Effects of Nitrous Oxide–Curare, Ether and Cyclopropane on Postoperative Respiratory Adequacy

*Azmy R. Boutros, M.D.**

Postoperative ventilatory status was studied in three groups of patients totaling 79: the first group anesthetized with N_2O and large doses of *d*-tubocurare followed by complete reversal with neostigmine, a second with N_2O-ether and a third with cyclopropane. Changes in arterial blood gases and inspiratory force were the criteria used.

Significant differences among the groups occurred only in the first hour postoperatively: (1) CO_2 retention in cyclopropane group compared to other groups and (2) less acidosis and higher inspiratory force measurements in female patients receiving curare, when a nerve muscle stimulator was used to define complete reversal of curarization.

POSTOPERATIVE ventilatory insufficiency, ranging from hypoventilation to apnea, has been a major argument against widespread use of large doses of muscle relaxants in anesthesia. Case reports of postoperative pulmonary complications,[1] prolonged apnea and irreversible curarization [2, 3, 4] and recurarization [5, 6] tended to strengthen the indictment against muscle relaxants.

Bendixen *et al.*,[7] comparing thiopental, N_2O, and succinylcholine with N_2O-ether, reported a suggestive difference in inspiratory force between cases with and without muscle relaxants, in favor of nonrelaxant techniques. Bunker *et al.*[8] concluded that the use of light general anesthesia with succinylcholine appeared to involve an increased incidence of atelectasis in the postoperative period.

On the other hand, anesthetic techniques utilizing large doses of muscle relaxants (particularly nondepolarizing drugs) are popular in Britain and Scandinavia. Favorable reports from these countries on the use of such techniques promote controversy concerning this approach and leave a certain sense of confusion.

There are marked differences between various techniques employing large doses of relaxants. Use of N_2O as the primary agent for maintaining anesthesia rather than use of cyclopropane or thiopental, and routine reversal of curarization with neostigmine as opposed to the reluctance to use neostigmine, are important variables.

Recent studies [9] have indicated that arterial blood gas analysis affords a more sensitive criterion of postoperative abnormalities of pulmonary function than clinical or radiological findings. The purpose of this study was to utilize changes in arterial blood gases to investigate postoperative respiratory effects of the following techniques on patients undergoing major abdominal surgery: (1) Nitrous oxide, oxygen with large doses of curare, induction doses only of thiopental, and routine reversal at the end of the operation. (2) Nitrous oxide, oxygen and ether with no relaxants except for intubation. (3) Cyclopropane and oxygen with no relaxants except for intubation.

Method

Seventy-nine patients scheduled for gallbladder, stomach or major colonic surgery were included in this study. They were all elective operations selected from the daily operative lists. The criteria used to assess respiratory function were Pa_{O_2}, Pa_{CO_2}, arterial *p*H (blood-gas and *p*H analyzing system Model 113, Instrumentation Laboratory, Inc., Boston, Massachusetts), and inspiratory force measurements using a pressure gauge as suggested by Wescott and Bendixen.[10] Arterial blood samples were obtained by percutaneous puncture of femoral artery using 23 gauge disposable needles. All patients were in the supine po-

* Department of Anesthesia, University of Iowa College of Medicine, Iowa City, Iowa.

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sition. Blood samples were processed within three minutes. Measurements were done on each patient at least four times: (1) the day before surgery, (2) first postoperative hour, (3) first postoperative day, and (4) third postoperative day. This was chosen to expose insidious or late developing changes in respiratory function.

Upon arrival in the recovery room the state of wakefulness of each patient was recorded by the nurses. Patients were classified as (*a*) wide awake and cooperative, (*b*) unconscious, (*c*) drowsy. Time taken for group *b* and *c* patients to become awake and cooperate was recorded.

Inspiratory force measurements and arterial blood sampling were done by the author on all patients, to standardize the procedure. At the time preoperative measurements were made, the author did not know what anesthetic technique was to be used. One hour postoperatively measurements were made in the recovery room.

On the first and third postoperative days, measurements were taken on the wards and each patient's oral temperature, as well as abnormal chest radiological findings, were recorded. We excluded only patients with hemorrhagic diathesis and extreme obesity, because we believed that repeated arterial punctures were hazardous in the former and technically difficult in the latter.

Anesthesia residents were notified the day before operation that a patient was chosen for the study. On the morning of the operation the resident discovered which technique to use by a random drawing from a set of three cards.

Anesthetic Techniques

All patients were premedicated with morphine and scopolamine in varying doses depending on age and weight. The actual dose was left to the discretion of the resident.

N_2O, O_2, Curare Technique. *d*-Tubocurare 30 mg. was given followed by thiopental sodium 100–250 mg. Controlled respiration was instituted using N_2O–O_2 7:3 liters/minute for approximately three minutes. The trachea was then sprayed with 4 per cent lidocaine and intubated following oxygenation for 15 seconds. Curare was repeated in 6 mg. doses every 30 minutes. The magnitude and frequency of repeated doses varied in some cases at the resident's discretion. However, it was impressed upon the residents that the last dose of curare should be given no later than 45–60 minutes before completion of the operation. Thiopental was not repeated after induction. Controlled ventilation with N_2O, O_2 7:3 liters/minute was carried out all through the procedure. Shortly before the end of the operation (usually when the anterior rectus sheath was being closed) two doses of 0.4 mg. atropine were given intravenously, 2–3 minutes apart. A minute or two before skin closure was completed, nitrous oxide was discontinued and high flow of oxygen was administered. At no time was the patient allowed to breathe unassisted. Patients were called by their names and asked to breathe and cough. Neostigmine was then given in doses of 0.5 mg. The end point of complete reversal was considered to be the patients' ability to touch their forehead. Extubation was performd and the patient taken to the recovery room. If the end point was not reached after 3 mg. of neostigmine, the endotracheal tube was left in place and respirations were assisted mechanically. Close adherence to this end point was insisted upon for the first 16 cases, even when it was believed that breathing was adequate before the end point was reached. However, on a suggestion by Dr. Churchill-Davidson, the end point was changed. Patients were not considered completely recovered until nerve-muscle stimulation indicated no signs of curarization at the motor end-plate as described by Churchill-Davidson.[11] The nerve stimulator we used is a modification of that described by Cohen.[12] Due to the fact that two end points were used, results obtained from this technique were divided into two groups: Curare Group I, with a clinical end point of touching the forehead, and Curare Group II, with recovery of neuromuscular conduction as the end point.

Ether. Anesthesia was induced with thiopental 100–250 mg. N_2O, O_2 7:3 liters/minute and ether vaporized in a Copper Kettle was then started. 10–15 minutes later flow rates of N_2O and O_2 were reduced to 3:2 liters/minute. A circle system with CO_2 absorption

TABLE 1

	Number of Cases	Age (years)	Weight (pounds)	Duration of Anesthesia (minutes)	Type of Operation	
					U.A.	Others
Curare I						
Total	16	53.7	137.6	135.6	75%	25%
Females	11 (68.75%)	49.2	125.7	129.1	72.7%	27.3%
Males	5 (31.25%)	63.8	163.6	150	80%	20%
Curare II						
Total	23	52.9	154.6	158.7	73.9%	26.1%
Females	19 (82.6%)	50.0	149.9	154.5	79%	21%
Males	4 (17.4%)	67.0	177.2	178.7	50%	50%
Ether						
Total	23	53.8	145.2	198.0	92.3%	8.7%
Females	12 (52.2%)	50.3	140.3	175.4	91.7%	8.3%
Males	11 (47.8%)	57.6	150.4	222.7	90.9%	9.1%
Cyclopropane						
Total	17	55.0	131.2	167.6	76.5%	23.5%
Females	13 (76.5%)	52.2	123	183.8	84.6%	15.4%
Males	4 (23.5%)	64.2	166.6	115.0	50%	50%

U.A.: Operations on gallbladder or stomach. Others: Major abdominal operations other than on gallbladder or stomach.

was used. One dose of succinylcholine was allowed for intubation, if necessary, in which case the patient was ventilated with oxygen for 15 seconds prior to intubation. Respiration was either assisted or controlled. Ether was discontinued when peritoneum was closed.

Cyclopropane. Anesthesia was induced with thiopental 100–250 mg. followed by cyclopropane and oxygen 500:200 ml./minute with controlled ventilation using a circle system with CO_2 absorption. Again, one dose of succinylcholine was allowed to facilitate intubation or closure of the abdomen or both. Cyclopropane flow rate was reduced to 50–100 ml./minute after 15 minutes, and was completely discontinued when anterior rectus sheath was closed. When closure of skin was started, high flow rates of oxygen were used.

Statistical significance of the results of both sexes combined and of females alone was calculated by analysis of variance on absolute changes from preoperative levels. Though statistical analysis of the results obtained from male patients alone was performed, we believed that the results were not meaningful due to the rather small number of male subjects in this study.

Results

A comparison of the total numbers, sex, average ages, average weights, average duration of anesthesia and type of operation performed in each of the four groups is shown in table 1.

A comparison of the doses of premedicant drugs and thiopental used for induction of anesthesia is shown in table 2. A few patients in each group received no thiopental for induction of anesthesia. These were two cases in the two curare groups, one case in the ether group and five cases in the cyclopropane group.

Succinylcholine was used in 56 per cent of cases in the ether group (average dose 57.69 mg.) and in 56 per cent of cases in the cyclopropane group (average dose 47.77 mg.).

A comparison between the total dose of *d*-tubocurare given in Curare I and Curare II sub-groups showed that patients in Curare I group required an average of 0.024 mg./minute/10 pounds body weight, while patients in the Curare II group required 0.025 mg./minute/10 pounds body weight.

Average doses of neostigmine required for reversal to the respective end points were 1.42

TABLE 2

	Morphine (mg.)	Thiopental (mg.)	Status on Arrival in Recovery Room		
			Awake	Drowsy	Unconscious
Curare I					
Total (16)	8.8	198.2	81.25%	18.75%	0
Females (11)	8.3	180.5	81.8%	18.2%	0
Males (5)	9.6	230.0	80.0%	20.0%	0
Curare II					
Total (23)	8.8	198.9	91.3%	8.7%	0
Females (19)	8.9	184.7	94.7%	5.3%	0
Males (4)	8.5	262.5	75.0%	25.0%	0
Ether					
Total (23)	9.3	188.6	8.7%	8.7%	82.6%
Females (12)	8.7	184.6	16.7%	8.3%	75.0%
Males (11)	10.0	234.1	0	9.1%	90.9%
Cyclopropane					
Total (17)	8.66	179.5	23.1%	12.0%	64.9%
Females (13)	8.8	162.5	23.0%	15.5%	61.5%
Males (4)	7.25	187.5	23.5%	70.6%	5.9%

mg. for the Curare I cases and 1.77 mg. for Curare II cases. The difference between the doses of neostigmine in the two groups was not statistically significant as shown by a *t* test.

PREOPERATIVE RESULTS

Average preoperative figures in 79 cases were as follows: Pa_{O_2} 78.56 mm. of mercury, Pa_{CO_2} 36.92, *p*H 7.474 and inspiratory force 36.82 cm. of water.

POSTOPERATIVE RESULTS

State of Wakefulness of Patients on Arrival in the Recovery Room (*Table 2*). Wide awake patients in Curare I group (81.25 per cent) and Curare II group (91.30 per cent) were comfortable and none complained of pain; 82.60 per cent of ether patients and 62.5 per cent of cyclopropane patients were unconscious. All regained consciousness within one hour with the exception of two patients in the ether group; these remained unconscious for two and three hours, respectively, and neither performed inspiratory force measurements in the recovery room. At the time femoral arterial blood samples were taken in the recovery room, all patients in the curare groups, all but one in the cyclopropane group and all but four in the ether group, were quite alert. We did not notice any appreciable degree of apprehension when the femoral artery was punctured.

Immediate Postoperative Respiratory Complications. CURARE GROUP: Two male patients required mechanical assistance of respiration in the recovery room. The first of these revealed no evidence of neuromuscular block when the nerve stimulator was used and responded favorably to levallorphan. The second patient had chronic renal disease and a previous nephrectomy but no azotemia. Total dose of *d*-tubocurare was 0.020 mg./minute/10 pounds body weight. Operation lasted 225 minutes and consisted of resection of recurrent retroperitoneal lymphosarcoma. Neostigmine 5 mg. failed to reverse his neuromuscular block. The lungs were ventilated mechanically for five hours. On a subsequent occasion, a similar operative procedure was repeated using the same anesthetic technique. Though the patient's status was essentially unchanged, this time he was given a much smaller total dose of *d*-tubocurare (0.012 mg./minute/10 pounds body weight. Operation lasted 150 minutes, and reversal with neostigmine was complete and uneventful.

CYCLOPROPANE GROUP: One patient had to be ventilated mechanically in the recovery

room. He was an 84 year old man, who, apart from being jaundiced, was essentially healthy. He received 5 mg. morphine and 0.2 mg. scopolamine for premedication. Anesthesia was induced with thiopental 125 mg. Succinylcholine 40 mg. was used to facilitate intubation. Respirations were controlled all through procedure which lasted for 100 minutes. Upon arrival in the recovery room, he was unconscious and breathing inadequately. Mechanically assisted ventilation was started. Levallorphan 1 mg. failed to produce any effect. Neuromuscular stimulation revealed no block. Mechanical ventilation continued for two and one-half hours. Patient became fully alert eight hours postoperatively. Two patients in this group had severe vomiting episodes, one of whom had laryngeal spasm and cyanosis upon arrival in the recovery room.

ETHER: Severe vomiting occurred in the recovery room in one patient in this group.

First Hour Results (Tables 3 and 4). Pa_{O_2}: The means of all determinations for all four groups reflected a fall in oxygen tension compared to preoperative figures. The difference between groups was not statistically significant. Analysis of results of female and male patients separately did not show significant differences among groups.

Pa_{CO_2}: Combined results of patients of both sexes showed a significant incidence of CO_2 retention in the cyclopropane group as compared to the other three groups ($P < 0.01$). The difference between other groups was not significant. Female patients' results reflected the same significant CO_2 retention in the cyclopropane group ($P < 0.01$). Male patients' results showed no significant difference between groups.

*p*H: All patients in all groups exhibited a decrease in arterial *p*H following anesthesia and operation. The difference between all four groups was not significant. Results of male patients alone also showed no difference between groups. However, when female patients' results were analyzed separately, there was significantly less acidosis in Curare II group compared to the other three groups ($P < 0.05$).

INSPIRATORY FORCE: All groups showed a drop in inspiratory force. Results of female patients showed significantly less reduction in inspiratory force in Curare II group than in the other three groups ($P < 0.05$). Results of male patients alone and males and females combined did not show significant difference between groups.

First Day Results (Tables 3 and 4) (applicable to both sexes individually and combined). Pa_{O_2}: All groups showed additional lowering in average Pa_{O_2} compared to preop-

TABLE 3. Mean Absolute Changes of Pa_{O_2} and Pa_{CO_2} in mm. of Mercury Compared to Preoperative Figures

	Number of Cases	Pa_{O_2}		
		First Hour	First Day	Third Day
Curare I				
Total	16	−7.53	−8.00	−6.75
Females	11	−8.00	−5.03	−7.80
Males	5	−6.25	−12.80	−5.20
Curare II				
Total	23	−4.06	−6.21	−6.40
Females	19	−2.00	−5.10	−5.00
Males	4	−13.83	−11.50	−11.40
Ether				
Total	23	−6.22	−11.02	−9.84
Females	12	−8.25	−8.75	−10.50
Males	11	−4.00	−14.60	−9.10
Cyclopropane				
Total	17	−9.28	−9.61	−6.84
Females	13	−9.80	−8.96	−6.50
Males	4	−7.00	−11.75	−7.70
		$Paco_2$		
Curare I				
Total	16	−0.06	−2.07	−0.75
Females	11	−0.40	−3.30	−1.90
Males	5	+1.00	+0.10	+0.90
Curare II				
Total	23	−0.43	−2.30	−0.93
Females	19	−0.78	−2.80	−1.00
Males	4	+1.25	+0.12	−0.37
Ether				
Total	23	+0.96	−2.34	−1.20
Females	12	+1.90	−2.00	−1.90
Males	11	+1.86	−2.70	−0.50
Cyclopropane				
Total	17	+5.31	−0.55	−1.87
Females	13	+5.80	−1.00	−1.40
Males	4	+3.16	+0.87	−3.10

TABLE 4. Mean Absolute Changes of *p*H and Inspiratory Force Compared to Preoperative Figures

	Number of Cases	Arterial *p*H		
		First Hour	First Day	Third Day
Curare I				
Total	16	−0.085	+0.010	−0.004
Females	11	−0.094	+0.024	−0.012
Males	5	−0.060	−0.005	+0.001
Curare II				
Total	23	−0.046	+0.020	+0.020
Females	19	−0.040	+0.020	+0.019
Males	5	−0.075	+0.019	+0.022
Ether				
Total	23	−0.066	+0.017	+0.019
Females	12	−0.076	+0.006	+0.029
Males	11	−0.056	+0.031	+0.013
Cyclopropane				
Total	17	−0.071	+0.015	+0.029
Females	13	−0.072	+0.020	+0.036
Males	4	−0.066	+0.001	+0.007
		Inspiratory Force (cm. of water)		
Curare I				
Total	16	−12.3	−5.4	−2.0
Females	11	−12.6	−6.0	−1.0
Males	5	−11.5	−5.2	−3.0
Curare II				
Total	23	−8.9	−6.8	−1.4
Females	19	−7.43	−6.4	−1.8
Males	4	−16.2	−9.6	+0.5
Ether				
Total	23	−13.6	−7.5	−3.6
Females	12	−13.6	−4.8	−4.2
Males	11	−13.5	−10.7	−3.1
Cyclopropane				
Total	17	−15.8	−9.8	−3.3
Females	13	−16.8	−9.3	−3.2
Males	4	−9.0	−11.2	−5.0

erative, and first postoperative values. Differences between groups were not statistically significant.

Pa_{CO_2}: The means of all four groups showed decreased Pa_{CO_2} compared both to preoperative and first hour values. The significantly higher Pa_{CO_2} figures obtained in the cyclopropane group one hour postoperatively no longer existed.

*p*H: There was an increase in mean arterial *p*H in all groups compared to both preoperative and first hour levels. There were no group differences.

INSPIRATORY FORCE: Inspiratory force measurements increased in all four groups compared to first hour levels. They were still below preoperative figures. Again, there were no differences between groups.

CLINICAL COMPLICATIONS (First-third postoperative days): There were no deaths. Pneumonia and/or collapse of part of the lung, based on clinical and radiological examination, occurred in two cases in the Curare I group (12.4 per cent), one case in the ether group (4.3 per cent) and one case in the cyclopropane group (6.2 per cent). There was no case of pneumonia or pulmonary collapse in the Curare II group.

Oral temperatures of 101° F. or more on the first postoperative day occurred in one case of the Curare I group (6.2 per cent), two cases of the ether group (8.6 per cent) and one case of the cyclopropane group (6.2 per cent). None occurred in the Curare II group.

On the third postoperative day the incidence was Curare I, 12.4 per cent; ether, 4.3 per cent; cyclopropane, 6.2 per cent and Curare II, nil.

Third Day Results (*Tables 3 and 4*). The averages of all parameters in all groups changed towards preoperative values. The only exception was a slight further fall of Pa_{O_2} values for female patients in Curare I and ether groups.

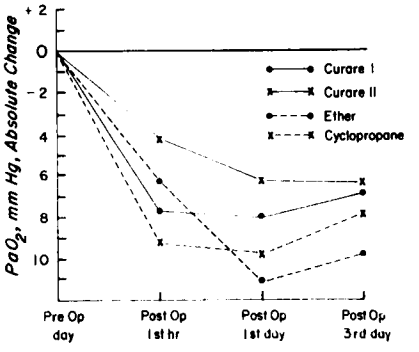

FIG. 1. Pa_{O_2}.

Discussion

In general, this study failed to demonstrate any marked superiority of any of the anesthetic techniques used, as far as postoperative respiratory function was concerned. Immediate postoperative results showed that when a nerve muscle stimulator was used to define complete reversal, significantly less acidosis and better inspiratory force measurement were obtained in female patients in Curare II group than in other groups. Combined male and female results of all measured parameters also showed less deviation from normal in Curare II group than in other groups, though a statistically significant difference could not be demonstrated (figs. 1, 2, 3, 4).

Significant CO_2 retention occurred only in the cyclopropane group as shown by the results of female patients alone and those of the combined sexes. The increase in arterial CO_2 tension in these patients represented a 14 per cent decrease in alveolar ventilation.

Inspiratory force measurements showed a remarkable lack of correlation between the ability of patients to inspire against a resistance and their corresponding blood gas tensions.

Early postoperative decrease in Pa_{O_2} emphasized that a measurable degree of hypoxemia commonly occurred postoperatively, no matter what anesthetic technique was used.

The first case of prolonged apnea and unconsciousness occurring in the curare group could not be attributed to persistent curarization, as neuromuscular conduction was shown to be intact. Indeed, this case presented a good example of the value of a nerve muscle stimulator in distinguishing between peripheral curarization and central depression. Use of relatively large doses of curare in the second case of prolonged apnea probably represented a bad choice of anesthetic technique in view of the evidence that elimination of *d*-tubocurare is largely dependent on adequate renal function.[18] The only case of prolonged apnea and unconsciousness following cyclopropane anesthesia remained essentially unexplained.

The ultimate success of any anesthetic regimen depends upon personnel as much as upon agents used. Anesthetic techniques reported here were performed by the same personnel with the same supervision. The observation that almost all patients anesthetized with ether were judged to be awake before the end of

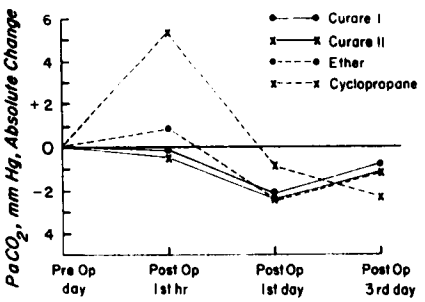

FIG. 2. Pa_{CO_2}.

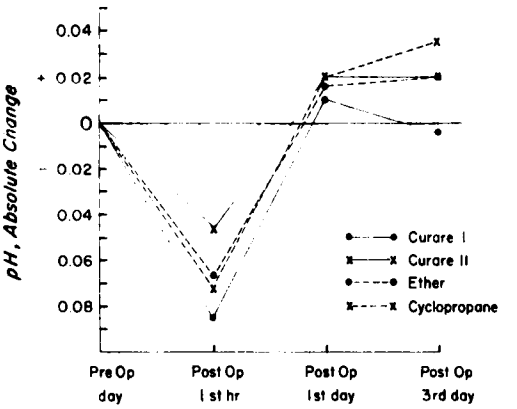

FIG. 3. *p*H.

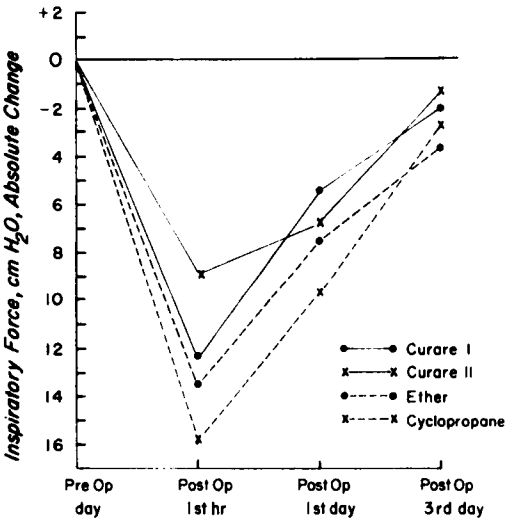

FIG. 4. Inspiratory force.

one hour in the recovery room is evidence that these patients were skillfully handled. Postoperative facilities and attention were the same for all groups.

To achieve favorable results with nondepolarizing muscle relaxants, the following concepts were observed:

(1) Nitrous oxide-oxygen, adequate doses of nondepolarizing relaxants, hyperventilation and complete reversal with neostigmine are all components of the same technique. The use of neostigmine is not an indication of excessive dose of curare, but rather an integral part of the technique.

(2) Nitrous oxide is maximally utilized. Flow rates of 7:3 liters/minute and hyperventilation provide rapid changes in inspired concentration and increase N_2O uptake during induction of anesthesia.[14]

(3) Meticulous reversal of neuromuscular block is essential and is best monitored with a nerve muscle stmiulator.

(4) Thorough knowledge of the factors that influence the mode and duration of action of muscle relaxants is mandatory before embarking on the use of large doses of these drugs in clinical anesthesia.

Summary

A study of effects of three anesthetic techniques on postoperative ventilatory status of 79 patients was conducted. The parameters used were arterial blood gases, *p*H and inspiratory force measurements. Measurements were made preoperatively and one hour, one day and three days postoperatively. The anesthetic techniques used were cyclopropane and oxygen; N_2O, O_2 and ether; and N_2O, O_2 and *d*-tubocurare.

Most postoperative measurements showed that there were no significant differences between the various anesthetic techniques used in this study. The only exceptions were: (1) Significant CO_2 retention in cyclopropane group in the first four postoperatively, as shown by the results of female patients alone and those of combined sexes. (2) Female patients' results showed significantly less acidosis and better inspiratory force measurements in the first hour postoperatively in the Curare II group as compared to other groups.

The study showed that N_2O-relaxants and reversal with neostigmine need not be followed by respiratory complications. The philosophy of the use of large doses of nondepolarizing muscle relaxants was discussed.

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