Pattern of inspiratory gas delivery affects CO_2 elimination in health and after acute lung injury

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Abstract

Objective: To avoid ventilator induced lung injury, tidal volume should be low in acute lung injury (ALI). Reducing dead space may be useful for example by using a pattern of inspiration that prolongs the time available for gas distribution and diffusion within the respiratory zone, the mean distribution time (MDT). A study was conducted to investigate how MDT affects CO_2 elimination in pigs at health and after ALI.

Design and setting: Randomised crossover study in the animal laboratory of Lund University Biomedical Center.

Subjects and intervention: Healthy pigs and pigs with ALI, caused by surfactant perturbation and lungdamaging ventilation were ventilated with a computer-controlled ventilator. With this device each breath could be tailored with respect to insufflation time and pause time (T_I and T_P) as well as flow shape (square, increasing or decreasing flow).

Measurements and results: The single-breath test for CO_2 allowed analysis of the volume of expired CO_2 and the volume of CO_2 re-inspired from Y-piece and tubes. With a long MDT caused by long T_I or T_P, the expired volume of CO_2 increased markedly in accordance with the MDT concept in both healthy and ALI pigs. High initial inspiratory flow caused by a short T_I or decreasing flow increased the re-inspired volume of CO_2. Arterial CO_2 increased during a longer period of short MDT and decreased again when MDT was prolonged.

Conclusions: CO_2 elimination can be enhanced by a pattern of ventilation that prolongs MDT. Positive effects of prolonged MDT caused by short T_I and decreasing flow were attenuated by high initial inspiratory flow.

Keywords

Pulmonary Gas Exchange · Respiration, Artificial · Capnography · Breath Tests · Swine

INTRODUCTION

During mechanical ventilation, oxygenation can in most instances be maintained at very low alveolar ventilation by increasing the fraction of inspired oxygen. Exchange of CO_2, however, depends upon alveolar ventilation. Enhanced CO_2 elimination without applying high airway pressure caused by high tidal volume (V_T) is an issue in some clinical situations. At acutely increased intracranial pressure a low $PaCO_2$ at low airway pressures may be desired, at least in an initial stage. In acute obstructive lung disease enhanced CO_2 elimination at low minute ventilation is often desired. Limitation of pressure and V_T is a strategy for lungprotective ventilation in acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) [1-6]. With respect to gas exchange, an optimal benefit from a particular V_T is an issue, whatever target values for arterial pH or $PaCO_2$ are chosen.

An optimal pattern of V_T delivery may enhance CO_2 elimination and an inspiratory pause may reduce respiratory dead space (V_D) or $PaCO_2$ [7-11]. Such positive effects have not always been observed, however [9, 12-14]. Diverging results may reflect methodological limitations.

Capnography in the format of the single-breath test for CO_2 ($SBT\text{-}CO_2$) allows accurate determination of CO_2 elimination and partitions of V_D [15]. Uttman et al. showed in healthy pigs that CO_2 elimination depends on time available for gas distribution and diffusion within the respiratory zone, mean distribution time (MDT) [16]. Variation of MDT was achieved by changing the duration of the postinspiratory pause (T_P). CO_2 elimination varied in proportion to the logarithm of MDT. Aboab et al. recently reported similar findings in ARDS patients [17]. In the latter study the concept of MDT was modified by taking into account the time required during inspiration to bring the fresh gas interface down to the respiratory zone. Furthermore, the concept of distribution was widened to include CO_2 exchange with alveolar blood. Still, knowledge is limited about how different combinations of duration of inspiratory gas insufflation (T_I) and T_P affect CO_2 elimination and ultimately $PaCO_2$.

The objective of the present study in pigs -healthy and after ALI- was to test the hypothesis that MDT describes how variation of inspiratory gas delivery affects breath-by-breath CO_2 elimination, when MDT is changed for one breath at a time. The study also explores whether a permanent lowering of MDT would constantly increase $PaCO_2$ and vice versa.

METHODS

Material

The local Ethics Board for Animal Research approved the study. Twenty-two pigs of the Swedish native breed, weighing 17-24 kg, were fasted overnight with free access to water. The animals were pre-medicated with azaperone (7 $mg \cdot kg^{-1}$) and anaesthetised with ketamine (5 $mg \cdot kg^{-1}$). Anaesthesia was maintained by continuous infusion of fentanyl (60 $\mu g \cdot kg^{-1} \cdot h^{-1}$) and midazolam (0.7 $mg \cdot kg^{-1} \cdot h^{-1}$).

ALI/ARDS was induced in 14 pigs by combining surfactant perturbation by inhalation of dioctyl sodium sulphosuccinate with very large V_T ventilation [18]. Details can be found in the electronic supplementary material (ESM) and in [19].

Pancuronium (0.5 $mg \cdot kg^{-1} \cdot h^{-1}$) was given only to healthy pigs. In ALI pigs, paralysis was avoided in order to allow judgement of anaesthesia depth during the longer experiments. With the anaesthesia practised no muscular movements were observed. Ventilation was maintained using a 7.0 mm ID tracheal tube connected to a ventilator (ServoVentilator 900C, Siemens-Elema, Solna, Sweden). A mainstream analyser (CO_2 Analyzer 930, Siemens-Elema, Solna, Sweden) measured partial pressure of CO_2 at airway opening ($PaoCO_2$). The ventilator/computer system used for data recording has previously been described [20]. Signals from the ventilator and CO_2 analyser representing flow rate, airway pressure and $PaoCO_2$ were sampled at the frequency of 100 Hz. The signals had a 50% response time of 12 ms and were synchronous within ± 8 ms. Compliance of the tracheal tube and ventilator tubing was measured *in vitro*. The system was tested for leakage.

For all pigs, the ventilator was at baseline set at volume control with square inspiratory flow, T_I 33% and T_P 10% of the respiratory cycle. Minute ventilation was adjusted to achieve $PaCO_2$ 5–6 kPa.

Protocol

Part 1 - Inspiratory gas delivery modified for one breath at a time

Eight healthy pigs were after preparation, stabilised for a period of 60 min at baseline ventilation at a fraction of inspired oxygen (F_IO_2) of 0.21. To combat the high tendency towards lung collapse in pigs, a positive end-expiratory pressure (PEEP) of 8 cmH_2O was used [21]. These pigs were studied at respiratory rate (RR) 20 min^{-1} and 40 min^{-1}, denoted $Health_{RR20}$ and $Health_{RR40}$. The non-linear influence of MDT on CO_2 exchange was considered to merit a primary exploration of particularly short MDT values at high RR, which may be used to reduce V_T in ARDS [19].

Six pigs were studied 24h after induction of ALI/ARDS. These pigs were part of another study comparing how different modes of ventilation affect lung function (see ESM). After stabilisation at PEEP 10 cmH_2O and F_IO_2 1.0, the effect of inspiratory flow patterns on CO_2 elimination of single breaths was studied at RR 20 min^{-1}. This group of pigs was denoted ALI_{RR20}.

For all groups of pigs ($Health_{RR20}$, $Health_{RR40}$ and ALI_{RR20}) the pattern of inspiratory gas delivery was modified for single breaths at a time, with respect to T_I (0.2-1.9 s), T_P (0.1-0.5 s) and inspiratory flow wave form (SHAPE), in different combinations. SHAPE was either square, increasing, or decreasing flow rate. The latter two shapes were linear ramps starting or ending at zero flow. V_T, PEEP and expiratory time were constant for all breaths. A recording sequence was pre-programmed in the computer that momentarily controlled the ventilator. Every 3rd breath out of 12 breaths comprising a recording sequence was modified. The breath immediately preceding a modified breath was defined as a control breath. Five different recording sequences, each with 4 modified breaths, gave 20

combinations of changes in T_I, T_P and SHAPE. In randomised order, the five recording sequences were repeated three times.

Part 2 - Prolonged periods of constant pattern of gas delivery

In 8 healthy pigs (the same animals as the healthy pigs of part 1) and eight other pigs studied 4 h after induction of ALI/ARDS (ALI_{TP}) alternative patterns of inspiratory gas delivery were maintained for prolonged periods in order to study the effect on $PaCO_2$. The reason for using a different group of ALI pigs than those used in part 1 was logistical; the total study time would otherwise have been too long. T_P was maintained at 17% for 40 min, then changed to 3%, which setting was again applied during 40 min and finally the initial 17% was set again and applied also during 40 min. Thereby, during the middle period, MDT was changed by a factor of 0.5, i.e. from 80 ms to 40 ms. A reciprocal change in expiratory time maintained RR unchanged. Also V_T was unchanged. $PaCO_2$ was measured every 5 minutes.

Data analysis

Sampled data of flow, pressure and $PaoCO_2$ were transferred to an Excel workbook (Microsoft, Redmond, WA, USA) and analysed according to Uttman et al. [22]. Tidal CO_2 elimination (V_TCO_2) represents the difference between expired volume of CO_2 (V_ECO_2) and that re-inspired from the Y-piece and adjacent tubing (V_ICO_2) (Fig.1). Variations in V_ICO_2, V_ECO_2 and V_TCO_2 resulting from variation of inspiratory pattern were expressed in percentage of average V_TCO_2 from the 4 control breaths in the same recording sequence immediately preceding the modified breaths and denoted ΔV_ICO_2, ΔV_ECO_2 and ΔV_TCO_2, respectively.

Airway dead space (V_{Daw}) was defined as the point of maximum slope of the SBT-CO_2. Over the alveolar plateau, $PaoCO_2$ was described by the equation:

$$PaoCO_2 = b + m \cdot \ln V_E$$

V_E is volume of expired gas. Alveolar P_{CO_2} (P_ACO_2) represents the midpoint of the plateau.

Variation in V_ECO_2 results from a shift of the ascending limb along the volume axis that reflects a change in V_{Daw} (ΔV_{Daw}) and a shift of the alveolar plateau along the PCO_2 axis (ΔP_ACO_2).

MDT was calculated from flow samples during T_I and T_P and with respect to V_{Daw} according to Aboab et al. [17]. Flow rate at onset of inspiration (F_{early}) was at square inspiratory flow V_T/T_I, at decreasing flow twice that value and zero for increasing flow. The sum of T_I and T_P (T_{I+P}) was calculated as it represents time for transfer of CO_2 from blood to alveolar gas.

Statistical methods

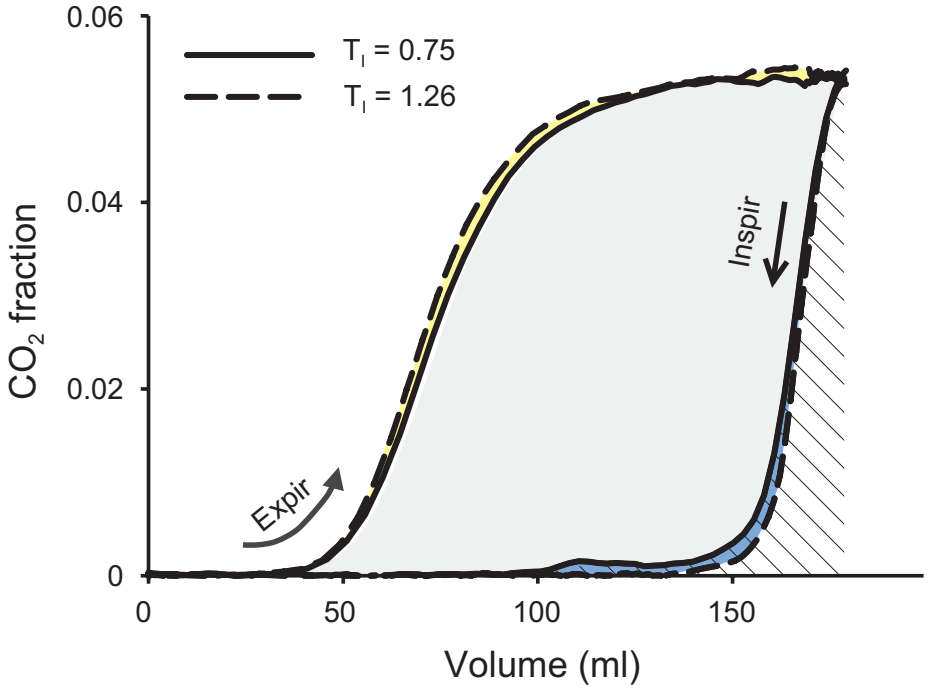
Data are presented as mean ± standard deviation (SD) or as mean ± standard error of the mean (SEM) when error of the mean is the issue. Regression analysis was used to study variations in volumes of CO_2 in relation to parameters describing inspiratory flow pattern. Student's paired two-tailed *t*-test was used to analyse changes in $PaCO_2$ during prolonged periods of altered T_P.

RESULTS

V_T and arterial blood gases are shown in Table 1. The ALI_{RR20} group was non-homogenous with respect to gas exchange as reported in ESM.

Part 1

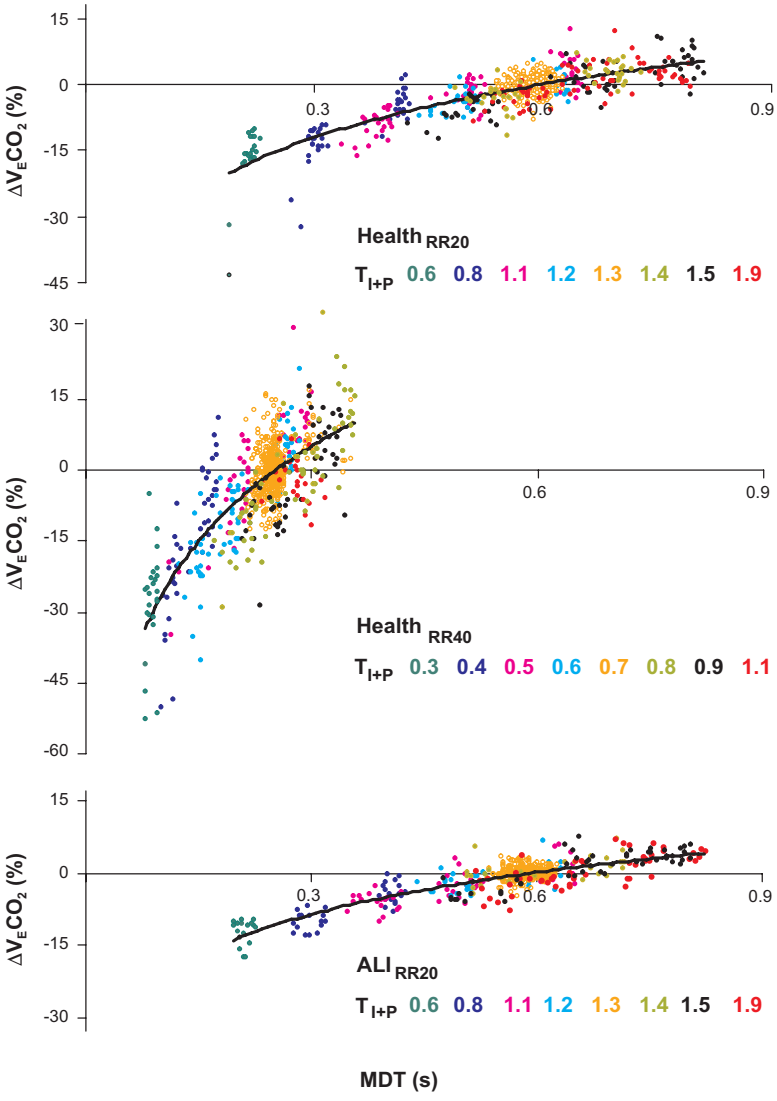
At $Health_{RR20}$, $Health_{RR40}$ and ALI_{RR20}, V_ICO_2 for control breaths was 16±1, 34±5 and 12±1 % of V_ECO_2, respectively. ΔV_ICO_2 showed a significant positive correlation to F_{early} that reflects T_I and SHAPE, Table 2, Fig. 1.



In breaths with square flow but varying T_I and T_P, ΔV_ECO_2 increased significantly at higher MDT at all conditions. A logarithmic relationship was slightly better than a linear relationship for all conditions, but significantly so only for $Health_{RR20}$ ($p<0.001$), Table 2, Fig. 2. Regression coefficient d, expressing the influence of lnMDT on ΔV_ECO_2, was significantly higher at $Health_{RR40}$ than at $Health_{RR20}$ ($p<0.001$). At ALI_{RR20} d was significantly lower than at $Health_{RR20}$ ($p<0.001$).

At $Health_{RR20}$ and ALI_{RR20}, 56--58 % of the change in ΔV_ECO_2 was caused by ΔV_{Daw} and the remaining 42--44 % by ΔP_ACO_2. At $Health_{RR40}$ the contribution to ΔV_ECO_2 by ΔV_{Daw} was 69% and by ΔP_ACO_2 31%.

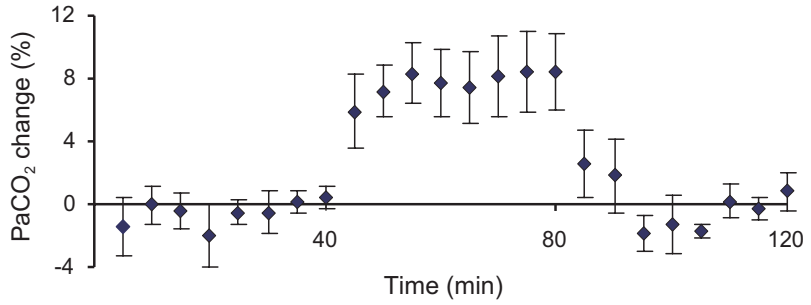
Differences between measured ΔV_ECO_2 and values calculated from the logarithmic equations in Table 2 were calculated. No significant correlation between T_{I+P} and these residuals was found for $Health_{RR20}$, $Health_{RR40}$ or ALI_{RR20}, as can be appreciated from Fig. 2. Accordingly, variations in T_{I+P} had no significant effect upon ΔV_ECO_2 apart from effects explained by MDT.



At $Health_{RR40}$, when MDT was varied by changing SHAPE, ΔV_ECO_2 varied similarly in relation to MDT as when T_I or T_P were varied. However, at $Health_{RR20}$, ΔV_ECO_2 varied significantly less when MDT was changed by varying SHAPE. At ALI_{RR20}, no significant effect on ΔV_ECO_2 was observed when SHAPE was varied. For breaths with square inspiratory flow, ΔV_TCO_2 varied with lnMDT and F_{early} as shown in Table 2. The coefficients f and g differed significantly between $Health_{RR20}$ and each of the conditions $Health_{RR40}$ and ALI_{RR20} ($p<0.001$)

Part 2

At $Health_{RR20}$ $PaCO_2$ increased at short MDT, Fig. 3. The average of the three last observations during each period of 40 min was considered to represent steady state. At $Health_{RR20}$ and ALI_{Tp}, average $PaCO_2$ increased significantly during the period of short MDT and decreased significantly when MDT was again prolonged, Table 3. The change in $PaCO_2$ was on average 75% of ΔV_TCO_2 resulting from changing MDT, estimated from equations in Table 2.



DISCUSSION

The previously described system based upon a computer-controlled ventilator was amended to allow changed pattern of a single inspiration at a time [20]. In part 1, T_I, T_P and SHAPE were modified while V_T, expiratory time and PEEP were unchanged. This allowed a comprehensive analysis of how different patterns of inspiratory flow affect CO_2 exchange by using SBT-CO_2. By comparing modified breaths with control breaths in the same recording sequence, influence from even minor deviations from a steady state was avoided. The technique for modification of single breaths allowed studies of 21 inspiratory flow patterns in a short time. Uttman et al. introduced the concept of MDT to explain how inspiratory flow pattern affects CO_2 exchange by its effect on distribution of inspired gas in the alveolar zone [16]. Aboab et al. stressed that MDT refers not only to time for gas distribution and diffusion within alveolar space but to time for all phenomena associated with transfer of CO_2 from circulating blood in the alveolar capillaries to the airways [17]. This may include movements caused by the heart and pulsating blood.

V_ICO_2 was larger than the volume of CO_2 in the Y-piece connecting ventilator tubing to the airway. This reflects mixing of gas in the inspiratory and expiratory lines shown by Fletcher et al. [23]. During the first part of inspiration, while CO_2 is present in both inspiratory and expiratory lines, a high flow rate increases turbulence and possibly also Coanda and Bernoulli effects around the Y-piece. This may explain the correlation between F_{early} and V_ICO_2. V_ICO_2 amounted to about 16% of V_ECO_2 at $Health_{RR20}$, and to 34% at $Health_{RR40}$. Re-inspiration of CO_2 is considerable. Within a low V_T strategy, reduction of V_ICO_2 can be achieved by one-way valves in the Y-piece as suggested by Fletcher et al., or by aspiration of dead space, as discussed by De Robertis et al. [24].

In accordance with the hypothesis based upon previous studies, ΔV_ECO_2 increased in relation to lnMDT [16, 17]. A better fit of a logarithmic equation rather than a linear one

agrees with concepts based upon physiology and morphology. As gas distribution in lung periphery and exchange with alveolar blood depends on diffusion, gas exchange would be negligible at zero MDT. A very long MDT would imply that the interface between resident alveolar gas and fresh inspired gas is by diffusion brought up to a level at which the summed surface area according to the model of Weibel is so small that further diffusion becomes negligible [25]. When MDT increases from zero to high values, one may accordingly expect a fast initial increase in ΔV_ECO_2 that becomes ever slower with further MDT increase. Patterns with particularly short MDT may severely reduce gas exchange, as the results at $Health_{RR40}$ shows. When increased RR is used in ALI/ARDS in order to limit V_T, it may be particularly important to maintain an adequate MDT by prolonging T_P and shortening expiration time.

At prolonged MDT, increasing ΔV_ECO_2 reflected both a decrease of V_{Daw} and a positive ΔP_ACO_2. This is in line with the results of Aboab et al. [17], who reasoned that a higher level of the alveolar plateau might, at least partially, be explained by continuing delivery of CO_2 by alveolar perfusion during a prolonged pause. T_{I+P} represents the time for alveolar perfusion during inspiration. In the present study we found that variation of T_{I+P} by different combinations of T_I and T_P did not significantly affect ΔV_ECO_2 above what was explained by MDT. This suggests that time for alveolar perfusion during inspiration is of low importance compared to time for distribution and diffusion within the alveolar zone as expressed by MDT. A possible explanation why T_{I+P} in itself did not affect ΔV_ECO_2 is that CO_2 delivered by alveolar perfusion late during inspiration does not, to a detectable extent, reach the upper respiratory zone in time to be expelled by the ensuing expiration.

A defined change in MDT had a similar effect on ΔV_ECO_2 regardless of whether the change was caused by varying T_I or T_P (Fig. 2). Mathematical analysis shows that for a given increase in T_P the effect on MDT is three times larger than a comparable increase in T_I (see ESM). Accordingly, it is much more efficient to prolong T_P than T_I.

The finding that at $Health_{RR20}$ and at ALI_{RR20}, ΔV_ECO_2 varied less and even insignificantly when MDT was changed by varying SHAPE implies that variation of SHAPE has effects on gas exchange that do not relate only to MDT. From studies based on flow oscillation techniques we know that sudden flow transients at airway opening lead to oscillations at frequencies around 5 Hz throughout the respiratory system. A hypothetical explanation for a maintained ΔV_ECO_2 at increasing flow in spite of a shorter MDT is the following: At increasing flow the sudden end-inspiratory flow cessation leads to enhanced diffusion by way of important oscillations in lung periphery. Correspondingly, at decreasing flow, absence of end-inspiratory oscillations may explain why CO_2 elimination was lower than expected on the basis of prolonged MDT at this SHAPE.

In part 2, when MDT was varied for periods of 40 minutes, $PaCO_2$ was expected to approach a steady state while CO_2 stores in the body became equilibrated [26, 27]. During the periods of changed T_P and thereby changed MDT, $PaCO_2$ changed in the direction expected. The effect of reduction of T_P and MDT was less marked in ALI_{Tp} than in $Health_{RR20}$, but not significantly so. We do not speculate about the reasons for the possible difference observed. The change in $PaCO_2$ was, for both $Health_{RR20}$ and ALI_{Tp}, 75% of the change in V_TCO_2 estimated by using the equations in Table 2. In man, the time constant for the change in $PaCO_2$ was 35min when ventilation was decreased [27]. Incomplete steady state partially explains why the change in $PaCO_2$ was <100% of predicted change in V_TCO_2. The period of changed T_P was limited to 40 min in order to limit interference from unavoidable changes in metabolism and other physiological factors affecting CO_2 exchange during prolonged experiments. Apart from incomplete steady state there may be other reasons why $PaCO_2$ did not change as much as estimated change in V_TCO_2. For example., increasing intrapulmonary P_{CO_2} may affect distribution of pulmonary ventilation and perfusion or may change bronchial tone and thereby modify CO_2 elimination.

In $Health_{RR20}$ the regression coefficient d was somewhat higher than in the non-homogenous ALI_{RR20} group, indicating that an increase in MDT results in a slightly higher increase in CO_2 elimination in healthy pigs than in pigs after ALI. The present findings are comparable to observations in ARDS patients [17]. It appears that the absence of collateral ventilation in pigs has limited importance with respect to effects of MDT [28]. This is in line with the concept that a longer MDT promotes gas exchange by allowing more time for diffusion of gases in the border zone between conductive airways and the respiratory zone of the lung. Selection of an inspiration pattern providing a longer MDT can be made only in patients who are not breathing spontaneously. The improvement in gas exchange caused by a pattern optimising MDT may lead to reduction of V_T in the range of not more than 5-8 % at ordinary RR. The non-linear relationship between CO_2 exchange and MDT implies that MDT becomes more important at increased rates. One should see optimisation of MDT as one way of reducing V_T which in combination with other means of reducing dead space, may be important. One should also consider that reduction of dead space by any means paves the way for using higher RR. Importantly, the clinical implication of this study remains unclear until further studies have been performed in patients of different categories.

This study confirms that changes in pattern of inspiratory gas delivery lead to important instant changes in CO_2 elimination and ensuing changes in $PaCO_2$. At square inspiratory flow, these changes relate to MDT in accordance with the hypothesis. At increasing and decreasing inspiratory flow rate, factors other than MDT must be further analysed. Flow rate early in inspiration affects the volume of re-inspired CO_2. The effects of changing MDT on CO_2 exchange are considerable, particularly at an increased RR. The findings merit further studies in critical care. The trade-off between improved gas exchange related to a prolonged MDT and potential negative effects of higher inspiratory flow rates and/or shorter expiration times should be investigated.

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Table 1 Tidal volume and arterial blood gases at the three conditions at start of measurements. In health PEEP was 8 and in ALI PEEP was 10 cm H_2O. Mean ± SD.

	V_T ml/kg	$PaCO_2$ kPa	PaO_2/F_IO_2 kPa
$Health_{RR20}$	8.8 ± 0.8	5.5 ± 0.5	63 ± 10
$Health_{RR40}$	5.9 ± 0.5	5.6 ± 0.3	62 ± 6
ALI_{RR20}	11.0 ± 1.7	5.9 ± 0.9	50 ± 17

Table 2 The relationship $\Delta V_ICO_2 = a + b \cdot F_{early}$, $\Delta V_ECO_2 = c + d \cdot \ln MDT$ and $\Delta V_TCO_2 = e + f \cdot \ln MDT + g \cdot F_{early}$, at square flow for the three conditions.

	$\Delta V_ICO_2 = a + b \cdot F_{early}$			$\Delta V_ECO_2 = c + d \cdot \ln MDT$			$\Delta V_TCO_2 = e + f \cdot \ln MDT + g \cdot F_{early}$			
	a	b	R^2	c	d	R^2	e	f	g	R^2
$Health_{RR20}$	-3.3	19	0.67	9.0	18	0.70	12	20	-8	0.75
$Health_{RR40}$	-13	54	0.50	40	29	0.59	56	36	-27	0.71
ALI_{RR20}	-2.8	14	0.77	6.5	12	0.74	10	13	-13	0.81

R^2 is correlation coefficient squared.

Table 3 $\Delta PaCO_2$ is the change in $PaCO_2$ after indicated change in MDT expressed as percentage of value before changing MDT (see Fig. 3). ΔV_TCO_2 is change in V_TCO_2 resulting from the change in MDT as estimated according to equations in Table 2. $\Delta PaCO_2$ was on average 75 % of $|\Delta V_TCO_2|$. Mean ± SEM.

		MDT 0.8 s → 0.4 s	MDT 0.4 s → 0.8 s
$Health_{RR20}$	$\Delta PaCO_2$, %	8.8 ± 2.8	-7.3 ± 1.5
	ΔV_TCO_2, % estimated	-11.8 ± 0.3	11.7 ± 0.3
ALI_{Tp}	$\Delta PaCO_2$, %	5.8 ± 2.1	-5.1 ± 0.8
	ΔV_TCO_2, % estimated	-6.6 ± 0.2	6.7 ± 0.2

Legends for the figures:

Fig. 1 An example of single-breath test for CO_2 from a healthy pig. Expired volume of CO_2 (V_ECO_2), is the area under the expiratory curve (*grey and hatched areas*). Volume of CO_2 re-inspired from Y-piece and adjacent tubing (V_ICO_2), is shown by the *hatched area*. The *grey area* represents tidal elimination of CO_2 (V_TCO_2). When inspiratory gas insufflation was prolonged from 0.75 s to 1.26 s, V_ECO_2 increased (*yellow area*) as a consequence of the increase in mean distribution time, from 0.51 s to 0.66 s. The decrease in V_ICO_2 (*blue area*) was due to the decrease in F_{early} from 0.37 l/s to 0.12 l/s. Accordingly, V_TCO_2 increased by the sum of the yellow and blue areas.

Fig. 2 Variations in expired volume of CO_2, expressed in percentage of average tidal elimination of CO_2 from control breaths (ΔV_ECO_2). ΔV_ECO_2 related to mean distribution time (MDT) for all breaths studied and corresponding regression lines (*black lines*). Healthy pigs ventilated at low ($Health_{RR20}$) and high ($Health_{RR40}$) respiratory rate and pigs after induction of ALI/ARDS (ALI_{RR20}). Breaths with similar total inspiratory time (T_{I+P}) are indicated in a specific colour. Distributions around regression lines were independent of T_{I+P}.

Fig. 3 Observed $PaCO_2$ when switching from a long to a short postinspiratory pause and back again resulting in a change in mean distribution time from 0.8 s to 0.4 s. For each pig the values are normalised to the mean value of the three measurements just before shortening the postinspiratory pause. Average ± SEM from 6 healthy pigs. During each period, the last three observations were used for calculation of data in Table 3.

Electronic supplement material

ARDS induction

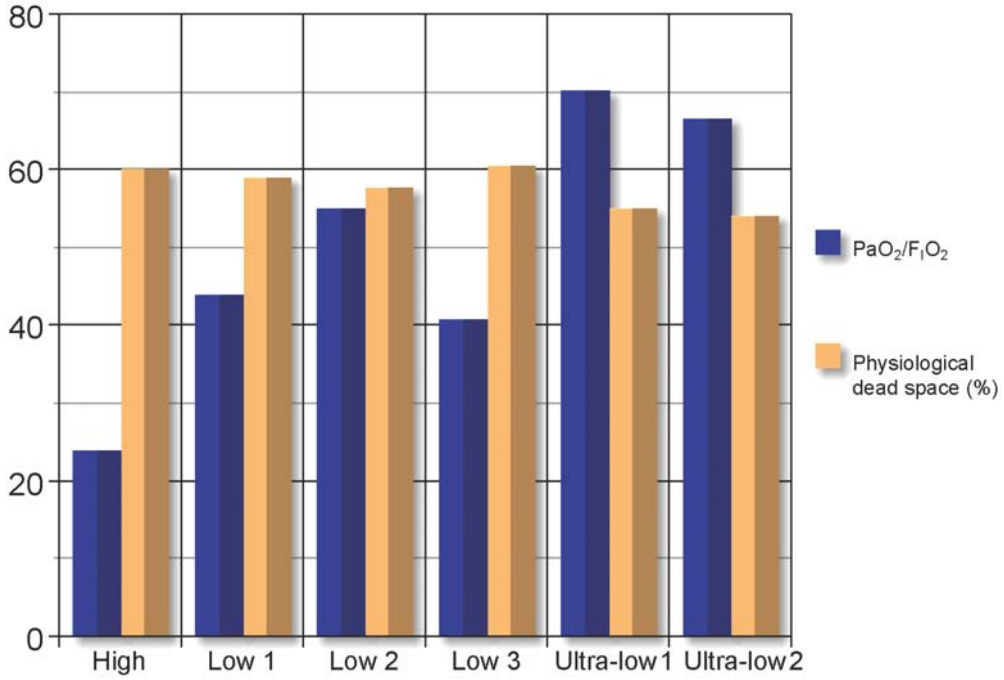
Surfactant perturbation was provoked by administration of the detergent dioctyl sodium sulphosuccinate in 5 % aerosol form for 200 breaths. Pressure-controlled harmful ventilation was started with a plateau pressure of 50 cmH_2O and end-expiratory pressure of -10 cmH_2O at 10 breaths/min. Dead space was added to maintain normocapnia. Harmful ventilation was continued for 90 min or until compliance (tidal volume/[plateau pressure – end-expiratory pressure]) decreased by 25%. Harmful ventilation was stopped when substantial exudates appeared in the tracheal tube. ARDS was diagnosed if PaO_2/F_IO_2 was less than 27 kPa after 5 min at basal ventilation at PEEP 0 cmH_2O. If this criterion was not met, harmful ventilation continued for another 30 min.

Twenty-four pigs fulfilling the ARDS criterion were randomised into 3 groups with different goals for mechanical ventilation. Ventilation proceeded for 24 hours. Values for measured parameters of ventilation are reported in table 1.

Group	High tidal volume	Low tidal volume	Ultra-low tidal volume
Tidal volume (ml/kg)	27 ± 5	13 ± 5	6 ± 0.4
Total PEEP (cmH_2O)	8 ± 1	9 ± 2	19 ± 1
Plateau pressure (cmH_2O)	41 ± 1	28 ± 3	30 ± 0.4
arterial pH	7.39 ± 0.04	7.38 ± 0.02	7.36 ± 0.02

Table 1. Average ± SD

Out of the 24 pigs 6 pigs were randomly selected for the present study (ALI_{RR20}). One pig was from group High, 3 pigs were from group Low and 2 pigs were from group Ultra-low. Measures of gas exchange at inclusion are reported in the figure below.



The effect of immediate changes in pattern of inspiratory gas delivery were studied in part 1.

The contribution of T_I and T_P to mean distribution time

A separate analysis of different combinations T_I and T_P was performed to investigate the relative contribution to mean distribution time (MDT). MDT was calculated from simulated breaths according to methods described in reference 16. Combination of T_P and T_I were simulated, resulting in values in table 2. V_T was 165 ml, airway dead space 60 ml, respiratory rate 20 min^{-1} and square inspiratory flow was used. Multipel regression was calculated on MDT with T_P and T_I as independent variables. The coefficient for T_I % is 0.0095 and for T_P % 0.030, i e the effect of T_P % is 3 times as high as for T_I %, Table 3.

MDT	T_P %	5	10	15	20	25	30
T_I %	15	0.284	0.434	0.584	0.734	0.884	1.034
T_I %	20	0.337	0.487	0.637	0.787	0.937	1.087
T_I %	25	0.382	0.532	0.682	0.832	0.982	1.132
T_I %	30	0.427	0.577	0.727	0.877	1.027	1.177
T_I %	35	0.479	0.629	0.779	0.929	1.079	1.229
T_I %	40	0.524	0.674	0.824	0.974	1.124	1.274

Table 2

	Coefficients	*Standard error*	*p-value*
Constant	-0.00709	0.001384	< 0.0001
T_I %	0.009549	4.1×10^{-5}	< 0.0001
T_P %	0.0300	4.1×10^{-5}	< 0.0001

Table 3