Partial Paralysis with d-Tubocurarine and the Ventilatory Response to CO₂:

An Example of Respiratory Sparing?

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d-Tubocurarine (dTe) was administered intravenously to six healthy unanesthetized volunteers to assess the effects of partial paralysis on ventilatory response to CO₂. Each subject received during a 40-minute period 0.2 mg/kg, consisting of five incremental doses at intervals 10 minutes apart. Isohypercapnia with PETCO₂ 6–7 torr above each subject’s resting level was maintained throughout dTe administration. Ventilation at this level of stimulus was 23.8 ± 1.1 l/min (mean ± SE) before administration of dTe, about three times resting levels. Steady-state minute ventilation measured during the period 4–6 minutes after each dose of dTe failed to decrease significantly; the levels of ventilation were maintained primarily by increased respiratory frequency, since tidal volumes declined significantly from an average of 1,550 ml to 1,050 ml (P < 0.025). Changes in the slope of the CO₂-response curve varied widely among subjects. Although the control slope of 2.03 ± 0.76 l/min/torr (mean ± SE) was reduced to 1.50 ± 0.36 l/min/torr after partial curarization, the change was not significant (P > 0.10). Ventilation was maintained at a time when grip strength was 60 per cent of control, vital capacity was 52 per cent of control, and maximum static respiratory pressures were 35–40 per cent of control. Nevertheless, the results suggest significant impairment of vital respiratory functions such as coughing, deep breathing, and the ability to maintain a patent airway in the absence of endotracheal intubation. (Key words: Neuromuscular relaxants, d-tubocurarine; Ventilation, carbon dioxide response; Carbon dioxide, ventilatory response.)

EARLY CLINICAL DESCRIPTIONS of general anesthesia supplemented with d-tubocurarine (dTe) often implied an apparent “respiratory-sparing” effect of dTe. This concept, that respiratory muscle function was unimpaired in the face of significant peripheral muscle weakness, arose largely from poorly quantitated unstressed measurements such as tidal volume at rest. More recent efforts to characterize the respiratory effects of d-tubocurarine have examined its influence on the response of the total respiratory apparatus to a stress in the form of a carbon dioxide stimulus. The results have been conflicting, however, and the effect of partial paralysis with d-tubocurarine on the ventilatory response to carbon dioxide has remained an area of controversy. Belleville hypothesized that d-tubocurarine by its peripheral action on respiratory muscles might decrease the slope of the CO₂ response curve.7 Johansen and Jørgensen’s findings,2 as well as those of Tyler and Cohen,1 confirmed this hypothesis. On the other hand, Riggs, Engel, and Ritchie3 found no significant change in the ventilatory response to CO₂ after slight or moderate paralysis.

In most of these studies, d-tubocurarine was administered by continuous infusion to achieve uniform paralysis as determined by intermittent measurements of grip strength, vital capacity, or head-lifting ability. Since CO₂ response curves require a certain amount of time to complete, it is dif-

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difficult to establish with certainty that the intensity of drug effect had not varied during the measurement periods. Furthermore, information about dose-related effects was difficult to discern.

We sought a different quantitative approach to establish whether the muscle weakness produced by incremental doses of d-tubocurarine altered the ventilatory response to CO₂. We recorded changes in minute ventilation at a fixed level of CO₂-stimulated breathing and thus provided a constant monitor of drug effect. Dose-related changes in respiratory muscle strength were quantified by serial measurements of maximum static respiratory pressures at several lung volumes. The less sensitive and less specific vital capacity was also measured for comparison. Measurements were obtained 4–6 minutes after each dose of dTc. This period represents the time of peak effect following intravenous administration of dTc and helps to obviate some of the problems inherent in continuous-infusion experiments.

Methods

Subjects of the study were six healthy male volunteers aged 21 to 30 years. Informed consent was obtained after fully explaining the nature, purpose, and risks of the study. Subjects were awake, fasting, and supine during the experiment. Atropine sulfate, 1.0 mg, was administered intravenously prior to dTc to minimize secretions. A total of 0.2 mg/kg d-tubocurarine was administered intravenously during a 40-minute period in the form of five incremental doses spaced at intervals 10 minutes apart. The individual doses of 0.026, 0.017, 0.029, 0.048, and 0.080 mg/kg formed a logarithmic progression to the total dose of 0.20 mg/kg. Serial measurements of ventilatory function and tests of muscle function (described below) were expressed in relation to the total cumulative doses of dTc, which after each of the five increments were 0.026, 0.043, 0.072, 0.12, and 0.20 mg/kg, respectively. These measurements were obtained before administration of dTc (control), 4 to 6 minutes after each intravenous dose, during the time of peak effect. The 10-minute interval between doses was necessary to allow for measurements at this time and also to allow ample time to re-establish a steady state of hypercapnia, which was interrupted by the tests of muscle function.

GAS ANALYSIS

A nonrebreathing circuit was utilized, with expired gases collected in a 10-liter recycling spirometer (Electromed #750). End-tidal CO₂ tension (PETCO₂) was determined by continuous sampling at the mouthpiece and analysis by infrared absorption (Godart Capnograph). The instrument was calibrated with three CO₂–O₂ mixtures previously analyzed by a micro-Scholander technique. Inspired oxygen concentration was monitored continuously with a Godart Rapox Analyzer; supplemental O₂ maintained the inspired concentration above 24 per cent. At the start of the study, the functional residual capacity (FRC) of each subject was determined by a closed-circuit nitrogen-dilution method. Analysis for nitrogen was performed by a 350 AR Nitralyzer (Med-Science). Outputs from the spirometer and all gas analyzers were simultaneously recorded on a Servo-Riter II (Texas Instruments).

VENTILATORY RESPONSE TO CARBON DIOXIDE

After allowing subjects a suitable period of rest and acclimatization to the apparatus, we recorded resting minute ventilation (VR), respiratory frequency (f), and PETCO₂. CO₂ challenge was then achieved with three different levels of inspired CO₂ (approximately 3, 4.5, and 5.5 per cent) to provide steady-state ventilatory-response curves. VR and f were recorded after PETCO₂ had been maintained for at least 5 minutes at each level. Upon completion of the response curve, inspired CO₂ was adjusted to achieve a stable PETCO₂, 6–7 torr above the subject's resting level. This constant stimulus of iso-hypercapnia was maintained during the period of drug administration. "Control" values for VR and f were recorded after stabilization, and 10 minutes after intravenous administration of a dose of atropine, 1.0 mg. Subsequent recordings of VR and f were made 4–6 minutes after each dose of
dTc. This represented the last 2 minutes of a 9-minute period of CO₂ breathing. Stability of PETCO₂ had always been achieved at the time each dose of dTc was administered. After measuring the effects of the total dose of dTc, we lowered inspired CO₂ to about 3 per cent and recorded steady-state ventilation at another point in order to obtain some information about the slope of the post-drug CO₂-response curve. Vₐ and f were recorded during the last 2 minutes of an 8-minute period of CO₂ breathing. Although this was 14 minutes after the last dose of dTc, the absence of demonstrable change in vital capacity and grip strength indicated that paralysis was comparable to that present at the higher CO₂ level. Additional points on the steady-state CO₂-response curve were not obtained because of the constraints of time and its effect on extent of paralysis.

TESTS OF MUSCLE FUNCTION

We evaluated respiratory muscle function with vital capacity and sequential measurement of maximal inspiratory and expiratory pressures at five different lung volumes. At the termination of each vital capacity maneuver, the mouthpiece was occluded and pressures generated by maximal effort on inspiration and expiration were recorded at residual volume (RV). Following several normal quiet breaths (indicated by the spirometer trace), the airway was occluded and pressures were measured at functional residual capacity (FRC). Subjects then inspired 1 liter from a giant syringe and then an additional liter, yielding pressure measurements at FRC + 1.0 liter and FRC + 2 liters. The final reading occurred after a maximal inspiration, i.e., at or near total lung capacity (TLC). Absolute lung volumes for plotting pressure-volume relationships were not determined but were constructed from the measurements of vital capacity and of FRC by closed-circuit nitrogen dilution. It was assumed that FRC does not change, and that RV approximates 25 per cent of TLC. Oral pressures were maintained for 1–2 seconds and a 2-mm orifice inside the mouthpiece minimized the contribution of the cheeks. The mouthpiece was connected by polyethylene tubing with an inside diameter of 2 mm to a Statham P23AA pressure transducer, the output of which was calibrated against a mercury column and displayed on the Servo Riber II. Before the start of the study a suitable practice period was allowed to obtain baseline values. Each series of measurements required 45 to 60 seconds to complete and was performed immediately after recording ventilatory responses to CO₂. Peripheral muscle power

![Graph](https://example.com/graph.png)

**FIG. 1.** Effects of increasing doses of d-tubocurarine on ventilatory responses during controlled hyperventilation. V̇ₑ = minute ventilation; Vₜ = tidal volume; f = respiratory frequency.
was assessed by grip strength registered in kilograms on a dynamometer (Stoelting and Company).

Results

Total doses of dTe received by the subjects were 17.0 ± 0.9 mg (mean ± SE). Ventilatory changes following the incremental doses are depicted in figure 1. Minute ventilation (V̇E) with controlled hypercapnia before dTe administration was 23.8 ± 1.1 l/min (mean ± SE), about three times the average resting value. Following atropine, V̇E was 26.2 ± 1.8 l/min. After the initial dose of dTe (0.026 mg/kg), V̇E was 27.2 ± 2.1 l/min. All subjects noticed visual blurring and most felt apprehensive. With the next three doses, producing cumulative totals of 0.043, 0.072, 0.12 mg/kg, V̇E's were 24.8, 26.2, and 26.8 l/min, respectively. The final dose (cumulative total 0.2 mg/kg) produced a gagging sensation and difficulty in swallowing in all volunteers. Two subjects experienced difficulty in maintaining an adequate airway and required chin support. Despite awareness of increased ventilation, most subjects indicated they had a desire to breathe more rapidly. Minute ventilation at this time was 22.5 ± 2.1 l/min (mean ± SE). The f ratio from analysis of variance indicated that the dTe-induced changes in minute ventilation were not significant (P > 0.10). As is evident from the lower half of figure 1, the level of ventilation was maintained principally by an increase in respiratory frequency, since tidal volumes decreased significantly from control levels of 1,550 ± 30 ml to 1,050 ± 80 ml with last dose of dTe (P < 0.025).

Although the slope of the ventilatory response curve was slightly decreased after dTe (fig. 2) from the control of 2.65 ± 0.76 l/min/torr BTPS (mean ± SE) to 1.80 ± 0.36 l/min/torr, paired t testing showed that this was not a statistically significant change (P > 0.10). One subject had a rather steep control slope (6.2 l/min/torr) and a virtually flat curve after dTe administration, albeit at an elevated V̇E. Two of the remaining five subjects had slight increases in slope following paralysis, while two others showed no change, and one a slight decrease.

Some of the changes in muscle power with increasing doses of dTe are shown in figure 3. Both grip strength and vital capacity were virtually unaffected by the initial three doses. The fourth dose (total 0.12 mg/kg), however, depressed grip strength from a control value of 56 ± 4 kg (mean ± SE) to 37 ± 3 kg. Vital capacity at this time showed minimal change from a control value of 5.5 ± 0.16 l to 5.1 ± 0.2 l. After the final dose, grip strength was 3.5 ± 1 kg, about 6 per cent of control, while vital capacity was reduced to 2.8 ± 0.1 l or about 52 per cent of baseline.

Limitation of respiratory muscle function by dTe was reflected in changes in respiratory pressures with maximum effort (fig. 4). The figure depicts a two-dimensional response with the ability of the respiratory muscle to generate effort (pressure) on the abscissa and the corresponding range of volumes (vital capacity) on the ordinate. Changes in respiratory pressures paralleled those found in other tests of muscle function, i.e., very little effect until dose 4 (0.12 mg/kg total), then marked impairment with the total dose, where values were approximately 35–40 per cent of control.

Discussion

The ventilatory response to a CO₂ stimulus expresses the ability of the respiratory sys-
tem to carry out its everyday role of CO₂ excretion while stressed by a CO₂ load. Although drug-induced changes are usually attributed to alterations in the sensitivity of the medullary chemoreceptors, they can also be modified by mechanical factors. These might include things that increase the work of breathing, such as increased airway resistance or anything that impairs the ability of the respiratory muscles to do work. It can be hypothesized, then, that respiratory muscle weakness resulting from partial curarization might decrease the ventilatory response to CO₂. The effect should arise purely from this peripheral mechanism, since Cohen’s data on dTc distribution⁵ and studies in awake subjects, which include Smith’s classic experiment,¹⁶ argue against any significant central action of dTc.

The present data again demonstrate that the muscles of the hand are more sensitive to the effects of dTc than are the muscles of respiration. Although this is in keeping with the concept of “respiratory sparing,” the extent of respiratory muscle impairment is hardly insignificant. Vital capacity decreased to about 50 per cent of control with the total dose of dTc, while maximum inspiratory and expiratory pressures were about 35-40 per cent of control. Although the latter pressures did not appear dramatically more sensitive than vital capacity in this group of healthy volunteers, they do provide better understanding of the altered respiratory function with muscle weakness, because unlike spirometric tests they are not affected by intrinsic pulmonary disease.¹⁷ Furthermore, they involve a work pattern that is essentially isometric, much like the test of grip strength. This affords a more uniform basis for comparing effects on the two muscle groups. Perhaps the greatest value in measurements of maximum inspiratory and expiratory pressures lies in the information these pressures provide about the work capability of the respiratory muscles, a function of their force and length. When translated to the thorax, force and length are represented by pressure and volume. If one then plots the maximum pressures against their corresponding lung volumes, as in figure 4, the maximum potential work available for breathing is given by the area enclosed within the resulting curves.¹²,¹³ The shaded area in figure 4 depicts the maximum work potential after partial curarization and serves to illustrate the impairment of respiratory muscle function in our subjects.

In the face of respiratory muscle weakness, how were the subjects able to maintain their stimulated levels of ventilation? The ventilatory volumes with controlled hypercapnia were more than three times the resting values for each subject. This level of stimulated breathing was considered adequate to magnify any drug-related change, although it did not approach the maximal levels attainable by the subjects, i.e., their
maximum breathing capacity. Figure 1 reveals how this level of ventilation was sustained during administration of dTc. With increasing paralysis there was a progressive reduction in tidal volumes accompanied by increasing respiratory frequency. This combination is advantageous in reducing the work required to overcome elastic resistance, which increases with the square of the tidal volume. Thus, the effort required by respiratory muscles to maintain a given alveolar ventilation decreases with increasing respiratory frequency and decreased tidal volumes. Increased increases in rate (more than 25/min) increase viscous or flow resistance, necessitating added work and limiting the effectiveness of the response. It is doubtful, however, that the latter factor played a major role in limiting our subjects' responses to the hypercapnic stimulus, since respiratory rates averaged 22/min with the total dTc dose. One might conclude, therefore, that partial curarization is associated with a normal ventilatory response to CO₂ to the point at which the advantage of increased respiratory frequency is offset by other factors. Beyond this point the response might be expected to "flatten out." Increasing the paralysis would probably reduce the stimulus level at which this occurs, while the slope up to that point remained similar to control. This does, however, require that upper airway obstruction be avoided. The latter was a problem with two of our subjects, and reflects the susceptibility of the neck and pharyngeal muscles to dTc. This may represent a more significant threat to respiration under clinical conditions than the weakness occurring in the principal respiratory muscles, the intercostals and diaphragm.

Our determinations of slope (V₅/Pco₂) showed no significant change after the total dose of dTc and tend to support the above-mentioned speculation about normal slope. Although the response curve was constructed from only two points, it provides reasonably valid information since the two points lie at elevated levels of Pbco₂. Therefore, they lie on the steeper linear portion of the response curve and avoid the lower "hockey stick" segment that results from including ventilation at resting levels of CO₂.

That our results failed to demonstrate either a significant decrease in ventilation or a change in slope of the curve of the ventilatory response to CO₂ does not imply that the partially curarized patient is free of respiratory depression, since the stimulus was not extreme. Although the respiratory muscle weakness was significant, it did not encroach upon the ability to generate appropriate ventilation in response to the hyper-

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**FIG. 4.** Maximum static respiratory pressures after administration of d-tubocurarine. Mean values from six subjects are plotted as a function of lung volume (V₅) in liters. TLC = total lung capacity; FRC = functional residual capacity; RV = residual volume. Shaded area indicates the maximum work capabilities of the respiratory muscles after curarization.
captive stimulus. Nevertheless, it would certainly interfere with deep breathing and in particular, coughing, as evidenced by the effects on maximum inspiratory and expiratory pressures. Furthermore, the pronounced weakening effect on neck and pharyngeal muscles poses a threat to upper airway integrity and handling of secretions, and provides further evidence for challenging the concept that d-tubocurarine has a truly "respiratory-sparing" action. Thus, while the weakness in the principal muscles of respiration, i.e., the intercostals and diaphragm, is less apparent than that in other muscle groups, and in this case was not sufficient to encroach upon the ventilation produced by a mild hyperventilatory stimulus, overall respiratory function is not truly spared.

References