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APNOEA FOLLOWING NORMOCAPNIC MECHANICAL VENTILATION IN AWAKE MAMMALS: A DEMONSTRATION OF CONTROL SYSTEM INERTIA

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SUMMARY

1. Inhibition of inspiratory muscle activity from volume-related feedback during mechanical ventilation has been shown previously. To determine if this neuromechanical inhibition displays a memory effect, the duration of expiration immediately following cessation of mechanical ventilation was assessed in eight normal subjects. The subjects were passively mechanically ventilated via a nasal mask until the end-tidal CO_2 (P_{ET,CO_2}) was a minimum of 30 mmHg and inspiratory effort was no longer detected, as evidenced by stabilization of mouth pressure and disappearance of surface diaphragm EMG activity. The ventilator output was held constant at a mean tidal volume (V_T) of 1·0 l and breath duration of 4·6 s and P_{ET,CO_2} was increased 1–1·5 mmHg/min (via increased inspired CO_2 fraction, F_{I,CO_2}) until inspiratory muscle activity returned. The P_{ET,CO_2} at which activation first occurred was defined as the CO_2 recruitment threshold ($P_{CO_2,RT}$). The mechanical ventilation protocol was repeated and the P_{ET,CO_2} increased 1–1·5 mmHg/min until it was a mean of 1·1 mmHg above spontaneous P_{ET,CO_2} and 3·6 mmHg below $P_{CO_2,RT}$. After 4–6 min of mildly hypercapnic mechanical ventilation, the mechanical ventilation was terminated.

2. Following termination of mechanical ventilation, the duration of the subsequent apnoea was $14·6 \pm 2·8$ s (mean ± S.E.M.) or 453 ± 123 % > spontaneous T_E and 178 ± 62 % > the T_E chosen by the subject during 'assist control' ventilation at $V_T = 1·0$ l.

3. To test the hypothesis that the apnoea following cessation of mechanical ventilation was due to a vagally mediated memory effect, the study was repeated in five double-lung transplant patients with similar $P_{CO_2,RT}$ to normal subjects. These pulmonary vagally denervated patients also displayed an apnoea ($14·5 \pm 4·0$ s) upon cessation of mechanical ventilation (at a P_{ET,CO_2} 2·0 mmHg > eupnoea and 2·4 mmHg < $P_{CO_2,RT}$), that was 367 ± 162 % > spontaneous T_E.

4. We also found significant apnoea in the awake dog immediately following mildly hypercapnic passive mechanical ventilation, and this was similar before and after bilateral vagal blockade ($15·7 \pm 1·3$ and $19·7 \pm 4·7$ s, respectively).

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5. We conclude that neuromechanical inhibition of inspiratory muscle activity, produced by passive mechanical ventilation at high V_T, exhibits a memory effect reflected in T_E prolongation, which persists in the face of substantial increases in chemoreceptor stimuli. This effect is not dependent on vagal feedback from lung receptors.

6. We hypothesize that this persistent apnoea represents an inherent 'inertia', characteristic of the ventilatory control system. This inertia contributes to the prolongation of apnoea, independently of the specific mechanism which initiated the apnoea and may explain why apnoeas are commonly terminated at higher P_{a,CO_2}s than those at initiation.

INTRODUCTION

Inhibition of respiratory motor output by mechanical feedback has been demonstrated numerous times, beginning with the observations of Hill & Flack in 1908, that rebreathing could be maintained longer, at a higher end-tidal P_{CO_2} and lower P_{O_2}, than voluntary breath-holding. Although these investigators did not recognize it at the time, the most likely explanation for this phenomenon was inspiratory inhibition mediated by mechanical feedback during active breathing (Godfrey & Campbell, 1968). Inspiratory muscle inhibition that is dependent upon the magnitude of the tidal volume (V_T) and independent of chemoreceptor stimuli has also been shown during controlled mechanical ventilation (CMV) (Altose, Castele, Connors & Dimarco, 1986; Simon, Skatrud, Badr, Griffin, Iber & Dempsey, 1991; Datta, Shea, Horner & Guz, 1991). In addition to inhibition of respiratory motor output *during* active or passive ventilation, inhibition *following* active breathing has been demonstrated in studies of breath-holding. The observation that breath-holding time was prolonged when brief periods of rebreathing were interspersed is an example of an inhibitory memory effect related to mechanical feedback during the period of rebreathing (Fowler, 1954). We hypothesized that the neuromechanical inhibition of inspiratory motor output produced during normocapnic CMV would display a memory effect manifest as a prolongation of expiratory duration (T_E) which persists once the source of the inhibition, i.e. CMV, has been removed. Because the inspiratory inhibition during CMV is dependent on V_T, we also hypothesized that any inhibitory memory would be mediated at least in part by vagal afferents.

To test these hypotheses, we used CMV at high V_T and mild hypercapnia, to inhibit the inspiratory muscles; assessed this inhibition via mouth pressure (P_m) and surface diaphragm EMG activity; terminated CMV and observed changes in breathing pattern. Studies were conducted in intact, awake humans and in lung transplant, vagally denervated patients. Awake dogs were subjected to a similar CMV protocol before and after cervical vagal blockade, to determine whether a species with a reportedly very strong inhibitory pulmonary stretch receptor reflex would respond to termination of CMV in a manner similar to humans.

METHODS

Human studies

Subjects

Eight healthy volunteers (six males and two females), aged 25–35 years, were studied. Five patients (two males and three females), aged 29–50 years, who had undergone a double-lung transplant within the last 6 months to 3 years, were also studied. As shown in Table 1, values for pulmonary function tests in the patients were within the normal range, with the exception of J.K., whose lung volumes showed some mild restriction (vital capacity, VC = 70% predicted), and R.B. whose arterial O_2 pressure (P_{a,O_2}) was below normal.

None of the subjects was initially aware of the primary objectives of the study. Informed consent was obtained in all cases. The study was approved by Human Study Committees at both the University of Wisconsin Center for Health Sciences and the Washington University School of Medicine and Barnes Hospital, St Louis, MO, USA.

Measurements

Subjects breathed through a standard, appropriately sized, nasal mask attached to a Puritan–Bennett 7200 ventilator (Puritan–Bennett, Boulder, CO, USA). Pressure at the airway opening and expiratory flow were measured by a differential pressure transducer and a hot-film anemometer, respectively, located within the ventilator. Three known volumes were entered daily through the ventilator and compared to the volume readings given by the ventilator, to confirm that volume measurements agreed. End-tidal gas was sampled from a port in the nasal mask and end-tidal CO_2 (P_{ET,CO_2}) was measured (Beckman LB-2 medical gas analyzer, Beckman Instruments, Fullerton, CA, USA). Diaphragm electrical activity (EMG_{di}) was obtained from surface electrodes (3M Red Dot) placed over the sixth and seventh intercostal space in the anterior axillary line. The raw EMG signal was amplified and band-pass filtered from 30 to 1000 Hz (Grass Model P511; Grass Instruments, Quincy, MA, USA). All measurements were displayed on an oscilloscope and recorded on photographic paper (16-channel polygraph; Electronics for Medicine, Honeywell, Pleasantville, NY, USA) and magnetic tape.

Experimental protocols

Determination of P_{CO_2} recruitment threshold. A 5 min period of steady-state spontaneous breathing with the mouth closed preceded each ventilator trial, during which eupnoeic V_T, breathing frequency (f_b) and P_{ET,CO_2} were determined. In every subject, P_{CO_2} recruitment threshold ($P_{CO_2,RT}$) was then determined by a technique which has been described previously (Simon *et al.* 1991). The subjects were placed on CMV and passively hyperventilated with a pre-set mean $V_T = 1{\cdot}05 \pm 0{\cdot}07$ l, frequency = 12–16 breaths/min and peak inspiratory flow rate ($\dot{V}$) of 40–50 l/min, until P_{ET,CO_2} was a minimum of 30 mmHg. Respiratory muscle inhibition was determined from specific criteria including absence of EMG_{di}, stabilization of the mouth pressure waveform and constancy of the peak positive end-inspiratory mouth pressure (P_m) (Simon *et al.* 1991). V_T and frequency were held constant and after 3–5 min of steady-state inhibition, P_{ET,CO_2} was increased 1–1·5 mmHg/min, by increasing the inspired CO_2 fraction (F_{I,CO_2}), until inspiratory effort returned. The P_{ET,CO_2} at initiation of inspiratory effort defined the $P_{CO_2,RT}$.

Cessation of controlled mechanical ventilation. To test for an inhibitory memory effect on respiratory motor output, a similar protocol was used. The subjects were hyperventilated in the CMV mode with the same V_T, $\dot{V}$ and frequency until respiratory muscles were inhibited (judged by EMG_{di} and P_m). After 3–5 min of steady state, F_{I,CO_2} was increased 1–1·5 mmHg/min until P_{ET,CO_2} was approximately 1–2 mmHg greater than eucapnia and 2–3 mmHg less than $P_{CO_2,RT}$. The P_{ET,CO_2} was held constant at this level for 4–6 min, during which time respiratory muscles remained inhibited. The ventilator mode was then switched during expiration to spontaneous breathing and F_{I,CO_2} was returned to that of room air.

Tidal volumes twice that of spontaneous breathing were used during CMV. Since T_E is dependent on V_T, it was necessary to determine the 'inherent' rhythm or frequency for the V_T and P_{ET,CO_2} at which the subject was being passively ventilated. 'Inherent' rhythm was determined for six normal subjects by switching the ventilator to 'assist control' mode, with the same V_T and $\dot{V}$ used during CMV, and allowing the subjects to adjust their own breathing rate. During mechanical ventilation

TABLE 1. Lung function and arterial blood gases of lung transplant patients

Subject	Sex	Age (years)	FEV_1 (l)	FEV_1 (%)	FEV_1/FVC (%)*		VC (l)	VC (%)	IC (l)	TLC (l)	TLC (%)	RV (l)	RV (%)	FRC (l)	FRC (%)	pH	P_{CO_2} (mmHg)	P_{O_2} (mmHg)
B.G.	M	50	2·79	91	84	74	3·29	81	2·21	4·47	80	1·18	62	1·99	71	7·47	35·0	84·0
R.B.	F	36	3·20	99	73	78	4·35	106	2·71	5·69	97	1·34	69	2·48	80	7·50	40·8	69·8
P.R.	M	42	4·06	113	90	76	4·52	97	2·38	5·65	91	1·13	61	2·97	92	7·42	34·6	87·6
J.K.	F	29	2·54	76	94	84	2·77	70	2·07	4·40	78	1·63	103	2·33	75	7·39	38·1	79·0
S.K.	F	41	2·24	87	97	85	2·84	94	2·37	4·03	88	1·19	83	1·66	66	7·48	31·2	96·5
Mean		39	2·97	93·2	87·6	79·4	3·55	89·6	2·35	4·85	86·8	1·29	75·6	2·29	76·8	7·45	35·9	83·4
S.E.M.		3	0·32	6·2	4·3	2·2	0·37	6·3	0·11	0·34	3·5	0·09	7·9	0·22	4·4	0·02	1·6	4·4

(%), percentage predicted normal values for age and size.

FEV_1, functional expiratory volume; FVC, functional vital capacity; VC, vital capacity; IC, inspiratory capacity; TLC, total lung capacity; RV, residual volume; FRC, functional residual capacity. * FEV_1 as a percentage of FVC

in the assist control mode, a fixed V_T was delivered at a pre-set, constant inspiratory flow rate when initiated by the subject. The subjects could change T_E by adjusting their frequency. Normocapnia was maintained by adding CO_2 to the inspired line and once a steady state was reached at this P_{ET,CO_2}, the subjects breathed on assist control for a further 5 min to ensure that their inherent T_E had been established.

Effects of apnoea. To determine the effects of apnoea on alveolar gases, breath-hold experiments were performed on four awake subjects lying supine. The subjects held their breath at their resting end-expiratory lung volume, for varying lengths of time, and then exhaled before inhaling. P_{ET,CO_2}, P_{ET,O_2} and arterial percentage O_2 saturation were measured for each breath-hold, plotted against time and regression analyses performed.

Animal studies

Animals

Three tracheotomized awake, female, mongrel dogs (20–25 kg) were studied. All surgical procedures were performed under general anaesthesia (thiamylal sodium–halothane in 100% O_2) using aseptic technique. The dogs were chronically instrumented with fine-wire EMG electrodes in the transversus abdominis and crural diaphragm (Smith, Ainsworth, Henderson & Dempsey, 1989). In a separate surgical session, bilateral cervical vagal loops were prepared by relocating both vagosympathetic trunks within skin folds (Phillipson, Hickey, Graf & Nadel, 1971). Once recovery from the surgical procedures was complete, each dog underwent a number of experimental trials. The study was approved by the Animal Care Committee of the University of Wisconsin, Madison, USA.

Measurements

The awake dogs breathed through the tracheostomy via a cuffed endotracheal tube which was attached to a Puritan–Bennett MA-1 ventilator (Puritan–Bennett, Boulder, CO, USA) during the mechanical ventilation protocols. Airway pressure was measured with a pressure transducer (Validyne, model MP45, range ± 50 cmH_2O) via a needle inserted into the endotracheal tube and airflow was measured by a pneumotachograph (Fleisch no. 1) attached to the endotracheal tube. End-tidal gas was sampled from a needle inserted in the endotracheal tube and P_{ET,CO_2} measured (LB-2 medical gas analyzer, Beckman Instruments, Fullerton, CA, USA). The raw diaphragm (EMG_{di}) and transversus abdominis EMG signals were amplified and band-pass filtered from 30 to 1000 Hz (Grass Model P511; Grass Instruments, Quincy, MA, USA). All measurements were displayed on an oscilloscope, recorded on photographic paper (16-channel polygraph; Gould ES2000 EW) and passed through an A–D board onto a microcomputer for storage.

Experimental protocols

Spontaneous breathing was established with the dog lying semi-recumbent in an air-conditioned, soundproof room on a raised, padded platform and breathing through the cuffed endotracheal tube. A 5 min period of steady-state spontaneous breathing preceded each ventilator trial, during which spontaneous V_T, f_b and P_{ET,CO_2} were determined. 'Inherent' rhythm was determined by attaching the endotracheal tube to the ventilator set in the 'assist control' mode with the same V_T and $\dot{V}$ used during CMV and allowing the dogs to set their own breathing rate at these settings, in the same manner as described previously for the human protocol. To maintain P_{ET,CO_2} at normocapnia, CO_2 was added to the inspired line when necessary.

To test for an inhibitory memory, essentially the same protocol was used for the dogs as that followed for the human subjects. Each dog was hyperventilated in the CMV mode, with the same V_T and $\dot{V}$ settings used during the AC mode, until inhibition of respiratory muscle activity (judged by EMG_{di} and P_m). After 3–5 min of steady state, F_{I,CO_2} was increased 1–1·5 mmHg/min until P_{ET,CO_2} was approximately 1–2 mmHg greater than eucapnia while inhibition of respiratory muscle activity persisted. Following 4–6 min of steady state at this P_{ET,CO_2} level, the ventilator mode was then switched during expiration to spontaneous breathing and F_{I,CO_2} was returned to room air.

To test the hypothesis that the inhibitory memory required vagal mediation, the experimental protocols were repeated in the same animals after bilateral, reversible cold block of the cervical vagus nerves (Ainsworth, Smith, Johnson, Eicker, Henderson & Dempsey, 1992). The intensity of pulmonary stretch receptor activity was evaluated in each dog prior to vagal blockade by two

methods. (1) Three 1 l passive lung inflations at end-expiration resulted in prolongation of T_E to an average of 3·5 times control T_E. (2) Occlusion of the airway at end-expiration caused an average 40% prolongation of inspiratory duration (T_I). Vagal blockade was achieved, for a maximum of 1 h per session, by circulating cold propylene glycol (−3 to −8 °C) through copper radiators placed around each vagosympathetic loop (Ainsworth *et al.* 1992). The effectiveness of the block was assessed by (1) the lack of significant prolongation of T_E following passive lung inflations, (2) the absence of T_I prolongation with end-expiratory occlusion and (3) the presence of bilateral Horner's syndrome.

Data analysis

Human studies. At the end of each steady state, ten consecutive breaths were analysed for V_T, P_{ET,CO_2} and timing. The data from each trial were averaged to give a single mean for each subject. Differences between means within a group were compared by using a paired t test. A one-way ANOVA was used to compare differences between means across groups ($P \leqslant 0.05$).

To test for the reproducibility of the post-CMV apnoea, a paired t test was used to compare trial 1 to trial 2 for all the subjects (and dogs) for which there were multiple trials and the coefficient of variation of the differences between trials was calculated.

Dog studies. Analysis of the flow signal was performed using custom software as described previously (Saupe, Smith, Henderson & Dempsey, 1992). For each experimental trial, a 2–3 min section of steady-state data was analysed. For each dog, the data from one or more trials were averaged and the overall means calculated.

RESULTS

Human studies

The overall protocol followed is illustrated by the representative tracing from a normal subject during spontaneous eupnoea and controlled mechanical ventilation (CMV), and immediately following cessation of CMV (Fig. 1). Respiratory muscle inhibition was induced by CMV as verified by the shape of the mouth pressure waveform and absence of diaphragm EMG (EMG_{di}). It can also be seen from Fig. 1 that respiratory muscle inhibition persisted when the P_{ET,CO_2} was greater than eucapnia.

During spontaneous breathing P_{ET,CO_2}, V_T, total breath duration (T_{TOT}) and T_E were compared between the normals and the lung transplant patients (Tables 2 and 3). Only T_I/T_{TOT} and P_{ET,CO_2} were significantly different between the two groups.

P_{CO_2} recruitment threshold

The V_T employed during CMV was 1·01 ± 0·03 l (mean ± S.E.M.) for the normal subjects and 1·08 ± 0·10 l for the patients, which was 190 and 170% of spontaneous V_T for the normals and patients, respectively (Tables 2 and 3). The mean frequency during CMV was not significantly changed from control. During CMV at these V_Ts and frequencies, P_{ET,CO_2} decreased and respiratory muscle inhibition was induced. Hypocapnia was limited to a minimum P_{ET,CO_2} of 30 mmHg (mean P_{ET,CO_2} = 32·5 ± 0·8 mmHg) by increasing F_{I,CO_2}. Following loss of inspiratory effort, V_T and frequency were held constant as P_{ET,CO_2} was slowly increased (by a mean of 1·1 mmHg/min), via increased F_{I,CO_2}, until resumption of respiratory muscle activity ($P_{CO_2,RT}$). $P_{CO_2,RT}$ was 46·4 ± 1·7 mmHg for the normal subjects (4·7 ± 1·0 mmHg > eupnoea) and 40·2 ± 0·9 mmHg for the lung transplant patients (4·0 ± 0·7 mmHg > eupnoea).

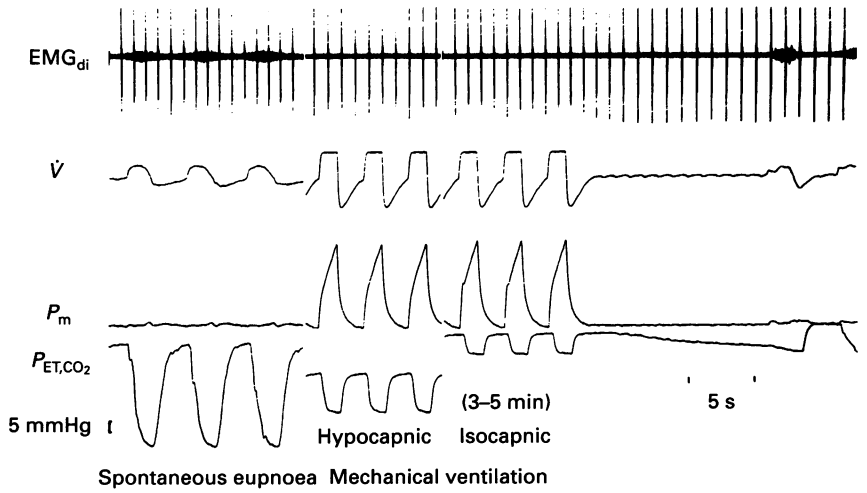

Fig. 1 Representative tracing from a normal subject showing diaphragm EMG (EMG$_{di}$), flow ($\dot{V}$), mouth pressure (P_m) and P_{ET,CO_2} during spontaneous eupnoea (left panel), during hypocapnic passive mechanical ventilation (CMV) (middle panel) and during and immediately following cessation of isocapnic CMV (right panel). Note: the EMG$_{di}$ is the low-level activity; the predominant signal is an ECG artifact.

TABLE 2. Breathing patterns in humans during spontaneous eupnoea (SE), assist control (AC) and controlled mechanical ventilation (CMV)

	V_T (l)			P_{ET,CO_2} (mmHg)			$P_{CO_2,RT}$ (mm Hg)	T_{TOT} (s)			T_E (s)			T_{apnoea} (s)
Subject	SE	AC	CMV	SE	AC	CMV		SE	AC	CMV	SE	AC	CMV	Post-CMV
K.S.	0·64	1·10	1·10	44·3	44·3	45·8	52·0	5·57	6·89	4·72	3·62	5·08	2·93	13·48
X.L.	0·46	1·05	1·05	43·9	43·9	45·3	53·0	4·18	7·39	4·90	2·59	5·50	3·30	28·1
D.A.	0·65	1·05	1·05	40·0	40·0	40·3	41·0	4·92	7·52	4·40	2·70	5·46	2·60	14·4
T.M.	0·60	1·00	1·00	41·5	41·5	41·5	44·0	6·06	6·83	4·80	3·38	4·86	3·00	6·9
L.S.	0·49	0·90	0·90	38·5	38·5	40·0	42·5	5·97	5·12	4·70	3·80	3·37	3·10	6·0
J.D.	0·61	1·10	1·10	44·5	44·5	45·8	52·0	5·16	8·93	4·25	2·73	7·53	2·56	24·39
A.G.	0·45	—	0·90	41·0	—	42·0	44·0	3·95	—	4·15	2·25	—	2·55	11·75
J.M.	0·45	—	0·95	40·0	—	41·0	43·0	4·50	—	4·80	2·45	—	3·40	11·85
Mean	0·54*	1·03	1·01	41·7	42·1	42·8	46·4†	5·04	7·11†	4·59	2·94	5·30†	2·93	14·61*
S.E.M.	0·03	0·03	0·03	0·8	1·0	0·9	1·8	0·28	0·51	0·10	0·20	0·50	0·12	2·77

$P_{CO_2,RT}$, CO_2 recruitment threshold (P_{ET,CO_2} at which the respiratory muscles activate).
T_{apnoea}, apnoea immediately following cessation of CMV.
* denotes significantly different from SE and AC ($P < 0·05$).
† denotes significantly different from SE ($P < 0·05$).

Cessation of mechanical ventilation

Once the $P_{CO_2,RT}$ was determined, the CMV protocol was essentially repeated, except that in this case CMV was terminated before reaching the $P_{CO_2,RT}$ and while inspiratory effort remained inhibited. To ensure that hypocapnia did not contribute to the inspiratory inhibition either during or after CMV, P_{ET,CO_2} was held constant prior to terminating CMV, for a mean of $5·5 \pm 0·5$ min. The P_{ET,CO_2} averaged 1–2 mmHg greater than eucapnia and 2–3 mmHg less than $P_{CO_2,RT}$ for both groups

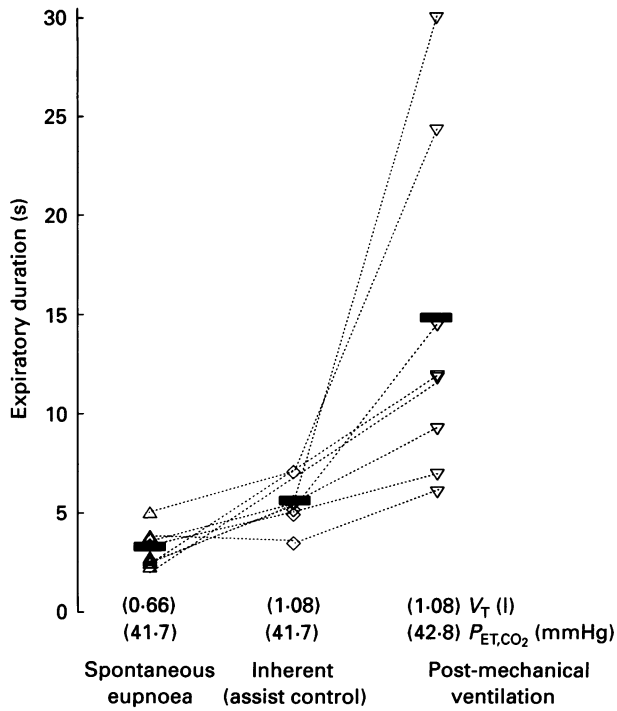

Fig. 2. Expiratory duration of the normal subjects during spontaneous eupnoea, during assist control ventilation at eucapnia (inherent) and following cessation of passive mechanical ventilation (P_{ET,CO_2} 1 mmHg above eucapnia).

TABLE 3. Breathing patterns in lung transplant patients during spontaneous eupnoea and during and after controlled mechanical ventilation (CMV)

	P_{ET,CO_2} (mmHg)		$P_{CO_2,RT}$ (mm Hg)	V_T (l)		T_{TOT} (s)		T_E (s)		T_{apnoea} (s)
Subjects	Eupnoea	CMV		Eupnoea	CMV	Eupnoea	CMV	Eupnoea	CMV	Post-CMV
R.B.	37·0	39·0	42·0	0·85	1·25	6·60	5·00	4·30	3·60	9·03
S.K.	32·0	35·0	37·0	0·40	0·75	4·40	4·15	3·28	2·85	5·80
J.K.	36·0	38·0	40·0	0·65	1·30	3·69	5·00	2·47	2·50	25·7
P.R.	36·0	39·0	42·0	0·60	1·00	4·55	4·30	2·75	2·40	8·10
B.G.	38·0	38·0	40·0	0·70	1·10	5·47	3·00	3·60	1·50	21·8
Mean	35·6*	37·8	40·2†	0·64	1·08†	5·14	4·52	3·45	2·68	14·53†
S.E.M.	1·0	0·9	0·7	0·07	0·10	0·62	0·49	0·39	0·35	3·99

$P_{CO_2,RT}$, CO_2 recruitment threshold (P_{ET,CO_2} at which the respiratory muscles activate).
T_{apnoea}, apnoea immediately following cessation of CMV.
* denotes significantly different between normals and lung transplant patients ($P < 0·05$).
† denotes significantly different from eupnoea ($P < 0·05$).

(Tables 2 and 3). Following cessation of mechanical ventilation, T_E was significantly prolonged relative to spontaneous T_E, in both the normal subjects and the lung transplant patients. T_E was 453 ± 123 and 367 ± 162% greater than spontaneous T_E, respectively (Figs 2 and 3 and Tables 2 and 3).

Because T_E is dependent on V_T, the large V_T used during CMV ($1{\cdot}01 \pm 0{\cdot}03$ l) was also employed during assist control ventilation in six normal subjects, to determine their 'inherent rhythm' at that elevated V_T. The representative tracing in Fig. 4 contrasts spontaneous eupnoea to assist control ventilation and shows the effect of

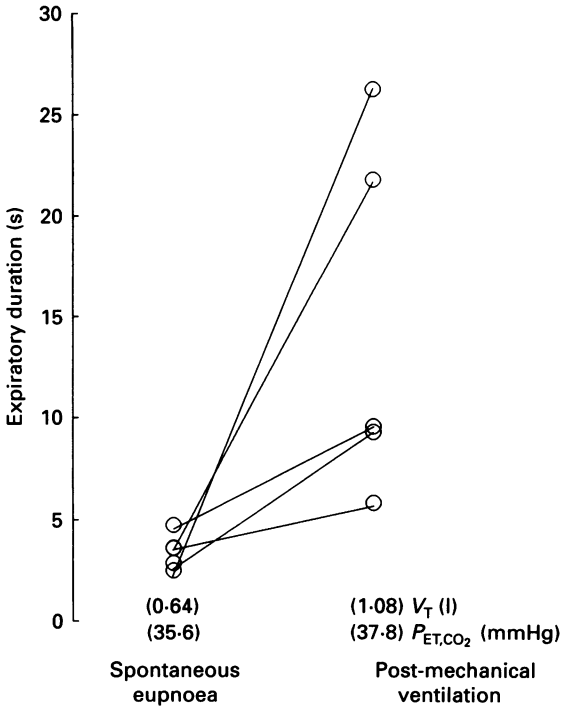

Fig. 3. Expiratory duration of the lung transplant patients during spontaneous eupnoea and following cessation of passive mechanical ventilation (P_{ET,CO_2} 1 mmHg above eucapnia).

large tidal volumes on T_E (inherent rhythm). Inherent T_E was significantly (approximately 180%) longer than spontaneous T_E (Table 2). The T_E following termination of CMV (T_{apnoea}) was compared to the T_E found during assist control ventilation. T_{apnoea} was significantly greater than inherent T_E (178 ± 62%) (Fig. 2 and Table 2).

The 'strength' of this inhibition of inspiratory motor output in the face of rising hypercapnia and hypoxaemia is demonstrated in Fig. 5 which shows the effects of T_E prolongation on end-tidal P_{CO_2} and P_{O_2} and arterial O_2 saturation. Regression analyses of P_{ET,CO_2}, P_{ET,O_2} and percentage O_2 saturation against time, determined from repeated breath-hold experiments, yielded Pearson correlation coefficients of $r = 0{\cdot}81$, $0{\cdot}88$ and $0{\cdot}92$, respectively. The T_{apnoea} of each subject was placed on the regression lines. The normal subjects' mean apnoea length of 14·7 s corresponded to a 4·5 mmHg increase in P_{ET,CO_2} and a 20 mmHg decrease in P_{ET,O_2}, which resulted in a drop in arterial percentage O_2 saturation to 92%.

Animal studies

Figure 6 is a representative tracing from a dog, showing spontaneous eupnoea, assist control ventilation and CMV and immediately post-CMV. The absence of diaphragm EMG and the mouth pressure waveform indicate inspiratory muscle

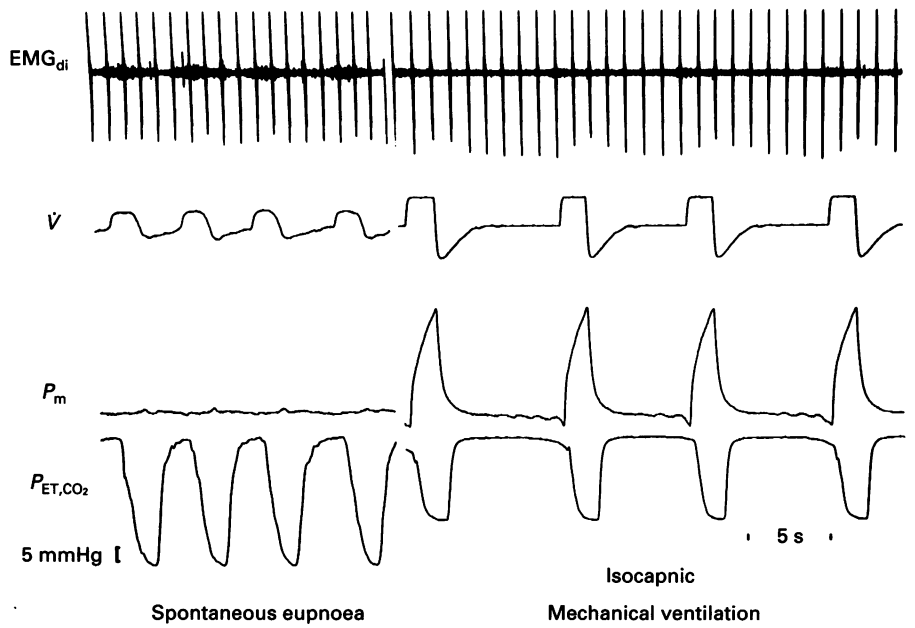

Fig. 4. Representative tracing from a normal subject showing diaphragm EMG (EMG_{di}), flow ($\dot{V}$), mouth pressure (P_m) and P_{ET,CO_2} during spontaneous eupnoea (left panel) and during assist control ventilation at the same tidal volume and inspiratory flow rate used during CMV (right panel). Note: the EMG_{di} is the low-level activity; the predominant signal is an ECG artifact.

inhibition during CMV. Note, however, that in this example tonic transversus abdominis EMG is present during both CMV and the apnoea, demonstrating that all respiratory muscle activity is not silent.

The ventilatory output during spontaneous breathing was compared between the intact and vagally blocked dogs. Except for a greater V_T in the vagally blocked dogs, there were no consistent differences between them (Table 4).

During CMV, the dogs were passively ventilated at V_Ts which were a mean of 273 and 156% of spontaneous V_T of the intact and vagally blocked dogs, respectively (Table 4). CMV at these large V_Ts decreased P_{ET,CO_2} to $32{\cdot}8 \pm 0{\cdot}9$ mmHg and respiratory muscle inhibition was induced. Once inspiratory muscle activity ceased, F_{I,CO_2} was increased until P_{ET,CO_2} averaged 0·8 mmHg above eucapnia (Table 4). P_{ET,CO_2} was held at this level for 5 min, during which respiratory muscle inhibition continued.

The same V_Ts used during CMV were also employed during assist control ventilation to determine the inherent T_E at these elevated V_Ts. The effect of the larger V_T during assist control ventilation was to lengthen T_E, as shown in Table 4.

When CMV was terminated, both the intact and vagally blocked dogs exhibited an apnoea (Table 4 and Fig. 7). T_{apnoea} was 444 ± 57 and $330 \pm 39\%$ of eupnoeic and assist control (inherent) T_E, respectively, in the intact dogs and 539 ± 188 and 283 ± 118, respectively, in the vagally blocked dogs (Table 4 and Fig. 7). Although

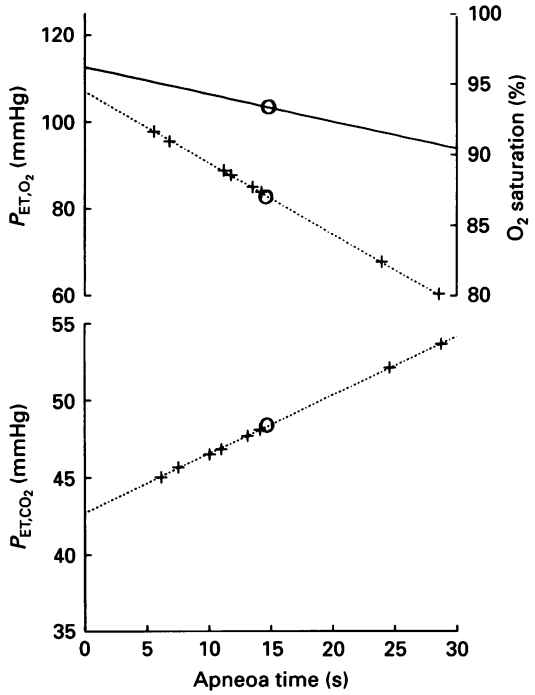

Fig. 5. Effects of breath-hold on P_{ET,CO_2}, P_{ET,O_2} and percentage arterial O_2 saturation in relation to apnoea lengths. Regression lines obtained from four subjects using voluntary breath-holding. The superimposed points represent the predicted P_{CO_2}, P_{O_2} and O_2 saturation, according to the average apnoea length following CMV obtained in each of the human subjects (see Figs 2 and 3). O, mean apnoea length.

the mean apnoea length was more variable in the vagally blocked dogs, there was no significant difference in T_{apnoea} between the intact and vagally blocked dogs.

Reproducibility of the apnoea

The reproducibility of T_{apnoea} was determined by comparing trial 1 and trial 2 apnoeas (as a percentage of spontaneous T_E) for all humans and dogs (Fig. 8). The correlation coefficient of apnoea length between trials was $r = 0{\cdot}85$. There was no significant difference between the means of trial 1 ($515 \pm 71\%$ of spontaneous T_E) and trial 2 ($449 \pm 64\%$), and the coefficient of variation of the differences between trial 1 and trial 2 was $\pm 26\%$ of the grand mean. Note also the unanimity in T_E prolongation > eupnoeic T_E for all trials (range = +75 to +1250% of spontaneous T_E) following passive, hypercapnic hyperventilation in both the vagally intact and vagally blocked or lung-denervated, and in both species.

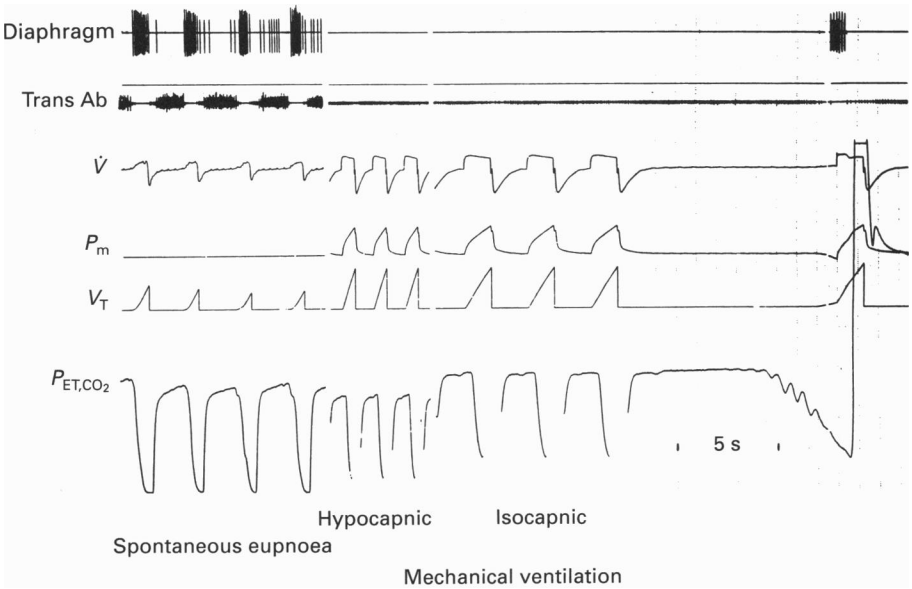

Fig. 6. Representative tracing from a vagally intact dog showing diaphragm EMG, transversus abdominis EMG (Trans Ab), flow ($\dot{V}$), mouth pressure (P_m) and P_{ET,CO_2} during spontaneous eupnoea (left panel) and during hypocapnic and isocapnic passive mechanical ventilation (CMV) (middle panel) and immediately following cessation of CMV (right panel). Note the continued tonic EMG activity of the expiratory transversus abdominis muscle when diaphragm EMG was silent during the apnoea period.

TABLE 4. Breathing pattern in dogs during spontaneous eupnoea (SE), assist control (AC) and controlled mechanical ventilation (CMV)

	V_T (ml)			P_{ET,CO_2} (mmHg)			T_{TOT} (s)			T_E (s)			T_{apnoea} (s)
Vagi intact	SE	AC	CMV	SE	AC	CMV	SE	AC	CMV	SE	AC	CMV	Post-CMV
O	367	800	800	39·4	39·4	42·0	5·18	3·98	3·10	3·74	2·53	1·90	13·1
T	143	600	600	34·6	34·6	34·6	4·12	6·20	3·70	2·84	4·72	2·50	17·1
X	271	667	667	39·5	39·5	40·4	4·49	5·65	3·38	2·96	3·89	2·13	15·7
Mean	244	667	667	37·9	37·9	38·7	4·48	5·55	3·43	3·05	3·94	2·22	15·7
S.E.M.	38	42	42	1·7	1·7	1·9	0·35	0·70	0·11	0·36	0·64	0·10	1·3
	V_T (ml)			P_{ET,CO_2} (mmHg)			T_{TOT} (s)			T_E (s)			T_{apnoea} (s)
Vagi blocked	SE	AC	CMV	SE	AC	CMV	SE	AC	CMV	SE	AC	CMV	Post-CMV
O	500	800	800	40·8	40·8	42·6	5·84	4·73	3·10	4·15	3·28	1·90	9·7
T	340	600	600	30·6	30·6	30·7	3·91	5·14	3·70	2·67	3·75	2·30	28·3
X	461	667	667	37·5	37·5	38·2	5·51	10·80	3·63	4·06	9·02	2·38	16·4
Mean	427	667	667	35·7	35·7	36·4	5·03	7·90	3·59	3·56	6·31	2·22	19·7
S.E.M.	37	42	42	1·8	1·8	2·0	0·51	1·57	0·12	0·44	1·44	0·10	4·7

T_{apnoea}, apnoea immediately following cessation of CMV. O, T and X indicate initials of each dog.

DISCUSSION

The results of this study can be summarized as follows: (1) the inhibition of inspiratory motor output induced by controlled hypercapnic, mechanical ventilation (CMV) continues when the source of the inhibition is removed in both awake humans

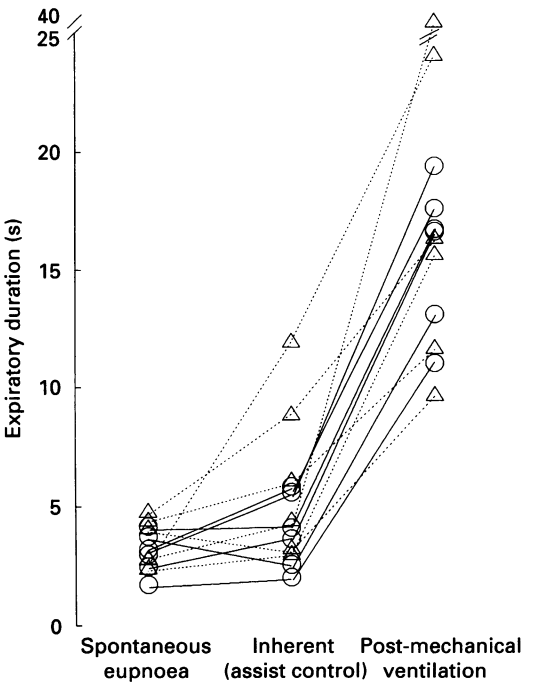

Fig. 7. Expiratory duration during spontaneous eupnoea, during assist control ventilation at eucapnia (inherent) and following cessation of passive mechanical ventilation (P_{ET,CO_2} 1 mmHg above eucapnia) of dogs before (○) and during (△) vagal blockade. The mean V_T was 244 ± 38 and 427 ± 37 ml during spontaneous eupnoea, 667 ± 42 ml during assist control ventilation and 667 ± 42 ml during CMV for the vagally intact and vagally blocked dogs, respectively. The mean P_{ET,CO_2} was 37·9 ± 1·7 and 35·7 ± 1·8 mmHg during spontaneous eupnoea, 37·9 ± 1·7 and 35·7 ± 1·8 mmHg during assist control ventilation and 38·7 ± 1·9 and 36·4 ± 2·0 mmHg during CMV for the vagally intact and vagally blocked dogs, respectively.

and dogs. This is evident by the prolongation of T_E following cessation of CMV; (2) this continued inhibition is not dependent on vagal feedback from the lungs and persists in the face of above-normal chemoreceptor stimulation.

Technical considerations

The difference between the CO_2 recruitment threshold ($P_{CO_2,RT}$) and eupnoeic P_{ET,CO_2} (approximately 5 mmHg) found in this study demonstrates substantial neuromechanical inhibition of inspiratory muscle activity during CMV as shown in recent studies (Henke, Arias, Skatrud & Dempsey, 1988; Pretcher, Nelson & Hubmayr, 1990; Simon *et al.* 1991). We believe we are able to determine inspiratory

muscle inhibition during CMV with accuracy and reliability. In the present study, respiratory muscle inhibition is evident from the absence of EMG_{di} and the peak height, shape and absence of negative deflection of the mouth pressure waveform. Since surface EMGs were recorded in the human subjects, it is possible that muscle

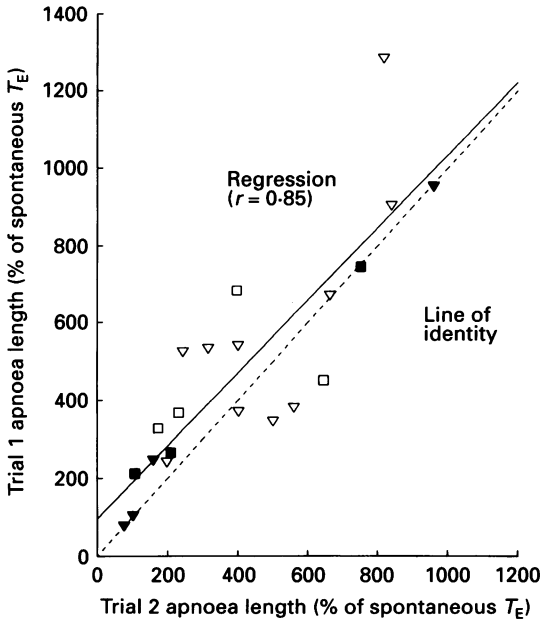

Fig. 8. Identity plot of trial 1 and trial 2 apnoea length as a percentage of spontaneous T_E for all the subjects and intact and vagally blocked dogs. ▽, normals; ▼, lung transplant patients; □, intact dogs; ■, vagally blocked dogs.

activity could have been underestimated. However, indwelling EMG electrodes were used in the dogs and they also showed a loss of phasic activity. The inspiratory muscle inhibition, indicated by the loss of EMG_{di}, does not imply complete absence of respiratory motor output or activity of the respiratory oscillator. Inspiratory activity may have been present in other respiratory motor nerves, such as the glossopharyngeal (Fukuda, 1992) and tonic expiratory EMG activity may have been present (Orem, 1991). In fact, tonic activation of the transversus abdominis during both CMV-induced inspiratory muscle inhibition and during the ensuing apnoea was found in one dog (Fig. 6). However, the best evidence that inspiratory motor output was indeed inhibited was the apnoea following the CMV.

The $P_{CO_2,RT}$ could be an artifact associated with a change in the arterial end-tidal P_{CO_2} difference when F_{I,CO_2} is increased. This possibility was examined in a previous study (Simon *et al.* 1991). They found no change in the arterial end-tidal P_{CO_2} relationship during the mechanical ventilation protocols when F_{I,CO_2} was raised.

It is possible that factors related to consciousness could have played a role in the apnoeas that were found following cessation of CMV. While we have not directly tested behavioural effects, we did find the post-CMV apnoea to be quite reproducible (Fig. 8). There was no consistent difference between trials and no apparent trend to

a lesser or greater apnoea with consecutive trials. Furthermore, in response to questions at the end of each study, all subjects denied consciously holding their breaths. The most frequent response was 'I felt no urge to breathe'. We have also previously observed the presence of neuromechanical inhibition *during* CMV in non-rapid eye movement (non-REM) sleep when similar differences were found between $P_{CO_2,RT}$ and eupnoeic P_{ET,CO_2} compared to wakefulness (Simon, Dempsey, Landry & Skatrud, 1993*a*).

One final technical consideration relates to the completeness of pulmonary stretch receptor inhibition in the lung transplant patients, since restoration of pulmonary stretch receptor activity has been demonstrated in chronically lung-denervated dogs (Clifford, Bell, Hopp & Coon, 1987). However, Iber and co-workers showed an absence of the Hering–Breuer reflex, at any passive increase in lung volume up to 80% of total lung capacity (TLC), during sleep in double-lung transplant patients compared to normals, who initiated inspiratory prolongation upon inflation at 40–50% of inspiratory capacity (Iber, Simon, Skatrud & Dempsey, 1991). In addition, in our dogs under acute vagal blockade, completeness of the block was confirmed by the absence of a Hering–Breuer reflex.

Source of respiratory muscle inhibition during controlled mechanical ventilation

Both chemical and neuromechanical feedback are potential sources of the respiratory muscle inhibition produced by CMV. There is ample evidence that hypocapnia leads to respiratory muscle inhibition, affecting both the amplitude (ramp generator) and timing (switching mechanisms) (Skatrud & Dempsey, 1983; Badr, Skatrud & Dempsey, 1992*a*, *b*). However, we do *not* believe that hypocapnia, acting at either the peripheral or central chemoreceptors, was the source of the inhibition found in this study. We have three types of evidence in support of this conclusion. (a) P_{ET,CO_2} was increased *slowly* (1·1 mmHg/min) and then held at a level 1–2 mmHg above eucapnia for at least 4 min (mean of 5·5 ± 0·5 min) and the inhibition continued. The slow increase in P_{ET,CO_2} and maintenance of the hypercapnia for 4–6 min should have allowed more than enough time to account for any circulatory delay and for equilibration of CO_2 between blood and brain (Bellville, Whipp, Kaufman, Swanson, Aqleh & Wiberg, 1979). (b) Our previously published data showed that, following the same protocol to slowly increase P_{ET,CO_2}, complete inhibition of respiratory output could be maintained over an additional period of 6–7 min, in which P_{ET,CO_2} was increased a *further* 6 mmHg above eucapnia (Simon *et al.* 1991; Simon, Griffin, Landry & Skatrud, 1993*b*). (c) Preliminary findings from an on-going study in our laboratory show that respiratory muscle activity during CMV can be completely inhibited *without* allowing P_{ET,CO_2} to fall below eucapnic levels.

Sources of neuromechanical inhibition explored in earlier studies included feedback from pulmonary stretch receptors, upper airway mechanoreceptors and ribcage (Simon *et al.* 1991, 1993*b*). Vagal feedback from pulmonary stretch receptors is a credible source of respiratory muscle inhibition during CMV, especially in view of the V_T and frequency dependence of the inhibition. In humans, a V_T of about 40% of inspiratory capacity (IC) activates the Hering–Breuer reflex during occluded inflation (Iber *et al.* 1991) and T_I prolongation during tidal breathing has been shown with airway occlusion at end-expiration (Polachek, Strong, Arens, Davies, Metcalf &

Younes, 1980; Iatridis & Iber, 1992). Since our subjects were passively ventilated at V_Ts which were 25–40% of their supine IC, they were within the lower range of pulmonary stretch receptor activation in humans (Iber *et al.* 1991). Furthermore, in dogs both tonic and phasic vagal influence is clearly operating within the tidal volume range (see Methods). However, in neither this study nor a previous one (Simon *et al.* 1991) was there any difference in neuromechanical inhibition during CMV between normal subjects and pulmonary-denervated, lung transplant patients. In addition, in the present study, complete neuromechanical inhibition was observed during mechanical ventilation in the vagally blocked dog, despite the dog's strong Hering–Breuer reflex.

Other potential sources of inhibition of inspiratory motor output are feedback from chest wall and/or diaphragm and/or upper airway mechanoreceptors. The effects of chest wall afferent feedback were examined by comparing the $P_{CO_2,RT}$ of C5–C6 quadriplegics to that of normal subjects (Simon *et al.* 1993*b*). Furthermore, the possibility of upper airway mechanoreceptor feedback as a source of the inhibition was explored by comparing the effects of positive *versus* negative pressure mechanical ventilation and by assessing the effects of upper airway anaesthesia during CMV on the inhibition (Simon *et al.* 1991). In addition, in the present study feedback from upper airway receptors was effectively eliminated in the dogs, since they were tracheotomized. Collectively, the data demonstrate that mechanoreceptor input from the upper airway or much of the chest wall is not an obligatory source of inspiratory muscle inhibition produced by CMV (Simon *et al.* 1991, 1993*b*). We have not yet determined with certainty whether receptors in the chest wall (including the diaphragm), which are mediated via neural pathways which enter the spinal cord above C6, might be required for this tidal volume-dependent inhibitory effect of CMV.

In summary, none of these mechanoreceptor feedback mechanisms was shown to play an obligatory role in the inhibitory effect induced by mechanical ventilation. Nevertheless, inspiratory muscle inhibition from neuromechanical feedback during CMV occurs independently of inhibitory effects from hypocapnia.

Continued inhibition of inspiratory motor output following cessation of controlled mechanical ventilation: memory or inertia?

We have observed apnoea initiated by neuromechanical, inhibitory influences accompanying mechanical ventilation at high V_T, which persisted for considerable time periods following the removal of the mechanical ventilation, despite substantial accumulation of otherwise powerful chemoreceptor stimuli. What is the nature of this continued inhibition of inspiratory motor output after the source of the inhibition (i.e. CMV) is removed? Is it a 'memory' phenomenon related specifically to the inhibitory influence of CMV at high V_T or would this prolonged inhibition occur regardless of the initiating influence, and is it more appropriately viewed as control system 'inertia'? Furthermore, what role might this continued inhibition play in physiological conditions in either the initiation or prolongation of apnoea?

Under physiological conditions, central apnoea frequently occurs following a hyperpnoea and is often unmasked in non-REM sleep or during shifts in states of consciousness (Dempsey & Skatrud, 1986; Younes, 1989). Two types of opposing influences appear to be operative in the period immediately following withdrawal of

the sensory stimulus (which caused the original hyperpnoea). Each of these types of opposing influences has been demonstrated in isolation. Firstly, a short-term potentiation or continued excitation of respiratory motor output was demonstrated following carotid sinus nerve electrical stimulation in the anaesthetized, vagotomized dog (Gesell & Hamilton, 1941) and in the unanaesthetized, decerebrate cat (Eldridge, 1976). Secondly, a continued brief inhibitory effect on phrenic nerve activity was shown to follow electrical stimulation of vagal afferents (pulmonary stretch receptor influence) and a longer lasting inhibition was demonstrated after withdrawal of electrical stimulation of the superior laryngeal nerve (Sullivan, Murphy, Kozar & Phillipson, 1978; Lawson, 1981). An example of the interaction of opposing excitatory and inhibitory effects was produced by simultaneous electrical stimulation of the superior laryngeal nerve and the carotid sinus nerve; ventilatory output was reduced upon termination of the stimulation(Lawson & Long, 1983).

The contribution of these opposing mechanisms under physiological circumstances has also been assessed by examining the post-stimulus ventilatory output in the unanaesthetized animal or human. An increase in respiratory drive via brief stimulation of vascularly isolated carotid chemoreceptors by hypoxia, followed by abrupt withdrawal of the hypoxia, caused a prolonged 'after-discharge' of ventilatory output in the awake goat (Engwall, Daristotle, Weizhen, Dempsey & Bisgard, 1991), as did transient whole-body isocapnic hypoxia in the awake (Georgopoulos, Shouty, Younes & Anthonisen, 1990) and sleeping human (Badr, Skatrud & Dempsey, 1992*b*). However, when systemic P_{a,CO_2} was allowed to fall during the chemoreceptor stimulation, the influence of the excitatory short-term potentiation was counteracted sufficiently so that the net effect was a marked and prolonged *reduction* in ventilatory output (to less than control) following removal of the excitatory carotid body stimulus (Engwall *et al.* 1991; Badr *et al.* 1992*b*). Additionally, in awake dogs, hyperpnoea produced actively by transient, normocapnic hypoxia resulted in a significant, although short-lived, apnoea; but under bilateral vagal blockade, the apnoea following the hypoxia was prevented and instead a slowly dissipating hyperpnoea (after-discharge) prevailed in the post-stimulus recovery period (Xi, Smith, Saupe & Dempsey, 1993). These data illustrate the presence of persisting excitatory and both chemo- and mechanoreceptor inhibitory influences; the relative strengths of these 'memory' effects will determine whether apnoea or hyperpnoea will occur following withdrawal of a stimulus.

Where does our observation of persistent apnoea fit into this schema of post-stimulus influences? Firstly, we emphasize that we used a contrived condition of passive mechanical ventilation to cause our hyperpnoea, rather than a normal actively induced hyperpnoea. None the less, we do think that the results from this experimental model of passive mechanical ventilation provide novel insights into the cause of post-hyperpnoea apnoea in physiological states. Our results imply that a strong non-chemical, neuromechanical effect does serve to inhibit respiratory motor output during high tidal volume CMV and that this inhibition does not require intact pulmonary stretch receptors *or* airway *or* chest wall muscle receptors, at least up to the level of C6 (Simon *et al.* 1991, 1993*b*). Secondly, and most pertinent to the problem of apnoea-causing mechanisms, is our observed persistence of apnoea *following* mechanical ventilation. Unlike the inhibitory 'memory' mechanisms described above, this prolonged inhibition is not dependent upon specific inhibitory

influences from either the vagally mediated pulmonary stretch receptors or upper airway pressure receptors; nor are inhibitory chemoreceptor influences implicated.

We propose two alternative explanations for the continued persistent apnoea. Firstly, it may be a 'memory' phenomenon reflecting the persistence of whatever inhibitory mechanisms linked to high tidal volume were involved in the initiation of inhibition *during* the mechanical ventilation. This specific apnoea-initiating mechanism remains unknown. As mentioned above, the persistent, very strong inhibitory memory effect obtained following superior laryngeal nerve electrical stimulation (Lawson, 1981, 1982) may be an example (under some circumstances) of a specific link of the persistent apnoea to the initiating inhibitory mechanism.

Alternatively, our preferred hypothesis is that this persistent apnoea represents an inherent 'inertia' characteristic of the control system, operant at the level of pattern generation of respiratory motor output. Once the pattern generator is reduced below threshold via sensory inhibition, it becomes very difficult to restore the phasic pattern. Indeed, as we observed, it requires substantial levels of chemoreceptor stimuli exerting their effect well above the apnoeic (initiation) threshold to turn phasic respiration back on again (Fig. 5). We emphasize that it is probably not sufficient to merely *reduce* respiratory motor output in order to demonstrate 'inertia'. For example, as previously shown during non-REM sleep in humans, markedly reducing – but not completely inhibiting – the magnitude of the inspiratory muscle EMG activity by means of mild levels of mechanical hyperventilation (-2 to -4 P_{ET,CO_2} and $+10$–15% $V_T >$ eupnoea), was not sufficient to cause apnoea in the post-hyperventilation period (Henke *et al.* 1988), although V_T was significantly reduced during the recovery period (Badr, Skatrud & Dempsey, 1992*a*). Other examples of 'inertia' in the human ventilatory control system include the hysteresis obtained during the progressive, ventilatory response to increasing *vs.* decreasing steady-state levels of inspired CO_2 (Bertholon, Carles, Eugene, Labeyrie & Teillac, 1988) and the observations some time ago, of Benchetrit and co-workers, that depth and duration of a breathing cycle were not independent of preceding cycles even in the absence of chemical and mechanoreceptor feedback (Benchetrit & Pham Dinh, 1973; Benchetrit & Bertrand, 1975).

In summary, we believe this inertial component of apnoea would not be tied to any specific, inhibitory sensory influence; rather, this inertia would be operative during any circumstance in which central apnoea was initiated by chemoreceptor or mechanoreceptor feedback or perhaps even by CNS hypoxia (Dempsey & Skatrud, 1986; Younes, 1989). Thus, the major influence of this mechanism under physiological conditions would be to *prolong apnoea* beyond the point where one would usually predict apnoea termination on the basis of the cessation of influences from the primary initiator – chemical and/or mechanical – of the apnoea. Accordingly, in physiological conditions, this inertia concept may explain in part why hyperventilation-induced apnoeas are commonly initiated at P_{a,CO_2}s which are significantly less than those present upon re-initiation of phasic respiration.

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REFERENCES

AINSWORTH, D. M., SMITH, C. A., JOHNSON, B. D., EICKER, S. W., HENDERSON, K. S. & DEMPSEY, J. A. (1992). Vagal contributions to respiratory muscle activity during eupnoea in the awake dog. *Journal of Applied Physiology* **72**, 1355–1361.

ALTOSE, M. D., CASTELE, R. J., CONNORS, A. F. JR & DIMARCO, A. F. (1986). Effects of volume and frequency of mechanical ventilation on respiratory activity in humans. *Respiration Physiology* **66**, 171–180.

BADR, M. S., SKATRUD, J. B. & DEMPSEY, J. A. (1992*a*). Ventilatory inhibition following mild hypocapnia in humans during NREM sleep. *American Review of Respiratory Disease* **145**, A405.

BADR, M. S., SKATRUD, J. B. & DEMPSEY, J. A. (1992*b*). Determinants of poststimulus potentiation in humans during NREM sleep. *Journal of Applied Physiology* **73**, 1958–1971.

BELLVILLE, J. W., WHIPP, B. J., KAUFMAN, R. D., SWANSON, G. D., AQLEH, K. A. & WIBERG, D. M. (1979). Central and peripheral chemoreflex loop gain in normal and carotid body-resected subjects. *Journal of Applied Physiology* **46**, 843–853.

BENCHETRIT, G. & BERTRAND, F. (1975). A short-term memory in the respiratory centres: statistical analysis. *Respiratory Physiology* **23**, 147–158.

BENCHETRIT, G. & PHAM DINH, T. (1973). Analyse d'une étude statistique de la ventilation cycle par cycle chez l'homme au repos. *Biométrie Humaine* **8**, 7–19.

BERTHOLON, J. F., CARLES, J., EUGENE, M., LABEYRIE, E. & TEILLAC, A. (1988). A dynamic analysis of the ventilatory response to carbon dioxide inhalation in man. *Journal of Physiology* **398**, 423–440.

CLIFFORD, P. S., BELL, L. B., HOPP, F. A. & COON, R. L. (1987). Reinnervation of pulmonary stretch receptors. *Journal of Applied Physiology* **62**, 1912–1916.

DATTA, A. K., SHEA, S. A., HORNER, R. L. & GUZ, A. (1991). The influence of induced hypocapnia and sleep on the endogenous respiratory rhythm in humans. *Journal of Physiology* **440**, 17–33.

DEMPSEY, J. A. & SKATRUD, J. B. (1986). A sleep-induced apneic threshold and its consequences. *American Review of Respiratory Disease* **133**, 1163–1170.

ELDRIDGE, F. L. (1976). Central neural stimulation of respiration in unanesthetized decerebrate cats. *Journal of Applied Physiology* **40**, 23–28.

ENGWALL, M., DARISTOTLE, L., WEIZHEN, N., DEMPSEY, J. A. & BISGARD, G. E. (1991). Ventilatory afterdischarge in the awake goat. *Journal of Applied Physiology* **71**, 1511–1517.

FOWLER, W. S. (1954). Breaking point of breath-holding. *Journal of Applied Physiology* **6**, 539–545.

FUKUDA, Y. (1992). Difference in glossopharyngeal and phrenic inspiratory activities of rats during hypocapnia and hypoxia. *Neuroscience Letters* **137**, 261–264.

GEORGOPOULOS, D., SHOUTY, Z. B., YOUNES, M. K. & ANTHONISEN, N. R. (1990). Hypoxic exposure and activation of the after-discharge mechanism in conscious humans. *Journal of Applied Physiology* **69**, 1159–1164.

GESELL, R. & HAMILTON, M. A. (1941). Reflexogenic components of breathing. *American Journal of Physiology* **133**, 694–719.

GODFREY, S. & CAMPBELL, E. J. M. (1968). The control of breath holding. *Respiration Physiology* **5**, 385–400.

HENKE, K. G., ARIAS, A., SKATRUD, J. B. & DEMPSEY, J. A. (1988). Inhibition of inspiratory muscle activity during sleep: chemical and nonchemical influences. *American Review of Respiratory Disease* **138**, 8–15.

HILL, L. & FLACK, M. (1908). The effect of excess of carbon dioxide and of want of oxygen upon the respiration and the circulation. *Journal of Physiology* **37**, 77–111.

IATRIDIS, A. & IBER, C. (1992). The role of neural reflex mechanisms in response to inspiratory resistive loads during sleep. *American Review of Respiratory Disease* **145**, A405.

IBER, C., SIMON, P. M., SKATRUD, J. B. & DEMPSEY, J. A. (1991). Pulmonary afferents mediate the lung inflation reflex in humans. *American Review of Respiratory Disease* **143**, 191.

LAWSON, E. E. (1981). Prolonged central respiratory inhibition following reflex-induced apnea. *Journal of Applied Physiology* **50**, 874–879.

LAWSON, E. E. (1982). Recovery from central apnea: effect of stimulus duration and end-tidal CO_2 partial pressure. *Journal of Applied Physiology* **53**, 105–109.

LAWSON, E. E. & LONG, W. A. (1983). Interaction of excitatory and inhibitory respiratory afterdischarge mechanisms in piglets. *Journal of Applied Physiology* **55**, 1299–1304.

OREM, J. (1991). Behavioral control of breathing. In *The Lung: Scientific Foundations*, ed. CRYSTAL, R. G. & WEST, J. B., pp. 1397–1404. Raven Press, Ltd, New York.

PHILLIPSON, E. A., HICKEY, R. F., GRAF, P. D. & NADEL, J. A. (1971). Hering–Breuer inflation reflex and regulation of breathing in conscious dogs. *Journal of Applied Physiology* **31**, 746–750.

POLACHEK, J., STRONG, R., ARENS, J., DAVIES, C., METCALF, I. & YOUNES, M. (1980). Phasic vagal influences on inspiratory motor activity in anesthetized humans. *Journal of Applied Physiology* **49**, 609–619.

PRETCHER, G. C., NELSON, S. B. & HUBMAYR, R. D. (1990). The ventilatory recruitment threshold for carbon dioxide. *American Review of Respiratory Disease* **141**, 758–764.

SAUPE, K. W., SMITH, C. A., HENDERSON, K. S. & DEMPSEY, J. A. (1992). Respiratory muscle recruitment during selective central and peripheral chemoreceptor stimulation in awake dogs. *Journal of Physiology* **448**, 613–631.

SIMON, P. M., DEMPSEY, J. A., LANDRY, D. M. & SKATRUD, J. B. (1993*a*). Effect of sleep on respiratory muscle activity during mechanical ventilation. *American Review of Respiratory Disease* **147**, 32–37.

SIMON, P. M., GRIFFIN, D. M., LANDRY, D. M. & SKATRUD, J. B. (1993*b*). Inhibition of respiratory activity during passive ventilation: a role for intercostal afferents? *Respiration Physiology* (in the Press).

SIMON, P. M., SKATRUD, J. B., BADR, M. S., GRIFFIN, D. M., IBER, C. & DEMPSEY, J. A. (1991). Role of airway mechanoreceptors in the inhibition of inspiration during mechanical ventilation in humans. *American Review of Respiratory Disease* **144**, 1033–1041.

SKATRUD, J. B. & DEMPSEY, J. A. (1983). Interaction of sleep state and chemical stimuli in sustaining rhythmic ventilation. *Journal of Applied Physiology* **55**, 813–822.

SMITH, C. A., AINSWORTH, D. M., HENDERSON, K. S. & DEMPSEY, J. A. (1989). Differential responses of expiratory muscles to chemical stimuli in awake dogs. *Journal of Applied Physiology* **66**, 384–391.

SULLIVAN, C. E., MURPHY, E., KOZAR, L. F. & PHILLIPSON, E. A. (1978). Waking and ventilatory responses to laryngeal stimulation in sleeping dogs. *Journal of Applied Physiology* **45**, 681–689.

XI, L., SMITH, C. A., SAUPE, K. W. & DEMPSEY, J. A. (1993). Effects of memory from vagal feedback on short-term potentiation of ventilation in conscious dogs. *Journal of Physiology* **462**, 547–561.

YOUNES, M. (1989). The physiologic basis of central sleep apnea and periodic breathing. In *Current Pulmonology*, ed. SIMMONS, D. H., pp. 265–326. Year Book Medical Publishers, Chicago.