Chapter 3.   Tidal volume, cardiac output and functional residual capacity determine end-tidal CO_2 transient during standing up in humans

Janneke Gisolf, Ronald Wilders, Rogier V. Immink, Johannes J. van Lieshout, and John M. Karemaker, *J Physiol 2004 Jan 15;554(Pt 2):579-90*

"The fact that the alveolar CO_2 tension is so dependent upon such factors as posture, indicates that alveolar CO_2 is not a physiologic constant, as originally believed by Haldane. Rather, it is a variable: the resultant of all factors affecting the respiratory center. Consequently, we cannot speak of an individual's alveolar CO_2 value unless we specify definitely the conditions under which it was taken."

R.J. Main, Am J Physiol 1937; 118,435-40

Reduction in end-tidal PCO_2 in the standing position is not solely due to hyperventilation. The effects of gravity on the circulation contribute to a relative hypocapnia in standing man, via a reduction in cardiac output (less blood flow through the lungs implies less CO_2 delivered to the lungs) and a regional ventilation-perfusion mismatch. Hypocapnia leads to vasoconstriction in the brain. In the following study we use a mathematical model to investigate the relative contribution of a number of respiratory and circulatory transients on end-tidal PCO_2 during posture change.

Introduction

In man the carbon dioxide (CO_2) content of the alveolar air is lower in the upright position than in the supine position [85]. In 1937 Main et al. confirmed this observation and explained it as being due to over-ventilation with resulting alkaemia [89]. However, Hitchcock and Ferguson [64] showed the drop in alveolar CO_2 partial pressure (PCO_2) upon assuming the erect posture to be independent of alterations in pulmonary ventilation. They attributed the lowered PCO_2 to an increase in functional residual capacity (FRC) in the upright position, and an impairment of CO_2 transport from the dependent parts of the body.

In man assuming the upright position, cardiac output (Q) decreases [116]. Variation in end-tidal partial PCO_2 ($PETCO_2$) reflects variation in Q in the same direction, for example during acute hemodynamic perturbations in anaesthetized patients during constant ventilation [111]. Airway CO_2 levels have been proposed as a monitor of Q during cardiovascular resuscitation [16]. We considered that the postural decrease in Q could well contribute to hypocapnia.

Previous studies have focused on the effect of gravity and body position on the distribution of ventilation [23; 93; 134], perfusion [3; 127] and ventilation-perfusion (V/Q) ratio [94; 126; 128] in the lung. Gravity induces a perfusion gradient in the upright lung, with a decrease in lung perfusion in apical regions and an increase in perfusion in basal regions. In the standing subject, air expired from alveoli active in gas exchange is diluted by air from apical lung segments which are relatively underperfused, resulting in a decrease in $PETCO_2$. In the upright position, FRC and tidal volume (VT) increase, due to lowering of the diaphragm and alveolar expansion due to the lungs' own weight. However, the relative contribution of each of these physiological phenomena to the postural decrease in $PETCO_2$ is unknown.

With the rising interest in cerebral autoregulation during posture change [14; 29; 43; 56; 67; 96], which is affected by PCO_2, we sought to determine the factors leading to transient $PETCO_2$ variation during standing up from the supine position. We hypothesized that the reduction in Q, and the V/Q mismatch determine the decrease in $PETCO_2$ upon standing up. To test this hypothesis, we developed a nine-compartment computer model of the lung to simulate breath-to-breath $PETCO_2$ variations during active standing up. The model includes an FRC, VT and anatomic dead space (VD). Lung perfusion is modelled using stroke volume (SV) and heart rate (HR). Regional V/Q ratios are modelled for each lung compartment, accounting for effects of gravity. Input data to the model are Fick-calibrated breath-to-breath SV of the heart, pulmonary O_2 uptake (VO_2), respiratory interval (T_{RESP}) and VT.

Methods

Model
To assess the underlying physiology determining $PETCO_2$ transients during posture change, we developed a breath-to-breath model, programmed in MATLAB® (Release 5.2, The MathWorks, Natick, MA). A detailed description of the mathematical model is given in the Appendix. The features of each breath (e.g. arterial and venous CO_2 concentrations) depend on the features of the previous breaths. Input data to the model are (Fick-calibrated) SV determined breath-to-breath, VO_2 and VT. The model is 'paced' by the respiratory interval.

Ventilation The model includes nine lung compartments (Fig. 3.1, right panel). Each compartment's share of the FRC and VT is determined by its position with the apical compartments smaller than the basal compartments. The distributions of VT and SV, in the supine and the upright position, are approximations based on observations by West [126] (Table 3.1). The model includes VD. Using an established relation between anatomic VD and height [58], we set the model VD for men at a greater volume compared to the VD for women (1.4 times), with the VD at 200 ml for men and 140 ml for women in the supine position. In the upright position, these values were increased by 70 ml (see below). The respiratory quotient (RQ), defined as the ratio of carbon dioxide production (VCO_2) to VO_2, normally between 0.7 and 1.0, was set at 0.9.

Circulation The model includes a simplified blood circulation with an arterial compartment (Va), a venous compartment (Vv) and lung capillary gas-exchange compartments (V_{cap}) (see Fig. 3.1, left panel). The lung capillary volume and the small venule volume are lumped, as gas exchange occurs in both. The major arteries of the lung are included in the venous compartment; the major veins of the lung are included in the arterial compartment. The total blood volume of 5.6 l is distributed over Vv (4.0 l), Va (1.3 l) and V_{cap} (200 ml) [27].

Effects of gravity The effects of gravity are modelled as a gravity-induced perfusion gradient in the lung. The distribution of perfusion and ventilation in each lung compartment are based on measurements by West [126]. Distributions of VT, SV, FRC and V_{cap} are summarized in Table 3.1. In the supine position, SV and VT are distributed equally over all compartments. With nine compartments, in the supine position each lung compartment receives one-ninth of the breath-to-breath SV and VT. In the upright position there is an apical to basal perfusion and ventilation gradient, with increased perfusion and ventilation at the lung base. The perfusion gradient is steeper than the ventilation gradient, resulting in a 7.9 to 0.8 apical to basal V/Q gradient. Furthermore, on going from supine to upright respiratory VD increases [15; 104]. Bjurstedt et al. [15] established an increase in VD in the upright position of +53 ml (anatomical) and +81 ml (physiological). In the model VD increases by 70 ml in the upright position.
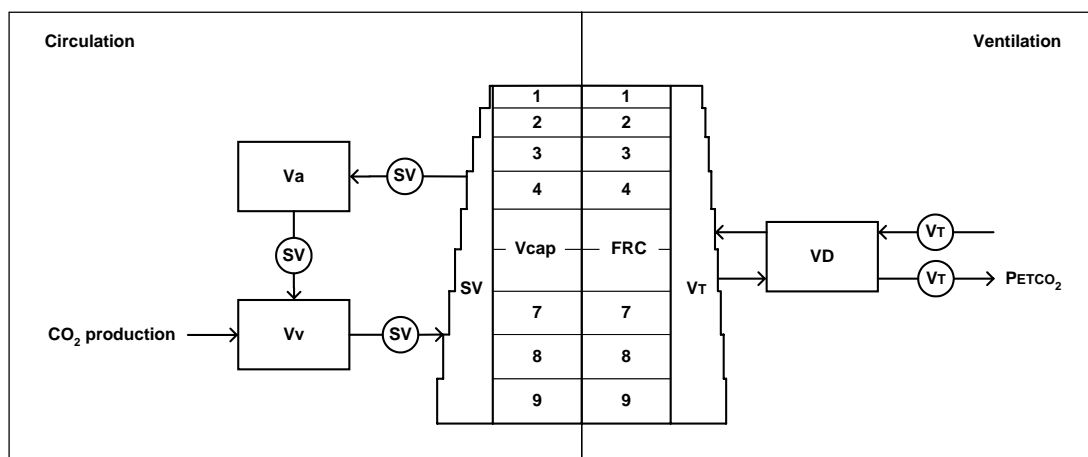

Figure 3.1
Diagram of the PETCO₂ model
The left panel represents circulation with an arterial volume Va, a venous volume Vv, a lung capillary volume V_{cap}, and circulating stroke volume per breath, SV. The right panel represents ventilation with a functional residual capacity FRC, a respiratory dead space VD, and a tidal volume VT. The distribution of SV and VT as shown here are for the upright position; in the supine position SV and VT are equally distributed over apical and basal lung segments (1..9).

Data set

The physiological data we used to test our model are of eight healthy young subjects (2 women; median age 24 years (21 to 38); median height 183 cm (162 to 191) and median weight 78 kg (50 to 85)) who participated in the study of van Lieshout *et al.* [124] for which informed consent had been obtained of all participants, which was approved by the ethics committee of Copenhagen (KF 01-120/96) and was performed according to the declaration of Helsinki. Instrumentation occurred as described previously; after five minutes of supine rest, each subject actively assumed the upright position and remained standing for five minutes while continuous finger arterial blood pressure (ABP) and breath-to-breath online gas concentrations were recorded. The data we analysed were from a recording of each subject standing up just once. For the purpose of tracking short-term PETCO₂ variations

with posture change, we selected data starting 150 second prior to standing up and ending after 150 seconds of standing up.

Mean arterial blood pressure was measured with a Finapres (Model 5; Netherlands Organization for Applied Scientific Research, Biomedical Instrumentation, TNO-BMI). The cuff was applied to the midphalanx of the middle finger of the dominant arm, which was placed at heart level. Beat-to-beat changes in SV were estimated by modelling flow from arterial pressure (Modelflow®, TNO-BMI). This method computes an aortic waveform from a peripheral arterial pressure signal using a non-linear 3-element model of the aortic impedance [57; 71]. Cardiac output was the product of SV and HR. To obtain absolute values of Q to calibrate Modelflow® Q, a Fick-determined Q was obtained from arterial and central venous O_2 content and the VO_2 in the supine and in the standing position. Absolute values of Q were used to calibrate Modelflow® Q, averaged during 150 seconds in the supine position, and during 150 seconds of standing.

Breath-to-breath online gas analysis was performed using a Med-Graphics CPX/D metabolic cart. Respiratory gas was sampled continuously from a mouthpiece and partial gas pressures were obtained from a Zirkonia oxygen analyzer (accuracy $\pm$ 0.03% O_2) and a nondispersive infrared sensor for CO_2 (accuracy $\pm$ 0.05% CO_2) that thus delivered VO_2, VCO_2 and $PETCO_2$.

Data processing and analysis The ventilatory gas analysis was recorded as one value for every breath. All data were stored on a hard disk for off-line analysis. Mean ABP, HR and the ventilatory data were expressed in absolute values. Mean ABP was the integral of one beat. Heart rate was the inverse of the inter-beat interval. Then, ventilatory data and Fick-calibrated Modelflow® SV data were time aligned. For the duration of each breath, the sum of stroke volumes was taken to obtain breath-to-breath SV data.

Experiments

To verify the contribution of the postural reduction in Q to hypocapnia in the standing position, the following protocol was carried out in seven healthy non-
smoking subjects aged 29±5 years, height 176±8 cm, and weight 71±11 kg. Informed consent was obtained in all participants. The study was approved by the ethics committee of the Academic Medical Center (MEC 01-147) and performed according to the declaration of Helsinki. First, the effect of increased ventilation was eliminated by using a protocol that involved standing up during controlled breathing. Second, we eliminated the effect of V/Q mismatch, FRC increase and increased ventilation. To achieve this we used a protocol involving standing with inflated leg splints (Pneumasplint, International deposit Nr. 844181), which augment venous return, followed by rapid leg splint deflation, with breathing frequency and VT controlled. The subjects breathed through a mouthpiece connected to a two-way respiratory valve, and were instructed to breathe at a metronome-paced frequency (0.15 Hz). For each subject the airflow was adjusted to a comfortable level (8.2±1 l/min). During expiration the inflow of air filled a bag, and during inspiration the subject was instructed to empty the bag, thus maintaining a constant VT. Keeping the breathing fixed, 5 minutes of supine recording were followed by 5 minutes of recording in the standing position. Next, while in the standing position inflatable hip-to-toe leg splints were inflated to 60 mmHg. After 5 minutes recording during standing with inflated splints, the splints were deflated to atmospheric pressure within 4 seconds, followed by 5 minutes recording in standing position with deflated splints. The respiratory frequency and VT were fixed throughout the procedures. We measured finger ABP (Finometer Model 1, TNO-BMI) and PCO_2 **(Hewlett Packard Airway Adapter 1436A)**. SV was derived from

the peripheral arterial pressure signal using Modelflow® as described above. Measurements of Q were carried out at the beginning and at the end of each procedure using the inert gas rebreathing technique (Innocor Model: SpO_2 & O_2 options [48]). Rebreathing episodes were marked and Modelflow® Q was level-corrected. The sum of FRC and VD was measured in the supine and standing position also using Innocor rebreathing technique. Calculation is based on the dilution of insoluble gas (SF_6). Measurement of FRC and VD combined, in both supine and standing positions, allowed us to analyse the effect of FRC increase as measured, on the $PETCO_2$.

Parameter sensitivity analysis
To assess the relative contribution of the various physiological phenomena contributing to $PETCO_2$ variations, the parameter sensitivity of the model was analysed. First, the effect of variations in VT, VD, SV, VO_2, RQ, FRC, Vv, Va, T_{RESP} and V/Q on model output (M-$PETCO_2$) were evaluated by carrying out a series of simulations in which a steady-state period of 200 s was followed by a 900 s period with one input parameter set at a value ranging from -10% to +10% of baseline value. An exception is the V/Q parameter sensitivity, which was determined starting with 200 s steady-state 'supine' settings, followed by 900 s with 'upright' settings. Steady-state values were: VT = 484 ml; VD = 200 ml; SV = 550 ml; VO_2 = 250 ml min^{-1}; RQ = 0.9; FRC = 2.5 l; Vv = 4.0 l; Va = 1.3 l; T_{RESP} = 4 s and V/Q = 'supine'. The output value used in the analysis was M- $PETCO_2$ at maximum value or at end-point. Second, the analysis was also performed with the input starting at baseline and varying each input variable as occurs during posture change with an increase in VT, VD and FRC, a reduction in SV, and a shift in V/Q.

Statistical analysis
Hemodynamic and respiratory variables were tested for normality (Shapiro-Wilk test) and, where distribution was not normal, the median was computed for each body position. Results were expressed as mean and standard deviation (SD) or as median and range, as appropriate. Supine and upright values were compared by paired t-test. Agreement between $PETCO_2$ and M-$PETCO_2$ was judged by plotting the difference between M-$PETCO_2$ and $PETCO_2$ against their mean, and computing Pearson's correlation coefficient. The mean difference (bias) and SD (precision) between M-$PETCO_2$ and $PETCO_2$ was tested by paired t-test. A P-value < 0.05 was considered to indicate a statistically significant difference.

Results

Input to the model
The group average hemodynamic and ventilatory responses to standing up from the test database are given in Table 3.2. Upon standing, Q decreased from 6.5±1.1 l min^{-1} to 4.0±0.9 l min^{-1} in the standing position. The Q response ranged from –0.6 l min^{-1} to –4.5 l min^{-1}. VT increased on standing up, while the respiratory rate decreased. VE increased on standing up in all subjects, with a range of 0.3 l min^{-1} to 5.9 l min^{-1}. The $PETCO_2$ decreased from 40±1 to 36±2 mmHg.

Table 3.1. Parameters of nine-compartment lung model

		Lung Compartment (Apical to Basal, Respectively)									
		1	2	3	4	5	6	7	8	9	Total
Supine	Perfusion (% SVk)	11.1	11.1	11.1	11.1	11.1	11.1	11.1	11.1	11.1	100
	Ventilation (%VTk)	11.1	11.1	11.1	11.1	11.1	11.1	11.1	11.1	11.1	100
	Alveolar Vol. (% FRCk)	6.58	8.64	10.11	11.16	11.90	12.43	12.81	13.08	13.27	100
	Lung Capil. (%V$_{cap}k$)	6.58	8.64	10.11	11.16	11.90	12.43	12.81	13.08	13.27	100
Standing	Perfusion (% SVk)	0.58	3.21	5.84	8.47	11.10	13.73	16.36	18.99	21.62	100
	Ventilation (%VTk)	4.58	6.63	8.48	10.13	11.62	12.96	14.17	15.25	16.22	100
	Alveolar Vol. (% FRCk)	6.58	8.64	10.11	11.16	11.90	12.43	12.81	13.08	13.27	100
	Lung Capil. (%V$_{cap}k$)	6.58	8.64	10.11	11.16	11.90	12.43	12.81	13.08	13.27	100

Distribution of stroke volume (SV), tidal volume (VT), functional residual capacity (FRC) and lung capillary blood volume (V$_{cap}$) per lung segment k, in the supine and standing position. Upright distributions are based on measurements by West [126].

Table 3.2. Hemodynamic and ventilatory responses to standing up in eight normal subjects

	Q (l min^{-1})	VCO$_2$ (ml min^{-1})	VO$_2$ (ml min^{-1})	PETCO$_2$ (mmHg)	R-R (min^{-1})	VT (ml)	VE (l min^{-1})
Supine	6.5±1.1	217±36	263±60	40±1	16±4	490±105	7.9±1.4
Standing	4.0±0.9	248±53	263±65	36±2	13±3	734±199	9.8±2.7
P value*	0.002	n.s.	n.s.	< 0.001	0.03	0.005	0.03

Group average values (mean ± SD) for cardiac output (Q), CO$_2$ output (VCO$_2$), oxygen uptake (VO$_2$), end-tidal CO$_2$ pressure (PETCO$_2$), respiratory rate (R-R), tidal volume (VT) and expired ventilation (VE) as determined from 150 s in the supine position followed by 150 s of standing. Data from the study of van Lieshout *et al.* [124] * Standing vs. supine, paired t-test.
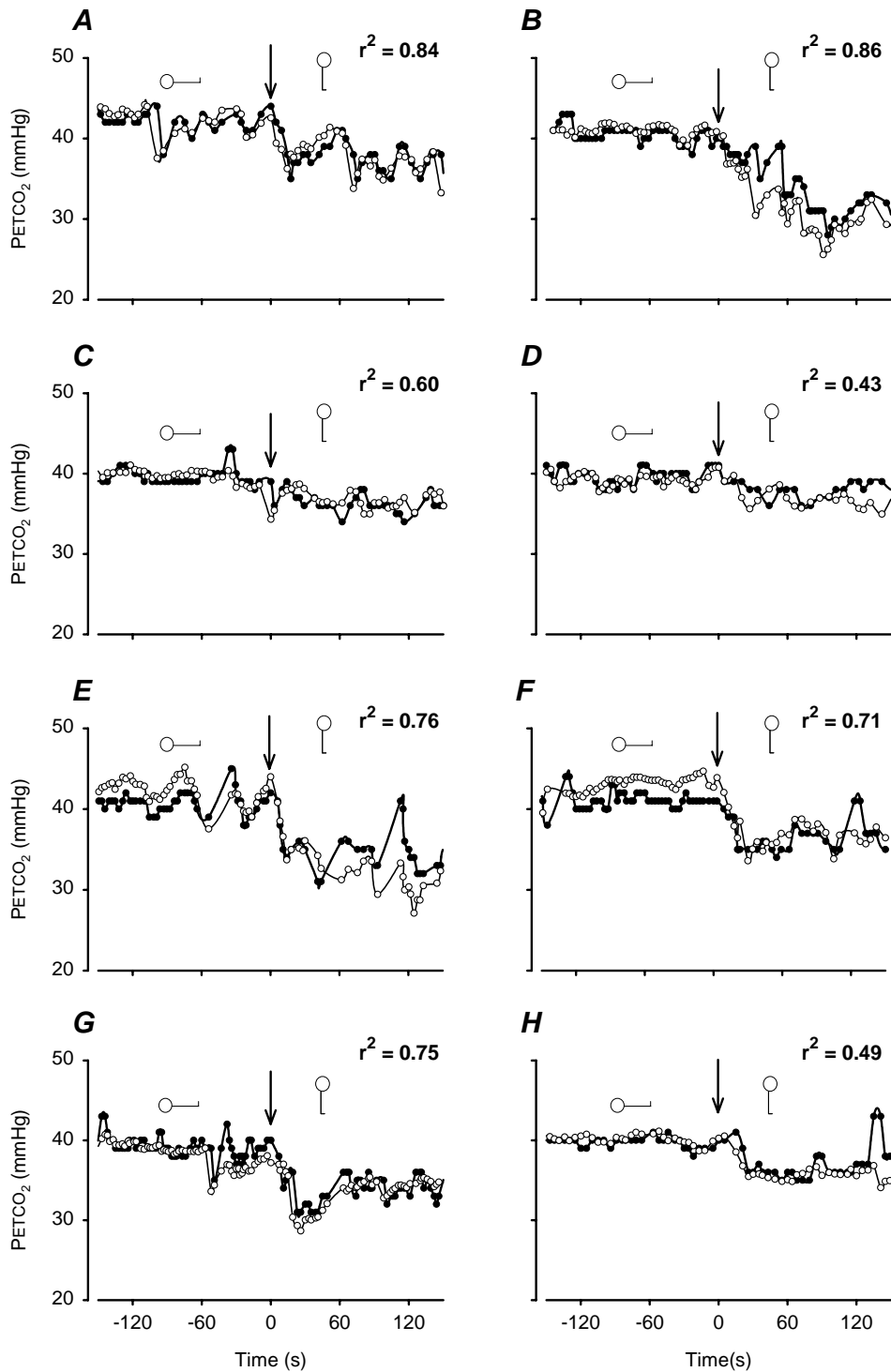
Figure 3.2.

Individual PETCO$_2$ recordings and model simulations during lying down and standing.

Plots of breath-to-breath PETCO$_2$ of each individual subject. Subjects 1 to 8 are represented in panels A to H, respectively. Each panel contains a plot of breath-to-breath PETCO$_2$ measurements (solid line with closed symbols) during 150 seconds supine and 150 seconds of standing, and a model simulation (thin solid line with open symbols) of the same period. Arrows indicate posture change from supine to standing at time zero.

Model simulation

Input to the model are (measured) breath-to-breath values of VT, SV (summed per breath) and VO_2. Starting values for PCO_2 in the venous and the arterial blood and in the various lung compartments are set for each test subject, corresponding to their starting measured $PETCO_2$. Venous CO_2 concentrations are set at a starting value ranging from 52 to 55%. The PCO_2 starting values in arterial blood and the lung compartments ranged from 40 to 42 mmHg. The first breaths of each model run are excluded from analysis. The $PETCO_2$ and the $M-PETCO_2$ during 150 s in the supine position followed by 150 s of standing of all individual subjects are given in Figure 3.2. The model tracks $PETCO_2$ during standing up, and it also follows non-posture related variations in $PETCO_2$ ($r^2 = 0.43$ to 0.86), with those registrations with the greatest variance in measured $PETCO_2$ resulting in the best correlations of $M-PETCO_2$ with $PETCO_2$ (P<0.01).
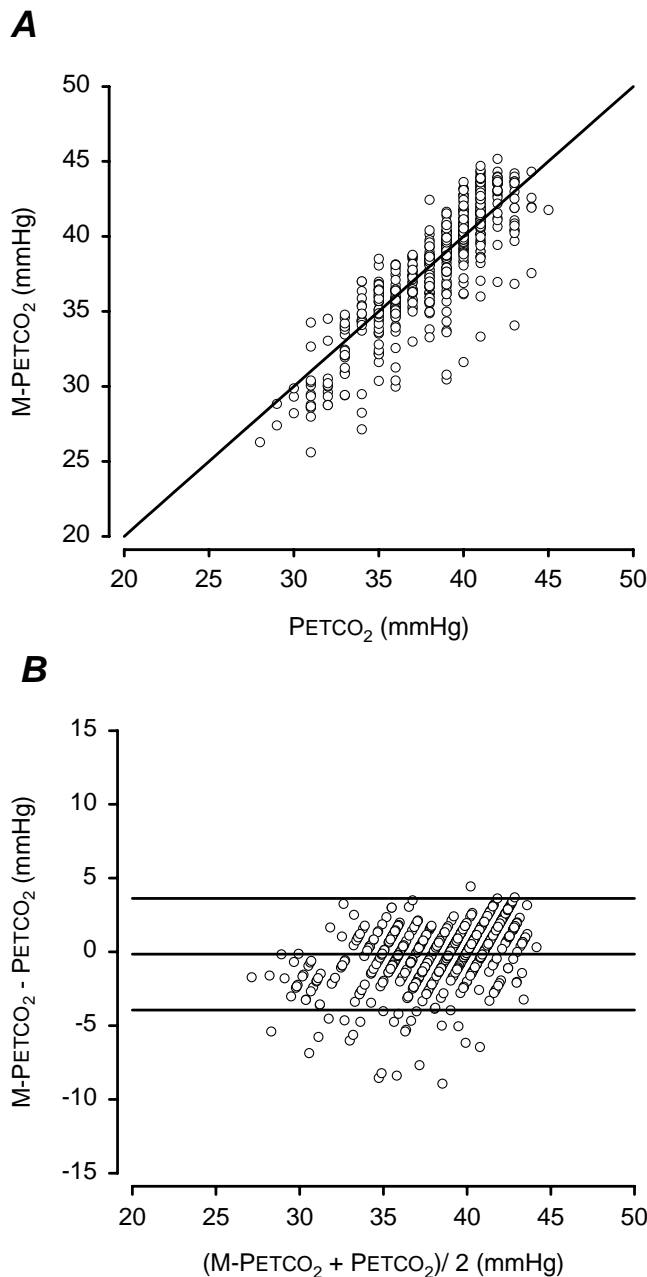
A

B

Figure 3.3.
Pooled data of 300 s of $PETCO_2$ recording in 8 subjects, 150 s supine and 150 seconds standing, plotted against the output of a model run of the same time period.
The number of data points is 583, representing the total of 583 breaths.
A, pooled data of computed $PETCO_2$ ($M-PETCO_2$) plotted against measured $PETCO_2$.
B, pooled data scatter diagram of differences between measured $PETCO_2$ and computed $PETCO_2$ ($M-PETCO_2$) against their mean. Horizontal lines indicate mean ± 1.96 SD.

Figure 3.3A shows the pooled results of breath-to-breath M-PETCO$_2$, plotted against the pooled PETCO$_2$ measurements. There was a significant correlation between M-PETCO$_2$ and PETCO$_2$ ($r^2 = 0.74$, P <0.05). The difference between PETCO$_2$ and M-PETCO$_2$, versus the average PETCO$_2$ is shown in Figure 3.3B. Accuracy (group-averaged M-PETCO$_2$ - PETCO$_2$ difference) and precision (SD of the M-PETCO$_2$ - PETCO$_2$ difference) of the model during the simulation were –0.16 and 1.93 mmHg respectively (95% limits of agreement were –3.95 and +3.63 mmHg).

Experiments

To verify the contribution of the postural reduction in Q to hypocapnia in the standing position, a protocol of standing up during controlled breathing, and the deflation of leg splints was applied on seven subjects. Throughout standing up and deflation of leg splints, the minute ventilation was fixed (the level ranged from 7 to 9.5 l/min) and breathing frequency was maintained at 0.15 Hz.

     Supine vs. standing   On average the sum of FRC and VD increased from 2.8±0.8 l in the supine position to 3.3±0.3 l in the upright position (p=0.22). The group average mean ABP was 84±8 mmHg supine vs. 87±13 mmHg standing (n.s.), whereas HR increased from 74±5 to 89±7 bpm (P<0.001). With VT and T$_{RESP}$ fixed, both Q (–0.6 to -3.1 l/min) and PETCO$_2$ (–2.3 to –3.5 mmHg) decreased on going from supine to standing, (Fig. 3.4). In other words, PETCO$_2$ decreased in the upright position even though the depth and rate of breathing were kept constant. However, the decrease in PETCO$_2$ and the decrease in Q showed a correlation coefficient (r^2) of only 0.06.

     Inflated vs. deflated leg splints   The group average mean ABP was 88±11 mmHg with inflated splints vs. 86±10 mmHg with deflated splints (n.s.), whereas HR increased from 80±8 to 93±10 bpm (P=0.02). Following deflation of splints, Q decreased (–0.1 to –1.1 l/min) and PETCO$_2$ decreased (ranging from –1.4 to –3.6 mmHg) in all subjects, while VT and T$_{RESP}$ were fixed (Fig. 3.4). The correlation between the decrease in Q and PETCO$_2$ yielded a correlation coefficient of r^2=0.80.

Figure 3.4.
PETCO$_2$ and *Q* during controlled breathing in 7 healthy subjects.
Results of protocol of supine and standing (A) and inflated and deflated leg cuffs. (B) protocols. Symbols represent average end-tidal PCO$_2$ (top) and cardiac output (*Q*, bottom) during 5 min. The black lines link the results of a particular subject. Asterisk indicates P<0.01.
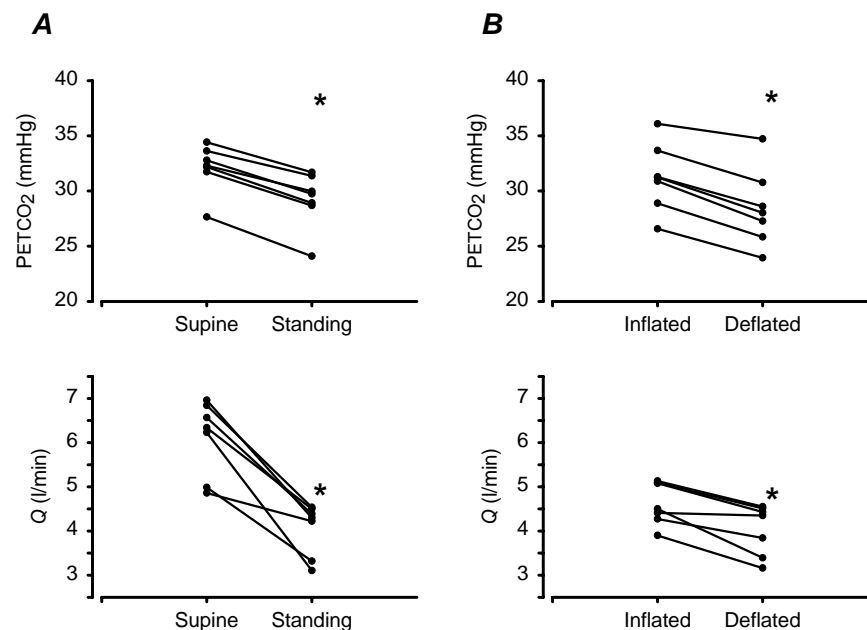
Parameter sensitivity analysis
The sensitivity of the model output to variations in parameters and model input was analysed. This resulted in a transient change in model output, a progressive variation or no variation in the output.

      Transient M-PETCO$_2$ change   A decrease in SV resulted in a transient reduction in PETCO$_2$ with a peak after six breaths (Fig. 3.5A). The model response to SV change was asymmetrical: a decrease in SV had a greater effect on PETCO$_2$ than an increase in SV of similar magnitude. The model response to an increase in FRC was transient, the peak response occurred at the first breath and rapidly decayed (Fig. 3.5B). The model response to FRC variation also showed asymmetry; an decrease in FRC yielded a greater M-PETCO$_2$ variation than an increase in FRC of the same magnitude.

      Progressive M-PETCO$_2$ change   A strong influence on model output was exerted by changes in VT, T_{RESP}, VO$_2$, RQ and VD (Fig. 3.6). The effects of T_{RESP}, VO$_2$ and RQ on M-PETCO$_2$ were equal, as can be expected from Eq. 4 (see Appendix), where the VCO$_2$ per breath is determined by VO$_{2,n}$, the RQ and the breath duration. The V/Q gradient was analysed by comparing a model run with homogeneous perfusion distribution (as in the supine position) to a model run with a gravity-induced lung-perfusion gradient (as in the standing position). The steady-state model run with 'supine' V/Q distribution resulted in a baseline PETCO$_2$ of 40 mmHg. After the model run with 'upright' V/Q distribution, the PETCO$_2$ was 38.4 mmHg after 900 s.

      No M-PETCO$_2$ change   A 10% increase or decrease in Vv or Va did not influence model outcome of PETCO$_2$. However, an increase in Va or Vv results in increased damping of breathing pattern-related variation in PETCO$_2$.

      Posture induced variations   The contribution of each parameter on PETCO$_2$ as is likely to occur during posture change is given in Figure 3.7. For example, a 20% increase in VT resulted in a progressive decrease in PETCO$_2$ which dropped from 40 to 34 mmHg after a 300 s model run. An increase in FRC resulted in acute hypocapnia which lasted for several breaths. After 300 s however, the PETCO$_2$ was only 1 mmHg below supine levels. The posture-dependent change in the V/Q mismatch per se had a limited effect on the decrease in PETCO$_2$.

      Computed effect of FRC and VD increase upon standing   We conducted an additional analysis of the increase in FRC and VD, which occur simultaneously during tilt. On average the sum of FRC and VD increased from 2.8±0.8 l in the supine position to 3.3±0.3 l in the upright position (p=0.22). We used model (male) supine steady state settings (see above) to analyse the effect on PETCO$_2$, where an FRC of 2.5 l and VD at 0.2 l results in a PETCO$_2$ of 40 mmHg. By increasing FRC to 2.93 l and VD increased to 0.27 (VD is known to increase by ≈70 ml in the upright position; together VD and FRC now amount to 3.2 l), computed PETCO$_2$ transiently decreased by 12% in the first breath. However, after 9 breaths the hypocapnia had completely disappeared, and after 13 breaths PETCO$_2$ had increased to above steady state levels. Therefore, an increase in FRC and VD combined induce hypocapnia only in the first 40 seconds.

Discussion

The present study determined the relative contributions of increased ventilation and FRC, slight V/Q mismatch, and decreased cardiac output to the postural decrease in PETCO$_2$. For this we developed a mathematical model based on respiratory and circulatory physiology,

which predicted PETCO$_2$ variations during the transition from supine to standing and for 2.5 minutes in the upright position. The model is sensitive to changes in VT, FRC and VD, SV, T$_{RESP}$, VO$_2$, RQ, and V/Q , all of which affect model output, i.e., PETCO$_2$ (Figs. 3.5, 3.6 and 7). Stroke volume transiently affects model PETCO$_2$ with a maximal effect after several breaths (Fig. 3.5A). This response is asymmetrical, with a greater effect from a decrease in SV compared to an increase in SV. An increase in FRC causes a transient decrease in model PETCO$_2$ (Fig. 3.5B). However, with the concomitant increase in VD, the FRC-induced hypocapnia is of limited duration ($\approx$40 s). A gravitation-induced slight V/Q mismatch as occurs during standing up (Fig. 3.1, Table 3.1) contributes to the decrease in PETCO$_2$. RQ affects model PETCO$_2$ levels, but does not vary on a breath-to-breath basis. Thus, the VT increase and SV reduction when standing up are the physiological events primarily responsible for the decrease in PETCO$_2$, whereas a gravity-induced V/Q mismatch and transiently, an increase in FRC contribute to hypocapnia.
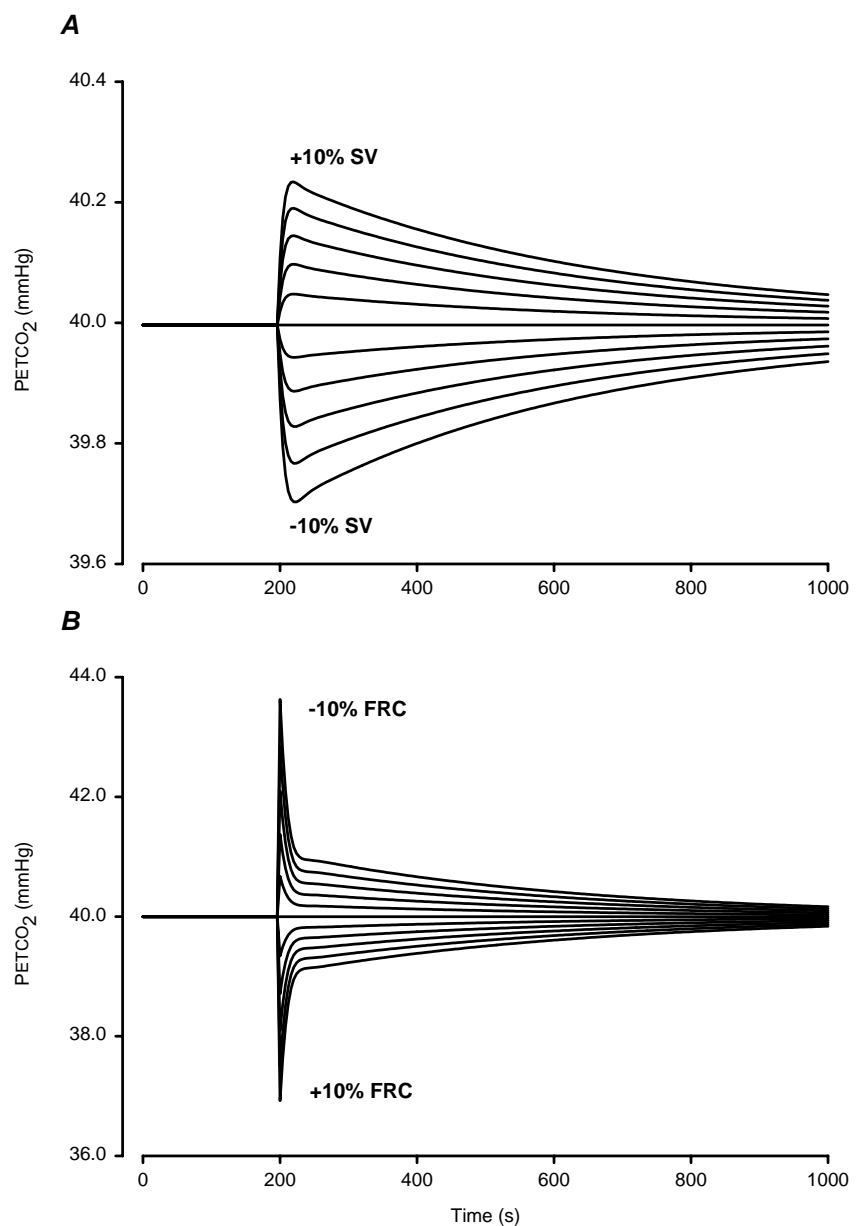

Figure 3.5. Parameter sensitivity analysis of SV and FRC.
Each line represents a model run where after 200 breaths under baseline conditions the input is changed from its baseline value by –10% to +10%, in steps of 2%. In A the input is SV of the heart, in B the input is FRC. Note difference in ordinate scale.

The predominant influence of Q on hypocapnia in the standing position was verified in experiments on human subjects, using a protocol in which first breathing alone and then breathing, FRC and V/Q were controlled. The correlation between the decrease in Q and in PETCO$_2$ (r^2=0.80), in the absence of alternations in breathing, FRC and V/Q indicates that the postural decrease in Q contributes to hypocapnia.
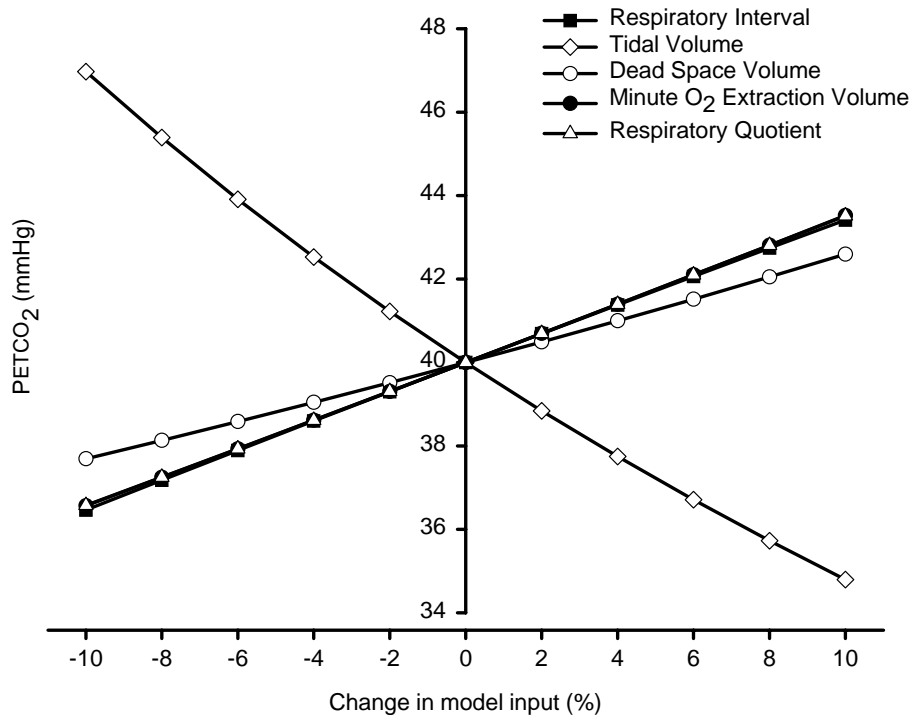

Figure 3.6.
Analysis of effect of each input variable on PETCO$_2$.
Parameter sensitivity analysis of model input (T$_{RESP}$, VT, VO$_2$) and model parameters (VD and RQ). Model input is changed from baseline by -10% to +10% (see Methods) and model output (PETCO$_2$) determined after 900 s.

Limitations
The lung model presented is, by design, a simplified representation of lung ventilation and perfusion, and has limitations. First, the model circulation is simplified into a venous, an arterial and a lung capillary compartment. There is no bronchial arterial shunt included, because its effect on the PETCO$_2$ is thought to be small and not likely to vary with posture change. Autoregulation of the lung is not included in our model, and the model circulation does not include a venous pooling reservoir, although venous pooling has profound effects on PETCO$_2$ [64]. We considered a pooled venous reservoir with high PCO$_2$ levels in blood and interstitium likely to affect the PETCO$_2$ when assuming the supine position after prolonged standing rather than on going from a supine position to standing up. When pooled blood with elevated PCO$_2$ returns to the heart and subsequently reaches the lungs, this will result in a PETCO$_2$ 'overshoot'. Interstitial space, and CO$_2$ transfer to and from extracellular space are not modelled, nor are changes in haemoglobin concentration due to haemoconcentration during standing. The model was designed for short-term PETCO$_2$ variability and we assumed that changes in haemoglobin concentration are minor.

The apex to base V/Q distribution inequality in the standing position results in a decrease in PETCO$_2$ because the air expired from alveoli active in gas exchange is diluted by air from apical lung segments which are relatively underperfused, suggesting that the reduction in PETCO$_2$ will be more pronounced than the reduction in arterial PCO$_2$ when standing up. In 1962 Bjurstedt et al. [15] observed that changing from the supine to the standing position was associated with a significant rise in the arterial to end-tidal PCO$_2$ difference. However, our current model and experimental data do not allow us to analyse the arterial to end-tidal PCO$_2$ difference due to the afore mentioned model limitations, including the absence of a bronchial arterial shunt, a venous pooling reservoir and lung-autoregulation.
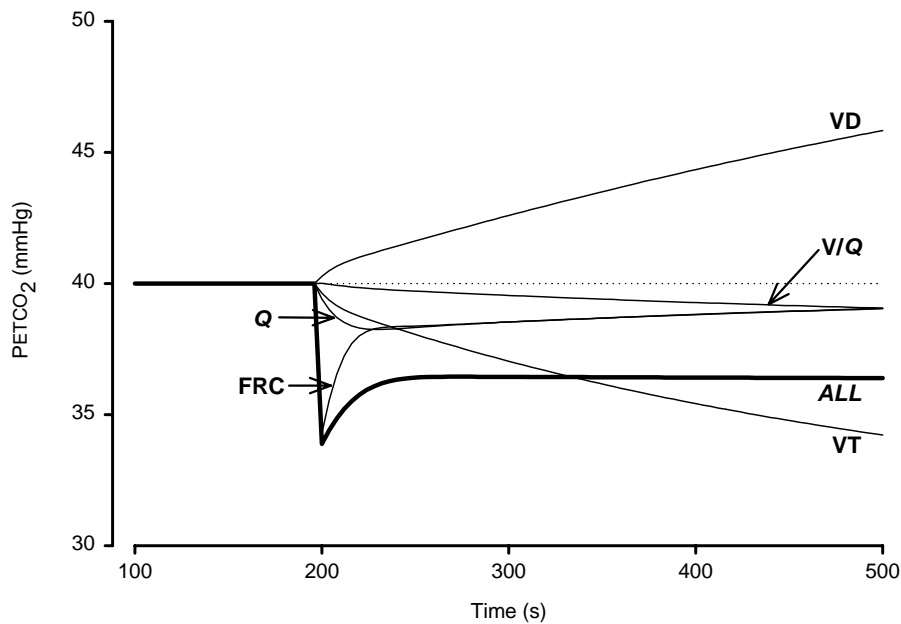

Figure 3.7.
Effect of active-standing induced variations in model input variables on PETCO$_2$.
Each thin line indicates the output of a model run starting with supine settings and with parameter settings varied 200 s as is likely to occur on standing up: Q, output when Q was reduced by 40%, VT, output when VT was increased by 20%, FRC, output when FRC was increased by 20%, VD, output when the VD was increased by 70 ml, V/Q, output when V/Q shifted from equal distribution to model settings for a gravitationally induced V/Q mismatch. The thick black line labelled *ALL* indicates model PETCO$_2$ levels when each of these changes occurred simultaneously.

To convert [CO$_2$] to PCO$_2$ and vice versa, we fitted blood CO$_2$ equilibrium curves (see Appendix), without accounting for O$_2$–dependency. We did not implement Kelman's digital computer procedure for conversion of PCO$_2$ into blood CO$_2$ content, which in our model would yield a linear relationship because haemoglobin concentration and temperature are assumed to remain constant ([76]).

Step changes in Vv and in Va did not influence PETCO$_2$ in the sensitivity analysis, where all other model settings were kept constant. This does not imply that settings for Vv and Va are of no consequence. These compartments act as buffers for PETCO$_2$ changes

brought about by variations in VT, SV, etc. Therefore, a larger Vv or Va will result in damping of $PETCO_2$ variations.

Several model parameters are estimated based on previous studies. The distribution of ventilation and perfusion in the upright position are based on measurements of West [126]. The distribution of ventilation and perfusion over the lung are influenced by a gravity-invoked hydrostatic pressure gradient (perfusion) and a pleural pressure gradient influencing the alveolar pressure/volume relationship (ventilation). Although in the supine position there is still some effect of gravity, this will be less because the vertical height of the lung is less than in the upright position. Therefore, we chose to model the distribution of ventilation and perfusion in the supine position as equally distributed from apex to base.

Conclusions

In human subjects assuming the upright position, end-tidal CO_2 levels drop. The present study shows that the CO_2 levels during posture change can be tracked using a mathematical model, with breath-to-breath values for tidal volume, stroke volume, pulmonary O_2 uptake and respiratory interval as input variables. We found that the decrease in end-tidal CO_2 level in the standing position is due to increased tidal volume and, transiently, decreased cardiac output increased FRC, and that the gravity-induced slight ventilation/perfusion mismatch contributes to the hypocapnia.

Acknowledgement

Appendix

Symbols	Definition	Units
$[CO_2]_a$	arterial CO_2 content	%
$[CO_2]_v$	venous partial CO_2 content	%
ABP	arterial blood pressure	mmHg
FRC	functional residual capacity	ml
HR	heart rate	bpm
$PETCO_2$	end-tidal partial CO_2 pressure	mmHg
$M\text{-}PETCO_2$	model output end-tidal partial CO_2 pressure	mmHg
$PkCO_2$	lung compartment 'k' partial CO_2 pressure	mmHg
$PtcCO_2$	PCO_2 of blood draining the lungs	mmHg
Q	cardiac output	$l\ min^{-1}$
RQ	respiratory quotient	unitless
R-R	respiratory rate	min^{-1}
SV	stroke volume per breath	ml
T_{RESP}	respiratory interval	s
Va	arterial blood volume	ml
V_{cap}	lung capillary blood volume	ml
VD	anatomical dead space	ml
VE	ventilation	$l\ min^{-1}$
VO_2	pulmonary O_2 uptake	$ml\ min^{-1}$
V/Q	ventilation-perfusion ratio	unitless
VT	tidal volume	ml
Vv	venous blood volume	ml

Model equations

    Conversion and weight functions   The CO_2 equilibrium curve relating blood CO_2 content ($[CO_2]$) to blood partial CO_2 pressure (PCO_2) is described as $[CO_2] = f(PCO_2)$, with

$$f(x) = 0.53 \cdot (1.266 - \exp(-0.0257x))$$

To compute PCO_2 from $[CO_2]$ in blood, we use the inverse function

$$f^{-1}(x) = -\ln(1.266 - (x / 0.53)) / 0.0257$$

To convert PCO_2 in air (mmHg) to $[CO_2]$ (%), we use the conversion factor c, which amounts to 0.1316 %/mmHg. The distribution of SV and VT over each lung compartment k (k = 1…9) is described by functions *g* and *h*, respectively. These functions, which are different for the supine and upright positions and yield the fractions for SV and VT listed in Table 3.2, are given by

$$g(k) = \begin{cases} 1/9 & \text{(in the supine position)} \\ -0.0205 + 0.0263\,k & \text{(in the upright position)} \end{cases}$$

and

$$h(k) = \begin{cases} 1/9 \ \text{(in the supine position)} \\ 0.226 \cdot (1.102 \ \exp(-0.1063\,k)) \ \text{(in the upright position)} \end{cases}$$

Each lung compartment's share of FRC, V_{cap} and VD is given by the weight function
$w(k) = 0.10055 \cdot (1.36708 - \exp(-0.3393k))$
which yields the fractions for FRC and V_{cap} listed in Table 3.2.

  Venous CO$_2$ For each breath n, the venous CO_2 content ($[CO_2]_{v,\ n}$) is calculated from its previous value $[CO_2]_{v,\ n-1}$ according to Eqs. 1-4. The amount of CO_2 in the venous compartment increases by the amount that arrives from the arterial compartment (A) and the amount created by the basal metabolism (B), and decreases by the amount that leaves the compartment (C). Thus, we have

  (Eq. 1) $[CO_2]_{v, n} = [CO_2]_{v, n-1} + (A + B - C) / Vv$

where

  (Eq. 2) $C = [CO_2]_{v, n-1} \cdot SV_n$

  (Eq. 3) $A = [CO_2]_{a, n-1} \cdot SV_n$

with $[CO_2]_a$ denoting the arterial CO_2 content, and

  (Eq. 4) $B = VO_{2, n} \cdot RQ \cdot (T_{RESP, n} / 60)$

where $VO_{2,\ n}$ is the oxygen extraction for breath *n* (in ml min^{-1}) and RQ is the respiratory quotient, which is set at 0.9 (the average as approximated from subject data, by dividing VCO_2 by VO_2). The term is multiplied by the breath duration in min ($T_{RESP,n} / 60$) to estimate the CO_2 produced per breath.

  Arterial CO$_2$ The arterial blood CO_2 content for breath *n* ($[CO_2]_{a,\ n}$) is calculated from its previous value $[CO_2]_{a, n-1}$ according to Eqs. 5 – 7. The amount of CO_2 in the arterial compartment increases by the amount of CO_2 arriving from the lungs (D) and decreases by the amount of CO_2 leaving the arterial compartment (E):

  (Eq. 5) $[CO_2]_{a, n} = [CO_2]_{a, n-1} + (D - E) / Va$

The amount D can be estimated from the end-tidal partial CO_2 pressure in each lung compartment *k* ($PkCO_2$, $k = 1\ldots9$) through

  (Eq. 6) $D = \sum_{k=1}^{9} f(PkCO_{2, n-1}) \cdot (g(k) \cdot SV_n)$

Where *f* is the above function that relates blood CO_2 content to the blood partial CO_2 pressure and *g* is the above function that defines the distribution of SV over the nine lung compartments. The amount E is given by

  (Eq. 7) $E = [CO_2]_{a, n-1} \cdot SV_n$

Lung CO₂   The PCO_2 of blood draining the lungs ($PtcCO_2$) is dependent on the gravity-induced perfusion and ventilation gradients, as described by the above functions g and h. For each breath, the PCO_2 in each lung segment k ($PkCO_{2,\,n}$) is calculated according to Eqs. 8 -13. At FRC, the amount of CO_2 in lung segment k (F) is determined by the CO_2 content in the lung capillaries, in the FRC and in the VD:

$$\text{(Eq. 8)}\quad F = f(PkCO_{2,\,n-1})\cdot\ w(k)\cdot\ V_{cap} + c\cdot\ PkCO_{2,\,n-1}\cdot\ w(k)\cdot\ FRC$$
$$+ c\cdot\ PETCO_{2,\,n-1}\cdot\ w(k)\cdot\ VD$$

with the weight function w and conversion factor c as described above. The contribution of CO_2 in dead space (the right-most term) is computed noting that end-tidal air from the previous breath is returned to the lungs from dead space. The amount of CO_2 carried to the lungs from the venous compartment (G) is given by

$$\text{(Eq. 9)}\quad G = [CO_2]_{v,\,n-1}\cdot\ SV_n\cdot\ g(k)$$

The ratio a of $[CO_2]$ in blood and $[CO_2]$ in air is approximated from the previous breath, n-1, according to

$$\text{(Eq. 10)}\quad a = f(PETCO_{2,\,n-1}) / (c\cdot\ PETCO_{2,\,n-1})$$

The ratio b of the end-tidal amount of CO_2 in air and the total amount of CO_2 is given by

$$\text{(Eq. 11)}\quad b = (w(k)\cdot\ FRC + h(k)\cdot\ VT_n)$$
$$/ \{a(w(k)\cdot\ V_{cap} + g(k)\cdot\ SV_n) + w(k)\cdot\ FRC + h(k)\cdot\ VT_n)\}$$

The end-tidal $[CO_2]$ in each lung compartment k is determined by the total amount of CO_2 (F+G), which is distributed over air and blood with ratio b, and the end-tidal volume of air in compartment k:

$$\text{(Eq. 12)}\quad [CO_2]_{k,\,n} = b\,(F + G) / (w(k)\cdot\ FRC + h(k)\cdot\ VT_n)$$

A simple conversion using the above constant c then yields $PkCO_{2,\,n}$. The $PETCO_2$ depends on the distribution of tidal volume, which is given by the fraction $h(k)$, k = 1..9, and differs between the supine and the standing position, and is computed as

$$\text{(Eq. 13)}\quad PETCO_{2,\,n} = \sum_{k=1}^{9} h(k)\cdot PkCO_{2,\,n}$$