Neostigmine as a Curare Antagonist A Clinical Study

D. A. Wescott, M.D., and H. H. Bendixen, M.D.

PRESENT methods of evaluating the reversal of curare* effect are mainly based on clinical judgment. In this study a quantitative measurement is used in an attempt to obtain more objective criteria for recovery of respiratory function following the use of muscle relaxants, and in particular for the clinical use of neostigmine methyl sulfate in anesthesia.

Background

In the early reports on the clinical use of curare, neostigmine reversal is hardly mentioned. Bennett[1] was the first to report, in 1940, the use of curare (Intocostrin) in preventing excessive muscle spasms in Metrazol shock therapy, but his report did not mention neostigmine. In 1941, Gray[2] reported on 50 cases, where Intocostrin had been used for the same purpose; three of these cases required artificial ventilation and the administration of neostigmine to counteract excessive respiratory depression. Griffith[3] in 1942 reported the first use of curare (Intocostrin) in clinical anesthesia; 25 cases received Intocostrin as a supplement to cyclopropane anesthesia, but apparently not assisted ventilation or neostigmine. It was recommended, however, that neostigmine be always on hand. In 1945 Gray[4] reported on the clinical use of curare in one thousand cases. The need for supported ventilation was strongly emphasized, but the use of physostigmine in three cases was described as unimpressive. In 1946 Prescott[5] stated that neostigmine is rarely necessary but if it is used the dose should be 5 mg., preceded by atropine sulfate 1.3 mg. This advice was based on a study in a conscious subject, using the vital capacity as a quantitative index of curare reversal.

As the use of neostigmine gained in popularity, reports began to appear of deaths following its use in reversing muscle relaxant effects (table 1); this set up lively discussions as to the likely cause of death. It appears from these reports[6,11] that it had become common practice to administer neostigmine and atropine simultaneously, often in the same syringe, by the intravenous route in doses of neostigmine 2.5 mg. and atropine 0.6 mg. The clinical picture was circulatory collapse or cardiac arrest and one explanation was offered by Bain,[12] who stated that the initial effect of atropine on the cardiac rate may be slowing; and that the full muscarinic blocking effects are not produced for several minutes. This is also mentioned by Goodman and Gilman.[13] Morton[14] questioned this and concluded from his study that only after small doses and slow injection will the *intravenous* administration of atropine cause initial bradycardia. Hunter[15] showed that cardiac slowing always follows the administration of neostigmine, regardless of timing of atropine injection, and he emphasized that the cardiac rate must be observed very carefully throughout reversal of curare effect, and for ten minutes after the last dose of neostigmine. In the report by a committee on anesthetic deaths, Edwards, Morton, Pask and Wylie[10] recommend that neostigmine be given in divided doses and not until a tachycardia has been produced by a relatively large dose of atropine. This technique has continued to be considered safe standard practice. Churchill-Davidson[16] emphasizes that adequate ventilation during reversal must be maintained; he considers it not justified to stop ventilation prior to the administration of neostigmine in

* The word "curare" is used throughout as a common denominator for drugs blocking neuromuscular transmission by prevention of depolarization.

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TABLE 1. Deaths Associated with Reversal of Curare by Neostigmine

Author	Number of Cases	Anesthesia Technique	Administration of Drugs	Author's Comments
MacIntosh[6]	1	Cyclopropane, curare, assisted ventilation	Atropine 0.6 mg., neostigmine 2.5 mg. *simultaneously*	General condition of patient: poor.
Clutton-Brock[7]	1	Kemithal, nitrous oxide-curare, assisted ventilation. Cyclopropane at end of procedure	Atropine 0.6 mg., neostigmine 2.0 mg. *simultaneously*	Patient deeply jaundiced; serious pulse irregularities.
Hill[8]	1	Open drop ether, curare 0.9 mg. ? spontaneous ventilation	Atropine 0.22 mg., neostigmine 0.25 mg. *simultaneously*	Patient's weight 2.9 kg. was jaundiced.
Lawson[9]	1	Nupercaine spinal, thiopental, meperidine, gallamine. ? spontaneous ventilation	Atropine 0.6 mg., neostigmine 2.5 mg. *simultaneously*	
Edwards[10]	5	Two cases had cyclopropane anesthesia	4 cases: atropine 0.6 mg. with or before neostigmine 2.5 mg. 1 case: 1.2 mg. atropine + 5 mg. neostigmine *simultaneously*	Might have been prevented by proper technique of administration.
Gray[11]	4	(1) N_2O, meperidine (2) N_2O, chlorpromazine (3) N_2O, meperidine (4) N_2O, trichlorethylene All with gallamine or curare	2 cases: atropine 0.6 mg., neostigmine 2.5 mg. *simultaneously* 2 cases: atropine 0.6 mg. 2 minutes before neostigmine 2.5 mg.	Too little atropine. Too much neostigmine in one dose.

order to allow carbon dioxide accumulation.

The attitudes of anesthetists to the use of neostigmine for reversal of curare-effect have largely evolved along two pathways: One group uses curare in relatively large doses, producing apnea requiring controlled ventilation, in association with light general anesthesia. This group tends toward the routine use of neostigmine as described above. The other group uses curare more rarely and generally in small doses as a supplement to deep or relatively deep general anesthesia. They, and the considerable number of anesthetists who do not use curare, find few indications for neostigmine and may even call its use an error in both technique and judgment.

Assessments of what constitutes normal ventilation following curarization have been relatively few. Artusio[17] used the minute ventilation as an index of recovery; and the use of grip strength as an index in the conscious was suggested by Macfarlane.[18] Cohen[19] measured minute ventilation and vital capacity in conscious subjects after a large dose of curare. He showed how the vital capacity takes considerably longer to return to normal than minute ventilation. This emphasized that restoration of adequate minute ventilation does not indicate full restoration of respiratory function. In a recent review Dam[20] recommends the "head-lift" test as a reliable index of recovery from curare effect. This of course is useful only in the awake and cooperative patient.

Previous concern has mostly been with restoring adequate minute ventilation. It seems necessary, however, to formulate the concept that adequate minute ventilation is not enough; a reserve of ventilatory effort is also needed. This reserve makes it possible to cough more effectively and to take the intermittent deep breaths, which Mead[21] and Ferris[22] have shown to be necessary for periodic reinflation of atelectatic pulmonary alveoli and for maintenance of normal pulmonary compliance. When the need for a reserve of ventilatory effort is considered in relation to the often prolonged effect of muscle relaxants, it would seem necessary to consider also a more frequent use of neostigmine in restoring such reserve. The only alternative would be for the anesthetist to support the ventilation in the postoperative period until he is satisfied that not only adequate alveolar ventilation, but also reserve of ventilatory effort is present.

Method and Procedure

The present study attempts the clinical use of inspiratory force measurements as a quantitative index, in the unconscious patient, of the reversal of curarization by neostigmine. The inspiratory force is defined[23] as the maximum negative pressure which is exerted

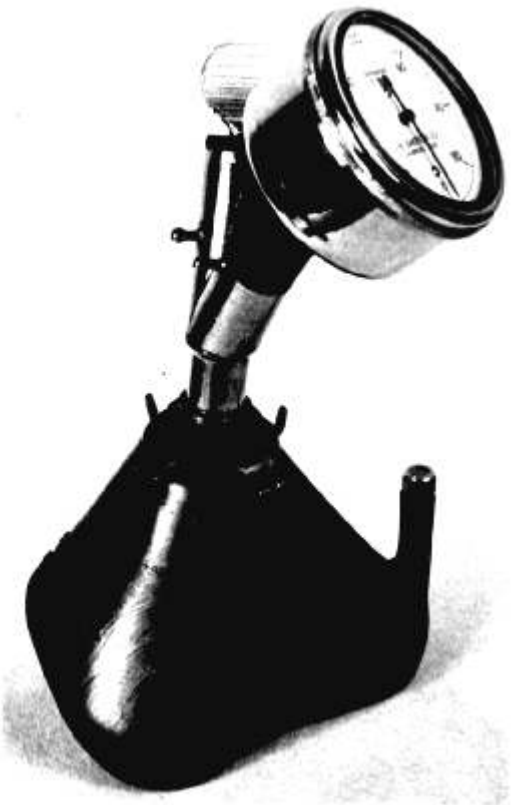

FIG. 1. The equipment needed for routine inspiratory force measurement: a face mask connected with a pressure gauge registering negative pressure. A stopper is used to make occlusion of the airway more abrupt; but it is strictly speaking not necessary.

against the completely occluded airway. In the first part of the study the emphasis was on determining the safety of this measurement in the clinical situation.

Thirty-five patients have been studied, all adults in good general health undergoing abdominal operations. Premedication was with pentobarbital and atropine sulfate, and induction of anesthesia with thiopental. Endotracheal intubation was facilitated by succinylcholine chloride. Maintenance of anesthesia was with nitrous-oxide and oxygen 2:1 in a semiclosed system and *d*-tubocurarine in doses large enough to produce profound relaxation and apnea throughout the operation. The use of opiates, as premedication or for supplementation of anesthesia was not permitted. The doses of succinylcholine (used for intubation only) ranged from 40 to 80 mg., thiopental from 125 to 1,200 mg. and *d*-tubocurarine from 18 to 74 mg. The length of anesthesia varied from one hour and 30 minutes to five hours. Ventilation was controlled by hand throughout. A radial artery was cannulated with a Cournand needle (no. 18) for collection of blood samples and for continuous monitoring of arterial blood pressure. The inspiratory efforts were measured during thirty seconds of airway occlusion as negative pressure changes in the endotracheal tube or under a well fitting mask.* Figure 1 shows the equipment needed for measurement of inspiratory force; in these studies the pressure gauge was removed and a pressure transducer used to allow a continuous recording. Electrocardiogram (usually lead 2) was monitored continuously, and in a few cases also a frontooccipital lead of electroencephalogram.

At the end of the surgical procedure, atropine 1 mg. was given intravenously, and when a rise in pulse rate had been observed, an inspiratory force measurement was carried out. Neostigmine 1 mg. was then given intravenously and the inspiratory force measurement repeated two minutes and again five minutes later. The administration of 1 mg. doses of neostigmine (followed by inspiratory force measurements two and five minutes later) was continued until there was no further improvement in inspiratory force or until the patient woke up. Additional atropine was given when the pulse rate fell appreciably or below 60. Assisted ventilation was continued until spontaneous respiration was judged to be adequate; and all patients received nitrous-oxide and oxygen 2:1 throughout the reversal. In some of the early cases the assisted ventilation was stopped one minute before the inspiratory force measurement in order to assure carbon dioxide accumulation for sufficient respiratory drive. This practice was abandoned.

In the first part of the study arterial blood was collected immediately before and at the

* In dogs, it was found [24] of importance that the occlusion of the airway occur at end expiration, since the lung volume at time of occlusion would influence the frequency of the inspiratory effort. This influence was eliminated by bilateral cervical vagotomy. A similar reflex influence has not been found active in humans.

end of the thirty second airway occlusion. This allowed determination of the changes occurring in arterial *p*H, oxygen saturation, concentration of carbon dioxide and tension of carbon dioxide. In the second part of the study arterial samples were collected at 60-second intervals whenever the ventilation had been adequate for two or more minutes by the judgment of two anesthetists. It was assumed that changes in arterial *p*H would reflect gross changes in ventilation, supporting or disproving the clinical judgment.

Pressure measurements were by Sanborn pressure transducers (model 267B) and amplification and recording by a four-channel Sanborn Polyviso, model 150. Oxygen satura-

TABLE 2. Arterial Blood Gas Changes During 30-Second Airway Occlusion

Case	SaO_2		*p*H		$Paco_2$		$Caco_2$	
	Before	At 30 Seconds	Before	At 30 Seconds	Before	At 30 Seconds	Before	At 30 Seconds
8	100	96	7.38	7.32	37	45	28.8	24.6
	97	96	7.38	7.28	37	50	22.5	24.9
	98	- -	7.32	- -	44	- -	23.7	-
	97	97	7.32	7.29	42.5	48.5	22.6	24.2
	99	- -	7.29	- -	47	- -	23.9	-
9	97	72	7.32	7.27	44	53	23.6	25.6
	94	88	7.31	7.25	46	52	24.3	24.0
	99	86	7.31	7.27	47	51	24.7	24.8
10	99	53	7.38	7.31	43	55	26.1	29.2
	98	77	7.34	7.29	47.5	58	26.1	29.2
	100	- -	7.29	- -	56	- -	27.7	-
	96	- -	7.37	- -	44	- -	25.8	-
11	- -	- -	7.40	7.36	40.8	47	26.2	27.7
	- -	- -	7.39	7.37	42.3	45	26.7	27.2
	- -	- -	7.41	7.38	40	44	26.2	27.8
12	100	100	7.38	7.32	38	46	23.6	24.6
	100	100	7.38	7.32	38	46	23.2	24.9
13	97	76	7.50	7.49	23.5	30.5	20.9	23.9
	98	58	7.54	7.46	23.7	33	20.5	24.0
	95	80	7.42	7.39	33.8	38	22.6	24.6
14	98	87	7.40	7.33	31.5	41.5	20.2	23.0
	97	93	7.40	7.33	32.5	41	20.9	22.7
	98	95	7.39	7.32	34	41.5	21.1	22.2
	98	96	7.37	7.33	35	40	20.9	21.8
15	78	71	7.50	7.50	34	35	27.4	27.7
	78	68	7.47	7.47	36	37	27.2	28.0
	97	89	7.42	7.42	41	42	27.8	28.1
16	85	- -	7.35	- -	43	- -	24.9	- -
	87	81	7.39	7.36	39	44	24.4	25.4
	76	70	7.34	7.32	46	50	26.0	26.7
17	95	87	7.55	7.34	25	43	22.2	24.2
	95	87	7.52	7.46	25.5	32	24.3	23.4
	95	90	7.41	7.39	34.5	36	22.9	22.6
	90	89	7.49	7.40	31	41	24.2	26.4
	90	84	7.50	7.41	31	40	25.0	26.2
	82	73	7.40	7.37	40	43	25.7	26.2
Mean* change	−10.7%		−0.05 *p*H units		+6.8 mm. Hg		+1.90 mEq./l.	

Samples for measurements of arterial *p*H, oxygen saturation and concentrations of carbon dioxide were drawn before and after 30 seconds of airway occlusion. All patients had been breathing nitrous oxide-oxygen 2:1. Some patients were "allowed to accumulate carbon dioxide" immediately before the measurement.

* The mean was calculated as the mean of the means for each patient.

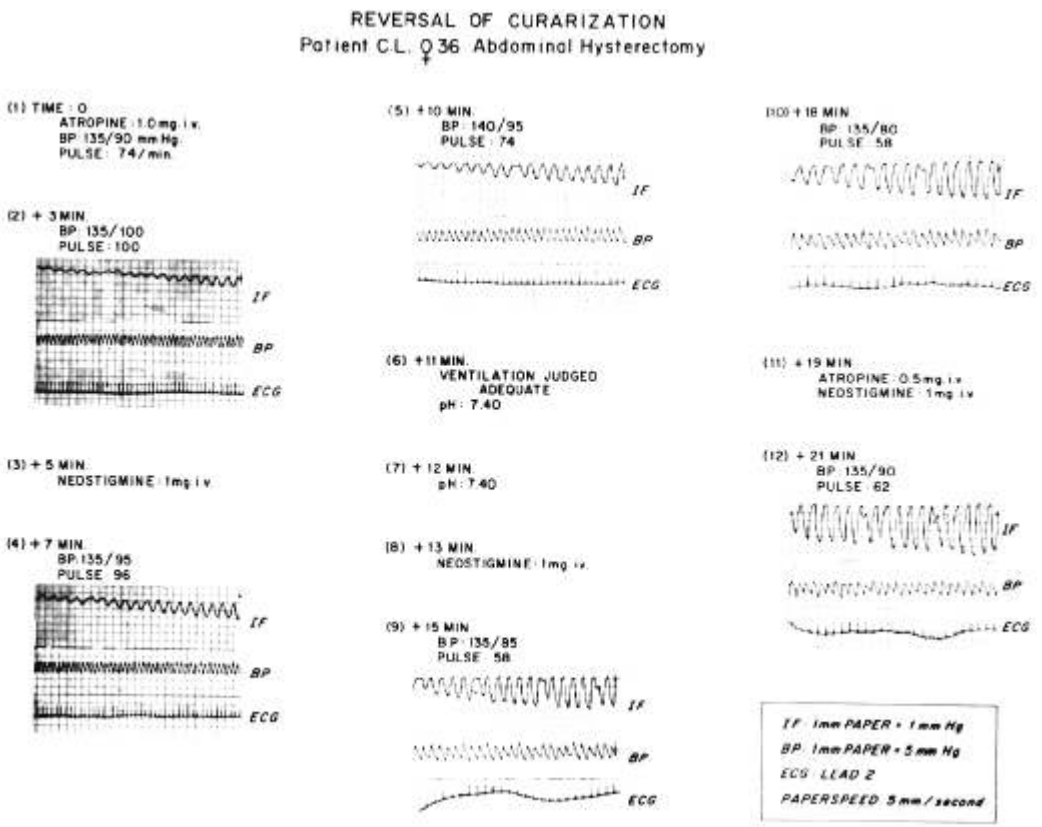

FIG. 2. Continuous tracings of inspiratory force, arterial blood pressure and electrocardiogram during reversal with neostigmine.

tions were determined by a Beckman spectrophotometer, the measurements of concentration of carbon dioxide were by the method of Van Slyke and *p*H was measured by a Beckman glass electrode used with a Sanborn *p*H amplifier and meter. The tension of carbon dioxide was derived from the Singer-Hastings nomogram.

Results

The changes in arterial blood gases during the thirty second period of airway obstruction were measured in eleven cases (table 2). Oxygen saturation fell to undesirable levels in some cases; these included the cases in which assisted ventilation was discontinued for sixty seconds immediately before the inspiratory force measurement, to allow carbon dioxide to "build up."

Arterial blood pressure and electrocardiogram were monitored in all 35 patients. There were no changes in blood pressure, except minor breath to breath variations of the type produced by mechanical or manually controlled ventilation (fig. 2). This was well defined only at an inspiratory force exceeding 20 mm. of mercury. There were no changes in pulse rate; in six patients, two of whom had arrhythmias before the reversal started, irregular rhythms were observed on the electrocardiogram during or immediately following the inspiratory force measurement. These were always ventricular ectopic beats (table 3) and gave no cause for concern. At no time was any irregular rhythm seen during or after inspiratory force measurements made prior to neostigmine administration.

The standard dose of atropine 1 mg. always produced an increase in pulse rate (table 4). Only six of 35 patients received extra atropine during neostigmine administration, and three of these were receiving unusually high doses of neostigmine. No electrocardiographic or blood pressure changes were thought to result

from atropine; two patients had arrhythmia before atropine (one auricular fibrillation and the other multiple premature auricular contractions). Neither of these irregularities were changed by atropine.

Neostigmine administration was not accompanied by adverse side effects. In a total of 84 single administrations of 1 mg., no change in blood pressure was seen. In one case, two simple ventricular extrasystoles were seen after the first dose, but no irregularities followed subsequent doses in the same patient. There was progressive slowing of the pulse rate with each dose (table 4). The pulse rate was never allowed to fall below 60 per minute without extra atropine being given; and the pulse rate always responded to further atropine. Neither bronchospasm nor excessive salivation was noted at any time. Table 4 shows the doses of atropine and neostigmine.

In all 35 patients the progressive reversal of curare was followed with inspiratory force measurements. The reversal was continued in each case until either no further increase in inspiratory force could be obtained (eight cases) or, more usually, until the patient woke up (27 cases), which ever happened first. The average initial inspiratory force was 2.5 mm. of mercury, and the average final inspiratory force was 21.2 mm. of mercury.

In thirteen patients we attempted to demonstrate that after minute ventilation has been restored to normal, by clinical judgment, a further increase in inspiratory force could be obtained. The results are shown in table 5; it is apparent that clinical judgment, or any assessment of minute ventilation, is not equivalent with complete reversal of curare effect. The evaluation of an individual case is apparent from figure 2, which shows the sequence of events in a typical patient.

Three cases in this series received totals of 4, 5 and 7 mg. of neostigmine, respectively, because an adequate inspiratory force could not be obtained with smaller doses and because by clinical judgment they appeared to be inadequately reversed. The patient who received 4 mg. (22) had a final inspiratory force of 8 mm. of mercury but this was probably a false low reading owing to a leak. In the other two cases, both apparently healthy females, though rather listless, the reason for the failure to measure a satisfactory inspiratory force was not clear although a leak could have occurred. They were both observed closely in the postoperative period, and their recovery was entirely normal. Consciousness was recovered immediately when 100 per cent oxygen instead of 2:1 nitrous oxide and oxygen was given. The further course was uneventful.

TABLE 3. ECG Changes* Associated with Inspiratory Force Measurement in Six Patients

	Preexisting Irregularity	Number of Times	Total Number Irregular Beats
1	Premature auricular beats	3	7
2	None	2	3
3	Auricular fibrillation	1	1
4	None	2	9
5	None	2	3
6	None	1	1

* All were ventricular ectopic beats.

TABLE 4.

Dose of Atropine and Neostigmine
35 Patients

	Atropine (mg.)	Neostigmine (mg.)
Average	1.4	2.7
Highest	2.5	7.0
Lowest	1.0	1.0

If 3 atypical cases are left out:
Doses of Atropine and Neostigmine
32 Patients

	Atropine (mg.)	Neostigmine (mg.)
Average	1.3	2.4
Highest	2.0	3.0
Lowest	1.0	1.0

Pulse Rate Changes

	Before Atropine	After Atropine	After Reversal
Average	83	110	79
Highest	120	150	100
Lowest	56	72	50

TABLE 5. Further Improvement in Inspiratory Force after Apparent Restoration of Normal Ventilation

Case	IF after Atropine: before Neostigmine	IF when Ventilation Apparently Normal	pH Measurements 60 Seconds Apart at Time when Ventilation Apparently Normal	Dosage of Neostigmine at this Time	Final IF Measurement	Total Dose of Neostigmine	Further Increase (%)	Comments
19	0	11	7.47 7.47	1	13	3	+18	
20	2	9	7.34 7.35	1	18	2	+100	
21	6	15	7.49 7.49	1	24	3	+60	
22	6	20	7.40 7.40	1	34	2	+70	
23	2	8	7.41 7.41	1	10	2	+25	
24	0	4	7.31 7.32	3	10	3		Leak suspected. Patient woke up before more neostigmine could be given.
25	11	15	7.40 7.40	1	27	3	+80	
26	6	15	7.33 7.35	1	28	2	+87	
27	0	10	7.33 7.33	3	15	3		Patient woke up before more neostigmine could be given.
28	0	6	7.41 7.41	2	8	3	+33	Leak suspected.
30	0	20	7.37 7.38	2	32	3	+60	
31	0	8	7.51 7.41	2	18	3	+125	pH change would suggest that ventilation was *not* normal.
32	2	15	7.34 7.33	2	25	3	+66	

Excluding cases 24, 27, 31 the mean further increase was 59.9 per cent.

Discussion

Appreciable oxygen desaturation was found to occur during thirty seconds of airway occlusion in patients breathing nitrous oxide and oxygen 2:1 (semiclosed system). This was particularly true if apnea had been allowed prior to the measurement in order to provide sufficient carbon dioxide tension for the respiratory drive. From oxygen saturation measurements in dogs breathing 100 per cent oxygen prior to the inspiratory force measurement,[24] and from the studies by Weitzner,[25] it appears safe to assume that the airway can be occluded with impunity for thirty seconds, provided the patient has been well ventilated with 100 per cent oxygen for two to three minutes prior to the airway occlusion. The carbon dioxide accumulation during the airway occlusion was of the same order of magnitude as the values found by others[26]; the individual variation was considerable, but it must be remembered that the ventilatory status just before the airway occlusion ranged from hyperventilation to apnea. The rise in carbon dioxide tension is thought to be of no significance as long as the tension is in the normal range before occlusion, and as long as no significant oxygen desaturation occurs.

The only technical disadvantage encountered with the inspiratory force measurement has been errors owing to leaks around the mask or endotracheal tube. An absolutely leakproof system is hard to obtain, but the anesthetist should rarely have difficulty in getting meaningful readings. These leaks will cause the inspiratory force measurements to be too low, but an error in this direction will give the patient the benefit of doubt and make the anesthetist pay extra attention to the ventilatory status of the patient. In routine use the only equipment required for the inspiratory measurement is a face mask attached to a pressure gauge registering negative pressure (fig. 1).

The particular clinical value of the inspiratory force measurement is to make possible quantitative monitoring of the return of respiratory muscle function in the unconscious or uncooperative patient. In its ability to reflect the reserve of ventilatory effort, it serves as a parallel to the vital capacity measurement in the conscious patient. It should

be made clear that neither the inspiratory force, nor the vital capacity measurement, is more than an index of one part of ventilatory performance: force (pressure) and volume respectively. They are both useful primarily when elastic and nonelastic resistance is in the normal range. It is unfortunate that a normal value for inspiratory force cannot be given; but the inspiratory force in the conscious and cooperative individual considerably exceeds (three to five times) the readings obtained in the unconscious or anesthetized, where the main drive for the inspiratory force is provided primarily by the gradual accumulation of carbon dioxide[24] during airway occlusion. Based on clinical observations, supplemented by this study, we expect that normal ventilation (defined *not* in terms of minute ventilation, but as the ventilation necessary to *maintain* a normal tension of carbon dioxide in arterial blood) may be present with the inspiratory force ranging from 6 to 12 mm. of mercury. With a reading of 15 mm. of mercury (20 cm. of water) a sufficient reserve of ventilatory effort is usually present and the patient may return to the recovery room. An exception is the patient with increased resistance to breathing (as in pulmonary emphysema); in such a patient a specific inspiratory force has no more meaning than a simple vital capacity measurement, and a considerable period of observation and assisted ventilation may be required. It should be emphasized that the inspiratory force measurement is not specific for muscle relaxants.[24] A decreased inspiratory force may also be caused by anesthetics and opiates. The inspiratory force measurement must be used only as a supplement to clinical judgment and be considered with all available pertinent information.

The results of this study do not appear to contraindicate the relatively extensive use of neostigmine as a curare antagonist, provided the outlined procedure is followed carefully; on the contrary, it has been possible to bring about considerable further reversal of curare effect by continued administration of neostigmine after adequate minute ventilation has been restored. We hesitate to recommend the routine use of reversal of curare effect by neostigmine, since it is possible that the patient would do as well or better if the anesthetist provided respiratory assistance for a prolonged time. If the choice is to be between returning the patient to the recovery room with adequate minute ventilation, but without adequate ventilatory reserve, or to use neostigmine for complete reversal then we do not hesitate to recommend the use of neostigmine in the patients' interest. The choice of neostigmine 1 mg. as the standard single dose in this study represented a compromise between a reasonably effective dose and our desire to study the effect of divided doses. It also represents a dose suitable as a single installment in the great majority of cases; under special circumstances the dose may have to be modified. In this study there have been no disturbing side effects of neostigmine, and no case deserving the label "neostigmine resistant curarization." The three cases, previously described, in which inspiratory force did not readily increase with increasing doses of neostigmine, are in no way so clear-cut as to allow them to be so labeled. No instance of so-called "recurarization" was seen, and the authors hesitate to employ this rather nebulous term. It seems more than likely that cases called "recurarization" had never been reversed in the first place, and these patients were either exhibiting the symptoms of carbon dioxide retention or were suffering from a steadily decreasing compliance, due to inability to re-expand collapsed alveoli, thus making hypoventilation the ultimate outcome.

It might be added that edrophonium (Tensilon) should not be considered a therapeutic drug in the reversal of curare effect, on the basis of its short action. For the very same reason it is a good diagnostic drug, in myasthenia gravis as well as in cases in which respiratory depression following muscle relaxants could be due to either a block by competition or a block by persistent depolarization.

No side effects of atropine were seen in this series. This is in agreement with a recent study by Jones and co-workers[27] who found no side effects when atropine was given during thiopental-nitrous oxide anesthesia. When given during cyclopropane or halothane anesthesia cardiac irregularities occurred frequently enough to advocate great caution in the use of both atropine and neostigmine whenever curare is used with cyclopropane or halothane.

Conclusions and Summary

It is not fully appreciated that to restore only the patient's minute ventilation at the end of the operation is not enough. A reserve of ventilatory effort must be provided to enable the patient to cough effectively and to take intermittent deep breaths.

In the conscious and cooperative patient the ability to raise the head, the grip-strength of the hand, the ability to take a deep breath and the vital capacity measurement may indicate the presence of a reserve of ventilatory effort. In the unconscious patient all tests requiring cooperation are useless, but the inspiratory force measurement has been found of value.

The effects and side effects of neostigmine have been studied in 35 healthy patients. When preceded by atropine and given in intermittent doses, neostigmine has been effective in restoring minute ventilation and also a reserve of ventilatory effort. No side effects have been encountered which contraindicate its use in the healthy patient.

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