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EXPERIMENTAL

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Tracheal gas insufflation during late exhalation efficiently reduces $PaCO_2$ in experimental acute lung injury

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Abstract *Objective:* Tracheal gas insufflation (TGI) reduces $PaCO_2$ by flushing the tracheal and mechanical deadspace, and may have its maximum benefit when TGI gas is unopposed by significant expiratory gas flow. Thus, limiting TGI to the late expiratory period may diminish tracheal exposure to TGI gas while preserving the efficacy of TGI. This study examined the gas exchange consequences of such late-expiratory TGI. *Design and setting:* Randomized controlled trial, animal study. *Materials:* Eleven pigs. *Interventions:* After stable lung injury was established using oleic acid 11 pigs were ventilated using a standardized lung protective strategy. Phasic expiratory TGI was applied for 30 min stages during the last 20%, 40%, 60%, and 100% of expiration in random sequence. $PaCO_2$ was continuously measured via an indwelling blood gas analysis system. *Measurements and results:* $PaCO_2$ at baseline was 86.1±4.7 mmHg, and decreased progressively with increasing TGI duration of 20%, 40%, and 60%, but not 100%, of expiration ($PaCO_2$=75.7±5.2, 68.8±3.6, 65.1±5.3 and 65.2±5.2 mmHg, respectively). For all stages the reduction in $PaCO_2$ relative to baseline was significant. Trends of increasing PaO_2 and airway pressure with increasing TGI duration were noted and most likely associated with a TGI-induced increase in lung volume. *Conclusions:* Under these conditions confining TGI to the final 60% of expiration achieved effective $PaCO_2$ reduction, not significantly different from panexpiratory TGI, while limiting exposure of the trachea to TGI gas, and reducing the potential for TGI-induced hyperinflation. These findings suggest that TGI is most effectively applied in a phasic manner in late expiration, with its duration titrated to effect.

Keywords Respiration, artificial · Insufflation, trachea · Pulmonary gas exchange · Lung Injury · Respiratory distress syndrome, adult

Introduction

As an adjunct to mechanical ventilation, tracheal gas insufflation (TGI), effectively reduces $PaCO_2$ by expelling CO_2-laden expired gas from the anatomical and mechanical deadspace and replacing it with fresh gas, thereby preventing rebreathing [1, 2, 3, 4, 5, 6, 7, 8, 9, 10]. TGI entails specific risks related to tracheal mucosal injury and hyperinflation [11]. While increasing the injected gas volume generally improves the effectiveness of TGI [9, 10, 11, 12], it may also exacerbate these problems. The competing priorities of efficacy and safety might be reconciled if a more efficient manner of delivering TGI gas could be defined, preserving its ventilatory benefit while minimizing adverse effects. It has been shown previously that expiration is the active segment of the tidal

cycle for TGI, and that the washout effect may operate mainly in the late portion of expiration [10, 11, 12, 13, 14]. Because the effectiveness of TGI is correlated best with the volume of fresh gas delivered during this late expiratory period [10], limiting TGI to late expiration may allow volume delivery to be reduced without seriously compromising its therapeutic effect.

This study examined the effects of varying TGI duration over the terminal portion of expiration. Our goal was to better define the dynamics of TGI in the treatment of acute lung injury.

Methods

The protocol and procedures were approved by the Animal Care and Use Committee of Regions Hospital. Eleven pigs (weight 26.1±2.5 kg) were anesthetized with pentobarbital (30 mg/kg as intravenous load followed by intravenous infusion of 15 mg/kg per hour) and paralyzed with pancuronium (0.1 mg/kg intravenously every 30 min). A 7.0 mm (inside diameter) endotracheal tube with an integral channel suitable for TGI (Hi-Lo, Mallinckrodt, Carlsbad, Calif., USA) was placed through a tracheostomy with its tip 2 cm above the main carina; proper position was confirmed bronchoscopically. Central venous and arterial lines were placed, and an indwelling, continuous arterial blood gas (ABG) sensor (Paratrend 7, Diametrics, St. Paul, Minn., USA) was inserted via the femoral artery.

Lung injury was induced by oleic acid infusion (0.10–0.20 mg/kg intravenously) titrated to a target PaO_2/FIO_2 ratio of 80–120 mmHg. During oleic acid infusion, each animal was ventilated (Model 840, Nellcor-Puritan-Bennett, Carlsbad, Calif., USA) in volume assist/control mode with f of 12/min, tidal volume (V_T) 10 ml/kg, positive end-expiratory pressure (PEEP) 5 cmH_2O, and FIO_2=1.0. Following injury a standardized lung-protective ventilatory strategy was initiated, utilizing decelerating-flow volume assist/control with V_T of 6–8 ml/kg. Frequency and PEEP were adjusted to achieve a $PaCO_2$ of approximately 80 mmHg and PaO_2 higher than 80 mmHg with FIO_2 and I:E ratio of 1.0 and 1:2, respectively. In all stages of the study the expiratory flow was observed to cease well before end-expiration.

TGI with pure oxygen was applied through the distal accessory port of the endotracheal tube in four randomly sequenced stages during the final 20%, 40%, 60%, and 100% of the expiratory phase using a controller designed for this investigation (Valley Inspired Products, Burnsville, Minn., USA). This controller sensed inspiratory/expiratory flow via a common-limb pneumotachometer (Fig. 1) and delivered time-controlled TGI flow (5 l/min) during the selected portion of the expiratory phase. TGI flow was terminated when the controller sensed the onset of inspiration. Each stage was maintained for at least 5 min of stable ABG values following a 30 min equilibration period. Baseline ABG values (without TGI) were obtained before the 1st stage, between stages 2 and 3, and after the 4th stage to evaluate the stability of the preparation.

$PaCO_2$ during TGI was compared between stages using paired *t* test with Bonferroni's correction for multiple comparisons (StatView, SPSS, Chicago, Ill., USA).

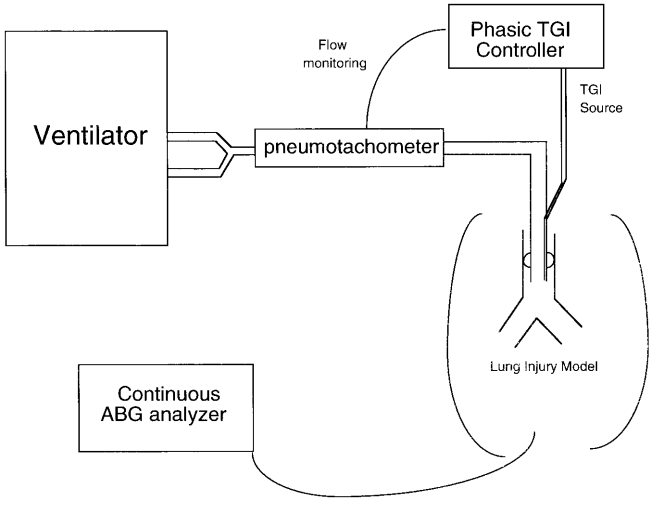

Fig. 1 Schematic of the experimental apparatus. The apparatus consisted of the ventilator, a common-limb pneumotachometer (Hamilton Medical, Reno, Nev., USA), the phasic TGI controller, the continuous ABG analyzer, and the animal model. The ventilator operated at baseline settings (a pressure-guarding strategy) throughout each study without adjustments or integration (electrical or pneumatic) with the TGI controller. The phasic TGI controller detected and "learned" the flow timing/direction from the in-line pneumotachometer and delivered TGI per protocol randomization. The ABG analyzer displayed the effects of setting changes throughout the protocol

Results

Subjects were ventilated with a mean V_T of 6.7±0.8 ml/kg, f 26.1±4.4/min, and PEEP 16.4±3.0 cmH_2O. Measurable expiratory flow was absent during the final 0.9±0.1 s (61±7%) of the expiratory period. In response to oleic acid injury prior to TGI mean arterial pH fell from 7.38±0.07 to 6.87±0.08 mmHg, $PaCO_2$ rose from 39.1±8.0 to 86.1±4.7 mmHg, and PaO_2 fell from 556.8±55.7 to 95.3±49.1 mmHg. The initial, midstudy, and final baseline $PaCO_2$ (85.4±4.2, 85.0±4.5, and 88.3±5.6 mmHg) and PaO_2 (93.1±39.6, 101.1±57.4, and 92.1±56.9 mmHg) did not differ significantly, suggesting a stable preparation and severity of injury throughout the study.

The responses of PaO_2, $PaCO_2$, and airway pressure to late-expiratory TGI are shown in Fig. 2. At all TGI durations the $PaCO_2$ values were reduced significantly from baseline ($p<0.05$). $PaCO_2$ tended to decrease with incremental increases in application time up to 60%, such that $PaCO_2$ at 60% was significantly less ($p<0.05$) than at 20% (Fig. 2A). There was no meaningful difference between $PaCO_2$ at 60% and 100%. PaO_2 tended to rise with increasing TGI duration ($p>0.05$; Fig. 2B). The effect of increasing TGI duration caused an increase in mean pH from the baseline of 6.87 to a range of 6.90–6.95.

Airway plateau (inspiratory pause) and airway mean pressures were observed to rise slightly in response to increasing TGI duration (Fig. 2C).

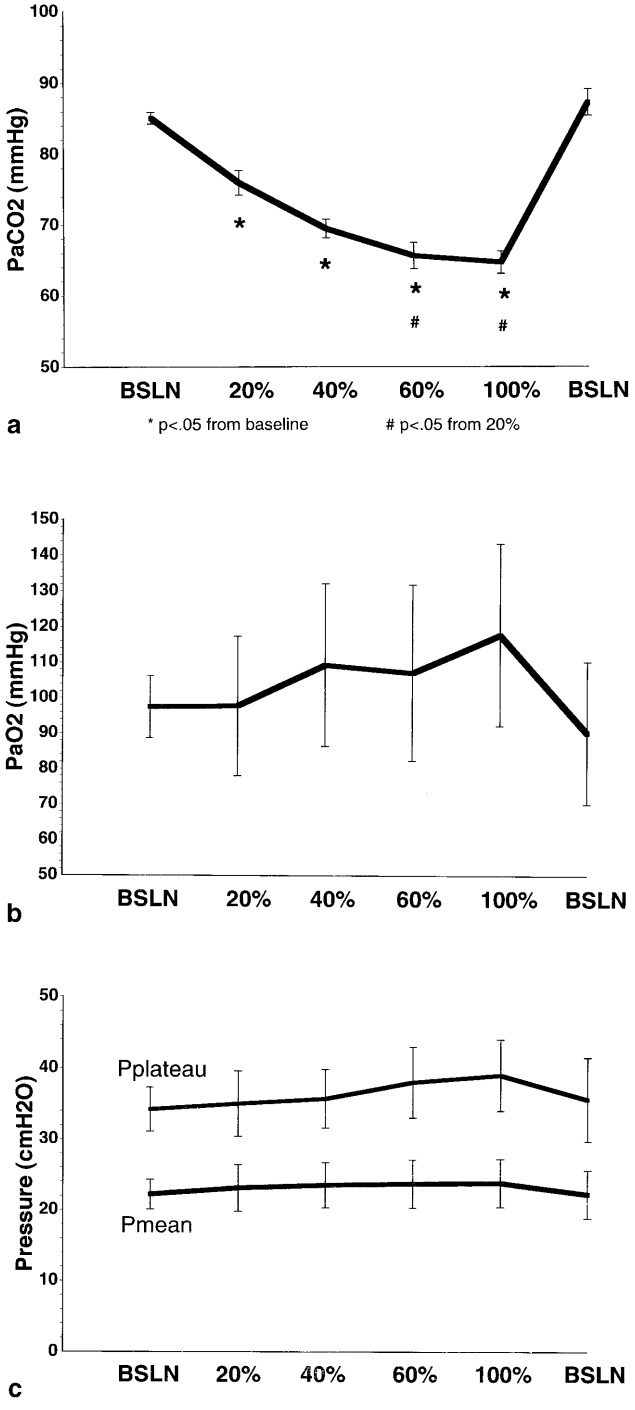

Fig. 2 a $PaCO_2$ response to expiratory TGI duration. $PaCO_2$ (±SE) is plotted vs. TGI duration, expressed as percentage of expiratory period, with end-expiration corresponding to 0%. $PaCO_2$ falls sharply with TGI duration set at 20% expiratory time. TGI duration provides incrementally less CO_2 reduction with increasing duration until no reduction occurs between 60% and panexpiratory application. **b** The effect on PaO_2 of increasing TGI duration. Change in PaO_2 (±SE) with increasing TGI time is not significant but trends upward as TGI duration is increased. **c** Mean airway and end-inspiratory plateau pressures (±SE) tend to increase with increasing TGI duration

Discussion

The overall efficacy of TGI in this animal model of severe acute lung injury is consistent with that observed by Belghith and colleagues [15] in human severe acute respiratory distress syndrome. Our results indicate that in the setting of lung injury and permissive hypercapnia, a TGI duration as short as 20% of expiration, corresponding to a TGI duration of only 0.31±0.05 s per breath, can augment CO_2 removal if applied selectively at the end of expiration. Furthermore, the therapeutic effect of fixed-flow rate TGI was essentially complete by 60% of expiration and did not increase with longer duration. The relationship of $PaCO_2$ to TGI duration that we observed is consistent with the inverse relationship of $PaCO_2$ to injected TGI volume described in our previous work conducted in healthy dogs [10]. The current results validate, in the setting of lung injury, our previous observations that (a) TGI benefit is reduced in the early expiratory period, when significant expiratory flow is present [10, 14], (b) a relatively short application of TGI may lower $PaCO_2$ significantly below baseline [10], and (c) in general, $PaCO_2$ decreases as the delivered TGI gas volume increases [10]. However, the current study also identifies a temporal constraint to TGI delivery in this setting. Increasing TGI volume by lengthening the injection period effectively augments CO_2 washout within late expiration, but further extension of TGI injection into the earlier period of ongoing expiratory flow may provide only marginal added benefit.

Mechanisms of late-expiratory TGI effect

Four mechanisms may account for the relative efficiency of TGI in the late-expiratory period. First and most importantly, late-expiratory TGI avoids bulk displacement of freshly insufflated gas mouthward by expired gas. While TGI gas insufflated early in expiration may be predominantly carried out of the airways, TGI gas injected in late-expiration persists in the anatomical and mechanical deadspace. Second, late-expiratory TGI more effectively dilutes CO_2-laden gas in the deadspace. As TGI gas exits its orifice(s), it undergoes turbulent mixing with expired alveolar gas. Therefore it acts not only by bulk displacement but also by dilution of CO_2 residing in the deadspace [14]. Theoretical and test lung models have shown the efficiency of this dilution to be inversely proportional to the mean expiratory flow occurring during the period of gas insufflation; CO_2 dilution increases in roughly exponential fashion as expiratory flow declines [14, 16]. Although not specifically tested in this study, the third and fourth proposed mechanisms apply to early vs. late expiratory TGI, Third, decreased expiratory flow during late expiration permits TGI gas to propagate substantially farther along the tra-

cheobronchial tree [14], increasing the flushed volume. Fourth, some portion of CO_2 reduction may be attributable to the "double inspiration" phenomenon [13]. Briefly, if TGI is turned on in the zero-flow period after the lungs have deflated, TGI may generate a small inspiratory flow of fresh gas. In volume control mode the ventilator adds an additional (albeit small) tidal volume; thus TGI increases total minute ventilation. Because respiratory compliance in our lung injury model was relatively low, the volume changes in response to TGI were expected to be small. Therefore we judge the "double inspiration" effect to have been of minimal significance in this model.

The first three mechanisms above may explain the results of Imanaka and colleagues [17], who found that when ventilating with I:E of 1:2, CO_2 reduction was greater with forward-directed than reverse-flow TGI, whereas with I:E of 2:1 there was no significant difference between them. It is plausible that when the expiratory phase is relatively long, the period of no-flow allows forward-directed TGI to penetrate further beyond the endotracheal tube, increasing the volume of flushed deadspace. With relatively short expiratory times such propagation is less likely; the volume in the ventilator circuitry behind the endotracheal tube tip becomes the principal volume flushed, and catheter direction is less important.

Adjusting the duration of late-expiratory TGI

In the present study CO_2 reduction occurred during the final 60% of expiration, with 82% of the total effect achieved in the terminal 40%. These percentages would be expected to vary depending on airway volume, mechanical deadspace volume in the ventilator circuit, I:E ratio, TGI flow rate, expiratory flow rate and profile. Therefore it is difficult to prescribe a universal duration for maximally efficient late-expiratory TGI. In general, durations of TGI that extend progressively into the period of detectable expiratory flow would be expected to provide diminishing additional gain. However, in the case of severe airflow obstruction, where the zero-flow period may be brief or absent – but expiratory flows are very low – longer TGI durations would be expected to yield greater benefit. Expiratory capnography, not measured in this study, may facilitate individualized adjustment of the TGI duration. The end-tidal PCO_2 should approach zero as deadspace flushing is completed [4, 18], so that as TGI duration is extended, the loss of further decline in end-tidal PCO_2 signals a point of diminishing returns.

Minimizing TGI duration should reduce certain hazards of its use. TGI increases end-expiratory lung volume by increasing end-expiratory plateau pressure [13]. Inadequately conditioned TGI gas has cooling and drying effects on the airways that are potentially injurious [12, 19]. There is also potential for direct mechanical trauma to the carina or tracheal wall caused by the TGI gas as it exits its delivery port(s) at high velocity. It is reasonable to assume that each of these potentially injurious mechanisms – drying, cooling and mechanical trauma – increases in proportion to the amount of TGI delivered, and that such adverse effects are minimized by limiting TGI flow, duration, or both. Another solution, careful conditioning of TGI gas, addresses cooling and drying but not mechanical trauma or auto-PEEP concerns.

It is worth noting that although the use of late-expiratory phasic insufflation allows a reduction in airway exposure to TGI gas, the safe threshold of unconditioned gas exposure remains unknown. Therefore, some degree of gas conditioning may be advisable regardless of the TGI delivery technique.

Study limitations

Our study has several limitations. It was conducted in animals with a characteristic type of experimental lung injury, employed an aggressive strategy of permissive hypercapnia, and focused on a narrow range of ventilatory (and TGI) conditions. As described, the monitoring of expiratory capnography and continuous lung volume status would have added further insight into the mechanisms of late expiratory TGI. Although the increases were not statistically significant, increases in PaO_2 with longer TGI duration corresponded to increases in plateau/mean pressures. This trend in PaO_2 and pressures and possibly a portion of the $PaCO_2$ reduction are probably due to a TGI-induced increase in lung volume [4] that was not measured in this study. Nonetheless, the concordance of our results with previous experimental and theoretical work, as discussed above, suggests that our conclusions have broad validity.

Conclusion

These results demonstrate that in the setting of acute lung injury the full therapeutic effect of phasic expiratory TGI may be realized while limiting its application to the terminal portion of expiration.

References

1. Marini JJ (1994) Tracheal gas insufflation: a useful adjunct to ventilation? Thorax 49:735–737
2. Marini JJ (1996) Adjunctive ventilation with tracheal gas insufflation – good vibrations. Crit Care Med 24:375–378
3. Nahum A, Burke WC, Ravenscraft SA, Marcy TW, Adams AB, Crooke PS, Marini JJ (1992) Lung mechanics during pressure-control ventilation in dogs. Augmentation of CO2 elimination by an intratracheal catheter. Am Rev Respir Dis 146:965–973
4. Ravenscraft SA, Burke WC, Nahum A, Adams AB, Nakos G, Marcy TW, Marini JJ (1993) Tracheal gas insufflation augments CO2 clearance during mechanical ventilation. Am Rev Respir Dis 1993:148:345–351
5. Nahum A, Shapiro RS, Ravenscraft SA, Adams AB, Marini JJ (1995) Efficacy of tracheal gas insufflation in a canine model of lung injury. Am J Respir Crit Care Med 152:489–495
6. Nakos G, Zakinthinos S, Kotanidou A, Tsagaris H, Roussos C (1994) Tracheal gas insufflation reduces the tidal volume while PaCO2 is maintained constant. Intensive Care Med 20:407–413
7. Cereda MF. Sparacino ME. Frank AR. Trawoger R. Kolobow T (1999) Efficacy of tracheal gas insufflation in spontaneously breathing sheep with lung injury. Am J Respir Crit Care Med 159:845–850
8. Kalfon P, Rao GS, Gallart L, Putbasset L, Coriat P, Rouby JJ (1997) Permissive hypercapnia with and without expiratory washout in patients with severe acute respiratory distress syndrome. Anesthesiology 87:6–17
9. Imanaka H, Kirmse M, Mang H, Hess D, Kacmarek RM (1999) Expiratory phase tracheal gas insufflation and pressure control in sheep with permissive hypercapnia. Am J Respir Crit Care Med 159:49–54
10. Ravenscraft SA, Shapiro RS, Nahum A, Burke WC, Adams AB, Nakos G, Marini JJ (1996) Tracheal gas insufflation: effectiveness determined by expiratory flush volume. Am J Respir Crit Care Med 153:1817–1824
11. Burke WC, Nahum A, Ravenscraft SA, Nakos G, Adams AB, Marcy TW, Marini JJ Modes of tracheal gas insufflation: comparison of continuous and phase-specific gas injection in normal dogs (1993) Am Rev Respir Dis 148:562–568
12. Marini JJ (1998) Phasic expiratory tracheal gas insufflation: short but sweet. Crit Care Med 26:825–826
13. Takahashi T, Bugedo G, Adams AB, Bliss PL, Marini JJ (1999) Effects of tracheal gas insufflation and tracheal gas exsufflation on intrinsic positive end-expiratory pressure and carbon dioxide elimination. Respir Care 44:918–924
14. Carter CS, Hotchkiss JD, Adams AB, Stone MK, Marini JJ (2000) Propagation and configuration of tracheal gas insufflation (TGI) flow when opposed by expiratory flow (abstract). Am J Respir Crit Care Med 161:A388
15. Belghith M, Fierobe L, Brunet F, Monchi M, Mira JP (1995) Is tracheal gas insufflation an alternative to extrapulmonary gas exchangers in severe ARDS? Chest 107:1416–1419
16. Hotchkiss JR Jr, Crooke PS 3rd, Marini JJ (1996) Theoretical interactions between ventilator settings and proximal deadspace ventilation during tracheal gas insufflation. Intensive Care Med 22:1112–1119
17. Imanaka H, Kirmse M, Mang H, Hess D, Kacmarek RM (1999) Expiratory phase tracheal gas insufflation and pressure control in sheep with permissive hypercapnia. Am J Respir Crit Care Med 159:49–54
18. Kuo P-H, Wu H-D, Yu C-J, Yang S-C, Lai Y-L, Yang P-C (1996) Efficacy of tracheal gas insufflation in acute respiratory distress syndrome with permissive hypercapnia. Am J Respir Crit Care Med 154:612–616
19. Shapiro RS, Ravenscraft SA, Nahum A, Adams AB, Marini JJ (1995) Tracheal Gas Insufflation (TGI) cools and dries gas in the central airways (abstract). Am J Respir Crit Care Med 151:A427