes between the best FEFV curve via FE_o versus FE_n were computed (Table 2).³² The bias and limits of agreement between the FEF_{50} , FEF_{25-75} , FEF_{75} and $FEV_{0.5}$ from the best FEFV curve via FE_o versus FE_n were calculated (Fig. 6).³²

RESULTS

Figures 2–4 demonstrate the passive (pEFV), passive forced (pFEFV) and, using repeated raised volume RTC with increasing jacket pressures (P_j), the forced (FEFV) expiratory flow-volume (EFV) curves from a lung volume raised to an airway opening pressure of 30 cm H_2O (V_{30}) that generated the IC, $jSVC$ and forced vital capacity (FVC), respectively, during a brief PHA. The abrupt increase in flow close to the end of the pFEFV curves is caused by late jacket (j) activation which generates a (partial) forced expiration to RV, producing the $jSVC$.⁶ All flow-volume curves are aligned at V_{30} (total lung capacity) in order to reveal their individual shape. When the FEFV curves were aligned along the descending portion or end-expiration (not shown), flow limitation was evident.^{6,11}

Figure 2: Infant no. 1: Curves no. 1n, 2n and 3n have decreased PF; low $V_{PEF}/\%FVC$: 6.1, 5.8 and 8.2%, respectively, indicate effective nasal airway ventilation. Nasal flow limitation is attained. The single FEFV curve no. 4 generated via FE_o has higher PF; $V_{PEF}/\%FVC$, 6.0%; the infant then woke up. Infant no. 2: Curves no. 1 to 4 have high PF; $V_{PEF}/\%FVC$: 3.4, 4.4, 4.6 and 4.9 %, respectively. Curves no. 5n and 6n have decreased PF; higher $V_{PEF}/\%FVC$: 12.4 and 10.5%, respectively. A flow transient at low lung volume in curves no. 1 and 3 reaching a nadir at volume points (arrows) of 245 and 228 ml, respectively, indicates dynamic airway collapse generated by forced expiratory airflow.^{33,34} Infant no. 3: High PF in curve no. 1 decreases in no. 2n and 3n; $V_{PEF}/\%FVC$: 5.4, 6.2 and 6.3%, respectively. Restoring FE_o generates curves no. 4, 5 and 6 with higher PF; $V_{PEF}/\%FVC$: 7.4, 5.4 and 5.9%, respectively. Nasal flow limitation is attained via FE_n but mid-expiratory flows are lower than those generated via FE_o . A comparable P_j generated high PF in curves no. 1 and 5 but a decreased PF in no. 2n. Infant no. 4: High PF in curve no. 1 gets lower in no. 2 ($FE_n > FE_o$), and lowest in no. 3n due to an entire FE_n ; $V_{PEF}/\%FVC$: 5.1, 4.4 and (highest) 19.7%, respectively. Re-opening of the mouth restores FE_o in curves no. 4 and 5 that have higher PF; $V_{PEF}/\%FVC$: 5.8 and 5.4%, respectively. A P_j of 58 cm H_2O generated curves no. 3n and 4 (see Fig. 7)

Figure 3: Infant no. 5: Curves no. 1, 2 and 3 have high PF; $V_{PEF}/\%FVC$: 3.2, 4.8 and 4.8%, respectively. With spontaneous mouth closure, curves no. 4n and 5n have decreased PF despite using higher P_j ; $V_{PEF}/\%FVC$: 16.7 and 14.2%, respectively. The highest and lowest FVC in this infant are within 7%. Infant no. 6: the assistant had to apply gentle pressure on the cheeks of this 6.9 weeks old infant to keep his mouth open during forced expiration. Curves no. 1, 2 and 3 have high PF; $V_{PEF}/\%FVC$: 7.1, 7.5 and 10%, respectively. Pulmonary flow limitation is achieved. However, when pressure was no longer applied on the cheeks, curves no. 4, 5n and 6n have lower PF ($FE_n > FE_o$); PF is most decreased in no. 6n which was entirely via FE_n ; $V_{PEF}/\%FVC$: 10, 5.2 and (highest) 18 %, respectively. A comparable P_j generated curves no. 5n and 6n. Infant no. 7: Curves no. 1–4 have high PF; $V_{PEF}/\%FVC$: 6.2, 4.6, 5.3 and 7.1%, respectively. Pulmonary flow limitation is achieved. Applying higher P_j generated flow transients in FEFV curves (not shown). With the mouth closing, curve no. 5n has decreased PF; $V_{PEF}/\%FVC$, 7.3%. A lower and an identical P_j used in curves no. 1 and 4, respectively, generated higher PF than in no. 5n. Significant alteration in the shape of curve no. 5n led to supramaximal flows at low lung volumes.¹¹ Infant no. 8: Curve no. 1n has low PF; $V_{PEF}/\%FVC$: 16%. After reopening the mouth, FEFV curve no. 2 has a high PF and flow transients (glottic closure); $V_{PEF}/\%FVC$: 2.4%. The head and neck were repositioned and using increasing P_j , FEFV curves no. 3, 4 and 5 (best) had prominent PF; $V_{PEF}/\%FVC$: 2.5, 2.9 and 2.9%, respectively. Using higher P_j generated flow transients in the FEFV curves (not shown). Mouth closure for a second time generated curve no. 6n that had lower PF; $V_{PEF}/\%FVC$: 13.5%. The lowest P_j of 42 cm H_2O generated a higher PF in curve no. 3 than 1n and 6n.

Figure 4: Infant no. 9: Curve no. 1, which was generated by the lowest P_j , has the highest PF; $V_{PEF}/\%FVC$: 3.01 %. The mouth closed spontaneously; despite applying progressively increased P_j , curves no. 2n to 6n have reduced PF; $V_{PEF}/\%FVC$: 11.7, 14.8, 15.0, 14.6 and 16.1, respectively. Nasal flow limitation is attained. Infant no. 10: Curves no. 1 (best), 2 and 3 have prominent PF; $V_{PEF}/\%FVC$: 3.3, 4.2 and 4.4%, respectively. Despite using a higher P_j , a closed mouth that was also partially covered with putty drastically reduced peak flow causing a flow transient which altered the shape of curve no. 4n significantly; note that a maximum flow of 764 ml/s is achieved at expired volume of 140 ml; $V_{PEF}/\%FVC$: 40.9%. Curves no. 5 and 6 were generated after reopening the mouth and placing a larger size facemask. Infant no. 11: Curves no. 1n to 4n have reduced PF; $V_{PEF}/\%FVC$: 20.8, 19.4, 19.9 and 17.5%, respectively. The closed mouth, which was also partially covered with putty, was reopened and a larger facemask was placed. Curves no. 5 and 6 (best) have higher PF

and were generated by lower P_j than curve no. 4n; $V_{PEF}/\%FVC$: 4.3 and 4.8%, respectively. Applying higher P_j generated flow transients in FEFV curve (not shown). Infant no. 12: Curves no. 1n to 3n have reduced PF; $V_{PEF}/\%FVC$: 21.5, 33.0 and 33.2%. After reopening the mouth, curves no. 4 to 8 (best) that have higher PF were generated.

In Figure 5, intrasubject $FEF\%$ via FE_o versus FE_n are compared: PF is higher in all; FEF_{25} is higher in all except no.7 and 9; FEF_{50} and FEF_{25-75} are higher in all except no.7 and 10. Intrasubject FEF_{25} via FE_o is even higher than the PF generated via FE_n in 8/11 infants and the difference was statistically significant ($p = 0.0337$). Thus, in all infants, the prominent peaks of maximum flow (PF) in the FEFV curves generated via FE_o were consistently decreased by FE_n which invariably altered the shape of the curve (Figs 2–7).

In infants no. 2–12, paired measurements from the best FEFV curve via FE_o and FE_n were compared (Table 2 and Figs. 2–6). Despite using comparable P_j ($p = 0.3188$), the PF, FEF_{25} , FEF_{50} , FEF_{25-75} as well as $FEV_{0.4}$ and $FEV_{0.5}$ were significantly decreased via FE_n than FE_o ($p < 0.05$). However, the FEF_{75} , FEF_{85} , FEF_{90} as well as the FVC and $\bar{FVC}$ were not different ($p > 0.05$). The $V_{PEF}/\%FVC$ ratio was significantly higher via FE_n than FE_o ($p = 0.0005$) (Fig. 5), exceeding 10% in infants no. 2, 4–6 and 8–12 (Table 2).

Infants no. 2, 5, 6, 7 and 12 woke up before an IC could be generated and in no.7, a $jSVC$ too. Intrasubject PF of FEFV curves generated via FE_o were higher than PF of passive ($pEFV$) ($p = 0.0391$) but not significantly different from PF of passive forced ($pFEFV$) expiratory flow-volume curves ($p = 0.0967$) that produced the IC and $jSVC$, respectively.⁶ PF of FEFV curves generated via FE_n were not different from PF of $pEFV$ ($p = 0.2891$) but lower than PF of $pFEFV$ ($p = 0.0186$) curves (Figs. 2–4).

DISCUSSION

As we hypothesized, FE_n consistently decreased PF ($p = 0.0005$) thus altered the shape of the FEFV curve in all infants and mid-expiratory flows were reduced ($p = 0.0269$), which an opened mouth (FE_o) resolved. This difference persisted even when a comparable or different intrasubject P_j was applied and the anterior jaw thrust was performed during FE_n versus FE_o (Figs. 2–4 and 7). Since FE_n diminished the maximum expiratory flow rate, flow limitation within the pulmonary airways would not be attained (Figs. 2–4).^{1,2,5,6,9,11,20,35–37}

The intrasubject $V_{PEF}/\%FVC$ ratio of the best FEFV curve was higher via FE_n than FE_o ($p = 0.0005$) (Table 2). The $V_{PEF}/\%FVC$ ratio via FE_n exceeded 10% in infants no. 2, 4–6 and 8–12 (Figs. 2–4 and 7). Supramaximal flows at very low lung volumes were occasionally observed when the nasal contribution to forced expiration became maximal with drastic reduction of PF, considerable alteration in the shape of the curve and significant increase in $V_{PEF}/\%FVC$ ratio (Fig. 3, infant no. 7, curve no. 5n; Fig. 4, infant no. 10, curve no. 4n). A $V_{PEF}/\%FVC$ ratio exceeding 10% that was associated with supramaximal flows at low lung volumes had previously been ascribed to late or slow application of RTC,^{6,7,11} which was clearly not the case in our study (Figs. 2–4 and 7). The FVC and $\bar{FVC}$ were not different via FE_o versus FE_n ($p > 0.05$) suggesting efficient nasal ventilation in infancy (Table 2 and Figs. 2–4 and 7). In healthy neonates, tidal breathing parameters were not different whether one or both nostrils were open.³⁸ Among 30 Caucasian infants aged 0.3–51.6 weeks, the reported range of nasal resistance (R_n) was 3.7 to 23.9 cm $H_2O/L/sec$.¹³ When plotted against thoracic gas volume (TGV), the absolute values of R_n decreased monotonically from birth to the end of the first year of postnatal life. Nasal resistance was significantly higher in Caucasian than in Negro infants because of anatomical differences in nasal structure.¹³ Different individual nasal airway resistances seemed to exist.^{20,21} The nasal pathway

contributed approximately half of the airway resistance in infants.^{13,26} The dimensions of the nasal airways in neonates increased significantly during the first year of life.¹⁷

The “jaw thrust”, which was first described in the 18th century, is critical for maintaining a patent airway in spontaneously breathing infants during sedation and anesthesia by lifting the tongue and the epiglottis.^{27,39–41} Compared to adults, infants have a relatively large tongue and a longer and thinner epiglottis. In addition, the larynx has a more anterior and cephalad position resulting in a short thyromental distance. Consequently, the tongue is bunched in the oropharynx.^{42,43} During inspiration, the upper airway is kept patent by the dilating action of the pharyngeal airway muscles. Therefore, drugs such as barbiturates, benzodiazepines and chloral hydrate that reduce the activity of pharyngeal muscles can reduce airway patency hence increase upper airway resistance.^{6,38,44–46} Jaw thrust generates tension on the suprahyoid muscles, ventrally pulling the hyoid bone towards the root of the tongue and ventrally displacing the insertion of the genioglossus muscle. These anatomic shifts lead to active widening of the pharynx.^{28,40,46–51} Opening the mouth without jaw thrust does not improve airway patency.⁴⁰ Reported objective measurements such as bronchoscopic photos and video endoscopy and image analysis of video recordings as well as increased tidal volume, minute ventilation and peak tidal inspiratory and expiratory flows in deeply sedated or anesthetized infants have established the increase in the oropharyngeal cross-sectional area during the jaw thrust.^{27,28,40,46,47,51,52} In our study, the anterior jaw thrust with an opened mouth improved in real time on the computer monitor screens the sedated infant’s tidal breathing,^{6,24,27,28} and increased the peak of maximum flow of raised volume passive and forced expirations. Consequently, FE_o generated smooth FEFV curves that had prominent peaks of maximum flow and flow limitation was readily achieved in the pulmonary airways (Figs. 2–4 and 7).⁶

In the present study, embedding the clear facemask in a thick roll of firm putty that was placed around the nose and an opened mouth was a must for raised volume RTC for the following reasons (Fig. 1): (1) it easily kept the infant’s mouth open during testing; (2) the need to apply only minimal pressure on the mask to prevent airleaks; (3) using both hands, the assistant, who firmly applied both hands against the body and ramus of the mandibles, could simultaneously perform a coordinated gentle anterior jaw thrust to decrease the upper airway resistance of the sedated infant sleeping supine by increasing the oropharyngeal cross-sectional area;^{27,28,40,46,47,51,52} (4) during manual hyperventilation, it enabled the investigator to adjust and, if the generated FEFV curve exhibited flow transients from glottic closure, re-adjust the head and neck.^{6,53} These tasks could not be accomplished with an air-filled cushioned mask because of frequent airleaks.^{5,11}

In the author’s opinion, if the infant’s mouth were to be kept open during raised volume RTC with the facemask embedded in firm putty placed around the mouth and nose as in our studies,⁶ then a mechanical arm⁵⁴ must never be used alone to hold the valve assembly inserted into the facemask port exerting pressure on the mask to prevent air leaks. If the infant were to vomit, inevitable aspiration would very likely occur since swallowing would be hindered by the opened mouth because of interference with lingual propulsion and lingual-mandibular coordination.^{55–59} Moreover, in the chin-down position, a mechanical arm would likely exert pressure through the facemask on the infant’s mandible and push the base of the tongue against the posterior pharyngeal wall.⁴² Consequently, the oropharyngeal cross-sectional area of the sedated infant would be diminished thus reducing the peak expiratory flow which in turn would likely lead an investigator to use higher jacket pressures during raised volume RTC.^{6,52,60} Furthermore, we think that an infant lung function setup, whose design does not enable the investigator to easily reach, hold and optimally adjust with both hands the infant’s head and neck in order to perform the anterior jaw thrust and maintain an opened mouth, would likely facilitate the generation of a FE_n rather than FE_o.

Following repeated raised volume RTC maneuvers, an inexperienced investigator might ascribe the progressive decrease in PF in the FEFV curves to the following: (a) gastric gaseous distension, (b) a paradoxical response to an administered bronchodilator drug, or (c) a presumed late or slow jacket activation if the $V_{PEF}/\%FVC$ ratio exceeded 10%,¹¹ while in fact the mouth was closing and/or increasingly getting obstructed by putty thus increasing the nasal airways' contribution to the forced expiration (FE_n).⁶ Actually, if the first FEFV curve were to be generated via FE_n in an infant, such investigator might think that the reduced PF was a true peak of maximum flow and not even realize that the achieved flow limitation in subsequent maneuvers was in the nasal rather than the pulmonary airways. In the present study, flow limitation seemed more readily achievable via FE_n than FE_o . Therefore, in the author's opinion, the mouth and nares must be routinely visualized through the facemask port before and immediately after each raised volume RTC maneuver (Fig. 1). The PF of the generated FEFV curve must also be assessed.

Published studies to date have not addressed FE_n which is an inherent physiological contributor to forced expiration in infants, hence a real potential confounding element too. Specifically, studies have not emphasized the importance of having an opened mouth or reported whether it had been kept open and monitored during the raised volume RTC technique or not. Moreover, vigilance about minimizing deadspace which is highly recommended during infant lung function testing would likely lead an investigator to use a small size facemask that may not allow the mouth to be opened.^{5-8,24,25,37,61-63} In the author's experience, spontaneous mouth closure and/or obstruction by putty have often occurred during raised volume forced expirations.⁶ Although the potential for a FE_n to reduce FEF and impact the bronchodilator response in infants has long been suspected, the magnitude of the problem and its impact on raised volume RTC studies have remained elusive and unresolved.^{5-7,11,13,14,26,35-37,51,54,64-71}

In the absence of an opened mouth, studies in acute bronchiolitis that employed raised volume RTC could be confounded by the respiratory syncytial virus causing nasal mucosal swelling with increased nasal airflow resistance superimposed on the nasal cycle.⁷² Whereas diminished FEF_{25-75} was documented across all ages in patients with CF, a prospective study reported that the $FEV_{0.5}$ only differentiated children with CF from healthy controls during infancy, not during preschool years.^{10,70} In another study, the FEF_{75} was reported as being the most sensitive marker of airway obstruction.⁷¹ Linnane et al. reported that the $FEV_{0.5}$ and FEF_{75} by raised volume RTC at V_{20} , which were normal at the time of diagnosis by newborn CF screening, diminished in children older than 6 years.⁷³ Using a commercial device, a large multicenter study reported that the functional residual capacity (FRC_{pleth}) measured by plethysmography and the RV were more sensitive than the FEF_{75} by raised volume RTC (V_{30}) in detecting lung function abnormalities in infants with CF. However, only about 25% of those with abnormal FRC_{pleth} and RV also had an abnormal FEF_{75} . In addition, CF infants had better average FVC and $FEV_{0.5}$ than historical controls during the first 18 months of life.⁶⁹ Using a different commercial device, Borrego et al. reported significantly lower z scores in $FEV_{0.5}$, FEF_{75} , FEF_{25-75} and FVC by raised volume RTC from V_{30} in wheezy infants, especially those at risk for subsequent asthma, than healthy controls.⁷⁴ Robin et al. reported that the $FEV_{0.5}$, FEF_{25-75} and FEF_{75} were decreased in infants with a history of prematurity and bronchopulmonary dysplasia.⁶⁸ In a study of infants with differing severities of respiratory symptoms, the $FEF_{\%}$, especially the FEF_{50} , identified a greater number of infants with abnormal lung function than measures of timed volume.⁷⁵ Taken together, infant lung function studies have reported different variables that varied in sensitivity in detecting airway obstruction. Indeed, infant lung function tests were deemed not ready to be used as primary efficacy endpoints in multicenter clinical trials in patients with cystic fibrosis, particularly at inexperienced sites.⁶⁹ In the present study, contrary to the $FEV_{0.4}$, $FEV_{0.5}$, as well as the FEF_{50} and FEF_{25-75} ($p < 0.05$),

differences between FEF₇₅, FEF₈₅ and FEF₉₀ via FE_o versus FE_n were statistically insignificant ($p > 0.05$) (Table 2 and Fig. 6). However, flows at these very low lung volumes have poor reproducibility hence do not routinely characterize levels of airway dysfunction as well as mid-expiratory flows do.^{12,76} In agreement with our recent report,⁶ applying the jaw thrust and keeping an opened mouth during forced expiration (FE_o) resulted in higher PF in the FEFV curves than the passive expiratory flow-volume (pEFV) curves of the IC ($p = 0.0391$); in the present study, although PF was higher than the PF of passive-forced expiratory flow-volume (pFEFV) curves of the jSVC in some infants, the difference was statistically insignificant ($p = 0.0967$) (Figs 2–4). PF of FEFV curves generated via FE_n were not different from PF of pEFV ($p = 0.2891$) but lower than PF of pFEFV ($p = 0.0186$) curves (Figs. 2–4).

The FEFV curves generated via FE_n in our infants (Figs. 2–4) resemble those obtained in adults with an increased external resistance placed at the airway opening, indicating that the effective dimensions of the nasal airways are smaller than those of the opened mouth.^{1,20} In adults, maximum expiratory flow was diminished via nasal than oral forced expiration in the upper 50–60% of the FVC.²⁰ In children aged 5.9–16 years, the PF and FEF₅₀ were decreased and the FVC slightly higher via nasal than oral forced expiration. Moreover, there was no difference in expiratory flow in the lower part of the FVC.⁵¹

Given the significant changes in nasal airway dimensions that occur in infancy, the present study is limited by the relatively small number of subjects, and the fact that it was not designed to undertake an in-depth investigation of the spectrum of potential modulating effects of FE_n on the FEF_% over a wide age range in healthy and wheezy infants or potential bronchodilator responses or to explore racial differences.^{13,15,16,17,22} Given the rapid lung growth and development in infants, their bronchodilator response has been poorly characterized hence not standardized and reportedly minimal or absent below 18 months of age.^{7,35–37,67,68} In the author's opinion, the anterior jaw thrust and an opened monitored mouth that minimize FE_n and maximize FE_o during raised volume RTC (Figs. 2–7) would increase the sensitivity and specificity of the variables of the FEFV curve in diagnosing pulmonary airways dysfunction in infants.^{6,69,74,77}

Conclusions

Although natural breathing is sufficiently sustained via the nose and rarely shared between the mouth and nose in healthy infants, the known higher nasal than the pulmonary airways resistance clearly affects raised volume forced expirations in infants, including the younger ones. By consistently decreasing PF, FE_n altered the shape of the FEFV curve in all infants. FE_n reduced FEF_%, especially mid-expiratory flows, which could also mask a potential bronchodilator response. Therefore, having an appropriate size transparent facemask applied around the infant's mouth and nose that is embedded in putty to achieve an airtight seal is inadequate for raised volume RTC unless it allows the infant's mouth to remain open. In fact, an opened and constantly monitored mouth as well as a gentle anterior jaw thrust ought to be physiologically integral to this sophisticated technique. Consequently, the smooth FEFV curves would have a prominent peak of maximum flow and flow limitation would be easily achieved without having to apply needless higher jacket pressures or use higher jacket driving pressures.⁶ Three critical aims would then be accomplished: (a) to maximize the oral and (b) minimize the inherent nasal airways contribution to the forced expiration, as well as (c) drastically reduce the upper airway resistance of the sedated infant sleeping supine. Ultimately, the flow limitation by raised volume RTC would be in the pulmonary (FE_o) rather than the nasal airways (FE_n).

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Glossary of Abbreviations*

CF	cystic fibrosis
FE_n	nasal forced expiration (mouth closed)
FE_o	oronasal forced expiration (mouth open)
FEF_%	forced expiratory flow at fixed proportions of FVC (FEF ₂₅ , FEF ₅₀ , etc.)
FEFV	forced expiratory flow volume (curve); it generates FVC
FEV_t	forced expiratory volume-time: FEV _{0.4} or FEV _{0.5} expired volume during the first 0.4 or 0.5 sec after the start of forced expiration
FVC	forced vital capacity
tFVC	expiratory time of FVC (forced expiratory time)
IC	inspiratory capacity
jSVC	slow vital capacity
Pao	airway opening pressure
pEFV	passive expiratory flow volume (curve); it generates IC
PF	peak flow
pFEFV	passive-forced expiratory flow volume (curve); it generates jSVC
Pj	jacket (j) pressure
PHA	post-hyperventilation apnea
RTC	rapid thoracoabdominal compression
RV	residual volume
V_{20 or 30}	raised lung volume to a Pao of 20 or 30 cm H ₂ O
V_{PEF}/ %FVC	Ratio of the expired volume at peak expiratory flow and FVC as percent

* Volumes and capacities at V₃₀ are presented throughout the text without the subscript 30.

Figure 1.

Infant's airway opening. The mouth and nares are inspected through the facemask port before and immediately after each maneuver to ensure that they are not obstructed by putty and the mouth remains open (left) not closed (right).

Figure 2.

Flow-volume curves - FEV₀ versus FEV_n. The numbers at the horizontal lines indicate the order (left) of the FEV curve: 'n' refers to a curve generated via FEV_n; the other FEV curves were generated via FEV₀; the measured respective Pj (cm H₂O) plateau is shown (right).

Figure 3.

Flow-volume curves - FE₀ versus FE_n. The numbers at the horizontal lines indicate the order (left) of the FEV₀ curve: 'n' refers to a curve generated via FE_n; the other FEV₀ curves were generated via FE₀; the measured respective P_j (cm H₂O) plateau is shown (right).

Figure 4.

Flow-volume curves - FE₀ versus FE_n. The numbers at the horizontal lines indicate the order (left) of the FEV curve: 'n' refers to a curve generated via FE_n; the other FEV curves were generated via FE₀; the measured respective P_j (cm H₂O) plateau is shown (right).

Figure 5.

FEF%: FE_o versus FE_n. FEF% from the best FEFV curve via FE_o versus FE_n from infants no. 2–12 are plotted against the flow rate (ml/sec).

Figure 6.

Bland-Altman plots from the best intrasubject FEFV curve via FE_o and FE_n showing the distribution of the % difference versus average between the FEF₅₀, FEF₂₅₋₇₅, FEF₇₅ and the FEV_{0.5}. In each panel the horizontal solid line represents the % difference, and the broken lines the 95% limits of agreement of % differences.

Figure 7.

Raised volume RTC in infant no. 4. (A) FE_n versus (B) FE_o . Trace of flow, volume, Pao, and Pj: Inspiration is positive and expiration is negative. As the lung volume is raised, Pao rises to a preset Pao of 30.7 and 30.6 cm H₂O at 0.159 s and 0.159 s then the inflating airflow is halted with the airway simultaneously occluded for 0.20 s which ends at 0.359 and 0.359 s, respectively. Note a 'true' zero flow and volume plateaus and that the predetermined Pao drops to a 'true' actual Pao of 29.6 and 29.5 cm H₂O, respectively during this 0.20 sec period. Jacket inflation begins at 0.352 and 0.354 s. The rising Pj causes a second tiny rise in Pao (jacket driving pressure) to 31.4 and 32.4 cm H₂O, respectively. Forced expiration then starts and is completed at 1.318 and 1.427 s before the end of Pj

plateau, 57.6 and 58.4 cm H₂O; forced expiratory time (*t*FVC) is 0.950 and 1.045 s, respectively. Note that no volume is passively exhaled prior to jacket activation and there is no late or slow application of the forcing function in (A). Note the lower PF and higher V_{PEF}/FVC ratio (19.6% versus 5.8%) in (A) than (B). Respective FEFV curves no. 3n and 4 are in Fig. 2.

Table 1

Subjects Characteristics

Subject No.	Sex & Race ^a	Age (wks)	Length (cm)	Weight (kg)
1	FC	29.1	65.5	6.70
2	FC	26.4	68.0	7.40
3	FC	13.6	60.0	6.08
4	MC	36.6	73.7	10.18
5	MC	27.6	70.4	8.59
6	MB	6.9	56.1	4.89
7	FB	8.4	53.7	4.21
8	FC	74.0	83.2	10.6
9	FC	104.0	87.0	10.90
10	FB	57.0	76.4	9.64
11	MB	33.9	73.5	10.30
12	FB	13.0	58.3	5.69

^aM, male; F, female; C, Caucasian; B, Black;

Table 2Variables from the best FEFV curve via FE_o versus FE_n from infants no. 2–12

Variable	FE _o	FE _n	<i>p</i> ^a	%Difference ^b
PF	1102 (892.0–1239.0; 534.2–1588.0) ^c	763.8 (545.3–831.4; 369.0–1085.0) ^c	0.0005 ^d	37.6 (33.5–47.8; 13.1–83.0) ^c
FEF ₂₅	808.0 (660.3–1072.0; 420.8–1146.0)	737.0 (545.2–747.1; 355.6–1052.0)	0.0034 ^d	14.5 (6.2–36.5; –11.0–62.1)
FEF ₅₀	620.6 (427.1–770.9; 329.0–863.0)	537.7 (378.1–730.8; 223.2–806.0)	0.0415 ^d	11 (–3.5–18.2; –16.3–38.3)
FEF ₇₅	355.0 (186.8–410.7; 131.0–506.0)	322.5 (212.0–443.4; 158.0–462.9)	0.4492	–4.1 (–22.0–10.4; –22.1–27.2)
FEF ₈₅	189.5 (101.0–270.2; 82.0–333.0)	225.8 (128.5–259.0; 95.0–304.0)	0.2598	–1.3 (–34.7–9.1; –52.7–19.0)
FEF ₉₀	133.1 (66.4–204.0; 58.0–211.0)	148.7 (101.2–187.0; 68.5–227.0)	0.5195	–5.4 (–37.6–14.1; –54.3–21.7)
FEF _{25–75}	593.0 (376.0–699.7; 279.0–811.0)	507.0 (370.0–661.2; 227.5–750.0)	0.0269 ^d	10.4 (0.4–18.3; –10.9–24.6)
FVC	362.3 (175.9–431.6; 120.6–534.3)	332.0 (158.8–390.8; 115.6–556.4)	0.1392	7.0 (–3.3–9.9; –8.7–14.0)
<i>f</i> FVC (sec)	1.125 (0.925–1.465; 0.865–2.030)	1.120 (0.950–1.420; 0.660–2.095)	0.3501	
FEV _{0.4}	241.3 (143.5–280.0; 102.2–333.5)	236.0 (131.2–264.5; 89.7–291.0)	0.0024 ^d	11.6 (1.8–13.1; –5.9–17.1)
FEV _{0.5}	285.6 (154.5–328.9; 109.1–372.1)	276.5 (141.1–311.2; 103.1–328.4)	0.0010 ^d	7.5 (3.9–10.6; –4.1–12.5)
V _{PEF} /FVC	4.83 (3.30–5.28; 2.90–7.49)	16.70 (12.40–19.70; 6.20–40.90)	0.0005 ^d	
Pj (cm H ₂ O)	45.3 (43.0–50.0; 37.9–55.9)	51.6 (35.1–57.6; 33.3–59.4)	0.3188	

Units: FEF%, mL/s; volumes and timed volumes, mL.

^aWilcoxon paired-sample test, one-tailed test^b=(100*(FE_o–FE_n)/average)^cMedian (Interquartile range; Range)^dStatistically significant (*p* < 0.05)