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An appropriate inspiratory flow pattern can enhance CO_2 exchange facilitating protective ventilation of healthy lungs

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Short running title: CO_2 exchange enhanced by modified inspiratory flow

Summary

Background: In acute lung injury, CO_2 exchange is enhanced by prolonging the volume weighted mean time for fresh gas to mix with resident alveolar gas, denoted mean distribution time (MDT), and by increasing the flow rate immediately before inspiratory flow interruption, end-inspiratory flow (EIF). The objective was to study these effects in man without lung disease and to analyse the results with respect to lung-protective ventilation of healthy lungs.

Methods: During preparation for intracranial surgery, the lungs of eight subjects were ventilated with a computer-controlled ventilator, allowing breath-by-breath modification of the inspiratory flow pattern. The durations of inspiration (T_I) and post-inspiratory pause (T_P) were modified, as was the profile of the inspiratory flow wave (i.e. constant, increasing or decreasing). The single-breath test for CO_2 was used to quantify airway dead space (V_{Daw}) and CO_2 exchange.

Results: A long MDT and a high EIF augment CO_2 elimination by reducing V_{Daw} and promoting mixing of tidal gas with resident alveolar gas. A heat and moisture exchanger had no other effect than enlarging V_{Daw}. A change of T_I from 33 to 15% and of T_P from 10 to 28%, leaving the time for expiration unchanged, would augment tidal elimination of CO_2 by 14%, allowing a 10% lower tidal volume.

Conclusions: In anaesthetised human subjects without lung disease, CO_2 exchange is enhanced by a long MDT and a high EIF. A short T_I and a long T_P allow significant reduction of tidal volume when lung-protective ventilation is required.

Clinical trial registration: NCT01686984

Key words: capnography; intermittent positive pressure ventilation; pulmonary gas exchange

Introduction

Seminal studies show increased survival among patients with acute respiratory distress syndrome (ARDS) ventilated with low tidal volume (V_T).[1 2] More recent studies show that low-V_T ventilation may be protective against lung complications or organ failure in patients without prior lung disease, such as patients ventilated during major surgery.[3-5] For large groups of ventilated patients, low V_T has therefore been suggested as standard in several reviews and meta-analyses.[6-10] Ventilation with reduced V_T carries a risk of CO_2 retention. In this study, we explore how dead space can be reduced and CO_2 exchange enhanced simply by optimising the inspiratory flow pattern, thereby reducing the need for other interventions. These might include increasing respiratory rate (RR) or more complex remedies, such as using an active humidifier instead of a heat and moisture exchanger (HME) or flushing upper airways with fresh gas before inspiration.[11-15]

Some patterns of inspiratory flow promote mixing of tidal and alveolar gas thereby reducing dead space.[16 17] An adjustable inspiratory waveform was therefore introduced with the ServoVentilator 900 (Siemens-Elema AB, Solna, Sweden).[18] Computer control of inspiratory flow and volumetric capnography allow detailed studies on how the inspiratory pattern affects dead space and CO_2 exchange.[19-23] In large airways gas transport is convective, whereas diffusion predominates in the respiratory zone.[24] During inspiration, the time allowed for such diffusion is essential for gas exchange.[25] This time is represented by mean distribution time (MDT) which reflects the inspiratory time (T_I), duration of post-inspiratory pause (T_P), and profile of the inspiratory flow wave which can be constant, increasing or decreasing (Fig. 1). MDT is calculated as the volume-weighted mean time for fresh gas to mix with resident alveolar gas (Fig. 2). In healthy pigs, a prolonged MDT reduced airway dead space (V_{Daw}) and increased CO_2 elimination.[23] When flow rate immediately before

interruption of inspiration (end-inspiratory flow, EIF) was high, this also promoted CO_2 exchange in animal and human ARDS,[19 21] but the effect in healthy lungs on CO_2 exchange of increasing EIF or MDT has not previously been explored. The objectives of the present study were to quantify effects of inspiratory flow patterns on CO_2 exchange in humans without lung disease, and to analyse the results with respect to lung-protective ventilation of healthy lungs.

Methods

Eight subjects were studied after induction of anaesthesia and orotracheal intubation during preparation for elective intracranial surgery (Table 1). Lung disease and age <18 yr were exclusion criteria. The study was approved by the Institutional Review Board of the Regional Ethics Committee in Lund, Sweden (Dnr 2012/381), conducted in adherence to the declaration of Helsinki and registered with ClinicalTrials.gov (NCT01686984). Written informed consent was obtained from each subject.

Anaesthesia was induced with remifentanil (0.5 – 1 μg kg^{-1} i.v.) followed by propofol (1.5 – 2 mg kg^{-1} i.v.). Intubation was facilitated with rocuronium (0.5 mg kg^{-1} i.v.). Anaesthesia was maintained with remifentanil (0.1 – 0.15 μg kg^{-1} h^{-1} i.v.) and propofol (4.0 – 6.7 mg kg^{-1} h^{-1} i.v.). Volume-controlled ventilation was delivered with a ServoVentilator 900C equipped with a mainstream CO_2 Analyzer 930 (Siemens-Elema AB, Solna, Sweden). Positive end-expiratory pressure (PEEP) was 5 cm H_2O and RR bpm. Ordinary breaths were delivered with constant flow, T_I was 33% and T_P 10%. Volumes and flow rates are expressed as measured at body temperature, standard barometric pressure, and gas saturated with water vapour (BTPS).

The ServoVentilator 900C was connected to a personal computer for instant and continuous ventilator control.[26 27] Six sequences of 12 breaths were recorded. Breaths number 3, 6, 9 and 12 were modified with respect to T_I (20 – 53%), T_P (3 – 18%) and the profile of the inspiratory flow wave, which was square (constant flow) or triangular (increasing or decreasing flow rate). V_T, PEEP and expiratory time were constant for all breaths. In total, 21 inspiratory flow patterns were studied (Fig. 1). An ordinary breath preceded each of the four modified breaths in a recording, and average values from

the four ordinary breaths served as the reference for the modified breaths in the same sequence. All breaths were analyzed with the single breath test for CO_2, as previously detailed.[19]

Subjects were studied in the supine position when end-tidal CO_2 concentration had stabilized. The six sequences were conducted with and without an HME between the CO_2 analyser and the subject (HCH 5708, Vital Signs Inc., Totowa, NJ, USA). When the HME was not used, tidal volume was reduced by the manufacturer-specified dead space contribution of the HME, 50 ml. Signals representing airway flow and fraction of CO_2 at the Y-piece of the ventilator tubing were sampled at 100 Hz. Each sequence was analyzed using Excel (Microsoft Corporation). Studied breaths were characterized by their MDT and EIF. The MDT refers to the volume-weighted mean time during which consecutive partitions of fresh inspired gas mixes by diffusion with resident alveolar gas (Fig. 2).[19] The EIF is flow rate at the end of inspiration immediately before the post-inspiratory pause (Fig. 1).

Tidal CO_2 elimination (V_TCO_2) and its variation attributable to changes in V_{Daw} and alveolar CO_2 fraction (F_ACO_2) were determined (Fig. 3). The V_{Daw} was calculated as previously described.[28] For V_TCO_2, V_{Daw} and F_ACO_2 the change relative to ordinary breaths was expressed as a percentage of the mean of the four ordinary breaths in the same recording sequence and denoted $\Delta V_TCO_2\%$, $\Delta V_{Daw}\%$ and $\Delta F_ACO_2\%$, respectively. Static compliance of the respiratory system (C) was determined as V_T divided by the difference between airway pressure at the end of post-inspiratory pause and PEEP. The effects of inspiratory flow pattern on ΔV_TCO_2, ΔV_{Daw} and ΔF_ACO_2 were expressed by applying multiple regressions with EIF, MDT and lnMDT as independent variables.[19 21]

Statistical analysis

Results are presented as mean values (SD). Single or multiple regression analysis was performed using the Analysis ToolPak of Excel. Student's paired two-tailed t-test was used to analyse differences between residuals. A *P* value of <0.05 was considered to indicate statistical significance.

Results

For breaths with and without an HME, V_{Daw} was 174 (19) and 113 (17) ml, respectively. The difference was 61.3 (7.3) ml. Internal volume of the HME was precisely measured *post hoc*. It was 53.2 ml measured at ambient temperature and barometric pressure, gas saturated with water vapour (ATPS) or 57.5 ml BTPS. Average MDT was lower with than without an HME, 0.74 (0.13) compared to 0.81 (0.14) s ($P<10^{-200}$). The HME did not affect how inspiratory patterns influenced V_TCO_2%, V_{Daw}% or F_ACO_2%.

In 32 breaths with EIF similar to the ordinary reference breaths, ΔV_TCO_2 was in each subject correlated with MDT but significantly closer with lnMDT. The following analysis therefore focuses on lnMDT.

Effects of mean distribution time and end-inspiratory flow on V_TCO_2, V_{Daw} and F_ACO_2

For all breaths, effects of MDT and EIF were analysed according to equation (1)

$$Y = a \times \text{lnMDT} + b \times \text{EIF} + c \qquad (1)$$

where Y represents ΔV_TCO_2%, ΔV_{Daw}% or ΔF_ACO_2% (Table 2). Equation (1) was applied to all breaths of each individual subject.

For ΔV_TCO_2% coefficient a and b differed significantly from zero, implying that ΔV_TCO_2% was influenced by lnMDT and EIF, $P<10^{-16}$ and $<10^{-4}$, respectively (Table 2, left columns). The coefficient b, representing the influence of EIF, was correlated significantly with individual values of compliance, as follows: $b = 0.26 \times C - 0.99$, (P=0.03).

For ΔV_{Daw}%, coefficients *a* and *b* (Table 2, middle columns) differed significantly from zero in each subject, implying that also ΔV_{Daw}% was influenced by lnMDT and EIF ($P<0.02$).

For ΔF_ACO_2%, coefficient *a* differed significantly from zero in all subjects ($P<0.001$), while *b* did so in six out of eight subjects (Table 2, right columns). A composite analysis based on all breaths in all subjects showed that ΔF_ACO_2% was influenced by both lnMDT ($P<10^{-57}$) and by EIF ($P<0.001$).

Effects of alternative inspiratory flow patterns on ΔV_TCO_2

Table 2 details how inspiratory pattern influences CO_2 exchange. However, the coefficients in Table 2 do not clearly illustrate to what extent CO_2 elimination is influenced by different inspiratory patterns. In order to make clinical consequences easier to comprehend, from the data in Table 2 ΔV_TCO_2% was recalculated for some patterns. These calculations are presented in Table 3 where the change of V_TCO_2 as a percentage of the value represented by ordinary unmodified breaths is given for these patterns. At ordinary T_I and T_P, it was shown that the flow profile does not significantly affect CO_2 exchange (Table 3, left columns). At constant flow, with a prolonged T_P and equally shortened T_I, V_TCO_2 would be augmented by 14% as a result of higher EIF and longer MDT and by 23% at increasing flow (middle columns). If total inspiratory time is prolonged at the expense of expiration, V_TCO_2 is further enhanced (right columns).

Discussion

In anaesthetised, mechanically ventilated patients with healthy lungs, we have demonstrated that a simple resetting of the inspiratory flow pattern of a ventilator with respect to T_I and T_P, without increasing respiratory rate, can improve CO_2 elimination, allowing a lower tidal volume for lung protection.

Our system uniquely allows studies, in a short time, of CO_2 exchange with many inspiratory flow patterns. Modified breaths were compared to reference breaths in the same recording sequence to avoid problems related to steady state and to make observations specifically reflecting a varying inspiratory pattern.

The HME increased V_{Daw} by 61 ml BTPS (i.e. 56.5 ml ATPS), 4 ml higher than its internal volume. The difference can be explained by the HME delaying entry of fresh gas to the respiratory zone, thereby shortening MDT. The HME did not have any other effect.

As in previous studies in patients with acute lung injury, longer MDT and higher EIF enhance CO_2 exchange.[19] The effect of MDT on $\Delta V_T CO_2$% varied little between subjects (Table 2). Coefficient *a* was 24% higher than in patients with acute lung injury (P=0.006) while coefficient *b* reflecting the effect of EIF was 270% higher (P<0.003).[19] Rather than MDT, lnMDT is the relevant parameter because diffusion gradients decrease exponentially.[19 20] During the post-inspiratory pause, movement of the fresh gas interface towards proximal airways with smaller total cross-sectional area most likely contributes to the non-linear effect of MDT. The positive effect of a high EIF on CO_2 exchange reflects conversion of kinetic energy to flow and pressure oscillations travelling down the

airways.[21 29-31] The effect on F_ACO_2 shows, for the first time, that this phenomenon reaches into the alveolar space. The main effect of MDT is attributable to diffusion over the interface where fresh inhaled gas from conductive airways meets resident alveolar gas. The effect of EIF, in contrast, involves the whole pulmonary gas volume. The two different mechanisms may explain why EIF is efficient even in when diffusion has slowed down during a post-inspiratory pause.

Variation in V_TCO_2, the loop area in Fig. 3, is attributable to V_{Daw}, affecting loop width, and F_ACO_2, with effect on loop height. An analysis showed that there was no difference in these two effects (*P*=0.91).

Although the effect of MDT was rather similar among our subjects, the effect of EIF varied more, and was less in subjects with low compliance. In patients with ARDS, in whom compliance is low, the effect of EIF was only about one-third of that observed in the present study.[19] That coefficient *b* for ΔF_ACO_2% was not significant in two subjects illustrate the variable effect of EIF. The effect of MDT is more stable within and among populations. This is not surprising, because diffusion between fresh inhaled gas and resident alveolar gas is a relatively simple process compared with transmission of pressure and flow oscillations through the airways and into the alveolar zone. The latter process depends on distribution of elastance, resistance, and capacitance all along the airways and into the alveolar space.[29 30]

To elucidate a potential clinical use of a modified inspiratory flow pattern, the coefficients in Table 2 were used to illustrate effects on CO_2 elimination for a number of alternate patterns (Table 3). At T_I 33% and T_P 10%, the flow profile was unimportant for CO_2 exchange. This reflects that with

increasing flow, positive effects of a higher EIF are balanced by negative effects of a shorter T_P. The opposite is true with decreasing flow. Shortening of T_I and prolongation of T_P importantly increased V_TCO_2, particularly with increasing flow. This reflects that when T_I is shortened, and T_P equally prolonged, MDT increases. This is because T_P is three times more important for MDT than T_I, given that all fractions of gas entering the alveolar space benefit to the same extent from a longer T_P.[21] In addition, a short T_I augments EIF. We illustrate that a further increased T_P boosts CO_2 exchange, but if this excessively shortens T_I, inspiratory peak pressures may be too high. If, in contrast, it is done at the expense of time for expiration, a higher auto-PEEP may develop. By prolonging T_P at a fixed V_T and constant flow, CO_2 elimination can be increased by ~15%. When a new steady state has been established after ~30 min, arterial and end-tidal PCO_2 will have been reduced accordingly.[22 32] However, it is often more important to reduce V_T than arterial PCO_2. An enhancement of CO_2 elimination by 15% gives room for a V_T reduction of ~10% because dead space takes its share of each breath. Furthermore, dead space reduction paves the way for a higher RR and a further reduction of V_T, as has recently been emphasized.[33] In early ARDS, reduction of V_T by 1 ml (kg body weight)$^{-1}$ might reduce mortality by 15%.[34] When lung-protective ventilation is needed, ventilator resetting appears to be easier to accomplish than some alternatives (e.g. replacing the HME with an active humidifier or gas flushing of upper airways).

In recent studies, it has been emphasized that also in patients without ARDS high tidal volumes may induce lung injury.[5-10] Examples are major abdominal surgery and heart surgery, particularly in obese patients. “Generalization of lung protective ventilation prophylactically to almost all mechanically ventilated patients beginning immediately following intubation” has been proposed.[35] In organ donors, lung-protective ventilation improves lungs for transplantation.[36] It has also been emphasised that lung-protective ventilation is by no means equivalent to low tidal volumes but rather a

combination of mechanical breath parameters.[8] The authors of that review conclude: "Preventing rather that treating ARDS may be the way forward in dealing with this recalcitrant condition and would represent a paradigm shift in the way mechanical ventilation is currently practiced."

The present study is limited to effects on CO_2 exchange. Anything that influences alveolar CO_2 tension will also, according to the alveolar gas equation, affect oxygen tension. Oxygen exchange will benefit from a pattern of inspiration that favours CO_2 exchange. During mechanical ventilation, oxygenation is upheld by oxygen enrichment of inhaled gas and by PEEP rather than by a specific degree of alveolar ventilation. This limits the interest in how oxygenation relates to patterns of inspiration.

Several studies indicate that the influence of the inspiratory flow pattern on CO_2 exchange is governed by some general principles. A field worth exploring is chronic obstructive lung disease in which large inhomogeneity of intrapulmonary gas mixing would in theory increase the influence of inspiratory flow patterns on gas exchange.[16] The significant influence on gas exchange by EIF in the present study shows that distribution of inspired gas within resident alveolar gas depends not only on diffusion, as is often proposed. In addition, transmission of gas flow and pressure pulses through the airways play a role, and this is analogous to the physical phenomena enabling ventilation by high-frequency oscillation. The present study adds to our understanding of gas exchange in healthy lungs. It also produces new questions, for instance, about the potential importance of similar factors during heavy exercise when diffusion is hampered by high respiratory rates causing short periods for diffusive gas mixing.

In conclusion, the present study shows that in mechanically ventilated human subjects without lung disease, CO_2 exchange is enhanced by a long MDT and a high EIF. These factors reduce airway and alveolar dead space by moving the interface between inspired gas and resident alveolar gas orally and by enhancing gas mixing within the alveolar zone. During volume-controlled ventilation, this is accomplished by shortening inspiratory time and prolonging post-inspiratory pause. With a more efficient inspiratory pattern, tidal volume can be reduced, potentially in favour of less ventilation-induced lung injury.

Authors' contributions

Study design: L.W.S., G.M., M.B., B.J.

Patient recruitment: L.W.S., M.B.

Data collection: L.W.S., S.A., M.C.

Data analysis: S.A., M.C., B.J.

Writing up the first draft of the paper: M.C., M.B.

Writing up the manuscript: L.W.S., G.M., S.A., B.J.

Declaration of interests

L.W.S: None declared.

G.M.: None declared.

S.A.: None declared.

M.C.: None declared.

M.B.: None declared.

B.J.: None declared.

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Tables

Subject	Sex	Age (yr)	Height (m)	Weight (kg)	BMI (kg m^{-2})	Smoker	Tidal volume with HME (ml)	Static compliance (ml cmH_2O^{-2})
1	M	75	1.87	97	28	No	363	71
2	M	32	1.93	79	21	No	510	62
3	F	32	1.80	92	28	No	477	48
4	M	49	1.77	140	45	No	570	36
5	F	75	1.65	70	26	No	370	46
6	M	50	1.69	99	35	Yes	475	57
7	F	25	1.72	57	19	No	401	62
8	F	57	1.78	89	28	No	443	53

Table 1: Characteristics of the subjects. HME, heat and moisture exchanger

Subject	Coefficients for $\Delta V_T CO_2$%			Coefficients for ΔV_{Daw}%			Coefficients for $\Delta F_A CO_2$%		
	lnMDT	EIF ($L\ s^{-1}$)	Constant	lnMDT	EIF ($L\ s^{-1}$)	Constant	lnMDT	EIF ($L\ s^{-1}$)	Constant
	a	***b***	***c***	***a***	***b***	***c***	***a***	***b***	***c***
1	18.2	17.3	-0.2	-11.2	-15.8	0.7	3.6	2.6	0.2
2	15.9	14.3	-2.9	-15.3	-18.6	4.7	3.5	1.8	0.0
3	14.2	8.7	-0.3	-12.0	-10.1	1.2	2.9	0.2	0.7
4	17.1	6.4	1	-8.9	-8.0	1.9	6.5	0.5	1.5
5	19.4	16.2	-0.1	-12.3	-15.1	0.9	4.5	2.8	0.5
6	18.4	14	-1.3	-12.5	-5.1	-0.7	6	5.4	-0.5
7	15.9	14.6	0.3	-19.2	-14.5	-1.6	2.1	2.6	-0.1
8	20.4	12.7	1.9	-8.9	-6.3	-1.3	3.8	2.1	0.7
Mean	*17.4*	*13.0*	*-0.2*	*-12.5*	*-11.7*	*0.7*	*4.1*	*2.3*	*0.4*
SD	*2.1*	*3.7*	*1.4*	*3.4*	*5.0*	*2.0*	*1.5*	*1.6*	*0.6*

Table 2. Coefficients for the equation $Y = a \times \text{lnMDT} + b \times \text{EIF} + c$ where Y is $\Delta V_T CO_2$%, ΔV_{Daw}%, and $\Delta F_A CO_2$% respectively. $\Delta V_T CO_2$%, ΔV_{Daw}%, and $\Delta F_A CO_2$% are the change of $\Delta V_T CO_2$, ΔV_{Daw}, and $\Delta F_A CO_2$ respectively relative to ordinary breaths, expressed as a percentage of the mean of four ordinary breaths in the same recording sequence. EIF, end-inspiratory flow; MDT, mean distribution time

	T_I 33%, T_P 10%			T_I 15%, T_P 28%			T_I 15%, T_P 35%		
Flow profile	**Incr.**	**Const.**	**Decr.**	**Incr.**	**Const.**	**Decr.**	**Incr.**	**Const.**	**Decr.**
EIF (ml s^{-1})	717	358	0	1576	788	0	1576	788	0
MDT (s)	0.59	0.76	1.03	1.16	1.23	1.36	1.42	1.50	1.62
lnMDT	-0.52	-0.28	0.03	0.15	0.21	0.31	0.35	0.40	0.49
Change in V_TCO_2 (%), mean (SD)	0 (1)	-1 (0.5)	0 (1)	23 (3)	14 (2)	5 (2)	27 (3)	17 (2)	8 (2)

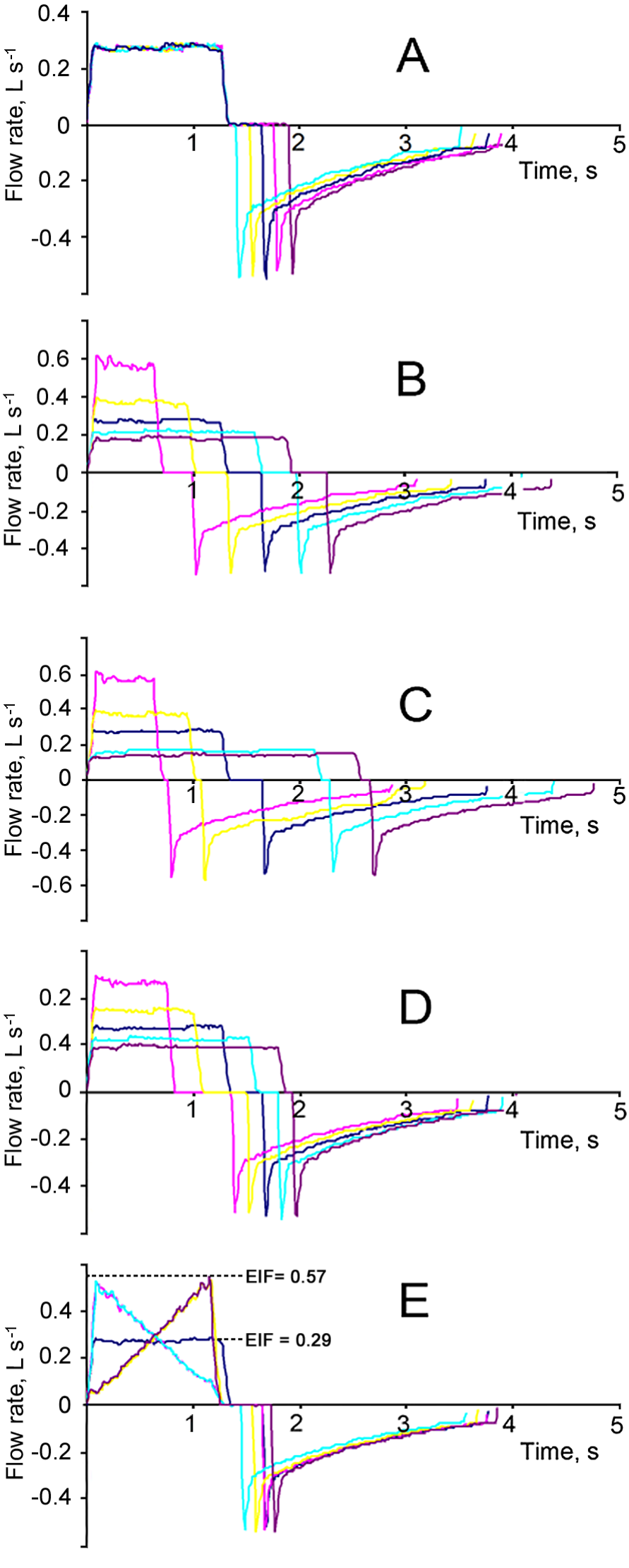
Table 3. Mean values for each inspiratory pattern of EIF, MDT and lnMDT. The change of V_TCO_2 as a percentage of the value of ordinary unmodified breaths was calculated from these means and individual coefficients in Table 2. The flow profile of inspiration was increasing (Incr.), constant (Const.) or decreasing (Decr.). EIF, end-inspiratory flow; MDT, mean distribution time, T_I, duration of inspiration; T_P, post-inspiratory pause

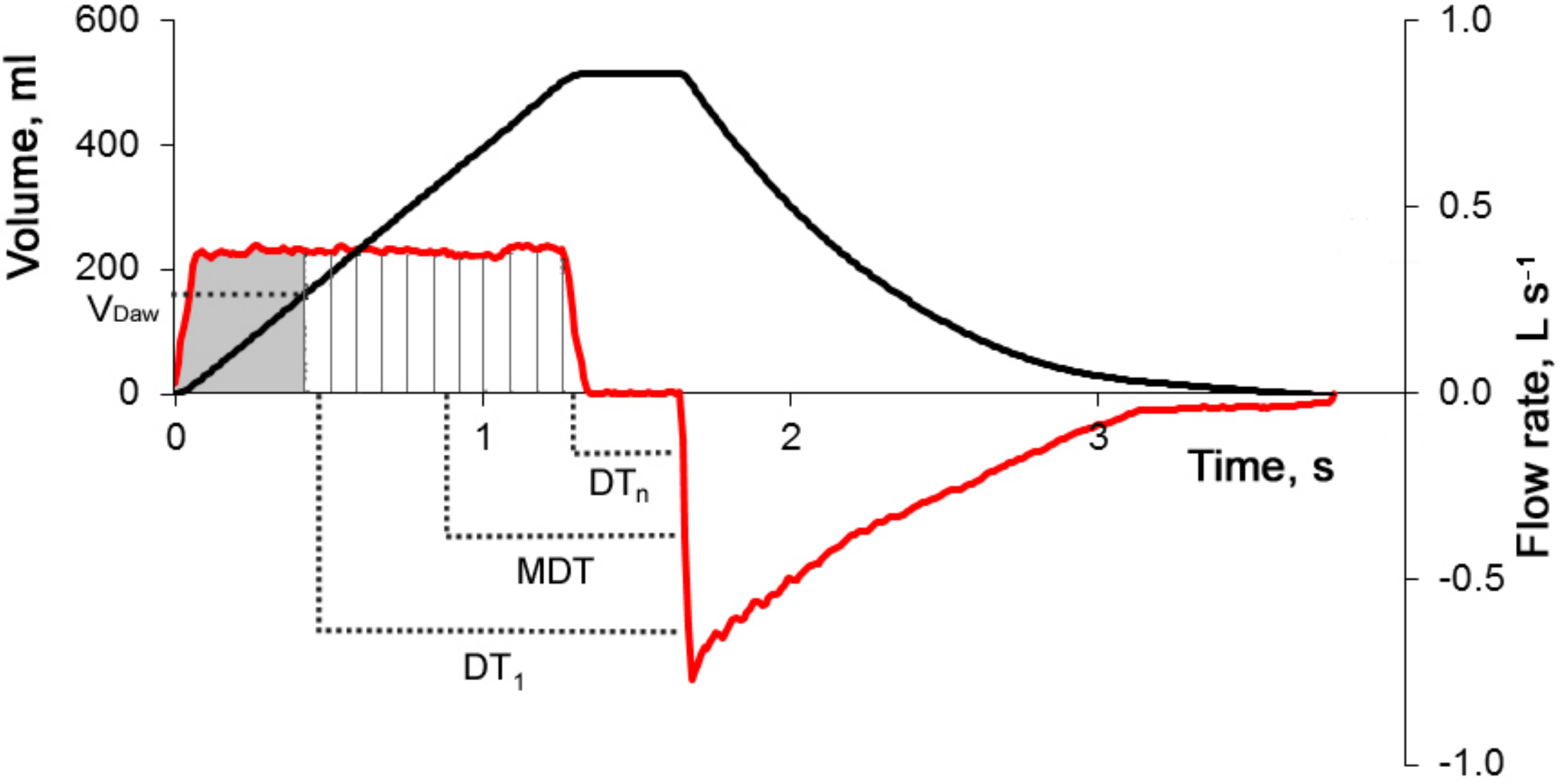
Legends to illustrations

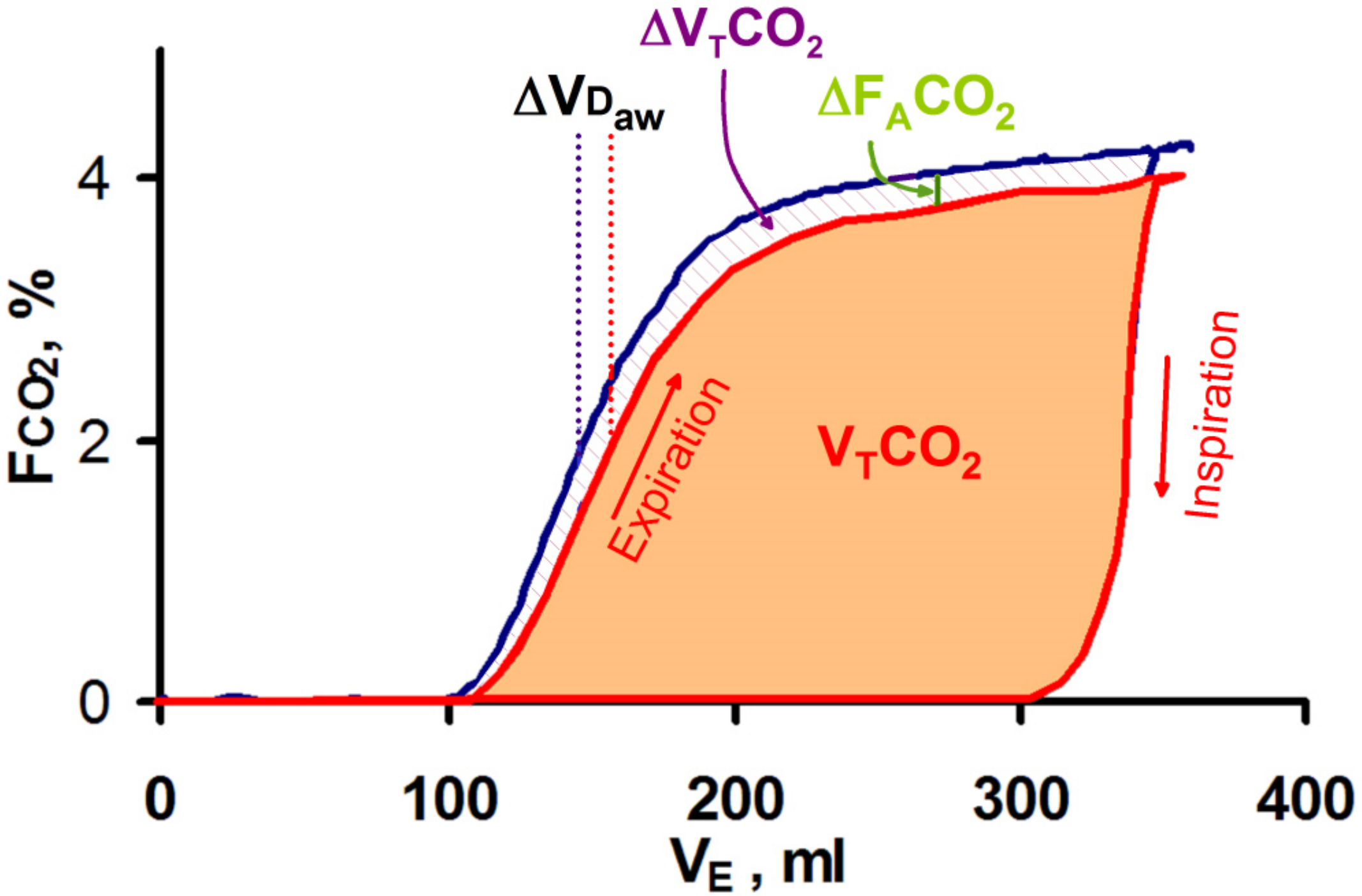
Fig 1. The 21 types of breath delivered, all having different inspiratory flow patterns but identical tidal volumes. In each panel, the dark blue trace shows the pattern of ordinary breaths to which all other patterns were compared. (A) Breaths with ordinary insufflation at constant flow but with varying post-inspiratory pause. (B) Breaths with varying inspiratory time, all with an ordinary pause. (C) Breaths with varying inspiratory time and pause time. (D) Breaths with varying inspiratory time and pause time all with similar mean distribution time. (E) Breaths with constant, increasing and decreasing flow profile, and also illustrating how end-inspiratory flow (EIF) was measured.

Fig 2. Flow rate (red line), and its integral volume (black line) against time. Initially, during inspiration, gas from airway dead space returns to the alveolar zone. When a volume of gas equal to airway dead space (V_{Daw}, grey area) has been inhaled, the first partition of fresh gas reaches the respiratory zone of the lung. Later consecutive partitions of fresh inspired gas (vertical lines) reach this zone. The first portion mixes by diffusion with resident alveolar gas during the distribution time DT_1, and the last portion has the distribution time DT_n. The volume weighted mean for alveolar gas distribution of portions 1 through n is the mean distribution time, MDT. Calculation of MDT ceases at the start of expiration because no further mixing between inspired and resident alveolar gas takes place thereafter.

Fig 3. The single breath test for CO_2. The red curve shows fraction of CO_2 at the Y-piece (FCO_2) plotted against expired volume (V_E). The descending limb of the loop reflects the next inspiration. The orange area represents the volume of CO_2 eliminated during the ordinary breath (V_TCO_2). The blue curve represents the expiratory limb of a breath with a prolonged pause. ΔV_{Daw} shows how airway dead space (V_{Daw}) was reduced by a volume represented by the difference between the vertical dotted red and blue lines. ΔF_ACO_2 shows how the level of the alveolar plateau increased. The reverse-hatched area indicates how ΔV_TCO_2 increased as a consequence of ΔV_{Daw} and ΔF_ACO_2.


A
B
C
D
E
Flow rate, L s-1
Time, s
EIF= 0.57
EIF = 0.29


600
400
200
0
Volume, ml
V_{Daw}
0
1
2
3
Time, s
1.0
0.5
0.0
-0.5
-1.0
Flow rate, L s^{-1}
DT_n
MDT
DT_1


ΔVTCO2
ΔVDaw
ΔFACO2
4
2
0
FCO2, %
Expiration
VTCO2
Inspiration
0
100
200
300
400
VE , ml