Effect of respiratory muscle weakness on $P_{0.1}$ induced by partial curarization

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HOLLE, ROLF H. O., ROBERT B. SCHOENE, AND EDWARD J. PAVLIN. *Effect of respiratory muscle weakness on $P_{0.1}$ induced by partial curarization.* J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 57(4): 1150–1157, 1984.—Mouth occlusion pressure 0.1 s after onset of inspiration ($P_{0.1}$) reflects central respiratory drive (CRD), but its dependence on respiratory muscle strength is unknown. To clarify this relationship, we produced progressive levels of respiratory muscle weakness by infusion of *d*-tubocurarine in eight supine spontaneously breathing normal subjects. Hypercapnic ventilatory response (HCVR) was measured before curarization and at mild (mean inspiratory effort 62 ± 3% of control), moderate (42 ± 3%), and severe (23 ± 1%) weakness. At the severe level of weakness *1*) supine functional residual capacity was not significantly changed from base line, *2*) the percent of base-line slope of $\Delta P_{0.1}/\Delta P_{CO_2}$ (122 ± 27%) was significantly greater ($P < 0.01$) than that for change in expired minute ventilation ($\Delta \dot{V}_E$)/ΔP_{CO_2} (39 ± 10%), *3*) the percent of base-line $\Delta P_{0.1}/\Delta \dot{V}_E$ (381 ± 46%) during HCVR was significantly increased ($P < 0.01$), *4*) the $P_{0.1}$ response was significantly increased from base line at two out of three specific levels of P_{CO_2} while the $\dot{V}_E$ was unchanged or significantly decreased, and *5*) peak inspiratory resistance did not significantly change. Thus $P_{0.1}$, unlike $\dot{V}_E$, did not decrease with even severe respiratory muscle weakness. Indeed, $P_{0.1}$ increased at two out of three levels of P_{CO_2} under circumstances when higher CRD is expected. One potential explanation for the results is that $P_{0.1}$ may at least qualitatively reflect CRD up to the level of severe respiratory muscle weakness attained in this study.

mouth occlusion pressure; respiratory drive; curare

MOUTH OCCLUSION PRESSURE ($P_{0.1}$) is the pressure generated after the first 0.1 s of inspiration when the airway is briefly occluded at functional residual capacity (FRC) (31). $P_{0.1}$ has been shown to be proportional to phrenic nerve output in cats (10) and to expired minute ventilation ($\dot{V}_E$) in normal humans (17) and is thought to reflect central respiratory drive (CRD). Because it occurs before there is significant airflow, the measurement of $P_{0.1}$ has been thought to be largely independent of lung mechanics and respiratory muscle force-velocity relationships (21). The dependence of $P_{0.1}$ on respiratory muscle strength, however, is at present unknown. It is possible that $P_{0.1}$ is proportional to respiratory muscle strength, resulting in significant underestimation of CRD in subjects with respiratory muscle weakness.

In two recent studies $P_{0.1}$ values in patients with respiratory muscle weakness were much higher than anticipated on the basis of their $\dot{V}_E$ levels during both resting and stimulated ventilation (1, 3). This finding led us to hypothesize that $P_{0.1}$ was less affected by respiratory muscle weakness than $\dot{V}_E$ was and may be a better measure of CRD in these circumstances. The purpose of this study was to test the dependence of $P_{0.1}$ and $\dot{V}_E$ on respiratory muscle strength by simultaneous measurements of $P_{0.1}$ and $\dot{V}_E$ in response to CO_2 stimulation during progressive steps of respiratory muscle weakness induced by partial curarization. The advantage of this model is that subjects with normal lung mechanics and physiological reflexes could be used as their own controls.

METHODS

Eight normal volunteers, aged 25–34 yr, gave informed consent to participate in the study. The protocol was approved by the University of Washington Human Subjects Review Board. All subjects were nonsmokers with normal spirometry, had no history of cardiopulmonary disease, and were not taking medications. All were medical personnel who had participated in previous respiratory drive studies and were familiar with the procedures.

Subjects reported to the laboratory at 8:00 A.M. after an overnight fast. Two pediatric catheters (3 mm OD) with balloons attached to the distal ends were passed through one nostril anesthetized with 1–2 ml 2% lidocaine hydrochloride jelly. Pressure tracings were used to place one balloon in the stomach and one in the esophagus for determination of transdiaphragmatic pressure. The subjects then reclined on a couch with the upper body angled at ~10° for the duration of the study. An intravenous line infusing D_5W at a low rate was inserted into a right hand vein, and 0.6 mg atropine was given intravenously to decrease oral secretions. After at least 10 min of restful breathing lung volumes were measured by the N_2-washout method.

The subsequent procedures were designed to measure hypercapnic ventilatory response (HCVR) before curarization and then at several levels of respiratory muscle weakness. Subjects breathed quietly through mouthpieces with noseclips in place in a darkened room, while white noise with quiet music in the background delivered through earphones was used to provide auditory distraction. End-tidal CO_2 and O_2 were monitored at the mouth by a mass spectrometer calibrated with gases of known concentration. Tidal volume (V_T) and $\dot{V}_E$ were measured

with a pneumotachograph which was calibrated each morning with a 1-liter syringe. Inspiratory time (T_I) and total respiratory cycle duration (T_T) were determined from the pneumotachograph tracing. Each of these measurements and the subjects' electrocardiograms were continuously monitored and recorded on a multichannel recorder. The $P_{0.1}$ was measured in a random pattern every 7–20 s with inaudible closures of the inspiratory portion of the airway with a pneumatically driven solenoid shutter. $P_{0.1}$ was measured on an oscilloscope as the pressure generated at 100 ms, which was electronically timed from initial inspiration. After 20 min of quiet breathing the base-line HCVR was measured by the Read rebreathing method (24). A 7% CO_2-40% O_2-balance N_2 initial mixture was used in the rebreathing bag. After completion of the HCVR, determinations of the vital capacity (VC), inspiratory effort (IE), and handgrip strength (HG) were made from the average of three trials of each. The VC was obtained with a Collins spirometer. The IE, measured with a Mannholdt vacuum gauge, was determined from the maximal plateau value that the subjects could hold for greater or equal to 1 s without using facial muscles. The HG was obtained using a Jamar Adjustable Dynamometer with the left hand supported in the same position each time.

Two to four steps of respiratory muscle weakness were then produced in each subject by partial curarization. An initial bolus of 0.05–0.07 mg/kg *d*-tubocurarine was administered intravenously. A constant infusion of 0.2–0.4 mg/min *d*-tubocurarine was delivered by a Harvard Infusion Pump throughout the entire period of curarization. The amounts of the initial bolus and the infusion were adjusted so that the IE of the first step was ~60% of control. Successive steps of respiratory muscle weakness were produced at 20–25 min intervals with additional boluses of 0.02–0.05 mg/kg *d*-tubocurarine. Using the percent of base-line IE for each step, the progressive steps of weakness were classified as mild (IE 51–75% of base line), moderate (IE 26–50%), and severe (IE < 25%) weakness. The number of steps in each subject was determined by individual sensitivity to curare. During each step a stable level of weakness was attained when repeat determinations of HG and IE did not appreciably change. At that point, after a 7–10 min period of resting breathing while on the mouthpiece, a repeat HCVR followed by measurements of IE, VC, and HG was performed. At the maximal level of weakness FRC was again determined after the other tests were completed. After these procedures the effects of curare were reversed by the intravenous injection of 1.0 mg atropine followed by 2.5 mg physostigmine.

An anesthesiologist (*EP*) was present during all studies to monitor the subjects during partial curarization. As a precaution the heads of the subjects were gently supported in the sniffing position (mild flexion of the neck and extension of the head with the jaw pulled up) to maximize airway patency throughout the study period. Significant partial obstruction of the upper airway could be detected by elevation of the ratio of transdiaphragmatic pressure to V_T. Such episodes were not detected during the measurement period.

Analysis of data. During the HCVR all $P_{0.1}$ measurements obtained during the 15- to 30-s period used to determine $\dot{V}_E$ were averaged to give the corresponding value. Time was allowed for estimated equilibration of end-tidal and mixed venous P_{CO_2} at the beginning of HCVR measurements before $P_{0.1}$ and $\dot{V}_E$ values were used for analysis. In determining the $P_{0.1}$ or $\dot{V}_E$ values in response to specific levels of P_{CO_2}, the best-fit line was drawn through the points. All values of $P_{0.1}$, $\dot{V}_E$, $\Delta P_{0.1}/\Delta P_{CO_2}$, $\Delta\dot{V}_E/\Delta P_{CO_2}$, and $\Delta P_{0.1}/\Delta\dot{V}_E$ were converted to percent of base-line response for comparison.

T_I, T_T, and T_I/T_T were determined by the method of Milic-Emili (20). Inspiratory flow at the point of peak esophageal pressure was determined from the slope of volume per unit time on the pneumotachograph tracing. A 15- to 20-s segment from the pen recorder at fast speed during a $P_{A_{CO_2}}$ of 52–55 Torr was used for determination of inspiratory timing and peak inspiratory airway resistance. Peak inspiratory airway resistance was calculated by subtracting calculated lung elastic pressure and mouthpiece pressure from peak esophageal pressure on nonoccluded breaths and dividing the difference by the corresponding inspiratory flow. The lung elastic pressure was calculated by assuming 1 cmH_2O inflation pressure for each 260 ml, using the volume corresponding to the instant of peak esophageal pressure (2).

All slopes were determined by linear regression analysis. Base-line responses were compared to the severe level of weakness by Student's paired *t* test. An analysis of variance was used to evaluate trends at base-line, moderate, and severe levels of weakness in those subjects having a step at each of these levels. Statistical variance is reported as ± SE (32).

RESULTS

Side effects of partial curarization. The subjects received an average total dose of 0.38 ± 0.03 mg/kg *d*-tubocurarine over a period of 70 ± 4 min. Approximately half of this total dose was delivered as a constant infusion in each case. The side effects of partial curarization have been adequately described in a previous study (15). In our study all subjects experienced some feelings of apprehension during the final level of weakness. Most required chin support to maintain their airway during the peak effect of the final bolus, but there was no evidence of airway obstruction during the measurement period. One subject noted pruritis and developed hives along the vein used for infusion following the first bolus of curare, but this resolved within 3 min. No wheezing or significant airway obstruction was noted during subsequent spirometry.

Effects of partial curarization on IE, HG, VC, and FRC. Four subjects had a step at mild weakness, six at moderate weakness, and seven at severe weakness. Five subjects had a step at both moderate and severe weakness, whereas only three had a step at three levels. Not all subjects had a step at each level because of unpredictability of response to partial curarization (16).

At all levels of weakness HG decreased more than IE, whereas IE decreased more than VC (Table 1). During

the control state average supine VC was 5.4 ± 0.4 liters, left hand HG (all subjects were right-handed) was 106 ± 8 lb, and IE was −91 ± 4 Torr. At the severe level of weakness attained by seven subjects, average supine VC was 2.1 ± 0.3 liters, HG was 4 ± 2 lb (0 in 3 subjects), and IE was −21 ± 1 Torr. There was no significant difference between the average base-line supine FRC of 2.80 ± 0.20 liters and the value of 2.86 ± 0.20 liters obtained at the maximal level of weakness in eight subjects.

Effects of partial curarization on $P_{0.1}$ and $\dot{V}_E$ during individual HCVR responses. Expired minute ventilation during HCVR with progressive weakness decreased during the severe step in all subjects (Figs. 1*A*, 2*A*, and 3*A*), resulting in a blunted $\dot{V}_E/CO_2$ response. Responses of $P_{0.1}$ fit one of these patterns. In the first pattern illustrated by *subj 2* (Fig. 1*B*), the $P_{0.1}$ response remained unchanged during increasing weakness. *Subj 6* had a similar pattern increasing only slightly. In the second pattern illustrated by *subj 4* (Fig. 2*B*), the $P_{0.1}$ response substantially increased. *Subj 1, 3, 7,* and *8* demonstrated this pattern. In the third pattern, illustrated solely by *subj 5* (Fig. 3*B*), the absolute values of $P_{0.1}$ increased while the slope actually decreased due to rising resting responses. This subject had the most brisk response to rising CO_2. The HCVR response of $P_{0.1}$ with increasing weakness was greater than $\dot{V}_E$ when directly compared in all eight subjects (Figs. 1*C*, 2*C*, and 3*C*).

TABLE 1. *Percent of base-line IE, VC and HG during increasing weakness*

Level of Weakness	IE	VC	HG
Base-line ($n = 8$)	100%	100%	100%
Mild ($n = 4$)	62 ± 3	95 ± 5	37 ± 13
Moderate ($n = 6$)	42 ± 3	72 ± 7	15 ± 4
Severe ($n = 7$)	23 ± 1	39 ± 6	4 ± 2

IE, inspiratory effort; VC, vital capacity; HG, handgrip strength.

Group results. In addition to slopes $P_{0.1}$ and $\dot{V}_E$ responses obtained from best-fit lines were compared at specific levels of P_{CO_2}. The percent of base-line $P_{0.1}$ and $\dot{V}_E$ responses to three levels of increasing P_{CO_2} and decreasing levels of respiratory muscle strength are illustrated in Fig. 4. The average $P_{0.1}$ response is higher than base-line and the average $\dot{V}_E$ response at all levels of weakness and all levels of P_{CO_2} stimulation. When base-line and severe level of weakness $P_{0.1}$ responses were compared ($n = 7$), the increases were significant at P_{CO_2} levels of 45 and 50 Torr. When base-line, moderate, and severe level of weakness $P_{0.1}$ responses were compared ($n = 5$) using an analysis of variance, the increases were also significant at P_{CO_2} levels of 45 and 50 Torr. The $P_{0.1}$ response was significantly higher than the $\dot{V}_E$ response during severe weakness at all levels of P_{CO_2} and during mild and moderate weakness at a P_{CO_2} of 45 Torr. In contrast, the response of $\dot{V}_E$ decreased significantly from baseline during severe weakness at a P_{CO_2} of 55 Torr.

Slopes. The percentages of base-line $P_{0.1}$ and $\dot{V}_E$ HCVR slopes with increasing weakness are compared in Table 2. When comparing the base-line to severe weakness values, the slope of $\Delta\dot{V}_E/\Delta P_{CO_2}$ decreased significantly (39 ± 10%), while the increase in $\Delta P_{0.1}/\Delta P_{CO_2}$ was not statistically significant (122 ± 27%). The percent of base-line $\Delta P_{0.1}/\Delta\dot{V}_E$ in response to P_{CO_2} during severe weakness increased significantly (381 ± 46%, $P < 0.01$) when the two were directly compared. When comparing base-line, moderate, and severe levels of weakness using an

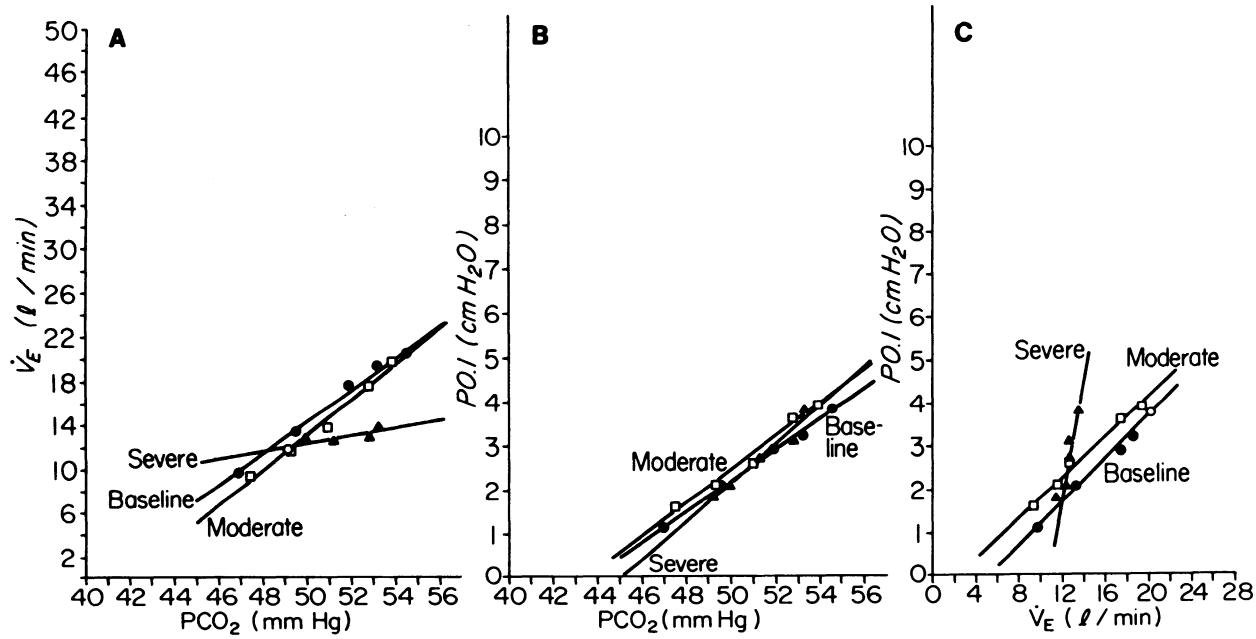

FIG. 1. Expired minute ventilation ($\dot{V}_E$) and mouth occlusion pressure 0.1 s after onset of inspiration ($P_{0.1}$) as a function of P_{CO_2} during progressive weakness in *subj 2*. *A*: $\dot{V}_E$ vs. P_{CO_2}. *B*: $P_{0.1}$ vs. P_{CO_2}. *C*: $P_{0.1}$ vs. $\dot{V}_E$. ●, base line; □, moderate weakness; ▲, severe weakness. $\dot{V}_E$ response decreased while $P_{0.1}$ remained stable.

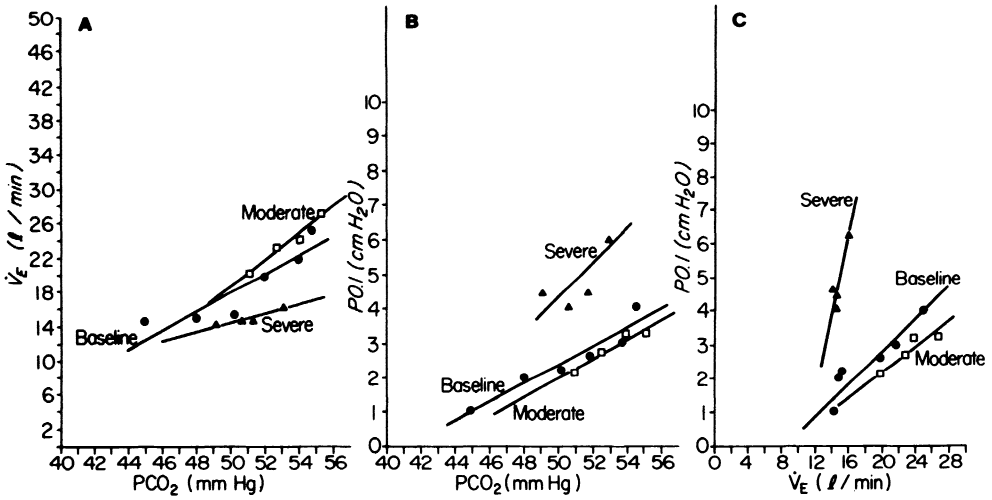

FIG. 2. Expired minute ventilation ($\dot{V}E$) and mouth occlusion pressure 0.1 s after onset of inspiration ($P_{0.1}$) as a function of PCO_2 during progressive weakness in *subj 4*. *A*: $\dot{V}E$ vs. PCO_2. *B*: $P_{0.1}$ vs. PCO_2. *C*: $P_{0.1}$ vs. $\dot{V}E$. ●, base line; □, moderate weakness; ▲, severe weakness. $\dot{V}E$ response decreased slightly while $P_{0.1}$ increased.

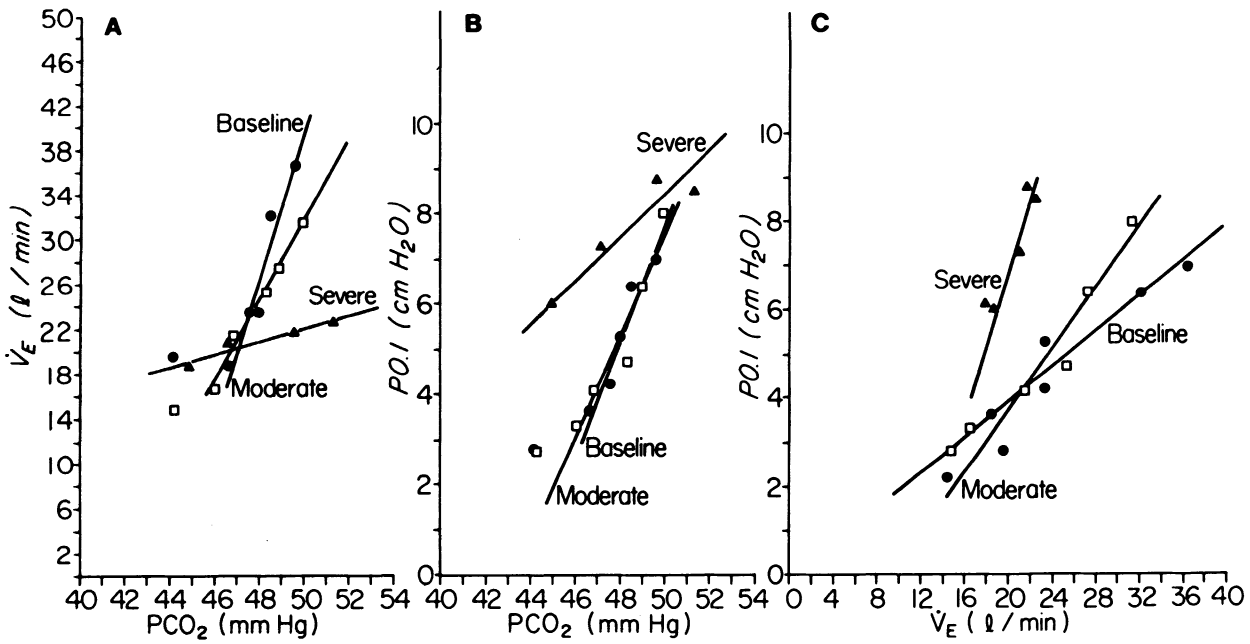

FIG. 3. Expired minute ventilation ($\dot{V}E$) and mouth occlusion pressure 0.1 s after onset of inspiration ($P_{0.1}$) as a function of PCO_2 during progressive weakness in *subj 5*. *A*: $\dot{V}E$ vs. PCO_2; *B*: $P_{0.1}$ vs. PCO_2; *C*: $P_{0.1}$ vs. $\dot{V}E$. ●, base line; □, moderate weakness; ▲, severe weakness. $\dot{V}E$ response decreased while absolute $P_{0.1}$ response increased. Decrease in slope of $P_{0.1}$ with severe weakness was due to increased resting values.

analysis of variance, the increase in $\Delta P_{0.1}/\Delta \dot{V}E$ was significant ($P < 0.01$), while the decrease in $\Delta \dot{V}E/\Delta PCO_2$ was not.

Effects of partial curarization on peak inspiratory resistance, transdiaphragmatic pressure, and TI/TT. The effects of partial curarization at the maximal level of weakness during near-maximal CO_2 stimulation (PCO_2 52–55 Torr) on peak inspiratory resistance, peak diaphragmatic pressure, and respiratory duty cycle were compared to base-line values in all eight subjects. The small decreases in average inspiratory flow rate (1.00 ± 0.27 to 0.87 ± 0.14 l/s) and peak transdiaphragmatic pressure (−16.7 ± 4.8 to −13.8 ± 2.7 cmH_2O) did not attain significance. The slight increase in average calculated peak inspiratory resistance (8.4 ± 1.3 to 9.5 ± 1.5 $cmH_2O \cdot l^{-1} \cdot s$) also was not significant. When the percent change in peak inspiratory resistance was correlated to the percent change in $P_{0.1}$ from base-line to maximal weakness in each individual subject, no significant relationship ($R = -0.04$) was found.

With progressive weakness inspiratory time shortened, and subjects developed peak esophageal and transdiaphragmatic pressures earlier during inspiration (Table 3). Respiratory frequency during maximal stimulation increased significantly from 15.8 ± 1.8 at base line to 23.3 ± 2.5 during maximal weakness, while TI/TT did not significantly change (0.44 ± 0.3 to 0.42 ± 0.04).

DISCUSSION

These results demonstrate that the absolute value of $P_{0.1}$ measurements during HCVR significantly increased in response to severe respiratory muscle weakness at two of three specific levels of PCO_2. The slope of $P_{0.1}/PCO_2$ failed to decrease with progressive weakness. In contrast, simultaneously obtained $\dot{V}E$ measurements significantly

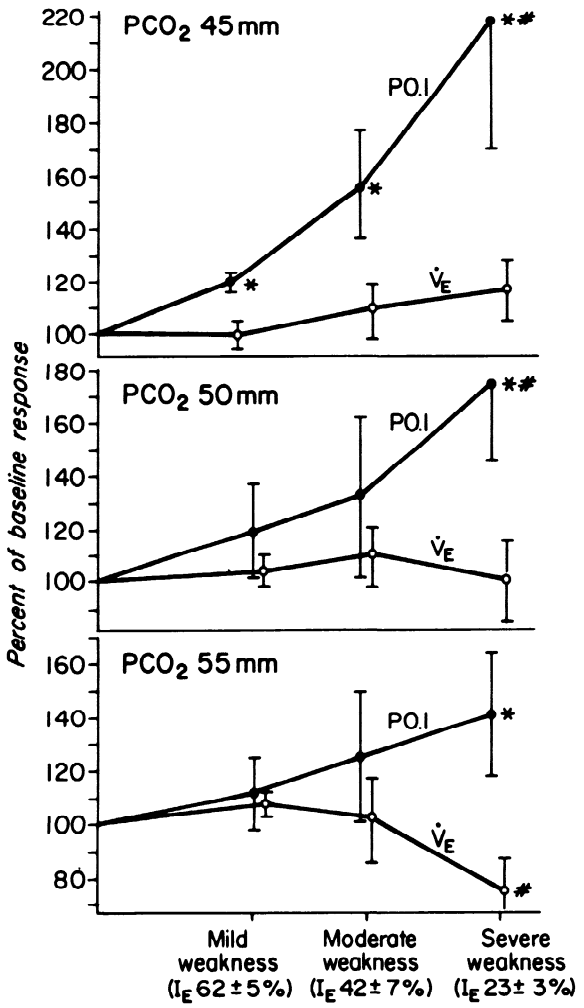

FIG. 4. Percent of base-line expired minute ventilation ($\dot{V}E$) and mouth occlusion pressure 0.1 s after onset of inspiration ($P_{0.1}$) responses during progressive weakness in response to P_{CO_2} levels of 45, 50, and 55 Torr. * $P_{0.1}$ response was significantly greater than $\dot{V}E$ response ($P < 0.05$); # Response was significantly increased or decreased from base line. $P_{0.1}$ response is significantly greater than $\dot{V}E$ response at all levels of P_{CO_2} with severe weakness and $P_{0.1}$ base-line response at 45 and 50 Torr. $\dot{V}E$ response significantly decreased from base line at maximum level of weakness with P_{CO_2} of 55 Torr. IE, inspiratory effort ($P < 0.05$).

TABLE 2. *Percent of base-line slope during HCVR of $\dot{V}E$ and $P_{0.1}$ in response to increasing weakness*

Level of Weakness	$\Delta\dot{V}E/\Delta P_{CO_2}$	$P_{0.1}/\Delta P_{CO_2}$	$\Delta P_{0.1}/\Delta\dot{V}E$ (during 1 h)
Base-line	100%	100%	100%
Mild	119 ± 15	102 ± 18	116 ± 30
Moderate	103 ± 28	88 ± 14	142 ± 41
Severe	39 ± 10*†	122 ± 27	381 ± 46*

HCVR, hypercapnic ventilatory response; $\dot{V}E$, expired minute ventilation; $P_{0.1}$, mouth occlusion pressure 0.1 s after onset of inspiration. * $P < 0.01$ compared with base-line level of weakness. † $P < 0.005$ compared with $P_{0.1}/\dot{V}E$ response.

TABLE 3. *Effects of partial curarization on TI/TT*

Subj	Level of Weakness	Maximal Frequency	TI/TT
RS	B	13	0.41
	M	20	0.55
DM	B	10	0.37
	M	10	0.39
RH	B	14	0.42
	M	20	0.48
GG	B	14	0.41
	M	27	0.41
LG	B	17	0.47
	M	30	0.51
RD	B	20	0.60
	M	23	0.46
RR	B	25	0.42
	M	30	0.34
MS	B	13	0.40
	M	26	0.25
Mean	B	15.8 + 1.8	0.44 + 0.03
	M	23.3 + 2.5	0.42 + 0.04
		($P < 0.05$)	(NS)

TI, inspiratory time; TT, respiratory cycle duration; b, base-line level of weakness; m, moderate level of weakness.

decreased with severe respiratory muscle weakness. When directly compared, $P_{0.1}$ measurements became progressively greater than $\dot{V}E$ measurements with increasing levels of weakness.

Weakened respiratory muscles should require greater neural input to maintain alveolar ventilation and thereby a constant P_{CO_2}. This assumption is supported by the findings of Paton and Aaimis (23), who demonstrated significantly increased phrenic nerve discharge despite a 40% decrease in $\dot{V}E$ in spontaneously breathing cats in response to partial curarization. In addition, the anxiety experienced during the final stage of weakness may have acted to increase CRD. These two effects should have resulted in increased CRD with increasing respiratory muscle weakness. The lack of change or significant decrease in $\dot{V}E$ measurements under these conditions suggests that $\dot{V}E$ is not an accurate measure of CRD in subjects with severe or possibly moderate respiratory muscle weakness. The significant increase of $P_{0.1}$ relative to $\dot{V}E$ measurements demonstrates that these two measurements are not comparable under these circumstances.

Although we did not directly measure CRD, the significant trend of increasing $P_{0.1}$ measurements with increasing weakness suggests that $P_{0.1}$ may reflect an intact CRD which would be anticipated with increasing muscle weakness. At some level of respiratory muscle weakness as complete paralysis is approached, $P_{0.1}$ must begin to underestimate CRD. Because the $P_{0.1}$ response increased from moderate to severe weakness at P_{CO_2} levels of 45 and 50 Torr, it is possible that the degree of underestimation was still small at the severe level of weakness. Without phrenic nerve tracings we are not able to quantitate CRD as the divergence between $P_{0.1}$ and $\dot{V}E$ increases.

In Fig. 3*B* the absolute $P_{0.1}$ values during severe weakness increased from base-line and moderate weakness, while the slope actually decreased. The decrease in slope, seen in several subjects, resulted from higher resting isocapnic values and suggests there may be a maximal $P_{0.1}$ value that is approached asymptotically with increasing respiratory muscle weakness and CO_2 stimulation. This phenomenon may have decreased the potential

increase in $P_{0.1}$ at a P_{CO_2} level of 55 Torr, possibly accounting for the failure to attain statistical significance at this level. This phenomenon decreases the value of slopes as a method of expressing respiratory drive under these circumstances and accounts for our inclusion of an analysis of the absolute values.

It is not clear from our results whether this $P_{0.1}$ ceiling is affected by progressing respiratory muscle weakness beyond the level of weakness investigated in this study. At some point of progressing muscle weakness the maximal $P_{0.1}$ must begin to decrease as muscle strength approaches zero. There is no evidence in our study that we attained these levels, as the maximal $P_{0.1}$ values in each subject were attained at maximal CO_2 stimulation during severe weakness.

Considerable experience with the effects of partial curarization has accumulated in prior studies involving awake nonintubated subjects (8, 12–15, 25). De Troyer and Bastenier-Geens (8) found that FRC decreased by 15% in response to partial curarization in the sitting position. Gal and Arora (13), however, found no significant change in FRC from a mean value of 2.80 ± 0.17 liters in partially curarized supine normal subjects. Our results in eight normal subjects also demonstrate that FRC does not decrease in response to partial curarization producing severe respiratory muscle weakness in the supine position. The lack of change of FRC implies that end-expiratory muscle length did not change and that comparison of $P_{0.1}$ values obtained at different levels of weakness is valid (26). De Troyer and Bastenier-Geens (8) also found no change in specific airway conductance, suggesting that partial curarization does not alter airway mechanics and that comparison of $P_{0.1}$ to $\dot{V}_E$ responses is justified.

Our calculations of peak inspiratory airway resistance during near-maximal CO_2 stimulation failed to show a significant change from base line to the maximal level of weakness. These calculations are at best only an approximation of inspiratory resistance during the first 0.1 s of inspiration. However, the failure to find a significant increase in resistance later during inspiration suggests that there was not a significant increase in early inspiration. In addition, the complete lack of correlation between the change in airway resistance and $P_{0.1}$ in individual subjects demonstrates that the observed increase in average $P_{0.1}$ did not result from increases in airway resistance in a few subjects.

Gal and Arora (13) found evidence for increased inspiratory resistance during partial curarization in six subjects during maximal inspiratory effort maneuvers. These authors, who noted that four of their subjects exhibited husky voices and that one had inspiratory stridor, do not state in their report if they supported the heads of their subjects during the measurement period. Our failure to find significant increases in inspiratory resistance may have been due to the careful attention paid to head positioning and monitoring of the transdiaphragmatic pressure-to-V_T ratio by our anesthesiologist. In addition, Gal and Arora used boluses only without constant infusions of curare. This method could have led to rapidly changing respiratory muscle strength during periods when several different measurements were made and to greater potential for partial airway obstruction.

Prior studies have shown that curare has no direct effects of its own on CRD. Cohen (6) has shown that curare does not cross the blood-brain barrier. The classic study of Smith and Reese (29), who used large doses of *d*-tubocurarine in awake subjects, also argues against any central effects. Although Molbech and Johansen (22) noted that *d*-tubocurarine may block the muscle spindle γ-efferents and thereby decrease respiratory muscle tone, it seems unlikely that this effect played a significant role in our results because we observed no change in FRC.

Our results have shown that with maximal weakness there was no significant change in peak inspiratory resistance, no change in T_I/T_T, and a small but not statistically significant decrease in peak transdiaphragmatic pressure. This implies that the trend towards increasing $P_{0.1}$ resulted from an increased rate of force generation during early inspiration, which we observed qualitatively on our tracings. This increased initial rate of force generation in response to respiratory muscle weakness could have a number of different causes and implications. It may simply be proportional to increased phrenic nerve output and CRD, implying that $P_{0.1}$ at least partially reflects CRD under these circumstances. Increasing anxiety in response to increasing respiratory muscle weakness should act through stimulation of CRD, thereby having a theoretically similar effect on $P_{0.1}$ and $\dot{V}_E$. Conscious or subconscious responses or reflexes that alter the pattern of respiratory muscle contraction and rate of force generation in response to respiratory muscle weakness independent of CRD cannot, however, be excluded by the present study design.

How severely weakened respiratory muscles can respond with an initially increased rate of force generation is not easily explained. Because partial curarization may paralyze the slow-twitch fibers of the diaphragm more than the fast-twitch fibers, this may result in an initially faster contraction that is less sustained (7, 19, 23). Another potential explanation involves the possible similarity of partial curarization and muscle fatigue (5). If fatigue were to occur within a single inspiratory cycle, relative preservation of the less fatigue-prone initial inspiration might occur. Finally, it has been shown that fatigue is less likely to occur with submaximal than with maximal $\dot{V}_E$ (11, 18, 19, 30, 33). If this phenomenon occurs within a single inspiration, it seems possible that fatigue of respiratory muscles is less evident during the submaximal contraction of the 1st 0.1 s of inspiration. Even at the severe level of weakness maximal $P_{0.1}$ values were usually only 10% and at most 30% of the maximal IE.

It is not clear whether results obtained during partial curarization are applicable to other types of muscle weakness. Edwards (9) has written that partial curarization is analogous to the high-frequency fatigue seen in muscles during ischemic exercise or in myasthenia gravis, while the type of fatigue seen in the diaphragm during respiratory failure appears to be low-frequency fatigue. The pattern of respiratory muscle weakness may also have some influence on the measurement of CRD by

varying techniques. Partial curarization weakens the thoracic muscles more than the diaphragm (12, 14, 25), whereas patients with chronic obstructive pulmonary disease (COPD) appear to have greater weakness of the diaphragm due to increased FRC. Respiratory muscle incoordination in such patients further complicates the pattern of respiratory muscle weakness (4, 27, 28) and may have a variable effect on the pattern of initial force generation. Whether or not these various differences affect the possible reflection of CRD by $P_{0.1}$ during respiratory muscle weakness is unknown.

In our study $\dot{V}E$ measurements remained constant or significantly decreased during increasing respiratory muscle weakness when increased CRD is expected. In contrast, $P_{0.1}$ measurements tended to increase, suggesting that $P_{0.1}$ may be a better indicator of CRD in these circumstances. These trends were evident even at the severe level of respiratory muscle weakness with an average IE of -21 ± 1 Torr, at which our subjects attained a level of weakness commonly observed in patients who have respiratory insufficiency or who fail to wean from mechanical ventilation. Two recent studies in patients with abnormal respiratory muscle strength support these conclusions. In hypercarbic bronchospastic patients with COPD admitted to an intensive care unit with respiratory failure, Aubier et al. (1) found $P_{0.1}$ values four times higher than in normal controls despite similar $\dot{V}E$ levels. Several studies have demonstrated that diaphragmatic fatigue and respiratory muscle weakness are commonplace in such patients (4, 28). This study demonstrated that very high $P_{0.1}$ values could be obtained despite respiratory muscle weakness and implied that respiratory muscle fatigue and abnormal lung mechanics may be more significant problems than decreased CRD in many of these patients. In another study Begin et al. (2) demonstrated that patients with respiratory muscle weakness due to myotonic dystrophy had resting and CO_2-stimulated $P_{0.1}$ values that were 1.5–2 times higher than those of normal controls, while $\dot{V}E$ levels were similar. These two studies also illustrate the possible underestimation of HCVR when using $\dot{V}E$ to measure CRD in patients with abnormal lung mechanics or respiratory muscle weakness.

The results in our normal subjects and the clinical studies presented above demonstrate that in spite of increasing muscle weakness and decreasing $\dot{V}E$, $P_{0.1}$ does not decrease, suggesting that $P_{0.1}$ may reflect an intact central respiratory drive. Presumably, with further progressive diaphragmatic weakness $P_{0.1}$ would begin to decrease despite increasing CRD. The mechanism of relative sparing of the $P_{0.1}$ response is unknown but appears to be due to an increased rate of initial inspiratory force generation. Demonstration of specific correlation of these elevated $P_{0.1}$ measurements to CRD must now be accomplished in a study where $P_{0.1}$ and phrenic nerve output can be directly compared during increasing muscle weakness. These results also demonstrate that $\dot{V}E$ is not an accurate measure of CRD under conditions of significant respiratory muscle weakness.

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