Effects of Succinylcholine on Respiratory and Nonrespiratory Muscle Strength in Humans

John P. Williams, M.D.,* and Denis L. Bourke, M.D.†

Succinylcholine was administered to 10 healthy unanesthetized volunteers to assess its effect on respiratory and nonrespiratory muscle strength and the ventilatory response to CO₂. Isohypercapnia with P₄CO₂ 8–10 mmHg above control was maintained throughout the study, succinylcholine infusion rates were increased from 20 µg·kg⁻¹·min⁻¹ until grip strength (GS) was 20% of control. CO₂-stimulated ventilation was 16.1 ± 1.8 l/min (mean ± SD), approximately three times control, and remained at that level throughout the study because of nonsignificant decreases in tidal volume and increases in respiratory frequency. Respiratory strength, as measured by maximum inspiratory pressure (IP), maximum expiratory pressure (EP), and forced vital capacity (FVC), was spared relative to GS. When GS = 50% of control, IP = 86 ± 8% of control, EP = 78 ± 15%, and FVC = 86 ± 9%. Wide variation occurred from subject to subject in the succinylcholine versus GS dose–response curve position. However, in all subjects the slope of the dose–response curve was very steep. (Key words: Carbon dioxide: ventilatory response. Neuromuscular relaxants: succinylcholine. Ventilation: carbon dioxide response.)

ESPINOZA AND ARTUSIO¹ demonstrated in 1954 that 50–70 µg·kg⁻¹·min⁻¹ of succinylcholine produced complete respiratory arrest in anesthetized humans. Although they did not attempt to quantify the extent of peripheral muscular blockade, they concluded, “We doubt whether any muscle relaxant drug will spare respiration and simultaneously produce adequate muscular relaxation.” Nevertheless, in other studies, depolarizing and nondepolarizing relaxants did appear to demonstrate a respiratory sparing effect.²⁻⁷ However, technical problems such as the comparison of isotonic contraction of respiratory muscles (e.g., forced vital capacity) with isometric contraction of peripheral muscles and the lack of end-tidal CO₂ stimulus control precluded valid conclusions. In 1974, Gal and Smith⁸ reported the first unequivocal demonstration of respiratory sparing during administration of low-dose curare. They used isohypercapnic respiratory stimulation and compared inspiratory and expiratory pressures with isometric grip strength measurements. Since then, other nondepolarizing muscle relaxants have been shown to produce similar effects.⁹⁻¹¹ Possibly because of anticipated difficulties in producing and maintaining partial relaxation, similar studies of the depolarizing agents have not been reported.‡ For our study, therefore, we used succinylcholine to examine the effects of partial paralysis on respiratory and peripheral musculature, using techniques similar to those of Gal and Smith.

Methods

With institutional approval and informed consent, we studied 10 healthy men who ranged in age from 22 to 42 yr and in weight from 51 to 93 kg. The subjects fasted for a minimum of 8 h before their study session. At the beginning of each session, we made anthropomorphic measurements¹² and then placed a blood pressure cuff on the nondominant arm, applied ECG leads, and inserted an 18-gauge intravenous catheter in the nondominant hand. Subjects then breathed through a low-resistance nonbreathing circuit for a 15-min acclimatization period. The breathing circuit design permitted the addition of oxygen and CO₂ to inspired air and included a spirometer (Med Science wedge spirometer) and sampling sites for inspired CO₂ (PᵢCO₂) and end-tidal CO₂ (P₄CO₂). Sampled gas was delivered to an infrared CO₂ analyzer (Gould Godart capnograph) and returned to the circuit. CO₂ and spirometer data were recorded continuously on a two-channel recorder (Hewlett-Packard).¹³ The respiratory circuit was modified further to permit the measurement of inspiratory and expiratory pressures (Boehringer pressure gauges) using the method described by Black and Hyatt.¹⁴ To assess peripheral muscular strength, we measured grip strength (GS). Subjects held a dynamometer (Jamar isometric grip dynamometer) in their dominant hand with the wrist stabilized in a neutral position. After the acclimatization period, with subjects in the semirecumbent position, inspired CO₂ was increased to 4%. The end-tidal CO₂ observed after 10 min of 4% inspired CO₂ was maintained throughout the rest of the study by varying inspired CO₂. During the next several minutes, control measurements of respiratory and peripheral muscle strength were made in the following sequence, which was repeated throughout the study: GS, forced

* Instructor in Anesthesiology, The University of Texas Medical School.
† Associate Professor of Anesthesiology, Boston University Medical Center.

Received from the Departments of Anesthesiology of Boston University Medical School and the University of Texas Medical School at Houston. Accepted for publication April 29, 1985. Presented at Anesthetic Research Society Meeting, Sheffield, England, November 1982.

Address reprint requests to Dr. Bourke: Department of Anesthesiology, University Hospital, 75 E. Newton Street, Boston, Massachusetts 02118.

‡ Personal communication, Thomas Gal, M.D.
vital capacity (FVC), 15-s rest, inspiratory pressure at residual volume (IP), 15-s rest, maximum expiratory pressure at total lung capacity (EP), and final GS. After control measurements were completed, the succinylcholine infusion was begun with the use of a Critikon 2100® infusion pump. The initial dose of succinylcholine was 20 μg·kg⁻¹·min⁻¹. This and each subsequent dose rate was maintained for a 12-min period, after which the dose rate was increased by either 5 or 10 μg·kg⁻¹·min⁻¹, depending on the response to the previous infusion rate. Measurements according to the sequence described above were made beginning at 5 and 10 min (scheduled observations) during each succinylcholine infusion and when either the subject or the investigator perceived a significant change in either respiratory strength or GS (unscheduled observations). We continued to increase the succinylcholine infusion rate until either vital capacity was reduced by 50%, handgrip was reduced by 80%, or the subject desired to terminate the infusion. Once either end point was reached, the infusion was discontinued and measurements were recorded every 5 min until subjects had 90% recovery of GS. Throughout the study, subjects' subjective comments were recorded.

For each subject we converted raw values of GS, EP, IP, and FVC to per cent of control. We then performed a least-squares linear regression on ln (%GS) versus ln (%FVC), ln (%EP), and ln (%IP) individually for each subject. The results shown in figures 1–4 are the exponential form of the regression equations obtained. The mean curve and standard deviations were obtained by evaluating the individual regression equations at 1% grip strength increments from 20 to 100%. Results are reported as mean ± 1 SD. Except for control values, IP, EP, FVC, and GS are reported as per cent of control.

Our rationale for this analytic approach follows. Be-
cause of the wide variation in intersubject dose–response, no useful plot of response versus dose could be made. However, when the measures of respiratory strength were plotted against GS, all of the individual plots were remarkably similar, the main source of variability now being the absolute values. Converting absolute values to per cent of control greatly improved comparability among subjects. Because it was impossible to control responses precisely enough to obtain observations at specific, predetermined grip strengths, we attempted to fit curves to each subject’s data. Empirically, the ln-ln conversion produced an excellent fit, as evidenced by the correlation coefficients. These manipulations are intended to produce illuminating descriptive statistics, not inferential statistics.

Results

Control measurements were GS = 40.8 ± 9.5 kg, IP = −91 ± 21 cmH₂O, EP = 101 ± 17 cmH₂O, and FVC = 5.1 ± 0.7 l. Figures 1, 2, and 3 depict the entire range of responses in shaded areas and show the mean curve. Figure 4 shows the three mean curves plotted together for comparison. Because of the difficulty in controlling relaxation precisely, six subjects progressed beyond 80% reduction in GS. Observations under these conditions were made when possible. For the subjects who continued beyond 80% reduction of GS, GS was between 10 and 20% of control GS (GS = 14 ± 3%). Respiratory measurements for these subjects were IP = 65 ± 16%, EP = 63 ± 11%, and FVC = 71 ± 16%. In two subjects, additional observations were made at 5% of control GS, where IP = 72% and 56%; EP = 84% and 75%; and FVC = 50% and 80%.

After termination of the succinylcholine infusion, seven of the subjects recovered to 90% GS within 5 min and demonstrated no deficit in respiratory strength at that time. Two subjects made a similar recovery by the 10-min observation. One subject required 20 min to recover to 90% GS. In all cases the ratio of GS to respiratory strength during recovery was similar to that observed during the succinylcholine infusion.

Table 1 shows the estimated succinylcholine infusion rates for several representative grip strengths. We emphasize that these are estimated infusion rates, since approximately 25% of the observations were unscheduled and it is therefore unlikely that a steady state succinylcholine level existed. The total dose of succinylcholine administered was 161 ± 108 mg or 2.2 ± 1.6 mg/kg. The wide range in all dosage data was not improved by adjusting for lean body mass.

Control minute ventilation (VE) was 5.35 ± 0.73 l/min at PETCO₂ 38 ± 3 mmHg. While breathing 4% CO₂ before succinylcholine infusion, VE = 16.1 ± 1.8 l/min and PETCO₂ = 48 ± 1.6 mmHg. Neither VE nor PETCO₂ changed significantly in any subject throughout the remainder of the study period. Tidal volume showed a nonsignificant decrease and respiratory rate a nonsignificant increase with increasing paralysis.

Subjects’ blood pressure and ECG remained normal throughout the study sessions. Subjects did not report difficulty with secretions. In only one instance did respiratory difficulty occur. In one subject soft tissue upper airway obstruction developed when his GS was 28% of control. The obstruction was immediately relieved when the mandible was elevated slightly, at which time respiratory strength measurements were: IP = 63%, EP = 46%, and FVC = 65%.

Throughout most of the study, subjects expressed no anxiety; most, in fact, were amused by the loss of peripheral muscle strength. Three subjects, however, terminated their sessions at GS between 30% and 25% of control because of rapidly progressing paralysis and fear of total paralysis. The final measurements on these

<table>
<thead>
<tr>
<th>Grip Strength (per cent of control)</th>
<th>Number of Observations</th>
<th>Estimated Dose (μg·kg⁻¹·min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>80 ± 3</td>
<td>10</td>
<td>29 ± 7</td>
</tr>
<tr>
<td>50 ± 4</td>
<td>10</td>
<td>37 ± 9</td>
</tr>
<tr>
<td>14 ± 3</td>
<td>6</td>
<td>42 ± 5</td>
</tr>
<tr>
<td>5/5*</td>
<td>2</td>
<td>45/50*</td>
</tr>
</tbody>
</table>

* N = 2, both values given.
three subjects were between 30% and 20% of control grip strength. Within 5 min of beginning the initial infusion rate of 20 μg·kg⁻¹·min⁻¹ of succinylcholine and before any decrement in GS could be detected, all subjects reported a sense of pressure in their eyes and visual difficulties. These visual problems were resolved in all instances when the subject closed one eye. Once GS was approximately 70% of control, and thereafter, all but two subjects reported a sense of weakness and a feeling of twitching over the anterolateral, lateral, mid, and lower thirds of the rib cage bilaterally. No other remarkable subjective information was elicited.

Discussion

Our study provides data that can be compared with studies of nondepolarizing relaxants. Grip strength, an isometric measurement, measures force as opposed to work and is more directly comparable to the isometric measurements of inspiratory force and expiratory force. Wrist position affects grip strength. The issue of subject effort (i.e., subject motivation) cannot be excluded as a source of error. However, the following mitigate against effort as a major source of error in our study: 1) the agreement in grip strength results just before and after respiratory measurements; and 2) the intersubject similarity, especially since four of the subjects were not pharmacologically knowledgeable while the rest were anesthetists.

Our results with the depolarizing muscle relaxant succinylcholine appear to demonstrate a respiratory sparing effect similar to that demonstrated for curare. Low doses of either drug that cause peripheral strength to decrease to 40–50% of control causes only minor decreases in respiratory strength as measured by IP, EP, and FVC. We were unable to determine accurate dose–response data for several reasons. First, we observed considerable intersubject variation in dose response, as previously reported. Second, once peripheral strength was reduced below 70% of control, small changes in infusion rates frequently caused large changes in relaxation, precluding accurate steady state dose determinations. During these instances, unscheduled measurements often were made; however, the fact that the difference between initial and final GS was always less than 10% during unscheduled observations suggests that the respiratory measurements and the mean of the two GS measurements can be reasonably considered simultaneous observations. For the reasons stated previously, we were unable to plot GS and respiratory values as a function of dose and, therefore, our results are presented as per cent of control respiratory strength measurement versus per cent of control handgrip strength.

Our study further suggests that there is little clinical application of succinylcholine's respiratory sparing effect. A number of factors determine the rate at which succinylcholine is metabolized; however, once the infusion rate exceeds metabolism, complete paralysis rapidly ensues. The dose range not only varies widely from subject to subject but also is very narrow for an individual subject. The mechanism that allows differential effects on respiratory strength and peripheral strength by low doses of both succinylcholine and nondepolarizing muscle relaxants has not been explained. However, our results indicate that the mechanism is not a property solely of nondepolarizing muscle relaxants. The appealing explanation invoking the unique geometry of the diaphragm appears not to be the case, since the length–tension relationship seems to be more important than curvature in determining the effectiveness of this muscle as a pressure generator, nor does the known differential effect of depolarizing and nondepolarizing muscle relaxants upon red and white musculature seem important. The ability of the diaphragm to sustain activity against a resistive force for an indefinite period of time seems to be identical to other intermittently contracting muscles. Further, the histocomposition of all of these muscles seems to contain equivalent amounts of the slow-twitch high oxidative (red) types of fibers.

In a study using anesthetized rats with peripheral musculature 4°C cooler than diaphragm, decamethonium produced differential blockade qualitatively similar to our results but of considerably less magnitude. It is unlikely that in our awake subjects a similarly large temperature difference could have occurred. Although blood flow can affect the onset and initial degree of blockade, the effects are less pronounced during continuous infusion and the relatively greater blood flow to the diaphragm would have produced results opposite from ours.

Since none of the causes described above adequately explain the differential block, we are left with the speculation that there are relatively more acetylcholine receptors available at postjunctional diaphragmatic fibers.

These are only a few of the numerous mechanisms that have been invoked to explain the differential effects of nondepolarizing muscle relaxants on respiratory and nonrespiratory muscle groups. Our results indicate that these mechanisms also must take into account the depolarizing muscle relaxants. Within this context the most obvious similarity between these two drug classes is the “phase II” effect of depolarizing relaxants. We did not assess any comparative signs of neuromuscular blockade (i.e., train-of-four or tetanic responses); thus it is difficult for us to make an objective statement about presence or absence of “phase II” blockade. However,
the most profound disparities between respiratory and nonrespiratory strength occurred early during each trial at times short enough and doses low enough to preclude any possibility of "phase II" blockade. The development of "phase II" blockade depends on the following: time or duration of exposure (>42 min), total dose (>2.3 mg·kg\(^{-1}\)), anesthetic technique, and route of administration.\(^{18}\) Only four of our subjects met even both of the first two criteria by the end of their study session, and only one had a recovery period longer than 15 min. A "phase II" blockade would have resulted in a considerably longer recovery period. Therefore, it is difficult to ascribe many of our observations to a "phase II" block. The presence of a pure depolarizing blockade also makes untenable the supposition of excess acetylcholine release being present in the diaphragm, since this would only contribute to the degree of depolarization and provide results contrary to ours. Further, regardless of the issue of "phase II" block, from the phenomenologic viewpoint, our subjects clearly demonstrate differential blockade qualitatively similar to that of the nondepolarizing relaxants at doses far below those that cause "phase II" blockade. The differential block progressed continuously as succinylcholine dose increased, thus producing a qualitatively similar differential block even if "phase II" block ensued at the higher doses.

Our results are not to be interpreted as encouraging the use of succinylcholine infusions to provide surgical relaxation during spontaneous ventilation. Intersubject dose responses vary widely and, once respiratory weakness begins, the dose–response curve becomes very steep. There is very little room for error. Maintenance of diaphragmatic strength does not ensure airway patency (see "Results"), the ability to handle secretions, or laryngeal competency, all of which can be intrinsic to the safe conduct of general anesthesia.

The authors acknowledge the valuable contribution of Robert G. Merin, M.D., in serving as a Judas goat. Without him they could not have completed this study.

References

2. Paton WDM, Zaimis EJ: The action of d-tubocurarine and decamethonium on respiratory and other muscles in the cat. J Physiol (Lond) 112:311–331, 1951