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

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In man assuming the upright position, end-tidal P_{CO_2} (P_{ETCO_2}) decreases. With the rising interest in cerebral autoregulation during posture change, which is known to be affected by P_{ETCO_2}, we sought to determine the factors leading to hypocapnia during standing up from the supine position. To study the contribution of an increase in tidal volume (V_T) and breathing frequency, a decrease in stroke volume (SV), a ventilation–perfusion (V/Q) gradient and an increase in functional residual capacity (FRC) to hypocapnia in the standing position, we developed a mathematical model of the lung to follow breath-to-breath variations in P_{ETCO_2}. A gravity-induced apical-to-basal V/Q gradient in the lung was modelled using nine lung segments. We tested the model using an eight-subject data set with measurements of V_T, pulmonary O_2 uptake and breath-to-breath lumped SV. On average, the P_{ETCO_2} decreased from 40 mmHg to 36 mmHg after 150 s standing. Results show that the model is able to track breath-to-breath P_{ETCO_2} variations ($r^2 = 0.74$, $P < 0.05$). Model parameter sensitivity analysis demonstrates that the decrease in P_{ETCO_2} during standing is due primarily to increased V_T, and transiently to decreased SV and increased FRC; a slight gravity-induced V/Q mismatch also contributes to the hypocapnia. The influence of cardiac output on hypocapnia in the standing position was verified in experiments on human subjects, where first breathing alone, and then breathing, FRC and V/Q were controlled.

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In man the carbon dioxide (CO_2) content of the alveolar air is lower in the upright position than in the supine position (Lilijestrand & Wollin, 1914). Main *et al.* (1937) confirmed this observation and explained it as being due to over-ventilation with resulting alkaemia. However, Hitchcock & Ferguson (1938) showed the drop in alveolar CO_2 partial pressure (P_{CO_2}) upon assuming the erect posture to be independent of alterations in pulmonary ventilation. They attributed the lowered P_{CO_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 (Stead *et al.* 1944). Variation in end-tidal partial P_{CO_2} (P_{ETCO_2}) reflects variation in Q in the same direction, for example during acute haemodynamic perturbations in anaesthetized patients during constant ventilation (Shibutani *et al.* 1994). Airway CO_2 levels have been proposed as a monitor of Q during cardiovascular resuscitation (Blumenthal & Voorhees, 1997). 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 (Zardini & West, 1966; Bryan *et al.* 1966; Milic-Emili *et al.* 1966), perfusion (West & Dollery, 1959; Anthonisen & Milic-Emili, 1966) and the ventilation–perfusion (V/Q) ratio (West, 1962; West *et al.* 1963; Musch *et al.* 2002) 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 P_{ETCO_2}. In the upright position, FRC and tidal volume (V_T) increase, due to lowering of the diaphragm and

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alveolar expansion due to the lungs' own weight. However, the relative contribution of each of these physiological phenomena to the postural decrease in P_{ETCO_2} is unknown.

With the rising interest in cerebral autoregulation during posture change (Birch *et al.* 1995; Cencetti *et al.* 1997; Novak *et al.* 1998; Harms *et al.* 2000; Hughson *et al.* 2001; Edwards *et al.* 2002), which is affected by P_{CO_2}, we sought to determine the factors leading to transient P_{ETCO_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 P_{ETCO_2} upon standing up. To test this hypothesis, we developed a nine-compartment computer model of the lung to simulate breath-to-breath P_{ETCO_2} variations during active standing up. The model includes an FRC, V_T and anatomic dead space (V_D). 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 ($\dot{V}_{O_2}$), respiratory interval (T_{RESP}) and V_T.

Methods

Model

To assess the underlying physiology determining P_{ETCO_2} transients during posture change, we developed a breath-to-breath model, programmed in MATLAB (Release 5.2, The MathWorks, Natick, MA, USA). 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, $\dot{V}_{O_2}$ and V_T. The model is 'paced' by the respiratory interval.

Ventilation. The model includes nine lung compartments (Fig. 1, right panel). Each compartment's share of the FRC and V_T is determined by its position with the apical compartments smaller than the basal compartments. The distributions of V_T and SV in the upright position, are approximations based on observations by West (1962) (Table 1). The model includes V_D. Using an established relation between anatomical V_D and height (Hart *et al.* 1963), we set the model V_D for men at a greater volume compared to the V_D for women (1.4 times), with the V_D 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 ($\dot{V}_{CO_2}$) to $\dot{V}_{O_2}$, normally between 0.7 and 1.0, was set at 0.9.

Circulation. The model includes a simplified blood circulation with an arterial compartment (V_a), a venous compartment (V_v) and lung capillary gas-exchange compartments (V_{cap}) (see Fig. 1, left panel). The lung capillary volume and the small venule volume are lumped together, 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 5.5 l is distributed over V_v (4.0 l), V_a (1.3 l) and V_{cap} (0.2 l) (Burton, 1972).

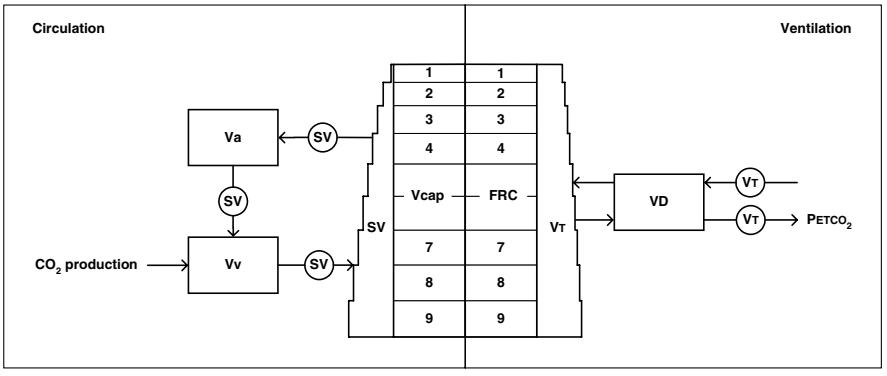

Figure 1. Diagram of the P_{ETCO_2} model
The left panel represents circulation with an arterial volume V_a, a venous volume V_v, a lung capillary volume V_{cap}, and circulating stroke volume per breath SV. The right panel represents ventilation with a functional residual capacity FRC, a respiratory dead space V_D, and a tidal volume V_T. The distribution of SV and V_T as shown here are for the upright position; in the supine position SV and V_T are equally distributed over apical and basal lung segments (1–9).

Table 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 (% SV*k*)	11.1	11.1	11.1	11.1	11.1	11.1	11.1	11.1	11.1	100
	Ventilation (%$V_T k$)	11.1	11.1	11.1	11.1	11.1	11.1	11.1	11.1	11.1	100
	Alveolar vol. (% FRC*k*)	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 (% SV*k*)	0.58	3.21	5.84	8.47	11.10	13.73	16.36	18.99	21.62	100
	Ventilation (%$V_T k$)	4.58	6.63	8.48	10.13	11.62	12.96	14.17	15.25	16.22	100
	Alveolar vol. (% FRC*k*)	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 (V_T), 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 (1962).

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 (1962). Distributions of V_T, SV, FRC and V_{cap} are summarized in Table 1. In the supine position, SV and V_T 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 V_T. 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 7.9–0.8 apical-to-basal *V/Q* gradient. Furthermore, on going from supine to upright respiratory V_D increases (Bjurstedt *et al.* 1962; Rea *et al.* 1977). Bjurstedt *et al.* (1962) established an increase in V_D in the upright position of +53 ml (anatomical) and +81 ml (physiological). In the model, V_D increases by 70 ml in the upright position.

Data set

The physiological data we used to test our model are from eight healthy young subjects (2 women; median age 24 years (21–38 years); median height 183 cm (162–191 cm); median weight 78 kg (50–85 kg)), who participated in the study of van Lieshout *et al.* (2001) for which informed consent had been obtained from all participants, and which was approved by the ethics committee of Copenhagen (KF 01-120/96) and was performed in accordance with the guidelines laid down in the Declaration of Helsinki. Instrumentation occurred as previously described; after 5 min of supine rest, each subject actively assumed the upright position and remained standing for 5 min 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 P_{ETCO_2} variations with posture change, we selected data starting 150 s prior to standing up and ending 150 s after 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 (Jellema *et al.* 1999; Harms *et al.* 1999). 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 $\dot{V}_{O_2}$ in the supine and in the standing position. Absolute values of *Q* were used to calibrate Modelflow *Q*, averaged during 150 s in the supine position, and during 150 s of standing.

Breath-to-breath online gas analysis was performed using a Medical-Graphics CPX/D metabolic cart. Respiratory gas was sampled continuously from a mouthpiece and partial gas pressures were obtained from a Zirkonia oxygen analyser (accuracy ± 0.03% O_2) and a non-dispersive infrared sensor for CO_2 (accuracy ± 0.05% CO_2) that thus delivered $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$ and P_{ETCO_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 interbeat interval. Then, ventilatory data and Fick-calibrated Modelflow SV data were time aligned. For

Table 2. Haemodynamic and ventilatory responses to standing up in eight normal subjects

	Q (l min^{-1})	$\dot{V}_{CO_2}$ (ml min^{-1})	$\dot{V}_{O_2}$ (ml min^{-1})	P_{ETCO_2} (mmHg)	R-R (min^{-1})	V_T (ml)	V_E (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 ± S.D.) for cardiac output (Q), CO_2 output ($\dot{V}_{CO_2}$), oxygen uptake ($\dot{V}_{O_2}$), end-tidal CO_2 pressure (P_{ETCO_2}), respiratory rate (R-R), tidal volume (V_T) and expired ventilation (V_E) as determined from 150 s in the supine position followed by 150 s of standing. Data from the study of van Lieshout *et al.* (2001). *Standing *versus* supine, paired t test.

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, weight 71 ± 11 kg). Informed consent was obtained from all participants. The study was approved by the ethics committee of the Academic Medical Center (MEC 01-147) and performed in accordance with the guidelines laid down in 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 V_T 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^{-1}). During expiration the inflow of air filled a bag, and during inspiration the subject was instructed to empty the bag, thus maintaining a constant V_T. Keeping the breathing fixed, 5 min of supine recording were followed by 5 min 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 min recording during standing with inflated splints, the splints were deflated to atmospheric pressure within 4 s, followed by 5 min recording in standing position with deflated splints. The respiratory frequency and V_T were fixed throughout the procedures. We measured finger ABP (Finometer Model 1, TPD-BMI) and P_{CO_2} (Hewlett Packard Airway Adapter 1436 A). SV was derived from the peripheral arterial pressure signal using Modelflow as described above. Measurements of Q were carried out at the beginning and end of each procedure using the inert gas rebreathing technique (Innocor Model: SpO_2 & O_2 options; Gabrielsen *et al.* 2002). Rebreathing episodes were marked and Modelflow Q was level-corrected. The sum of FRC and V_D was measured in the supine and standing positions, also using the Innocor rebreathing technique. The calculation is based on the dilution of insoluble gas (SF6). Measurement of FRC and V_D combined, in both the supine and standing positions, allowed us to analyse the effect of FRC increase, as measured, on the P_{ETCO_2}.

Parameter sensitivity analysis

To assess the relative contribution of the various physiological phenomena contributing to P_{ETCO_2} variations, the parameter sensitivity of the model was analysed. First, the effect of variations in V_T, V_D, SV, $\dot{V}_{O_2}$, RQ, FRC, V_v, V_a, T_{RESP} and V/Q on model output (M-P_{ETCO_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: V_T = 484 ml; V_D = 200 ml; SV = 550 ml; $\dot{V}_{O_2}$ = 250 ml min^{-1}; RQ = 0.9; FRC = 2.5 l; V_v = 4.0 l; V_a = 1.3 l; T_{RESP} = 4 s and V/Q = 'supine'. The output value used in the analysis was M-P_{ETCO_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 V_T, V_D and FRC, a reduction in SV, and a shift in V/Q.

Statistical analysis

Haemodynamic 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 means and standard deviation (S.D.) or as median and range, as appropriate. Supine and upright values were compared by paired *t* test. Agreement between P_{ETCO_2} and M-P_{ETCO_2} was judged by plotting the difference between M-P_{ETCO_2} and P_{ETCO_2} against their means, and computing Pearson's correlation coefficient. The mean difference (bias) and S.D. (precision) between M-P_{ETCO_2} and P_{ETCO_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 haemodynamic and ventilatory responses to standing up from the test database are given in Table 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}. V_T increased on standing up, while the respiratory rate decreased. V_E increased on standing up in all subjects,

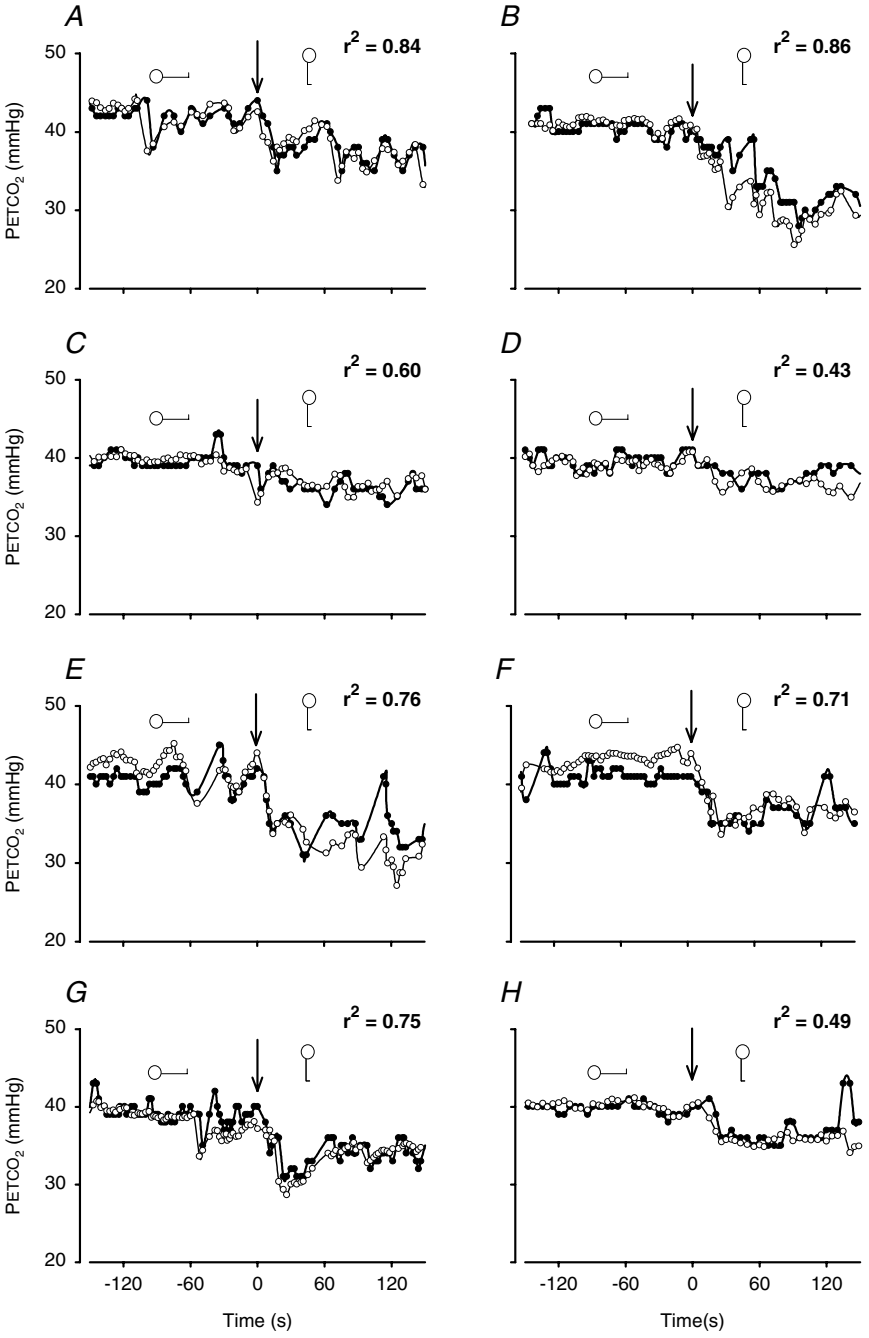

Figure 2. Individual P_{ETCO_2} recordings and model simulations during lying down and standing
Plots of breath-to-breath P_{ETCO_2} of each individual subject. Subjects 1–8 are represented in panels *A*–*H*, respectively. Each panel contains a plot of breath-to-breath P_{ETCO_2} measurements (●) during 150 s supine and 150 s of standing, and a model simulation (○) of the same period. Arrows indicate posture change from supine to standing at time zero.

with a range of 0.3–5.9 l min^{-1}. The P_{ETCO_2} decreased from 40 ± 1 to 36 ± 2 mmHg.

Model simulation

Inputs to the model were (measured) breath-to-breath values of V_T, SV (summed per breath) and $\dot{V}_{O_2}$. Starting values for P_{CO_2} in the venous and the arterial blood and in the various lung compartments were set for each test subject, corresponding to their starting measured P_{ETCO_2}. Venous CO_2 concentrations were set at a starting value ranging from 52 to 55%. The P_{CO_2} starting values in arterial blood and the lung compartments ranged from 40 to 42 mmHg. The first breaths of each model run were excluded from analysis. The P_{ETCO_2} and the M-P_{ETCO_2} during 150 s in the supine position followed by 150 s of standing of all individual subjects are given in Fig. 2. The model tracks P_{ETCO_2} during standing up, and it also follows non-posture-related variations in P_{ETCO_2} ($r^2 = 0.43$–0.86), with those registrations with the greatest variance in measured P_{ETCO_2} resulting in the best correlations of M-P_{ETCO_2} with P_{ETCO_2} ($P < 0.01$).

Figure 3*A* shows the pooled results of breath-to-breath M-P_{ETCO_2}, plotted against the pooled P_{ETCO_2} measurements. There was a significant correlation between M-P_{ETCO_2} and P_{ETCO_2} ($r^2 = 0.74$, $P < 0.05$). The difference between P_{ETCO_2} and M-P_{ETCO_2}, *versus* the average P_{ETCO_2} is shown in Fig. 3*B*. Accuracy (group-averaged M-P_{ETCO_2} – P_{ETCO_2} difference) and precision (S.D. of the M-P_{ETCO_2} – P_{ETCO_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^{-1}) and breathing frequency was maintained at 0.15 Hz.

Supine *versus* standing. On average the sum of FRC and V_D 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 *versus* 87 ± 13 mmHg standing (n.s.), whereas HR increased from 74 ± 5 to 89 ± 7 beats min^{-1} ($P < 0.001$). With V_T and T_{RESP} fixed, both Q (–0.6 to –3.1 l min^{-1}) and P_{ETCO_2} (–2.3 to –3.5 mmHg) decreased on going from supine to standing (Fig. 4). In other words, P_{ETCO_2} decreased in the upright position even though the depth and rate of breathing were kept constant. However, the decrease in P_{ETCO_2} and the decrease in Q showed a correlation coefficient (r^2) of only 0.06.

Inflated *versus* deflated leg splints. The group average mean ABP was 88 ± 11 mmHg with inflated splints *versus* 86 ± 10 mmHg with deflated splints (n.s.), whereas HR increased from 80 ± 8 to 93 ± 10 beats min^{-1} ($P = 0.02$). Following deflation of splints, Q decreased (−0.1 to −1.1 l min^{-1}) and P_{ETCO_2} decreased (ranging from –1.4 to −3.6 mmHg) in all subjects, while V_T and T_{RESP} were fixed

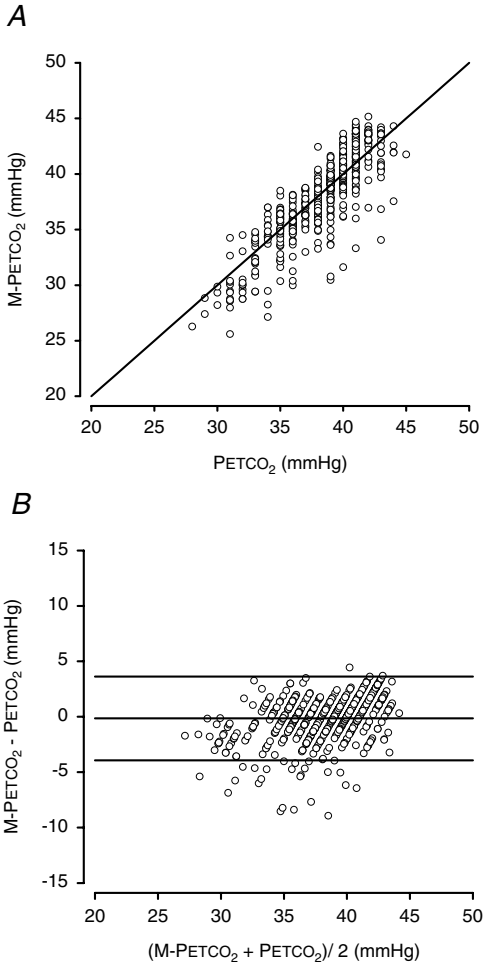

Figure 3. Pooled data of 300 s of P_{ETCO_2} registration in 8 subjects, 150 s supine and 150 s standing, plotted against the output of a model run of the same time period
The number of data points is 583, representing the total of 583 breaths. *A*, pooled data of computed P_{ETCO_2} (M-P_{ETCO_2}) plotted against measured P_{ETCO_2}. *B*, pooled data scatter diagram of differences between measured P_{ETCO_2} and computed P_{ETCO_2} (M-P_{ETCO_2}) against their mean. Horizontal lines indicate mean ± 1.96 S.D.

(Fig. 4). The correlation between the decrease in Q and P_{ETCO_2} yielded a correlation coefficient of $r^2 = 0.80$.

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-P_{ETCO_2} change. A decrease in SV resulted in a transient reduction in P_{ETCO_2} with a peak after six breaths (Fig. 5*A*). The model response to SV change was asymmetrical: a decrease in SV had a greater effect on P_{ETCO_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. 5*B*). The model response to FRC variation also showed asymmetry; a decrease in FRC yielded a greater M-P_{ETCO_2} variation than an increase in FRC of the same magnitude.

Progressive M-P_{ETCO_2} change. A strong influence on model output was exerted by changes in V_T, T_{RESP}, $\dot{V}_{O_2}$, RQ and V_D (Fig. 6). The effects of T_{RESP}, $\dot{V}_{O_2}$ and RQ on M-P_{ETCO_2} were equal, as can be expected from eqn (4) (see Appendix), where the $\dot{V}_{CO_2}$ per breath is determined by $\dot{V}_{O_2,n}$, 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 P_{ETCO_2} of 40 mmHg. After the model run with 'upright' V/Q distribution, the P_{ETCO_2} was 38.4 mmHg after 900 s.

No M-P_{ETCO_2} change. A 10% increase or decrease in V_v or V_a did not influence model outcome of P_{ETCO_2}. However, an increase in V_a or V_v results in increased damping of breathing pattern-related variation in P_{ETCO_2}.

Posture-induced variations. The contribution of each parameter on P_{ETCO_2} as is likely to occur during posture change is given in Fig 7. For example, a 20% increase in V_T resulted in a progressive decrease in P_{ETCO_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 P_{ETCO_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 P_{ETCO_2}.

Computed effect of FRC and V_D increase upon standing. We conducted an additional analysis of the increase in FRC and V_D, which occur simultaneously during tilt. On average the sum of FRC and V_D 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

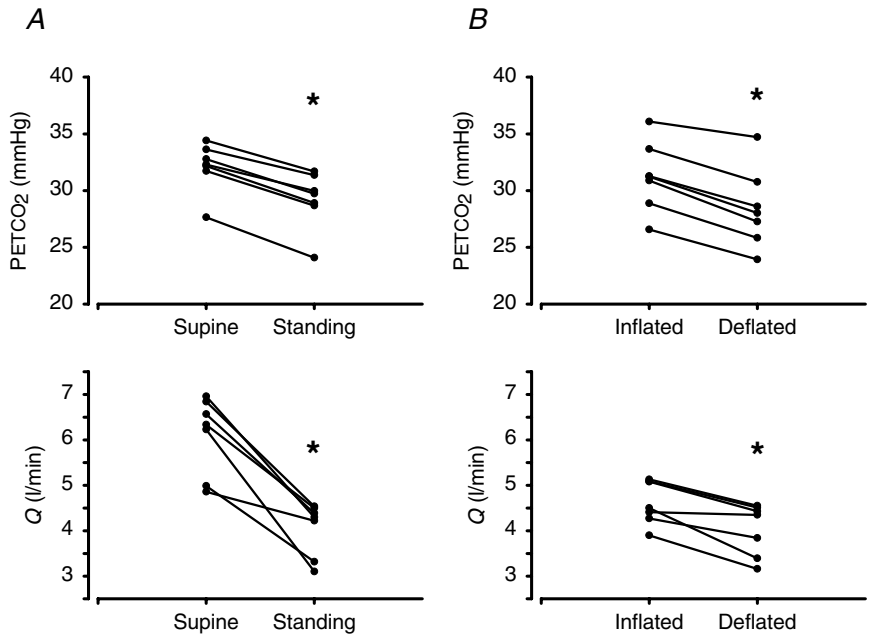

Figure 4. P_{ETCO_2} and Q during controlled breathing in 7 healthy subjects
Results of supine and standing (*A*) and inflated and deflated leg cuffs (*B*) protocols. Symbols represent average end-tidal P_{CO_2} (top) and cardiac output (Q, bottom) during 5 min. The lines link the results of a particular subject. Asterisk indicates $P < 0.01$.

state settings (see above) to analyse the effect on P_{ETCO_2}, where an FRC of 2.5 l and V_D at 0.2 l results in a P_{ETCO_2} of 40 mmHg. By increasing FRC to 2.93 l and V_D increased to 0.27 (V_D is known to increase by ~70 ml in the upright position; together V_D and FRC now amount to 3.2 l), computed P_{ETCO_2} transiently decreased by 12% in the first breath. However, after 9 breaths the hypocapnia had completely disappeared, and after 13 breaths P_{ETCO_2} had increased to above steady state levels. Therefore, an increase in FRC and V_D combined induce hypocapnia only in the first 40 s.

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 P_{ETCO_2}. For this we developed a mathematical model based on respiratory and circulatory physiology, which predicted P_{ETCO_2} variations during the transition from supine to standing and for 2.5 min in the upright position. The model is sensitive to changes in V_T, FRC and V_D, SV, T_{RESP}, $\dot{V}_{O_2}$, RQ, and *V/Q*, all of which affect model output, i.e. P_{ETCO_2} (Figs 5, 6 and 7). Stroke volume transiently affects model P_{ETCO_2} with a maximal effect after several breaths (Fig. 5*A*). 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 P_{ETCO_2} (Fig. 5*B*). However, with the concomitant increase in V_D, the FRC-induced hypocapnia is of limited duration (~40 s). A gravitation-induced slight *V/Q* mismatch as occurs during standing up (Fig. 1, Table 1) contributes to the decrease in P_{ETCO_2}. RQ affects model P_{ETCO_2} levels, but does not vary on a breath-to-breath basis. Thus, the V_T increase and SV reduction when standing up are the physiological events primarily responsible for the decrease in P_{ETCO_2}, whereas a gravity-induced *V/Q* mismatch and, transiently, an increase in FRC contribute to hypocapnia.

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 P_{ETCO_2} ($r^2 = 0.80$), in the absence of alternations in breathing, FRC and

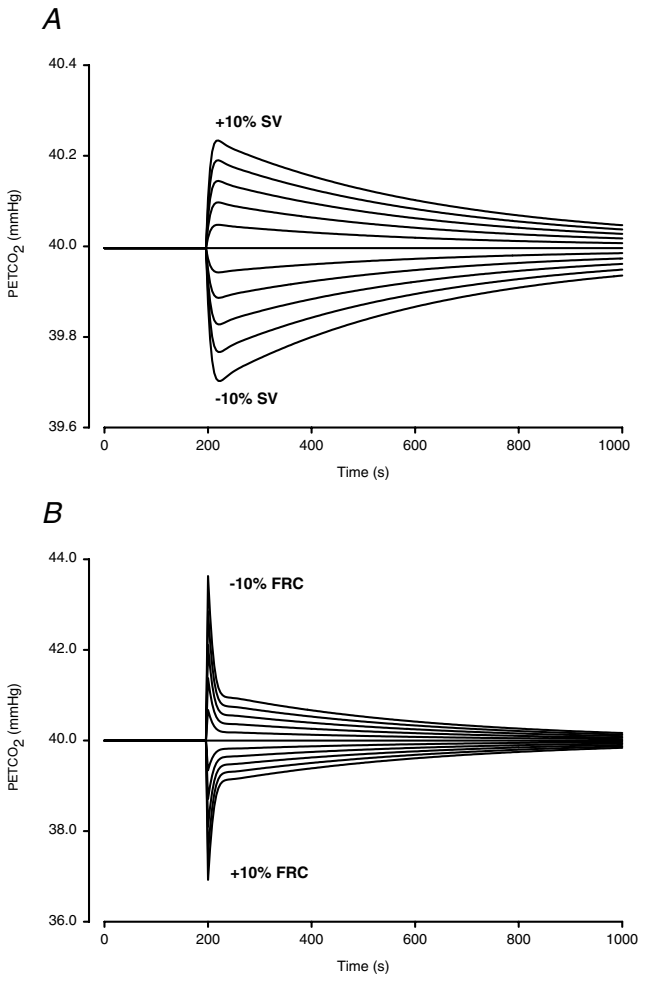

Figure 5. Parameter sensitivity analysis of SV and FRC
Each line represents a model run where after 200 breaths under baseline conditions the input is changed from its baseline value by –10 to +10%, in steps of 2%. In *A* the input is SV of the heart, in *B* the input is FRC. Note difference in ordinate scale.

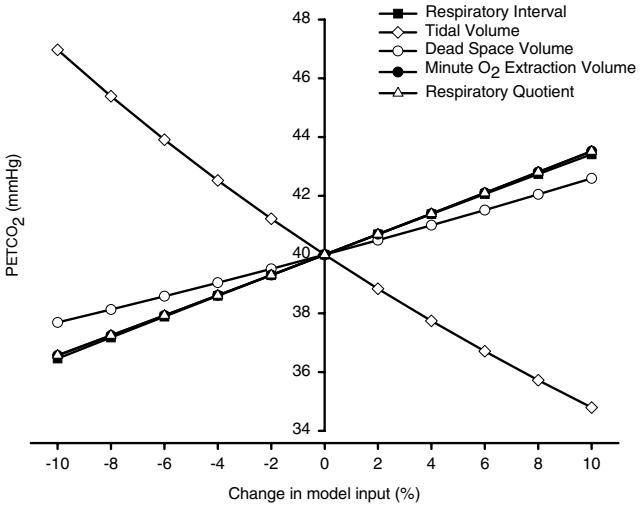

Figure 6. Analysis of effect of each input variable on P_{ETCO_2}
Parameter sensitivity analysis of model input (T_{RESP}, V_T, $\dot{V}_{O_2}$) and model parameters (V_D and RQ). Model input is changed from baseline by –10 to +10% (see Methods) and model output (P_{ETCO_2}) determined after 900 s.

V/Q indicates that the postural decrease in *Q* contributes to hypocapnia.

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 P_{ETCO_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 P_{ETCO_2} (Hitchcock & Ferguson, 1938). We considered a pooled venous reservoir with high P_{CO_2} levels in blood and interstitium likely to affect the P_{ETCO_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 P_{CO_2} returns to the heart and subsequently reaches the lungs, this will result in a P_{ETCO_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 P_{ETCO_2} variability and we assumed that changes in haemoglobin concentration are minor.

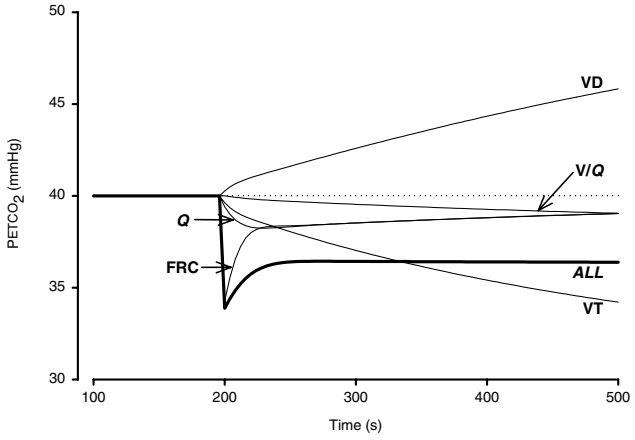

Figure 7. Effect of active-standing induced variations in model input variables on P_{ETCO_2}
Each thin line indicates the output of a model run starting with supine settings and with parameter settings varied at 200 s as is likely to occur on standing up: *Q,* output when *Q* was reduced by 40%, V_T, output when V_T was increased by 20%, FRC, output when FRC was increased by 20%, V_D, output when V_D 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 line labelled ALL indicates model P_{ETCO_2} levels when all of these changes occurred simultaneously.

The apex-to-base *V/Q* distribution inequality in the standing position results in a decrease in P_{ETCO_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 P_{ETCO_2} will be more pronounced than the reduction in arterial P_{CO_2} when standing up. In 1962 Bjurstedt *et al.* observed that changing from the supine to the standing position was associated with a significant rise in the arterial-to-end-tidal P_{CO_2} difference. However, our current model and experimental data do not allow us to analyse the arterial-to-end-tidal P_{CO_2} difference due to the aforementioned model limitations, including the absence of a bronchial arterial shunt, a venous pooling reservoir and lung-autoregulation.

To convert $[CO_2]$ to P_{CO_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 P_{CO_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 (Kelman, 1967).

Step changes in V_v and in V_a did not influence P_{ETCO_2} in the sensitivity analysis, where all other model settings were kept constant. This does not imply that settings for V_v and V_a are of no consequence. These compartments act as buffers for P_{ETCO_2} changes brought about by variations in V_T, SV, etc. Therefore, a larger V_v or V_a will result in damping of P_{ETCO_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 (1962). 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

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	beats min^{-1}
P_{ETCO_2}	End-tidal partial CO_2 pressure	mmHg
M-P_{ETCO_2}	Model output end-tidal partial CO_2 pressure	mmHg
P_{kCO_2}	Lung compartment k partial CO_2 pressure	mmHg
P_{tcCO_2}	P_{CO_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
V_a	Arterial blood volume	ml
V_{cap}	Lung capillary blood volume	ml
V_D	Anatomical dead space	ml
V_E	Ventilation	l min^{-1}
$\dot{V}_{O_2}$	Pulmonary O_2 uptake	ml min^{-1}
V/Q	Ventilation/perfusion ratio	unitless
V_T	Tidal volume	ml
V_v	Venous blood volume	ml

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, and increased FRC. The gravity-induced slight ventilation–perfusion mismatch contributes to hypocapnia.

Model equations

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

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

To compute P_{CO_2} from $[CO_2]$ in blood, we use the inverse function

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

To convert P_{CO_2} in air (mmHg) to $[CO_2]$ (%), we use the conversion factor c, which amounts to 0.1316% mmHg^{-1}. The distribution of SV and V_T 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 V_T listed in Table 2, are given by

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

and

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

Each lung compartment's share of FRC, V_{cap} and V_D is given by the weight function

$$w(k) = 0.10055(1.36708 - \exp(-0.3393k))$$

which yields the fractions for FRC and V_{cap} listed in Table 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 eqns (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

$$[CO_2]_{v,n} - [CO_2]_{v,n-1} + (A + B - C)/V_v \quad (1)$$

where

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

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

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

$$B = \dot{V}_{O_2,n}RQ(T_{RESP,n}/60) \quad (4)$$

where $\dot{V}_{O_2,n}$ 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 $\dot{V}_{CO_2}$ by $\dot{V}_{O_2}$). 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 eqns (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)

$$[CO_2]_{a,n} = [CO_2]_{a,n-1} + (D - E)/V_a \quad (5)$$

The amount D can be estimated from the end-tidal partial CO_2 pressure in each lung compartment k ($P_{kCO_2}k = 1...9$) through

$$D = \sum_{k=1}^{9} f(P_{kCO_2,n-1})(g(k)SV_n) \quad (6)$$

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

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

Lung CO_2. The P_{CO_2} of blood draining the lungs (P_{tcCO2}) is dependent on the gravity-induced perfusion and ventilation gradients, as described by the above functions g and h. For each breath, the P_{CO_2} in each lung segment k ($P_{kCO_2,n}$) is calculated according to eqns (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 V_D

$$F = f(P_{kCO_2,n-1})w(k)V_{cap} + cP_{kCO_2,n-1}w(k)FRC + cP_{ETCO2,n-1}w(k)V_D \quad (8)$$

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

$$G = [CO_2]_{v,n-1}SVng(k) \quad (9)$$

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

$$a = f(P_{ETCO_2,n-1})/(cP_{ETCO_2,n-1}) \quad (10)$$

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

$$b = (w(k)FRC + h(k)V_{Tn})/a(w(k)V_{cap} + g(k)SVn) + w(k)FRC + h(k)V_{Tn}) \quad (11)$$

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

$$[CO_2]_{k,n} = b(F + G)/(w(k)FRC + h(k)V_{Tn}) \quad (12)$$

A simple conversion using the above constant c then yields $P_{kCO2,n}$. The P_{ETCO_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

$$P_{ETCO_2,n} = \sum_{k=1}^{9} h(k)P_{kCO_2,n} \quad (13)$$

References

Anthonisen NR & Milic-Emili J (1966). Distribution of pulmonary perfusion in erect man. *J Appl Physiol* **21**, 760–766.

Birch AA, Dirnhuber MJ, Hartley-Davies R, Iannotti F & Neil-Dwyer G (1995). Assessment of autoregulation by means of periodic changes in blood pressure. *Stroke* **26**, 834–837.

Bjurstedt H, Hesser CM, Liljestrand G & Matell G (1962). Effects of posture on alveolar-arterial CO_2 and O_2 differences and on alveolar dead space in man. *Acta Physiol Scand* **54**, 65–82.

Blumenthal SR & Voorhees WD (1997). The relationship between airway carbon dioxide excretion and cardiac output during cardiopulmonary resuscitation. *Resuscitation* **34**, 263–270.

Bryan AC, Milic-Emili J & Pengelly D (1966). Effect of gravity on the distribution of pulmonary ventilation. *J Appl Physiol* **21**, 778–784.

Burton AC (1972). *Physiology and Biophysics of the Circulation. Year Book*. Medical Publishers, Chicago.

Cencetti S, Bandinelli G & Lagi A (1997). Effect of PCO_2 changes induced by head-upright tilt on transcranial Doppler recordings. *Stroke* **28**, 1195–1197.

Edwards MR, Shoemaker JK & Hughson RL (2002). Dynamic modulation of cerebrovascular resistance as an index of autoregulation under tilt and controlled $PETCO_2$. *Am J Physiol Regul Integr Comp Physiol* **283**, R653–R662.

Gabrielsen A, Videbaek R, Schou M, Damgaard M, Kastrup J & Norsk P (2002). Non-invasive measurement of cardiac output in heart failure patients using a new foreign gas rebreathing technique. *Clin Sci (Lond)* **102**, 247–252.

Harms MP, Colier WN, Wieling W, Lenders JW, Secher NH & van Lieshout JJ (2000). Orthostatic tolerance, cerebral oxygenation, and blood velocity in humans with sympathetic failure. *Stroke* **31**, 1608–1614.

Harms MP, Wesseling KH, Pott F, Jenstrup M, Goudoever J, Secher NH & van Lieshout JJ (1999). Continuous stroke volume monitoring by modelling flow from non-invasive measurement of arterial pressure in humans under orthostatic stress. *Clin Sci (Lond)* **9**, 291–301.

Hart MC, Orzalesi MM & Cook CD (1963). Relation between anatomic respiratory dead space and body size and lung volume. *J Appl Physiol* **18**, 519–522.

Hitchcock FA & Ferguson JKW (1938). Respiratory and circulatory adjustments to the erect posture. *Am J Physiol* **12**, 457–465.

Hughson RL, Edwards MR, O'Leary DD & Shoemaker JK (2001). Critical analysis of cerebrovascular autoregulation during repeated head-up tilt. *Stroke* **32**, 2403–2408.

Jellema WT, Wesseling KH, Groeneveld AB, Stoutenbeek CP, Thijs LG & van Lieshout JJ (1999). Continuous cardiac output in septic shock by simulating a model of the aortic input impedance: a comparison with bolus injection thermodilution. *Anesthesiology* **90**, 1317–1328.

Kelman GR (1967). Digital computer procedure for the conversion of PCO_2 into blood CO_2 content. *Respir Physiol* **3**, 111–115.

van Lieshout JJ, Pott F, Madsen PL, van Goudoever J & Secher NH (2001). Muscle tensing during standing: effects on cerebral tissue oxygenation and cerebral artery blood velocity. *Stroke* **32**, 1546–1551.

Lilijestrand G & Wollin G (1914). Einfluss der Körperstellung auf die Zusammensetzung der Alveolarluft des Menschen. *Zentralbl F Physiol* **27**, 1268–1270.

Main RJ (1937). Alterations of alveolar CO_2 in man accompanying postural change. *Am J Physiol* **118**, 435–440.

Milic-Emili J, Henderson JA, Dolovich MB, Trop D & Kaneko K (1966). Regional distribution of inspired gas in the lung. *J Appl Physiol* **21**, 749–759.

Musch G, Layfield JD, Harris RS, Melo MF, Winkler T, Callahan RJ, Fischman AJ & Venegas JG (2002). Topographical distribution of pulmonary perfusion and ventilation, assessed by PET in supine and prone humans. *J Appl Physiol* **93**, 1841–1851.

Novak V, Spies JM, Novak P, McPhee BR, Rummans TA & Low PA (1998). Hypocapnia and cerebral hypoperfusion in orthostatic intolerance. *Stroke* **29**, 1876–1881.

Rea HH, Withy SJ, Seelye ER & Harris EA (1977). The effects of posture on venous admixture and respiratory dead space in health. *Am Rev Respir Dis* **115**, 571–580.

Shibutani K, Muraoka M, Shirasaki S, Kubal K, Sanchala VT & Gupte P (1994). Do changes in end-tidal PCO_2 quantitatively reflect changes in cardiac output? *Anesth Analg* **79**, 829–833.

Stead EA Jr, Warren JV, Merrill AJ & Brannon ES (1944). The cardiac output in male subjects as measured by the technique of right atrial catherization. Normal values with observations on the effect of anxiety and tilting. *J Clin Invest* **24**, 326–331.

West JB (1962). Regional differences in gas exchange in the lung of erect man. *J Appl Physiol* **17**, 893–898.

West JB & Dollery CT (1959). Distribution of blood flow and ventilation-perfusion ratio in the lung, measured with radioactive CO_2. *J Appl Physiol* **15**, 405–410.

West JB, Dollery CT & Naimark A (1963). Distribution of blood flow in isolated lung; relation to vascular and alveolar pressures. *J Appl Physiol* **19**, 713–724.

Zardini P & West JB (1966). Topographical distribution of ventilation in isolated lung. *J Appl Physiol* **21**, 794–802.

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