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G. Dassieu
L. Brochard
E. Agudze
J. Patkaï
J.-C. Janaud
C. Danan

Continuous tracheal gas insufflation enables a volume reduction strategy in hyaline membrane disease: technical aspects and clinical results

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G. Dassieu · E. Agudze · J. Patkaï · J.-C. Janaud · C. Danan (✉)
Service de réanimation néonatale,
Hôpital Intercommunal de Créteil,
40 av. de Verdun,
94010 Créteil Cedex, France
Fax: + 33 (1) 45 17 54 73
email: nicucreteil@compuserve.com

L. Brochard
Service de réanimation médicale,
Hôpital Henri Mondor,
51 av. du Maréchal de Lattre de Tassigny,
94010 Créteil Cedex, France

Abstract *Objective*: Instrumental dead space wash-out can be used to improve carbon dioxide clearance. The aim of this study was to define, using a bench test, an optimal protocol for long-term use, and to assess the efficacy of this technique in neonates.
Design: A bench test with an artificial lung model, and an observational prospective study. Dead space wash-out was performed by continuous tracheal gas insufflation (CTGI), via six capillaries molded in the wall of a specially designed endotracheal tube, in 30 preterm neonates with hyaline membrane disease.
Setting: Neonatal intensive care unit of a regional hospital.
Results: The bench test study showed that a CTGI flow of 0.5 l/min had the optimal efficacy-to-side-effect ratio, resulting in a maximal or submaximal efficacy (93 to 100 %) without a marked increase in tracheal and CTGI circuit pressures. In the 30 newborns, 15 min of CTGI induced a significant fall in arterial carbon dioxide tension ($PaCO_2$), from 45 ± 7 to 35 ± 5 mmHg ($p = 0.0001$), and in 14 patients allowed a reduction in the gradient between Peack inspirating pressure and positive end-expiratory pressure from 20.8 ± 4.6 to 14.4 ± 3.7 cmH_2O ($p < 0.0001$) while keeping the transcutaneous partial pressure of carbon dioxide constant. As predicted by the bench test, the decrease in $PaCO_2$ induced by CTGI correlated well with $PaCO_2$ values before CTGI ($r = 0.58$, $p < 0.002$) and with instrumental dead space-to-tidal volume ratio ($r = 0.54$, $p < 0.005$).
Conclusion: CTGI may be a useful adjunct to conventional ventilation in preterm neonates with respiratory disease, enabling an increase in CO_2 clearance or a reduction in ventilatory pressure.

Key words Mechanical ventilation · Newborns · Very-low-birthweight · Dead space washout · Barotrauma

Introduction

Improving the survival of the most immature premature neonates takes conventional ventilation to its limits. In this population, the high ratio of volume of dead space to tidal volume of the most severe forms of restrictive respiratory diseases makes efficient CO_2 clearance more and more difficult to achieve. Part of the CO_2 to be cleared from the alveoli is trapped in the dead space. Increasing the elimination of CO_2 is thus often only possible at the price of increasing tidal volume (V_t). For the most immature premature neonates, however, the aggressiveness of artificial ventilation remains a limiting factor with respect to life expectancy and sequelae-free survival [1]. Under those conditions, tracheal wash-out of CO_2 could be a valuable adjunct to increase CO_2

elimination. As shown in previous work, continuous tracheal gas insufflation (CTGI) using a specially designed pediatric endotracheal tube with capillaries molded in its wall enables this objective to be achieved [2]. Moreover, this wash-out procedure allows the instrumental dead space volume to be maintained for easy nursing or for implementation of a pneumotachograph or CO_2 sensor.

The aim of this subsequent study was to determine both in vitro and in vivo which are the important factors for the efficacy of dead space wash-out and also to assess precisely the optimum conditions for prolonged clinical use [2]. Accordingly, the study consisted, first, of a technical phase on a bench test and, second, of the clinical evaluation of 30 newborn infants presenting with hyaline membrane disease. The aims of the technical phase were to define the optimum CTGI flow rate with regard to CO_2 elimination and to tracheal and CTGI circuit pressure rise, the optimum conditions for safety, and to determine the various parameters influencing CTGI efficacy. The aim of the clinical study was to evaluate the capability of CTGI to decrease ventilator pressure or the partial pressure of CO_2 (PCO_2) and to identify the determinants of its efficacy, in order to identify the patients most likely to benefit from this approach. The previous study did not provide such answers, due to the small sample of patients studied and to the relatively homogeneous degree of the respiratory distress [2].

Materials and methods

The clinical phase of the study was approved by the Henri Mondor Institutional Review Board, Créteil, France. The newborns were only enrolled in the study after the informed consent of both parents had been obtained.

Dead space wash-out technique

Dead space wash-out was ensured by an ancillary flow injected into the lower part of the endotracheal tube through six capillaries extruded in the wall of the tube (990.05.1024 EPRT, Vygon, 95 440 Ecouen, France). The endotracheal tube (ETT) internal diameter was 2.7 mm and the external diameter was 4.1 mm. CTGI gases entered six capillaries through a manifold welded to the proximal extremity of the tube. Two other independent capillaries were used, one to monitor pressure changes at the tube extremity, the other to inject surfactant. Pressure monitoring in the CTGI circuit and at the distal extremity of the tube (AST 142PC, Vanves, France) was designed to prevent hyperinflation. Any abnormal rise in the CTGI circuit pressure would trigger an alarm and cut the power supply to the pump while opening an electrovalve (Kuhnke 65231, Malente, Germany).

In order to control both the fractional inspired oxygen (FIO_2) and the relative humidity and temperature of the inspired gases, a silent pump (Sercom WBG 0221 LCB, Schiltigheim, France) was placed in the incubator and drew off 0.5 l/min from the inspiratory circuit downstream of the warmer-humidifier and fed the gases into the CTGI circuit (Fig. 1).

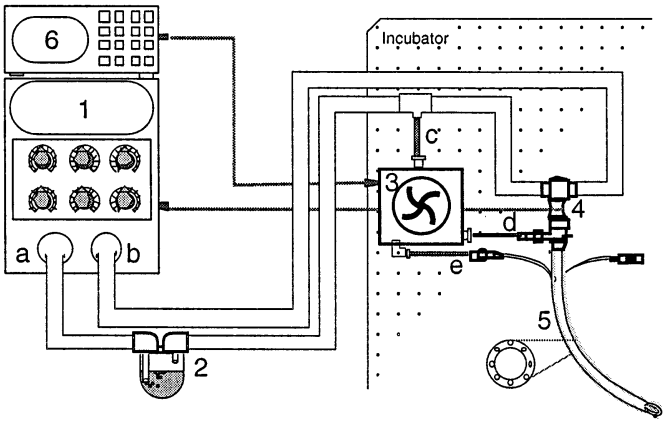

Fig. 1 Diagram of assembly for controlled positive pressure ventilation and CTGI. *1* Ventilator; *2* heater/humidifier; *3* CTGI pump; *4* flow sensor holder; *5* endotracheal tube; *6* monitoring and safety module. *a* Inspiratory circuit; *b* expiratory circuit; *c* CTGI circuit (inlet); *d* CTGI circuit (outlet); *e* tracheal pressure transducer

Bench testing

These tests were mainly selected to evaluate the optimal conditions for delivery, with regard to the efficacy of CO_2 elimination and the various foreseeable risks associated with tracheal insufflation.

Effect of CTGI flow rate on rise in intratracheal pressure and on upstream pressure

Using a test lung and CTGI flow rates ranging from 0.5 to 1.9 l/min, 10 ETT were tested to determine the pressure in the CTGI circuit and at the distal tip (distal pressure) of the tube, which was assessed inside the test lung. Sixty ETT were tested in the same way at a flow rate of 0.5 l/min.

Efficacy of CTGI on PCO_2 reduction in an artificial lung model

The test lung was provided with a continuous CO_2 supply. The PCO_2 in the test lung was determined (Ultracap 6000, Nellcor, Jouy-en-Josas, France) during ventilation, and the CO_2 flow in the test lung was adjusted to keep PCO_2 steady at 50 mmHg. CTGI was then added, and the reduction in PCO_2 induced by CTGI was analyzed. The same experiment was repeated by varying V_t (2–10 ml), instrumental dead space ($V_{D.Inst}$) (4.5 and 0 ml), expiratory time, inspiratory time, CTGI flow rate (from 0 to 1.5 l/min), and PCO_2 before CTGI, by varying the CO_2 flow rate.

These two first series of experiments allowed us to determine the optimal flow rate with regard to the best efficacy-to-side effects ratio.

Contribution of CTGI at 0.5 l/min to V_t

In this test, two different levels of FIO_2 were used, one for the ventilator (FIO_2 0.21) and the other for the CTGI circuit (FIO_2 1). Determination of the resulting FIO_2 in the test lung allowed the calcu-

lation of the contribution of CTGI to V_t as follows: the fraction of V_t contributed by CTGI = (FIO_2 –0.21)/(1 –0.21). V_t ranged from 2 to 10 ml.

Clinical tests

Population

Thirty premature neonates, tracheally intubated and receiving conventional mechanical ventilation (Babylog 8000; Dräger, Lubeck, Germany) for the clinical and radiological syndrome of hyaline membrane disease, were enrolled in the study. The only severity criterion was the requirement for mechanical ventilation. The mean gestational age was 28.5 ± 2.4 weeks, mean weight 1074 ± 365 g, and mean postnatal age 39 ± 28 h. After surfactant had been administered and before the tests were started, mean airway pressure was 11.5 ± 2.8 cmH_2O and FIO_2 was 0.33 ± 0.14.

Methods

Two immediate efficacy tests were conducted. (1) The capnia reduction test: the aim was to evaluate the ability of CTGI at 0.5 l/min to reduce PCO_2 while maintaining the same minute ventilation delivered by the ventilator. Three successive 15-min periods were used; the first to verify the stability of transcutaneous PCO_2 ($TcPCO_2$ (TCM3, Radiometer, Copenhagen, Denmark)), the second to analyze the effect of CTGI, and a third to reassess the effect of discontinuing CTGI. Ventilatory settings were not modified, except for FIO_2 if required. $TcPCO_2$ was monitored throughout the test, and two blood gas determinations were performed, the first immediately before CTGI initiation and the other immediately before discontinuing CTGI.

(2) Peack inspiratory pressure (PIP) reduction test: the aim was to evaluate the ability of CTGI at 0.5 l/min to reduce PIP, and thus V_t, while maintaining a constant $TcPCO_2$. After a 15-min observation period to ensure the stability of $TcPCO_2$, CTGI was given for 15 min. During that period, PIP was adjusted to maintain a constant $TcPCO_2$. The other ventilatory settings were not modified, except FIO_2 if required. After 15 min, CTGI was discontinued and the course of $TcPCO_2$ monitored, without any change in PIP.

If clinical tests were positive (i.e. a reduction in capnia or inflation pressure superior or equal to 10% of the baseline value) the newborn was enrolled for long-term treatment with GTGI.

Instrumental dead space

Under clinical conditions and during bench tests, the instrumental dead space was 4.5 ml, including the Y-piece (breathing circuit No. 7500–4S2, Baxter, Deerfield Ill., USA), the Babylog 8000 flow sensor (No. 8411130 Dräger, Lübeck, Germany), and the ETT. The $V_{D.Inst}$/ V_t ratio was calculated by dividing the instrumental dead space (4.5 ml) by the actual V_t.

Statistics

The results are expressed as mean ± standard deviation (SD). For bench tests, linear regression was used to analyze the relation between ΔPCO_2 and different settings. For clinical tests, paired *t*-tests were used to compare the values of PIP, arterial CO_2 tension ($PaCO_2$), and $TcPCO_2$ before and after CTGI. Linear regression was used to analyze the relation between $\Delta PaCO_2$ and clinical parameters recorded before initiation of CTGI (Statview 4.5, Macintosh).

Long-term treatment with CTGI was not analyzed for this study.

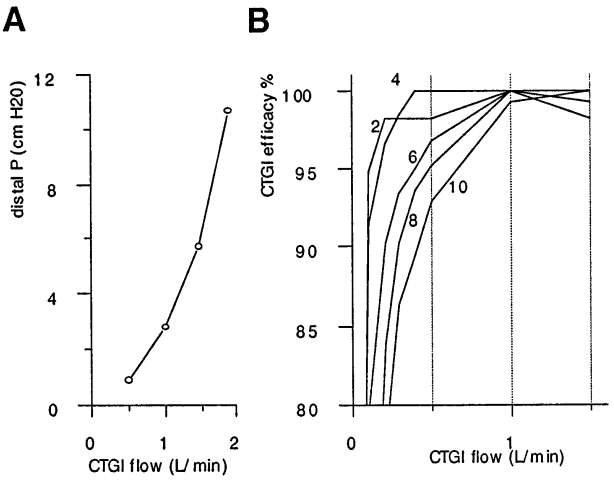

Fig. 2 **A** Measurements of the generated pressure in the test lung *distal P* according to the CTGI flow. **B** Each curve represents for each V_t *2, 4, 6, 8 and 10 ml* the percent of efficacy (calculated for each flow as the ratio between the observed ΔPCO_2 with this flow and the maximum possible ΔPCO_2 with any flow), as a function of CTGI flow (from 100 ml/min to 1 l/min)

Results

Results of the bench test

Effect of CTGI flow rate on rise in intratracheal pressure and on upstream pressure

Sixty ETT were tested to determine the driving pressure required for CTGI with a 0.5-l/min flow: the driving pressure was 48 ± 1 cmH_2O. Ten ETT were tested with different flow rates of CTGI from 0.5 to 1.9 l/min. Whereas with 0.5 l/min CTGI the distal pressure generated by CTGI in the tube was only 0.86 ± 0.04 cmH_2O, this pressure increased fairly rapidly with CTGI flow rate (Fig. 2A). For instance, at a flow rate of 1.9 l/min, the downstream pressure was 10.7 cmH_2O and the driving pressure was 280 cmH_2O.

Efficacy of CTGI on PCO_2 reduction in an artificial lung model

In the test lung model described, increasing CTGI flow from 0.5 to 1 l/min did not result in any significant additional efficacy for V_t up to 10 ml, though it increased the distal tube pressure threefold. For V_t below 4.5 ml (i.e.,

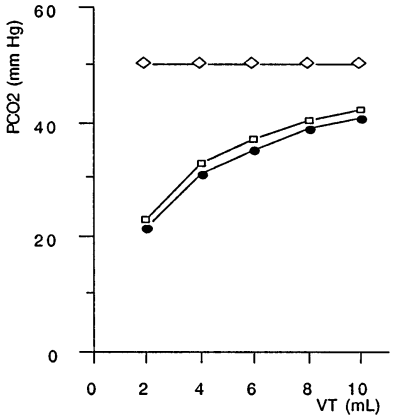

Fig. 3 CO_2 elimination bench tests: CTGI at 0.5 l/min efficacy against efficacy of total instrumental V_d removal. Baseline PCO_2 values with IPPV and with an instrumental V_d of 4.5 ml are represented by *open diamonds*; CO_2 flow in the test lung is set, for each V_t value, to reach a CO_2 baseline value within the test lung of 50 mmHg. PCO_2 values with intermittent positive pressure ventilation (IPPV) + CTGI at 0.5 l/min and with the same instrumental V_d and the same CO_2 flow are represented by *open squares*. PCO_2 values with IPPV and with instrumental $V_d = 0$ and the same CO_2 flow are represented by *closed circles*

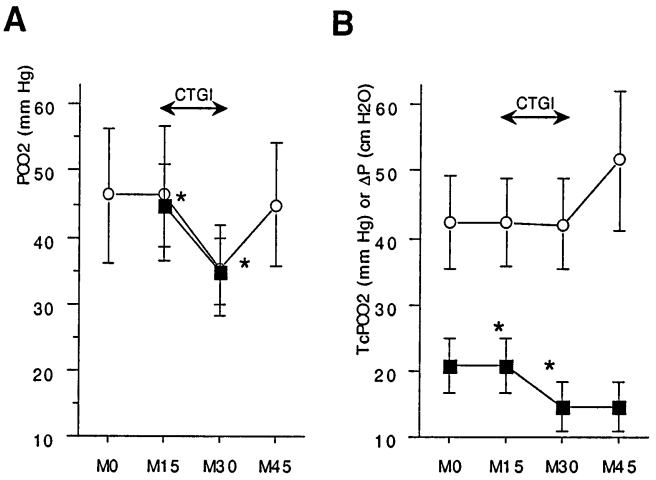

Fig. 4 Clinical tests. **A** PCO_2 reduction test ($n = 30$). After an observation period *M0 to M15*, CTGI at 0.5 l/min was initiated at M15 for 15 min and was discontinued at M30. All ventilator settings were kept constant. $TcPCO_2$ *open circles* and $PaCO_2$ *closed squares* are shown; $^*p < 0.0001$. **B** Pressure reduction test ($n = 14$). During the CTGI period, PIP was reduced in order to keep $TcPCO_2$ constant. At M30 the CTGI was removed and PIP was not modified during the following 15 min. $TcPCO_2$ *open circles* and ΔP (PIP –positive end-expiratory pressure closed squares are shown; $^*p < 0.0001$

the instrumental dead space value), a setting made possible by using CTGI, flow rates less 0.5 l/min could be used without any loss of efficacy (Fig. 2B).

The ability of CTGI to reduce PCO_2 in the test lung was inversely proportional to the PCO_2 before CTGI ($r = 0.99$, $p < 0.0001$) and to the $V_{D.Inst}/V_t$ ratio ($r = 0.99$, $p < 0.001$). The efficacy increased with CTGI flow rate, but was not sensitive to isolated changes in inspiratory or expiratory time.

Under the various test situations, CTGI at 0.5 l/min allowed an optimal efficacy equivalent to the performances of a test lung devoid of dead space (Fig. 3).

Contribution of CTGI at 0.5 l/min to V_t

At 0.5 l/min, CTGI contributed greatly to V_t in all test situations. The contribution of CTGI increased with decreasing tidal volumes (ranging from 40% for $V_t = 10$ ml to 100% for $V_t = 2$ ml) and decreasing respiratory rates. It increased with increasing CTGI flow rates.

Clinical results

CTGI at 0.5 l/min induced on average a 22% reduction in $PaCO_2$: from 45 ± 7 to 35 ± 5 mmHg ($p < 0.0001$) (Fig. 4A). For each of the 30 infants, the reduction in PCO_2 was at least equal to 10% of the baseline value.

The decrease in $PaCO_2$ correlated with the $V_{D.Inst}/V_t$ ratio ($r = 0.54$, $p < 0.005$) and to $PaCO_2$ before CTGI ($r = 0.58$, $p < 0.002$). The decrease was not significantly correlated with any of the following parameters: weight, gestational age, FIO_2, and oxygenation index ($FIO_2 \times 100 \times MAP/PaO_2$, where MAP = mean airway pressure and PaO_2 = arterial oxygen tension). The PIP reduction test was performed in 14 infants. It was not performed in the others because of hypercapnia ($n = 6$) or technical problems ($n = 10$) (Fig. 4B). The gestational age of the group was 28.4 ± 2.2 weeks, and the mean weight was 1131 ± 407 g. At the beginning of the test and after surfactant therapy, mean airway pressure was 11.3 ± 3.3 cmH_2O and FIO_2 was 0.32 ± 0.16.

After 15 min of CTGI, the ΔP [PIP-PEEP (positive end-expiratory pressure)] was reduced by 30%, from 20.8 ± 4.6 to 14.4 ± 3.7 cmH_2O ($p < 0.0001$). The ΔP reduction correlated well with baseline $TcPCO_2$ ($r = 0.6$, $p < 0.05$) and with baseline PIP ($r = 0.57$, $p < 0.05$).

Discussion

With the technique proposed herein, CTGI requires little change in conventional ventilatory practice and seems adequate for prolonged treatment. As shown both in vitro and in mechanically ventilated premature newborns, a CTGI flow rate of 0.5 l/min allows an optimal instrumental dead space wash-out without causing

significant hyperinflation; this flow rate may even be reduced for a smaller V_t.

A standard method of reducing total V_d is to minimize instrumental volume [3]. With this method, however, it is not possible to suppress completely instrumental dead space. Furthermore the new neonatal ventilators use flow sensors which represent mandatory additional instrumental dead space [4].

Because a reduction in dead space became an important goal in mechanical ventilation for adult patients with lung injury, Marini and his group developed the technique of tracheal gas insufflation in animals and in adult patients [5, 6]: continuous or expiratory wash-out of the lower trachea and the instrumental dead space was performed in combination with conventional mechanical ventilation by means of a catheter inserted through the ETT. Others have proposed a special ETT to avoid the use of a catheter which may reduce the internal lumen of the tube and which can facilitate endotracheal suctioning [7, 8]. Because in neonates the introduction of a catheter can result in a critical reduction of the inner ETT diameter, we adapted this method to neonatal ventilation and developed the technical solutions presented here. There is only a small advantage in using a catheter instead of the special ETT in terms of efficacy, since the effect of catheter position is small or even negligible close to the carina [9]. In patients, the tracheal gas insufflation has been proposed both to reduce $PaCO_2$ [6] and to reduce V_t while maintaining a constant $PaCO_2$ [10].

Kolobow and coworkers developed for neonatal use intratracheal pulmonary ventilation based on a different principle [11–13]: a catheter is placed in the ETT, with its distal end designed to direct gas flow from the distal to the proximal part of the ETT, creating a Venturi effect. In addition, all the gases used for ventilation are injected via the catheter, which thus fully bypasses the instrumental dead space. The flow and pressure dynamics generated by intratracheal pulmonary ventilation thus differ from those observed in conventional ventilation [14]. In an animal model of hyaline membrane disease, this technique enabled a substantial reduction in insufflation pressures and V_t [14]. Comparing our results to these, our test lung study suggests that CTGI with a flow rate of 0.5 l/min results in ventilation free of instrumental dead space and suggests that CTGI has a comparable efficacy to the total bypass achieved by Kolobow's technique.

Since the main goal of CTGI is to clear expired CO_2 from the instrumental dead space, expiratory wash-out only is required [15]. Ravenscraft et al. [16] showed that the effectiveness of TGI was primarly determined by the expiratory flush volume, whatever the fraction of expiration during which it was delivered. At conventional ventilation rates, the instrumental dead space used is totally washed out during expiration with a flow rate of 0.5 l/min. Use of continuous flow adds an inspiratory bypass effect [17]. The inspiratory contribution of CTGI, used alone, may be relatively pronounced for a very small V_t, while its effect is negligible if the tube has been totally washed out during the previous expiration, since the inspired gas will be free of CO_2. For simplicity, however, and because the ventilator provides continuous flow, we preferred to use continuous tracheal insufflation.

As demonstrated previously, the increase in distal pressure is due to a momentum transfer mechanism [18] created at the continuous flow exit in the endotracheal tube lumen. The distal pressure increases very rapidly with the velocity of the gas at the exit of the capillaries [18], and thus with rising CTGI flow rates. Consistent with previous findings, our bench tests demonstrated that CTGI flow rates greater than 0.5 l/min could generate unacceptable levels of tracheal pressure. It is important to stress that the distal pressure created by CTGI cannot be detected at the Y-piece level and thus cannot be displayed by the ventilator manometer. In addition, in order to generate CTGI flow without reducing humidity during gas expansion in the ETT, the driving pressure should not exceed 100 cmH_2O. This generates a 0.5-l/min flow, and therefore the pressure generated at the tracheal end of the tube does not exceed 1 cmH_2O.

Bench tests also confirmed that 0.5 l/min was almost always sufficient to obtain optimal CO_2 wash-out, even with respiratory rates of 90 cycles/min. Therefore, it seems that, for the ETT described in this study, a flow rate of 0.5 l/min has the optimal benefit/risk ratio.

Because maximum efficacy is obtained as soon as the wash-out enables a volume equal to the V_t to be cleared during expiration, CTGI flows of less than 0.5 l/min could be used for a small V_t (i.e., less than instrumental dead space volume). For a V_t greater than the instrumental dead space volume, the required CTGI flow has to wash out the instrumental dead space; this is achieved, as discussed above, with an 0.5-l/min CTGI. If the instrumental dead space is washed out during expiration by a volume equivalent to the next delivered V_t, the instrumental dead space can be increased without affecting $PaCO_2$. This has interesting possibilities for clinical applications, such as ease of nursing, baths, skin to skin, while keeping the baby connected to the respirator, or for interposition of monitoring sensors (flow or CO_2 sensor).

It is noteworthy that a CTGI at 0.5 l/min used with neonatal continuous flow ventilators does not modify minute ventilation or V_t volume (data not shown) as has been reported with volume-cycled but also pressure-limited ventilators for adults [19]. There is no modification of the inflation pressure. This may not be true if flow rates higher than 0.5 l/min are used, however, because of positive pressure generated in the lung.

Although CTGI does not modify the V_t, the gas provided by CTGI can contribute to the V_t composition, which makes it mandatory to achieve adequate humidity and warming. In an animal study, Shapiro et al. [20] showed that tracheal injection of dry gas substantially reduced airway temperature and humidity, and increased the incidence of tracheal lesions. With the present system, this risk is prevented by maintaining the humidity and temperature of the inspired gases, and by the fact that the CTGI delivery aperture is located 2.1 cm above the distal end of the ETT. This distance is sufficient for the jet of gas exiting from the distal end of the CTGI capillaries not to impact on the tracheal mucosa [21].

At a constant $TcPCO_2$, CTGI at 0.5 l/min allowed a 30 % decrease in the inflation pressure (PIP –PEEP) (from 20.8 to 14.3 cmH_2O). The decrease in V_t for a constant PCO_2 could not be directly measured but should be similar to the 30 % reduction in inflation pressure, if compliance remained constant. This potential 30 % decrease in V_t should allow a noticeable decrease in the mechanical stress (barotrauma and volutrauma) related to artificial ventilation, allowing the use of tidal volumes of about 3 ml/kg or even less in association with a moderate permissive hypercapnia strategy. The high efficacy of CTGI is due to the fact that the target population is particularly suitable for this type of technique, having a high V_d/V_t ratio and a high initial $PaCO_2$. This confirms in premature infants the data reported by Ravenscraft et al. and Nahum et al. in animals [6, 15]. Neonatal hyaline membrane disease is a restrictive lung disease with an increased V_d/V_t ratio and no marked increase in alveolar dead space. In other types of respiratory distress in which alveolar dead space is predominant, the efficacy of CTGI is reduced since the ventilated and poorly perfused alveoli induce a decrease in the CO_2 content of the airways [15]. Because CTGI mainly acts by washing expired CO_2 out of the respiratory prostheses, the efficacy of CTGI on $PaCO_2$ is proportional to the CO_2 content of the V_d and should be predictable on the basis of its immediate effect on tracheal capnography [6, 15].

During the weaning period, and particularly in low-birth weight children with a high $V_{D.Inst}/V_t$ ratio, CTGI may also allow a decrease in the work of breathing. This aspect deserves further assessment.

During the acute period of respiratory disease, CTGI, by increasing CO_2 clearance, enables infants to be less aggressively ventilated with reduced inflation pressure or V_t. In the context of a dual strategy associating optimized conventional mechanical ventilation and permissive hypercapnia, CTGI may perhaps contribute to decreasing the incidence of bronchopulmonary dysplasia and its use may be advisable for this purpose.

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