

Controlled versus Assisted Mechanical Ventilation Effects on Respiratory Motor Output in Sleeping Humans

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Central apneas occur after cessation of mechanical ventilation despite normocapnic conditions. We asked whether this was due to ventilator-induced increases in respiratory rate or V_T . Accordingly, we compared the effects of increased V_T (135 to 220% of eupneic V_T) with and without increased respiratory rate, using controlled and assist control mechanical ventilation, respectively, upon transdiaphragmatic pressure in sleeping humans. Increasing ventilator frequency +1 per minute and V_T to 165–200% of baseline eupnea eliminated transdiaphragmatic pressure during controlled mechanical ventilation and prolonged expiratory time (two to four times control) after mechanical ventilation. During and after assist control mechanical ventilation at 135–220% of eupneic V_T , transdiaphragmatic pressure was reduced in proportion to the increase in ventilator volume. However, every ventilator cycle was triggered by an active inspiration, and immediately after mechanical ventilation, expiratory time during spontaneous breathing was prolonged less than 20% of that observed after controlled mechanical ventilation at similar V_T . We conclude that both increased frequency and V_T during mechanical ventilation significantly inhibited respiratory motor output via nonchemical mechanisms. Controlled mechanical ventilation at increased frequency plus moderate elevations in V_T reset respiratory rhythm and inhibited respiratory motor output to a much greater extent than did increased V_T alone.

Keywords: neuromechanical inhibition; resetting of respiratory rhythm; assisted mechanical ventilation; controlled mechanical ventilation; sleep

Positive pressure mechanical ventilation applied to humans in non-rapid eye movement (NREM) sleep induces a loss of respiratory drive and an associated apnea after cessation of mechanical ventilation, despite normocapnic conditions (1–5). It is unclear whether these inhibitory effects are dependent on increases in V_T (i.e., Hering Breuer mechanism) or are caused by a resetting of the inherent respiratory rhythm by the raised ventilator frequency (3, 6–8). On the one hand, in a sleeping canine model, small increases in respiratory frequency achieved via controlled normocapnic mechanical ventilation (CMV) resulted in complete abolition of dia-

phragm electromyogram (EMGdi) (3). On the other hand, in sleeping (5) or awake (9, 10) humans, increases in V_T alone, as induced via normocapnic assist CMV (ACMV), resulted in reduced inspiratory effort with relatively little effect on breath timing.

Our aim was to determine the relative contributions of increased respiratory rate and V_T to the neuromechanical inhibition of respiratory motor output in the human. To this end, we compared the effects of CMV (at varying frequency and V_T) and ACMV (at varying V_T) on the amplitude and timing of transdiaphragmatic pressure (P_{di}). We maintained normocapnia and used normoxic and hyperoxic backgrounds to exclude the influence of changing chemical drives and studied subjects during NREM sleep to avoid behavioral influences on respiratory motor output. Based primarily on animal studies (3, 11) and estimates of the sensitivity of the Hering Breuer reflex in the human (12–15), we hypothesized that resetting of the respiratory rhythm and complete inhibition of respiratory motor output via normocapnic mechanical ventilation in the human would require an increase in ventilator frequency combined with substantial elevations in V_T .

METHODS

Subjects

Seven healthy adults, two women and five men, age of 36 ± 14 years, with no prior history of cardiopulmonary disease or sleep apnea participated in the study. Sleep architecture was staged during NREM sleep using standard electroencephalography (16). Each subject completed two to three nights of mechanical ventilation trials in stage II and stage III NREM sleep, and subjects were required to sleep on their back for the entire night. Each subject ingested 10 mg of zolpidem 10 to 20 minutes before the lights were turned out. In two subjects, we also completed several ventilator trials during NREM sleep before and after ingesting zolpidem. We observed similar effects of mechanical ventilation on P_{di} in trials with and without the zolpidem in these two subjects when studied in the same sleep states.

Subject Consent, Preparation, Ventilator Circuit, and Measurements

The ventilator circuit, the use of continuous positive airway pressure, and flow and pressure measurements have been previously described (1, 5) (see additional details in the online supplement).

CMV

We used a pneumatically powered, electronically controlled mechanical ventilator (Veolar; Hamilton Medical, Rhazüns, Switzerland) that allowed the control of V_T , breathing frequency, and inspiratory time (TI). We used three V_T settings, 1.3 to 2 times the eupneic V_T , and two fixed ventilator frequencies (f_R) (+1 and +3 breaths per minute above mean eupneic f_R) during 1 minute of normocapnic CMV. The TI was set at the TI observed during spontaneous breathing; thus, increases in V_T during CMV were achieved solely by increasing inspiratory flow rate. A square wave inspiratory flow pattern was selected. A servo-controlled flow valve in the ventilator opened during inspiration to supply gas to

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the subject and to control inspiratory flow rate, pattern, and duration. The ventilator delivered breath was terminated when the servo-controlled flow valve closed after delivering the preset V_T . The ventilator delivered V_T settings that were within 5 to 10% of the preset V_T .

Each CMV trial was preceded by 2 to 3 minutes of stable eupneic breathing. The subject was switched into the ventilator circuit in the CMV mode during expiration and CMV continued for 60 to 90 seconds with $F_{I_{CO_2}}$ increased sufficiently to maintain $P_{ET_{CO_2}}$ normocapnic. Then the ventilator was switched off during early expiration and $F_{I_{CO_2}}$ returned immediately to room air levels near zero CO_2 . Expiratory time (TE) after the last CMV cycle was calculated as the time from the end of inspiration to the onset of the next spontaneous inspiratory effort, as determined from a negative shift in esophageal pressure (Pes) and an increase in Pdi, which exceeded the cardiogenic artifact.

ACMV

With the ACMV, the subject triggered the ventilator by generating an inspiratory effort of 0.5 to 1 cm H_2O . Then the ventilator delivered a preset V_T at the preset average TI achieved in eupnea by augmenting inspiratory flow rate. Each subject completed two or three ACMV trials at each of three V_T settings, 1.3–2.2 times spontaneous control, during NREM sleep while normocapnia was maintained.

Data Analysis

For each CMV trial, 10 breaths from eupnea immediately before CMV, the entire 60–90 seconds of CMV, and the first three breaths of recovery were analyzed for volume, pressures, timing, and end-tidal gases. We selected for analysis one trial from each subject for each CMV V_T/f_R combination. The trial was selected for the most constant sleep state and end-tidal (partial) carbon dioxide pressure ($P_{ET_{CO_2}}$) closest to eupneic baseline conditions. This amounted to six CMV trials per subject (+1 and +3 f_R at V_T 135%, 165%, and 200% of eupnea). The same was done for each of the three V_T settings used during ACMV, and this resulted in three ACMV trials per subject. In addition, mean values for ΔP_{di} , ΔP_{es} , gastric pressure (ΔP_{ga}) and each of the ventilatory output variables obtained during 1 minute of baseline eupnea for each 15-second interval during CMV or ACMV and for each of the initial three spontaneous breaths after CMV or ACMV were compared using a repeated-measures two-way analysis of variance. When mean values differed significantly, paired post hoc comparisons were made using the Tukey test. Significance was accepted at $p < 0.05$.

RESULTS

Effects of CMV on Pdi and Breath Timing

A polygraph recording from a typical CMV trial is shown for one subject (K.H.) in Figure 1A. This trial was conducted at an f_R of three breaths per minute above the average spontaneous baseline frequency and a V_T that was 200% of spontaneous baseline. Note the cardiogenic artifact superimposed on the Pes and Pga traces, which was especially prominent in this subject. At the onset of CMV, $F_{I_{CO_2}}$ was added to maintain $P_{ET_{CO_2}}$ 1 to 1.5 mm Hg above baseline throughout the CMV trials. CMV caused an immediate positive shift in Pes and a marked reduction in Pdi, which was maintained over the 1-minute period of CMV. A transient increase in end-expiratory lung volume commonly occurred at the onset of CMV, but end-expiratory lung volume returned to or near baseline levels after the initial two to four ventilator cycles, as inferred from the constancy in end-expiratory Pes and Pga. At the cessation of CMV, a 17-second apnea ensued followed by resumption of spontaneous inspiratory efforts. Each of the initial two spontaneous breaths after the apnea had smaller V_T and Pdi relative to baseline eupnea (*see* additional recordings during CMV at smaller V_T settings in Figures E1 and E2 in the online supplement).

Single spontaneous and associated CMV breaths recorded at fast speed (28 mm/second) are shown in Figure 1B to illustrate the within-breath pressure changes. Note the typical development of negative Pes and positive Pga and Pdi during a spontane-

ous inspiration, as opposed to an unchanging Pes and Pdi during steady-state CMV at raised V_T and frequency (*see* examples recorded at fast speeds in an additional subject and at two V_T settings in Figures E3 and E4 in the online supplement).

Group mean values ($n = 7$) for ΔP_{di} are shown throughout all CMV trials in Figures 2A and 2B and for other key variables in Tables 1 and 2. In all CMV trials, as V_T was increased, TI was maintained at or slightly below baseline spontaneous TI; thus, mean (and peak) inspiratory flow rates during CMV averaged 1.6 to 3 times those at baseline. Mean \dot{V}_E was increased 1.4 to 2 times baseline, and mean $P_{ET_{CO_2}}$ was maintained an average of 0.5 ± 0.1 mm Hg greater than eupnea over all CMV trials.

At the smallest (i.e., 35%) increase in V_T during CMV and at +1 f_R , nadir inspiratory ΔP_{es} shifted from negative values in spontaneous baseline breaths to +4 to 5 cm H_2O during CMV; peak ΔP_{ga} increased 0.7 cm H_2O above baseline, and ΔP_{di} fell to within ± 1 cm H_2O of zero Pdi. TE was not prolonged significantly after the final ventilator cycle, and ΔP_{di} and V_T were reduced slightly but significantly below baseline on the first spontaneous breath after CMV.

At the two larger increases in V_T during CMV (65% and 100% relative to spontaneous eupnea), ΔP_{es} increased to +5.7 cm H_2O , ΔP_{ga} increased 0.5–2 cm H_2O , and mean ΔP_{di} fell markedly and varied from 0 to –2 cm H_2O . Negative values for ΔP_{di} (range = –0.6 to –5 cm H_2O) were observed in five of seven subjects.

After the final CMV cycle with V_T at two times eupnea, TE averaged 8–9 seconds or approximately 4.5 times the baseline spontaneous TE, and TE averaged 4–6 seconds when V_T was held at 1.6 times eupnea (Figure 3). On the first spontaneous breath after these post-CMV apneas, the mean ΔP_{di} and the V_T and V_T/TI were reduced 20 to 90% below baseline eupneic levels. At each CMV V_T , the reduction in ΔP_{di} during CMV and the prolongation in TE after CMV were not different when CMV was conducted at +1 f_R or +3/minute f_R above spontaneous eupnea.

In summary, normocapnic CMV at increased fixed f_R and V_T reduced ΔP_{di} during CMV and prolonged TE immediately after CMV. These effects were dependent on the V_T maintained during the CMV. Reductions in Pdi and V_T persisted for the first spontaneous breath immediately after the postventilator apneas.

Effects of ACMV with Increased V_T on Pdi and Breath Timing

Figure 4 is a polygraph tracing showing the effects of normocapnic ACMV at a V_T 195% of eupnea in subject 1. On the first ACMV breath, Pes shifted from negative to positive, Pga increased slightly, and Pdi was reduced to approximately 40% of spontaneous control. These changes remained throughout the ACMV trial. After cessation of ACMV, TE was prolonged less than 20% of baseline, but the first two or three spontaneous breaths showed a less negative Pes and reduced Pdi and V_T relative to spontaneous eupnea.

Figure 5 shows group mean values for ΔP_{di} and V_T during and after ACMV trials. $P_{ET_{CO_2}}$ averaged 0.4 ± 0.1 mm Hg greater than control (range = –0.9 to 2.8 mm Hg) over the three types of ACMV trials at increased V_T . TI during ACMV remained similar to baseline spontaneous breathing; thus, the increases in V_T were achieved by increases in inspiratory flow rate above baseline eupnea by 30% at the smallest increase in V_T and by twofold at the highest V_T . When V_T was raised to 135% of baseline control via ACMV, TE was unchanged, and ΔP_{di} was reduced to 40% of baseline eupnea. During ACMV at the two higher V_T settings, ΔP_{di} was reduced to less than 20% of eupnea (at 170% V_T) and to –1 to –2 cm H_2O (at 220% V_T). Mean

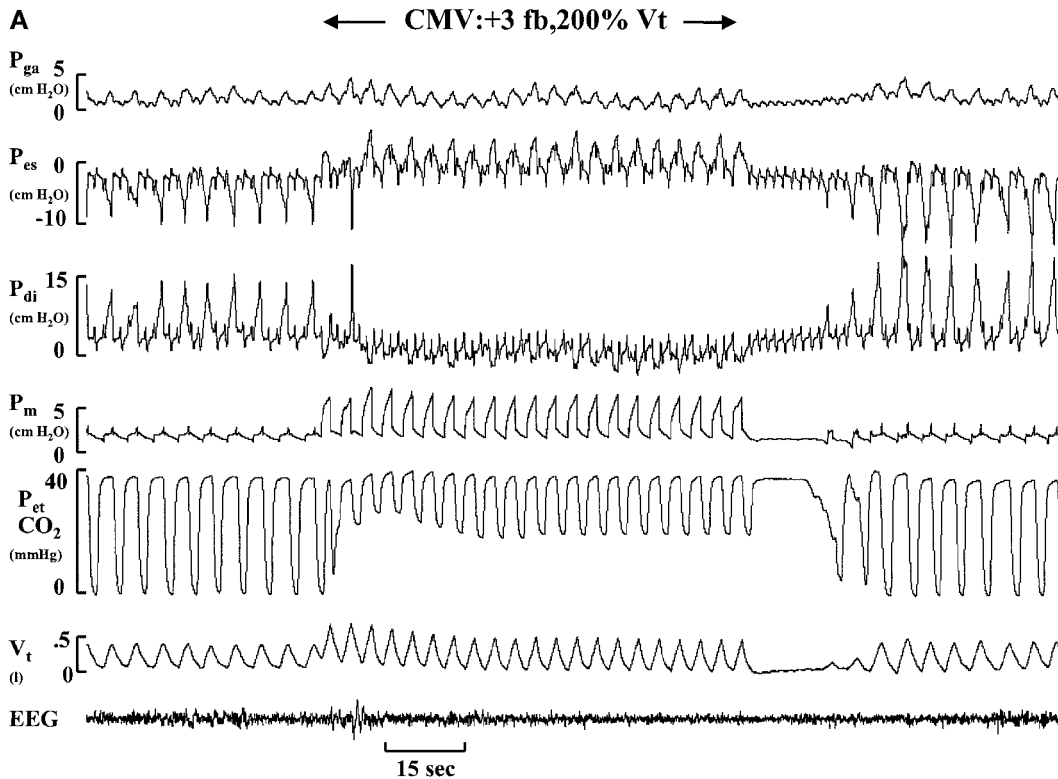
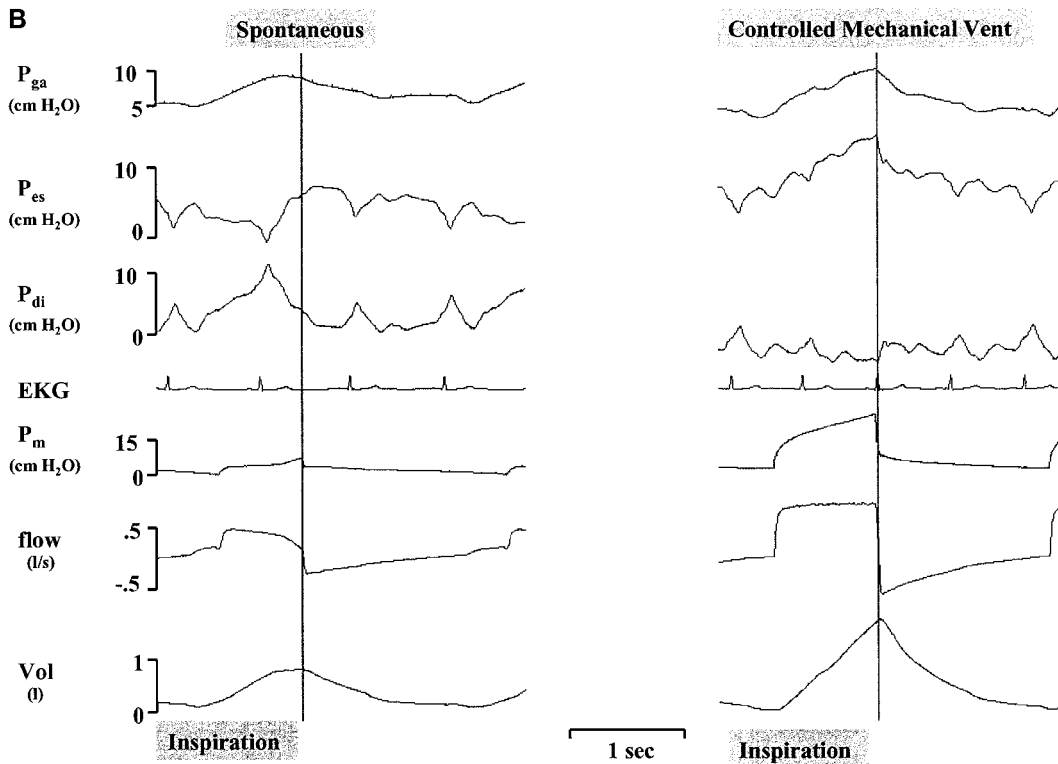


Figure 1. (A) Polygraph record of a trial of controlled mechanical ventilation (CMV) in Subject 1 at a breathing frequency that is three breaths per minute above spontaneous eupnea and a V_T that is 200% of spontaneous eupnea. EEG = electroencephalogram spontaneous breathing and continuous positive airway pressure (CPAP) precedes the CMV trial. The onset of CMV occurs with the increase in P_m . Note the immediate reduction in P_{di} at CMV onset and the apnea that followed the cessation of CMV. Also note the cardiogenic artifact on the P_{es} and P_{di} traces. Inspired CO_2 was added to prevent the P_{ETCO_2} from falling when V_T was raised with CMV. (B) A polygraph record of a spontaneous control breath and a single cycle of CMV at a higher V_T (200% of eupnea), both obtained from the same trial shown in (A) and recorded at fast speed (28 mm/second). Note the rise in P_{es} and absence of change in P_{di} during inspiration with CMV at high V_T .



TE was prolonged to 128% and 134% of baseline eupnea during ACMV at 170% and 220% V_T , respectively ($p < 0.5$).

On the first spontaneous recovery breath after cessation of ACMV, mean TE remained unchanged from baseline eupnea after the 135% V_T trial but was prolonged to 120% of baseline TE ($p < 0.05$) after the 165 and 220% V_T trials. These effects of ACMV on TE were less than 20–25% of the mean TE prolon-

gation observed after CMV at comparable V_T elevations (Figure 3). ΔP_{di} was 20–65% less than spontaneous control on the first two recovery spontaneous breaths and returned to near baseline levels by the third to sixth recovery breaths. Similarly, inspiratory flow rate and V_T were also reduced in magnitude significantly below control during the first spontaneous recovery breaths (Figure 5), and these reductions were greatest when the V_T delivered

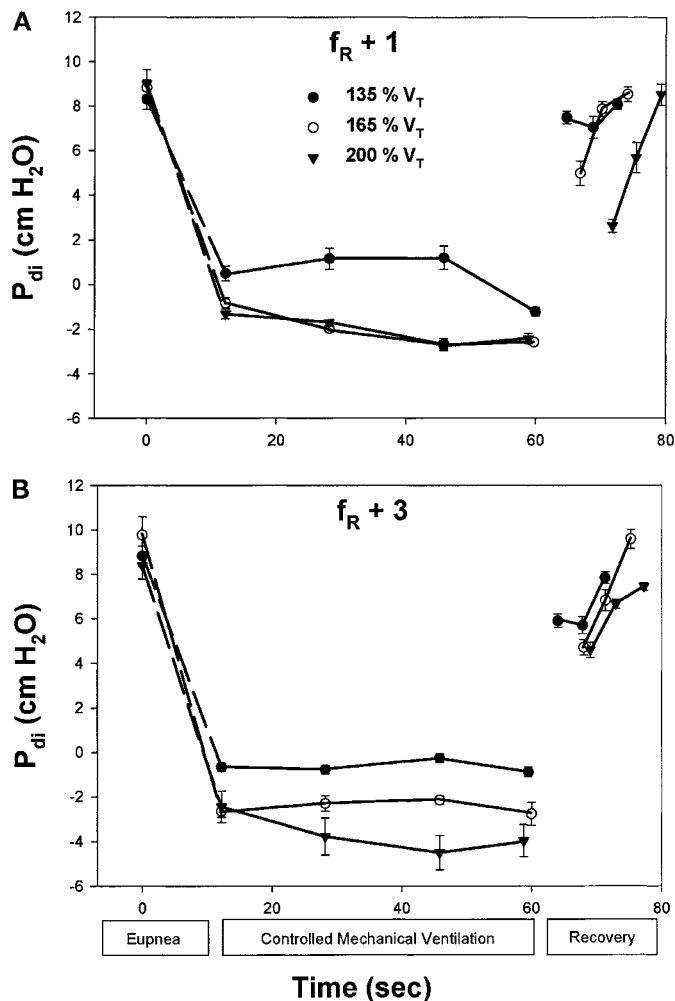


Figure 2. Changes in ΔP_{di} averaged over 15-second time intervals during CMV are shown at each of the three increases in V_T and at breathing frequencies that averaged three (B) and one (A) breath(s) per minute greater than spontaneous eupnea ($n = 7$). The first point on the left at zero time is spontaneous eupnea, followed by the four time points during CMV and then the first three breaths during spontaneous breathing in recovery. The break between the end of CMV and the first spontaneous breath indicates the average length of the TE after the final ventilator breath (Figure 3).

during the preceding period of ACMV equaled or exceeded 170% of eupneic control.

Effects of ACMV on Within-Breath P_{es} , P_m , and P_{di}

All ventilator cycles during ACMV were accompanied by inspiratory muscle efforts, as judged by a negative mask pressure (P_m) and P_{es} and a positive P_{di} immediately before the onset of inspiratory flow generated by the P_m ventilator. These spontaneous efforts generated during the ventilator trigger phase occurred over 0.1–0.2 seconds, with an average P_m of -0.5 ± 0.1 cm H_2O , P_{es} of -0.6 ± 0.4 cm H_2O , and P_{di} of 0.6 ± 0.3 cm H_2O .

Figures 6A and 6B show a single spontaneous breath + continuous positive airway pressure and associated ACMV cycles recorded at high speed to illustrate the within-breath pressure changes. Note first the typical development of a negative esophageal and positive P_{di} during a spontaneous inspiration. During ACMV, initial small changes occurred in P_m , P_{es} , and P_{di} before

the ventilator trigger. Then with the onset of ventilator-assisted inspiratory flow and positive P_m (I) at the 140% increase in V_T , negative swings in P_{es} and positive P_{di} were greatly reduced, relative to spontaneous, and (2) at the 200% increase in V_T , P_{es} moved in a positive direction and P_{di} in a slightly negative direction throughout inspiration.

Effects of Hyperoxia on P_{di} and Breath Timing during CMV and ACMV

In two subjects, inspired air was enriched with 60% O_2 at a flow rate sufficient to raise $P_{ET_{O_2}}$ to 310–325 mm Hg throughout six trials of normocapnic ACMV at V_T 180 to 200% of baseline eupnea and nine trials of normocapnic CMV at f_R ($+1f_R$) and V_T 150 to 180% of eupnea (data not shown). With normocapnic hyperoxic ACMV, reductions in P_{di} below spontaneous eupnea averaged 50–60% during the final 15 seconds and 30–40% on the first spontaneous breath after cessation of ACMV. These changes were within $\pm 10\%$ of those after normoxic normocapnic ACMV in these two subjects. Similarly, with hyperoxic normocapnic CMV trials, ΔP_{di} was reduced to 0 to 1 cm H_2O during the final 15 seconds of CMV and TE prolonged four times eupneic control after CMV, as in the normoxic trials.

DISCUSSION

Our findings in sleeping healthy humans have shown that inspiratory motor output, as indicated by ΔP_{di} , is reduced during controlled, normocapnic mechanical ventilation when ventilator frequency is increased as little as one breath per minute above spontaneous eupnea. The complete elimination of inspiratory motor output also required that V_T during CMV be raised 65% or more above eupnea. Prolonged TEs occurred after cessation of CMV, and their length increased in proportion to the magnitude of the V_T maintained during the CMV but were independent of further increases in CMV frequency. During assisted normocapnic mechanical ventilation synchronous with inspiratory effort (ACMV), inspiratory motor output was never completely eliminated, and TE was only slightly but significantly prolonged. However, during ACMV at raised V_T , P_{di} was reduced well below spontaneous control; furthermore, in recovery from ACMV, the initial spontaneous efforts produced P_{di} and V_T , which were 20–70% below baseline eupneic control breaths. These reductions in spontaneous P_{di} and V_T in recovery from ACMV were greatest at the two highest V_T s maintained during ACMV. Hyperoxia did not prevent the inhibitory effects of either CMV or ACMV on P_{di} or apnea during or after mechanical ventilation. We attribute the resetting of respiratory rhythm and apnea caused by CMV to the neuromechanical effects of repeated and augmented lung inflation and the reduced P_{di} during and after ACMV to the neuromechanical inhibitory effects on respiratory motor output associated with increased V_T .

Use of P_{di} to Assess Reduced Respiratory Motor Output during and after CMV and ACMV

The reduction and/or elimination of P_{di} during and after both types of mechanical ventilation were substantial and consistent and we believe qualitatively reflected reductions in phrenic motor output, especially when volumes and flow rates were not altered markedly from eupnea. For example, Beck and colleagues (17) used a multiple array of esophageal electrodes to measure crural EMG $_{di}$ in sedated humans and showed a tight coupling of reductions in EMG $_{di}$ to those in P_{di} during pressure support ventilation at small increments in V_T . However, during mechanical ventilation at high V_T and flow rate, there are other potential reasons why this mechanical index of respiratory motor output may have been reduced.

TABLE 1. EFFECTS OF CMV AT AN INCREASED RESPIRATORY FREQUENCY (+1 MORE THAN EUPNEA) AND V_T

	V_T L	P_{ETCO_2} mm Hg	TI sec	TE sec	V_T/TI L/sec	VE L/min	ΔP_{ga} cm H ₂ O \cong	ΔP_{es} cm H ₂ O \cong	ΔP_{di} cm H ₂ O
Eupnea	0.56 ± 0.1	41.2 ± 2.0	2.0 ± 0.4	2.1 ± 0.4	0.28 ± 0.0	8.2 ± 0.5	2.6 ± 1.0	5.7 ± 0.3	8.3 ± 0.5
CMV 135% eupnea V_T , final 15 sec	0.75 ± 0.1*	41.8 ± 2.5	1.9 ± 0.3	2.0 ± 0.3 2.7 ± 0.5	0.41 ± 0.1*	11.2 ± 1.4*	3.3 ± 0.9*	4.5 ± 3.1*	1.2 ± 0.2*
TE after last CMV cycle First recovery breath post-CMV	0.31 ± 0.2*		2.0 ± 0.7	2.1 ± 0.6	0.16 ± 0.1*	4.5 ± 2.0*	2.1 ± 1.4	-5.4 ± 1.0	7.5 ± 0.3*
CMV 165% eupnea V_T , final 15 sec	0.93 ± 0.2	42.0 ± 1.6	1.9 ± 0.4	1.9 ± 0.4 4.4 ± 3.7*	0.51 ± 0.1	14.0 ± 2.0*	2.9 ± 0.5*	5.5 ± 1.5*	-2.6 ± 0.1*
TE after last CMV cycle First recovery breath post-CMV	0.20 ± 0.1*		1.5 ± 0.7	1.9 ± 0.4	0.13 ± 0.1*	3.4 ± 1.8*	1.4 ± 1.0*	-3.6 ± 1.0*	5.0 ± 0.6*
CMV 200% eupnea V_T , final 15 sec	1.15 ± 0.2	40.7 ± 2.2	1.8 ± 0.4	1.9 ± 0.3 8.9 ± 5.4*	0.64 ± 0.1*	15.9 ± 2.4*	4.6 ± 1.6*	7.0 ± 1.4*	-2.4 ± 0.2*
TE after last CMV cycle First recovery breath post-CMV	0.09 ± 0.0*		1.7 ± 0.4	1.9 ± 0.4	0.04 ± 0.0*	1.1 ± 1.0*	1.0 ± 0.7*	1.6 ± 2.1*	2.6 ± 0.3*

Definition of abbreviations: CMV = controlled normocapnic mechanical ventilation; Pdi = transdiaphragmatic pressure; Pes = esophageal pressure; Pga = gastric pressure; TE = expiratory time; TI = inspiratory time.

Data are means ± SE (n = 7). Eupnea refers to the grand mean of the 10 spontaneous breaths that preceded each of the three CMV trials at a f_R of +1. Values for P_{ETCO_2} during recovery breaths were not measured because of excessively low flow rates.

* Mean values are significantly different from eupnea (p < 0.05).

First, the intrinsic mechanical properties of the diaphragm were changed during mechanical ventilation, both by the increased V_T , and therefore shortened muscle length, and by the increased flow rate, and therefore increased velocity of muscle shortening. Based on phrenic nerve stimulation studies at varying lung volumes and flow rates in humans (18, 19), we estimate that our increases in V_T and mean flow rates would have accounted for approximately 20% of the mean reduction observed in Pdi at the maximum V_T and flow rate and 5–10% of the reduction in Pdi at the smaller increase in V_T and flow rate. Second, phasic activation of expiratory muscles with relaxation of the diaphragm during subsequent inspiration could also have assisted in reducing diaphragmatic pressure development; however, this seems unlikely given the absence of changes in end-expiratory Pga or Pes throughout trials of ACMV. Third, changes in Pdi reflect primarily the activity of the diaphragm; thus, re-

duced or even eliminated Pdi during mechanical ventilation does not necessarily mean that motor output to all inspiratory pump muscles was similarly reduced. Finally, there were several circumstances during passive mechanical ventilation at high V_T where the increases in Pes during inspiration exceeded that in Pga, resulting in a negative Pdi. In these circumstances, the transmission of changes in pleural pressure to the abdominal compartment was attenuated. This may be explained by the retention of passive tension in the diaphragm, as demonstrated by Froese and Bryan (20) in the paralyzed human diaphragm during mechanical ventilation at raised V_T with subjects in the supine position. Alternatively, in the supine position, the abdominal contents may push on the diaphragm and impair transmission of all of the ΔP_{es} to the abdomen. Lake and colleagues (10) also reported negative Pdi during pressure support mechanical ventilation in subjects who were awake. Thus, the changes in

TABLE 2. EFFECTS OF CMV AT AN INCREASED RESPIRATORY FREQUENCY (+3 MORE THAN EUPNEA) AND V_T

	V_T L	P_{ETCO_2} mm Hg	TI sec	TE sec	V_T/TI L/sec	VE L/min	ΔP_{ga} cm H ₂ O \cong	ΔP_{es} cm H ₂ O \cong	ΔP_{di} cm H ₂ O
Eupnea	0.56 ± 0.1	41.6 ± 1.6	2.1 ± 0.4	2.0 ± 0.4	0.27 ± 0.0	8.3 ± 0.7	2.4 ± 1.0	-6.4 ± 2.3	8.8 ± 0.4
CMV 135% eupnea V_T , final 15 sec	0.78 ± 0.2*	43.0 ± 1.9	1.7 ± 0.2	1.8 ± 0.3 2.6 ± 0.9	0.46 ± 0.1*	13.5 ± 2.9*	3.0 ± 0.9*	2.1 ± 0.8*	-0.9 ± 0.2*
TE after last CMV cycle First recovery breath post CMV	0.32 ± 0.3*		1.6 ± 0.2	2.2 ± 0.5	0.19 ± 0.2*	4.9 ± 3.7*	2.1 ± 1.0	3.8 ± 1.0*	5.9 ± 0.3*
CMV 165% eupnea V_T , final 15 sec	0.91 ± 0.2	41.7 ± 1.6	1.8 ± 0.4	2.4 ± 0.8 6.3 ± 5.1*	0.52 ± 0.1*	15.0 ± 2.1*	2.9 ± 0.6*	5.7 ± 2.1*	-2.8 ± 0.5*
TE after last CMV cycle First recovery breath post CMV	0.20 ± 0.1*		1.5 ± 0.6	1.8 ± 1.0	0.14 ± 0.1*	3.7 ± 2.0*	1.4 ± 0.8*	3.3 ± 2.6*	4.7 ± 0.4*
CMV 200% eupnea V_T , final 15 sec	1.03 ± 0.4	41.2 ± 1.9	1.8 ± 0.3	2.9 ± 1.1 7.9 ± 4.8*	0.56 ± 0.2*	16.6 ± 4.8*	3.6 ± 1.4*	7.6 ± 3.4*	-4.0 ± 0.7*
TE after last CMV cycle First recovery breath post CMV	0.39 ± 0.4*		1.7 ± 0.4	2.6 ± 1.2	0.21 ± 0.2*	4.8 ± 3.4*	1.6 ± 0.8*	-3.0 ± 0.9*	4.6 ± 0.3*

For definition of abbreviations see Table 1.

Data are means ± SE (n = 7). Eupnea refers to the grand mean of the 10 spontaneous breaths that preceded each of the three CMV trials at a f_R of +1. Values for P_{ETCO_2} during recovery breaths were not measured due to excessively low flow rates.

* Mean values are significantly different from eupnea (p < 0.05).

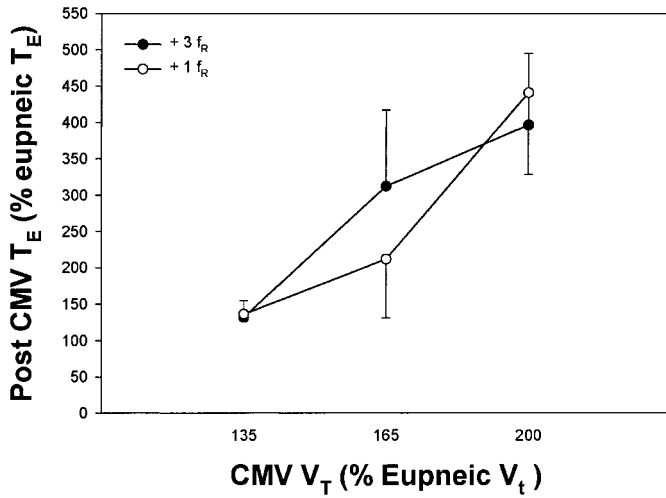


Figure 3. Average apnea lengths (relative to baseline spontaneous eupnea) after CMV at one and three breaths per minute more than eupnea and at each of the three V_T settings maintained during the CMV trials. The average absolute TE in control eupnea that preceded each of the CMV trials was 2.1 ± 0.4 seconds.

P_{di} during ACMV or CMV at raised V_T clearly overestimate the actual reduction in diaphragmatic activity and in the accompanying reduction in central respiratory motor output.

The recovery data obtained during spontaneous breathing in NREM sleep immediately after CMV or ACMV unequivocally demonstrate the significant inhibition of central respiratory motor output that occurred as a result of normocapnic mechanical ventilation. First, our interpretation that CMV completely elimi-

nated central respiratory motor output to all inspiratory muscles is shown by the substantial apneas that consistently followed CMV conducted at increased frequency and at V_T settings that were elevated 65% or more above eupnea. Furthermore, post-CMV apneic length was dependent on the magnitude of the V_T maintained during CMV. Second, immediately after normocapnic ACMV, TE was prolonged, but only to one-fifth the TE observed after CMV at comparable levels of V_T . However, we did consistently observe a significant reduction in P_{di} and in V_T in the initial two to four recovery spontaneous breaths when compared with the baseline spontaneous eupneic breaths, and these reductions after ACMV were greatest in trials with the higher V_T settings delivered during the ACMV. Finally, we note that our interpretation of P_{di} data during and after CMV in the human is consistent with previous studies in sleeping dogs, which showed that diaphragmatic EMG (as recorded from indwelling electrodes) was completely eliminated during and immediately after normocapnic CMV (at +1 f_R) (3).

Past versus Present Findings Using CMV and ACMV

CMV effects. Present findings extend previous results (discussed previously in this article) by showing in the sleeping human (1) that the increased frequency of CMV need only be as little as one breath per minute above spontaneous eupnea to eliminate respiratory motor output, but that V_T must also be increased at least 65% or more above eupnea and (2) that the duration of the post-CMV apnea lengthened in proportion to the V_T applied during CMV. When normocapnic CMV was conducted at average eupneic frequencies and relatively small V_T settings, anesthetized or sleeping intact humans entrained their diaphragm EMG to the ventilator (21, 22); accordingly, postventilator apnea did not occur (2, 23). Finally, in awake subjects, CMV trials conducted even at substantial increases in frequency and V_T did not always cause postventilator apnea, even when substantial

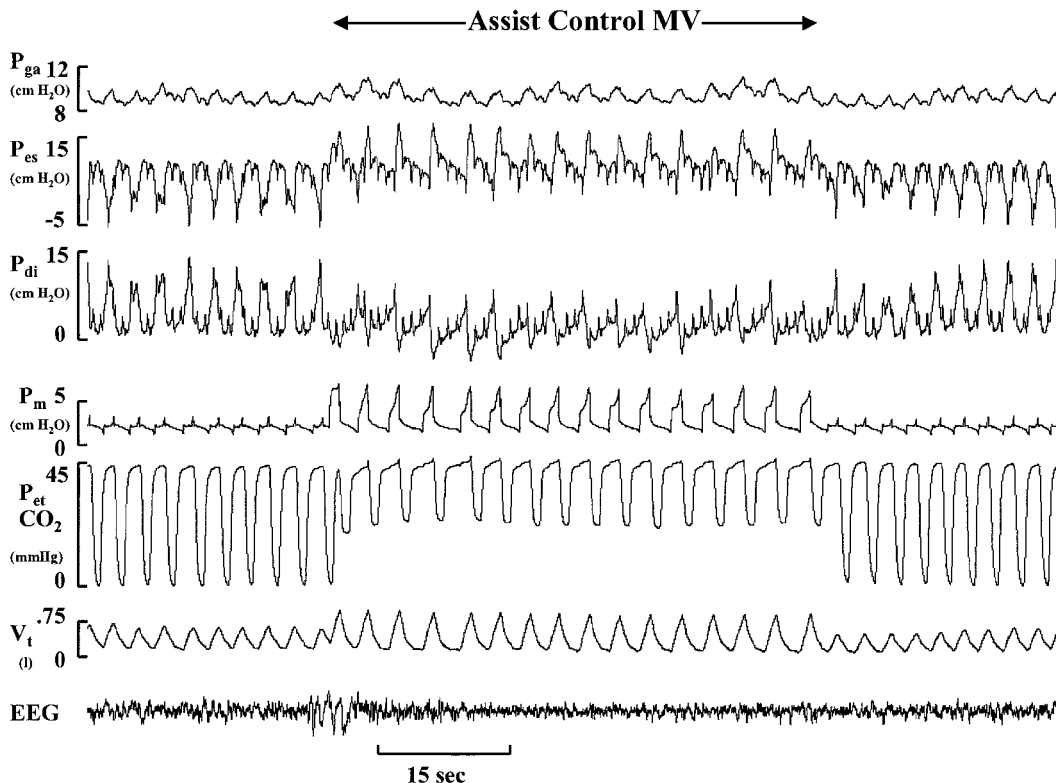


Figure 4. Typical example of the effects of assist control mechanical ventilation (ACMV) in subject 1 conducted at a V_T , which was 195% of spontaneous eupnea. All symbols are as in the legend for Figure 1. Spontaneous breathing plus CPAP precedes the ACMV trial. Note that ACMV begins with the increase in P_m and ceases when P_m returns to its baseline levels. Note the sudden reduction in P_{di} and increase in P_{es} at the onset of ACMV, which were maintained throughout ACMV and then gradually returned to normal during spontaneous breathing after the cessation of ACMV. P_{ETCO_2} was maintained at or slightly greater than eupneic levels by the addition of inspired CO_2 .

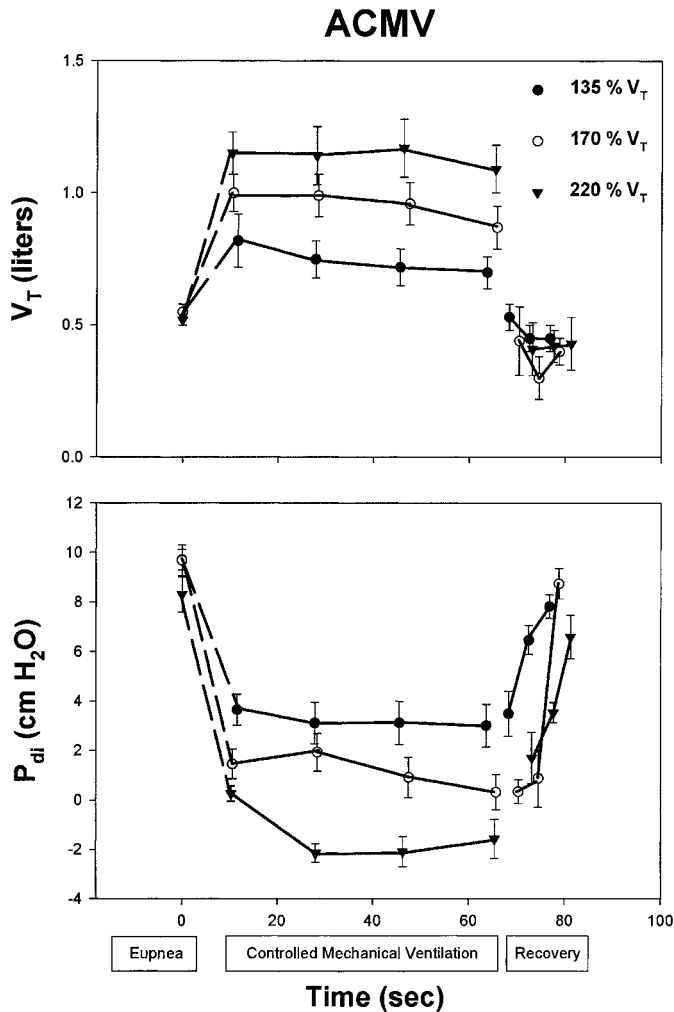


Figure 5. Group mean data ($n = 7$) for ΔP_{di} during spontaneous breathing (first data point), normocapnic ACMV averaged over 15-second intervals, and at three levels of V_T and during the first three spontaneous breaths after ACMV. The changes in ΔP_{di} are shown for ACMV at each of three V_T s.

hypocapnia was present (6, 23–25); however, one cannot exclude variable effects of wakefulness and behavioral responses to the mechanical ventilator on the control of breathing (15, 24), which were not factors in our present study conducted in NREM sleep.

Most of our findings in sleeping humans on CMV are similar to those in sleeping dogs (3), although there appears to be less volume-sensitive inhibition of respiratory motor output in the human versus the dog. For example, respiratory motor output in the human and dog was sensitive to both CMV frequency and V_T ; however, the dog required only a 10–20% increase in ventilator V_T at raised frequency to cause complete cessation of EMG_{di} and substantial postventilator apnea, whereas the human required a much larger percentage increase in ventilator V_T (Figure 3). At the same time, both species showed substantial V_T -dependent apneas after normocapnic CMV.

ACMV effects. We extend previous findings of normocapnic ACMV effects on reducing respiratory motor output in awake (9, 10, 26) and sleeping (5) subjects by showing that assisted synchronous ventilation will markedly reduce the amplitude of but not eliminate respiratory motor output both during and after ACMV and that this inhibitory effect is V_T dependent. TE is

also prolonged significantly at high V_T during ACMV, but these timing effects are relatively small compared with those elicited by CMV. In apparent contrast to our findings with normocapnic ACMV, Georgopoulos and colleagues (27) reported that P_{di} was unaffected by proportional assist ventilation, relative to spontaneous breaths, when comparisons were made during rebreathing at similar levels of raised P_{ETCO_2} and V_T in awake subjects. However, there are major differences between our studies including the variable effects of state of consciousness and chemoreceptor stimulation on respiratory motor output and the additional important influence (in our study) of a raised V_T during ACMV.

Chemoreceptor versus Nonchemoreceptor Influences

We prevented hypocapnia during mechanical ventilation by adding inspired CO_2 . Despite our control of P_{ETCO_2} , the question remains as to whether the P_{CO_2} was normocapnic at known peripheral and central chemoreceptor sites (7). First, we have shown that neither CMV (28) nor ACMV (5) at raised F_{ICO_2} in subjects who are awake causes systematic changes in the arterial to end-tidal P_{CO_2} difference, findings that agree with the consensus in the animal literature (29). Second, there are laryngeal and lung receptors sensitive to increases in inspired CO_2 . However, increased F_{ICO_2} to the isolated upper airway in intact anesthetized cats (30) or unanesthetized dogs (31) had no effect on phrenic motor output, and increases in lung CO_2 , *per se*, were shown to increase breathing frequency and minute phrenic motor output in the anesthetized dog (32).

Third, our increases in F_{ICO_2} and V_T likely had opposing effects on the amplitude of oscillations in arterial P_{CO_2} and pH (33). The effect of changes in arterial P_{CO_2} oscillation at constant mean P_{aCO_2} on ventilatory control are controversial (34, 35); however, in studies which both measured and controlled these oscillations, no effect on respiratory motor output was discernable, at least when V_{CO_2} was at resting levels (36). Certainly, we cannot attribute the reduced respiratory motor outputs after ACMV or CMV to alterations in CO_2 oscillations because F_{ICO_2} was reduced to room air levels in recovery.

We have additional types of evidence against a significant role for carotid chemoreceptors in accounting for reductions in respiratory motor output during isocapnic mechanical ventilation. First, we found equal amounts of resetting and/or inhibition of respiratory motor output during and after normocapnic CMV and ACMV in normoxia versus hyperoxia. Hyperoxia is known to markedly reduce the carotid chemoreceptor response to CO_2 (37, 38). Second, in the sleeping dog, we found that bilateral denervation of the carotid bodies also did not influence the magnitude of inhibition of EMG_{di} during and after normocapnic CMV or ACMV (unpublished findings from the authors' laboratory) or pressure support ventilation (39). Perhaps medullary chemoreceptor P_{CO_2} was reduced independently of arterial P_{CO_2} , but we know of no reason to expect such a dissociation to occur during normocapnic mechanical ventilation.

Our study also provides evidence that the inhibitory influences of mechanical ventilation will occur even in the presence of mild but significant hypercapnia. First, the initial few spontaneous inspiratory efforts after the termination of apneas in recovery from normocapnic CMV showed a V_T and P_{di} that were consistently reduced significantly below eupneic baseline values, despite a P_{aCO_2} that was undoubtedly significantly greater than eupnea. Second, during isocapnic ACMV at raised V_T , we occasionally observed very small inspiratory efforts that failed to trigger the ventilator to deliver the desired V_T (see the example in Figure 7 and, recorded at a faster speed, in Figure E5 in the online supplement). Note that despite the resultant transient increase in P_{ETCO_2} to 2–3 mm Hg above normocapnia after two successive untriggered efforts, the subsequent inspiratory effort

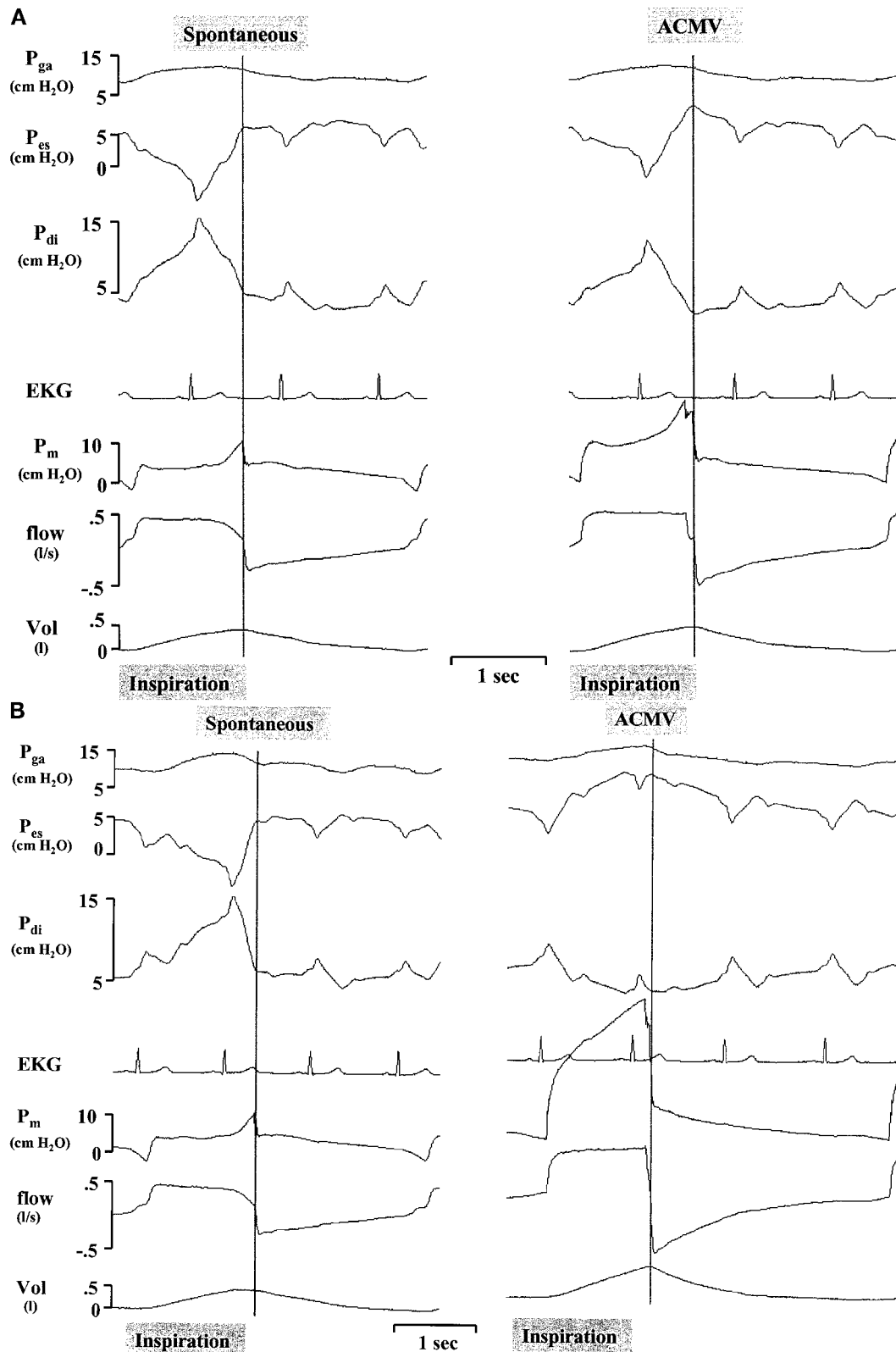


Figure 6. Polygraph records at a fast speed (28 mm/second) of a spontaneous control breath plus CPAP and a single cycle of ACMV, both obtained from subject 1 during an ACMV trial at $V_T = 140\%$ of eupnea (A) and at 200% of eupnea (B). Note the reduced fall in P_{es} and rise in P_{di} with inspiration during ACMV versus spontaneous breathing at $V_T 140\%$ of eupnea and the positive P_{es} and slight fall in P_{di} with inspiration during ACMV at 200% of eupneic V_T .

still remained well below those in baseline eupnea. Finally, in sleeping dogs, raising the P_{ETCO_2} 3–5 mm Hg above eupneic control during CMV at increased frequency and V_T did not prevent the elimination of EMGdi or postventilator apneas (3). Similarly, in sleeping humans, inspiratory effort was eliminated via hypocapnic CMV at raised V_T and did not return (as CMV

was continued) until P_{ETCO_2} was increased an average of 6 mm Hg above spontaneous eupnea (40).

In summary, although we acknowledge the apnea and hypoapnea-producing effects of even very small decrements in P_{aCO_2} in sleeping humans (2, 23, 41), we believe the evidence, as outlined previously here, speaks strongly in favor of nonchemoreceptor

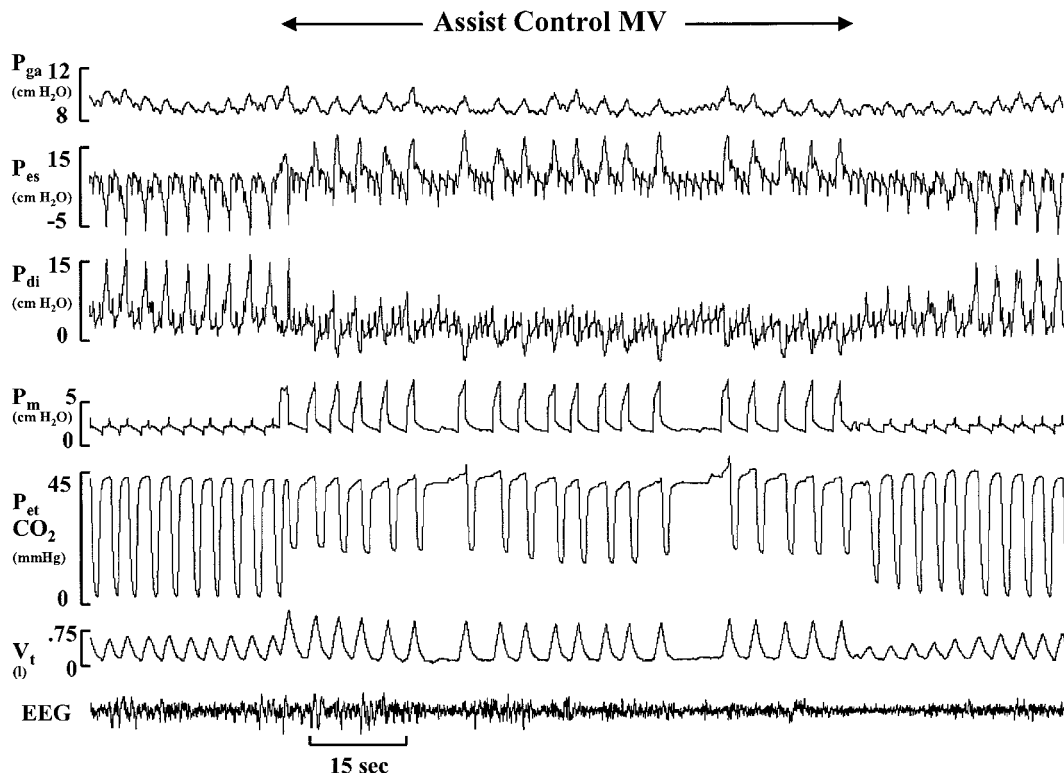


Figure 7. Example of a polygraph record from subject 1 showing the response to normocapnic ACMV at V_T 200% of control during which respiratory motor output was markedly reduced during the trial resulting in “untriggered” ventilator breaths and the transient accumulation of CO_2 . Note the increase in $P_{ET}CO_2$ after the untriggered breaths accompanied by a small increase in P_{di} . The “untriggered” ventilator cycles are those without a prominent increase in P_m and no V_t . The effects of the accumulation of CO_2 on within-breath P_{di} are shown in Figure E5 in the online supplement.

mediation of the observed elimination or reduction in respiratory motor output during and after isocapnic CMV or ACMV.

Mechanisms of Neuromechanical Inhibition during CMV and ACMV

With synchronous ACMV at increased V_T , the amplitude of respiratory motor output was reduced, both during and after mechanical ventilation, and the effect was V_T dependent and substantial. However, every ACMV cycle was triggered by an active inspiration, and TE prolongations were relatively small in the immediate postventilator period. Is the reduction in respiratory amplitude an effect of vagal inhibitory feedback from lung stretch? There is limited evidence in intact humans showing relatively small but significant effects on breath timing of dynamic lung volume changes either within or very close to the eupneic tidal range (14, 15). Furthermore, lung denervated lung transplant patients (42), unlike intact subjects (21), showed much difficulty in entraining their spontaneous rhythm to the mechanical ventilator during sleep. Thus, our observed effects of ACMV at high V_T primarily on the amplitude of respiratory motor output with relatively small effects on breath timing are consistent with these claims of a highly sensitive volume and perhaps vagal feedback effects on respiratory motor output.

The elimination of respiratory motor output in the human during and after CMV by means of increased ventilator frequency and V_T represents a “resetting” of the respiratory rhythm. Two types of powerful influences are responsible for this resetting effect, as previously documented in anesthetized or sleeping dogs and cats (3, 43). First, application of single ventilator breaths during early expiration, that is, in the so-called inflation-sensitive phase of the respiratory cycle, causes TE prolongation (3, 11) whose duration is dependent on the magnitude of the ventilator volume (3). Second, although these TE prolonging effects lasted only for one respiratory cycle (3, 42), repeated ventilator cycles performed at an increased frequency

above eupnea exerted a cumulative inhibitory effect on respiratory motor output, thereby lengthening the inflation sensitive phase of each respiratory cycle (3). This time-dependent cumulative inhibitory effect of CMV was manifested in postventilator apneas in both sleeping dogs (3) and humans (Figures 1 and 3) and was analogous to that originally reported in anesthetized piglets secondary to repeated electrical stimulation of the superior laryngeal nerve (44). In the sleeping dog, postventilator apneas first appeared after two or three CMV ventilator cycles, and apnea length increased progressively further as CMV was prolonged up through a duration of approximately 10 ventilator cycles (3). In the dog, tonic expiratory muscle EMG activity was also shown to occur simultaneously with a silent diaphragm EMG throughout the period of passive CMV, as well as during the subsequent apneic recovery period (3).

In the anesthetized cat, Knox (11) showed that TE prolongation via application of single ventilator breaths during neural expiration required intact vagal feedback. However, in lung transplant humans who were awake and vagally blocked dogs, we showed postventilator apneas after normocapnic CMV at raised frequency and V_T (45). Given the evidence cited previously here along with the potentially confounding effects of wakefulness, we propose that the role of vagal feedback in the resetting of respiratory rhythm during CMV needs testing in a sleeping state, where the effects of reflex inhibition may be more readily unmasked.

In summary, present evidence using both CMV and ACMV confirms and extends earlier work (8) that strong and sustained inhibition of the drive to breathe may be exerted by nonchemical feedback influences in the sleeping ventilated human. Furthermore, these inhibitory influences persist beyond the termination of the mechanical perturbations and in the face of rising chemical stimuli. The influence of either mode of mechanical ventilation was critically dependent on the magnitude of the ventilator V_T and likely on vagal feedback (discussed previously here). How-

ever, a raised f_R (with CMV) combined with a moderately augmented V_T showed substantially greater and more sustained inhibition of the amplitude and timing of respiratory motor output than did synchronous increases in V_T alone (as with ACMV). We attribute this potent cumulative inhibitory effect on breath timing during CMV to repeated application of the ventilator volume during the progressively prolonged inflation-sensitive phase of the respiratory cycle.

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