CLINICAL USE OF A PHYSIOLOGICAL RESPIRATOR PRODUCING N_2O AMNESIA-ANALGESIA

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This paper summarizes the clinical experience with a new type of apparatus which produced artificial respiration and nitrous oxide-oxygen anesthesia in 171 patients undergoing operation. In brief, the patients are rendered apneic by the skeletal muscle relaxant, succinylcholine, and are artificially respired with a fixed mixture of nitrous oxide and oxygen. The pressure used to inflate the lungs is servo-controlled to maintain the end-expiratory (and, hence, usually also the alveolar and the arterial) carbon dioxide concentration at any desired level. This type of regulation closely simulates important elements of the normal control of breathing.

This apparatus was originally developed in 1953 because of the following considerations: (1) Experiences here and elsewhere indicated that there are many clinical advantages associated with the combination of very light general anesthesia and immobility produced by a muscle relaxant (1, 2, 3). (2) Objective and quantitative measurements of both patient and apparatus should be more informative and useful than the essentially subjective appraisals which constitute current anesthesia practice. (3) Repetitive processes such as artificial respiration, the mixing of the anesthetic agent with O_2, and the measurement of gas concentrations can often be carried out more efficiently and accurately when performed mechanically rather than manually. (4) Objective measurements can often provide the signal for the self-regulating systems controlling such mechanically operated anesthesia devices.

Description of Technique

Anesthesia is induced with an intravenous injection of approximately 0.2 Gm. of thiopental. Immobilization and apnea are then produced and maintained for the surgical operation by the continuous intravenous infusion of 0.5 per cent succinylcholine chloride in a 0.9 per cent sodium chloride solution. A tracheal catheter is inserted and an air tight seal obtained with an inflatable cuff. The lungs are intermittently inflated through the catheter with a mixture of nitrous oxide

Accepted for publication November 5, 1956. From the Department of Anesthesiology, Columbia University College of Physicians and Surgeons and the Anesthesiology Service of The Presbyterian Hospital, 622 West 168th Street, New York 32, New York. Aided by grants from the National Foundation for Infantile Paralysis and the Burroughs Wellcome Company, (U.S.A.), Inc. This paper was presented in part before the annual meeting of the American Medical Association, Chicago, Illinois, June 13, 1956.

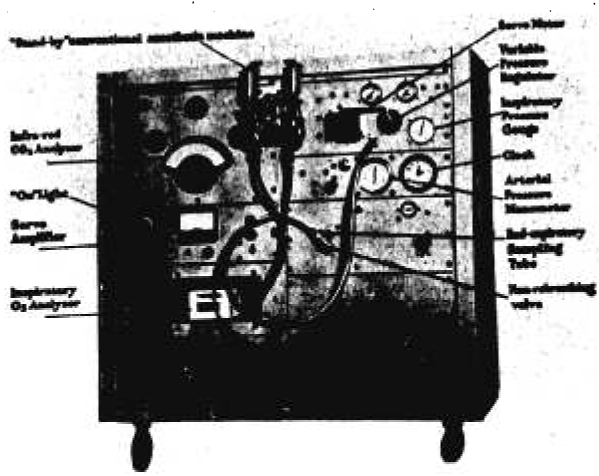

FIG. 1. Physiological respirator producing nitrous oxide amnesia-analgesia.

and oxygen delivered by a new type of apparatus (figs. 1 and 2). This apparatus * has been described in detail elsewhere (4).

Nitrous oxide and oxygen are delivered from large capacity manifolds to a specially designed mixer which blends the gases, fixing the

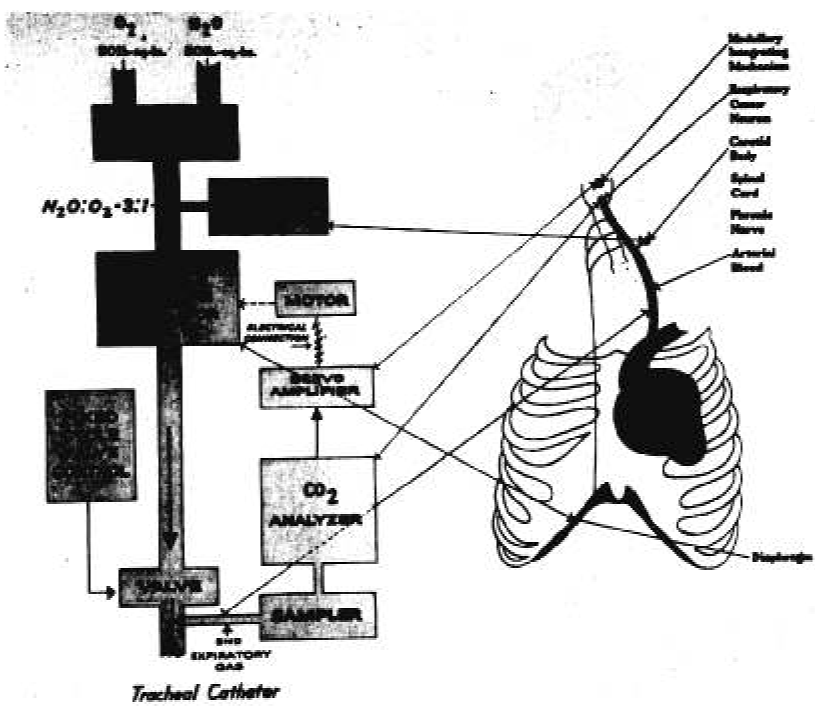

FIG. 2. Diagram of physiological respirator showing relationship to normal respiratory control.

* This instrument was engineered by A. S. J. Lee and is available from Invengineering, Inc., Belmar, New Jersey.

nitrous oxide concentration at any desired value. The oxygen concentration is continuously monitored with a Pauling analyzer. A variable pressure regulator then reduces the pressure of the gas mixture to that used for inflating the lungs. A new type of nonrebreathing valve attached to the tracheal catheter permits this gas mixture to enter the lungs to produce inspiration, and connects the catheter to ambient at-

TABLE 1

AGE DISTRIBUTION IN DECADES

Years	<10	10-19	20-29	30-39	40-49	50-59	60-69	>70	Total
Number of Patients	3	13	12	17	36	48	30	12	171

mosphere for passive exhalation. This valve is pneumatically actuated fifteen times a minute through a remote control system with inspiration occupying one-third of the cycle.

The only variable of the respirator is the inflating pressure. It is automatically adjusted by a series of sequential processes. A gas sample is obtained from the lumen of the tracheal catheter during the final

TABLE 2

RISK OF ANESTHESIA

Class	Good	Fair	Poor	Very Poor	Good Emergency	Poor Emergency	Moribund	Total
Number of Patients	105	48	9	1	5	2	1	171

0.2 of a second of the expiratory phase of the cycle with a small caliber sampling tube and a small pump. This end-expiratory sample usually consists of alveolar air. The partial pressure of carbon dioxide in this sample is therefore in equilibrium with that of the arterial blood. The pump delivers the sample to an infra-red gas analyzer for carbon dioxide analysis. The electrical output of this analyzer is then utilized

TABLE 3

LOCATION AND TYPES OF OPERATION

Location	Total	Most Frequent Type	Number
Head and Neck	19	Thyroidectomy	6
Thoracic	16	Pulmonary	5
Upper Abdominal	36	Cholecystectomy	11
Lower Abdominal	21	Hysterectomy	10
Extra-peritoneal	24	Inguinal Herniorrhaphy	12
Extremity	28	Arthrotomy	7
Perineal	27	Dilatation and Curettage	11
Total	171		

TABLE 4

DURATION OF ANESTHESIA

Hours	<1.0	1-1.9	2.0-2.9	3.0-3.9	4.0-4.9	5.0-5.9	>6.0	Total
Number of Operations	17	38	51	28	18	8	11	171

in a servo-system for adjusting the variable pressure regulator controlling the inflating pressure and ultimately the amount of carbon dioxide exhaled. For example, if the end-tidal carbon dioxide concentration exceeds the value which the system is set to maintain, then the inflating pressure is automatically increased, deeper respirations ensue and more carbon dioxide is exhaled. These small adjustments in inflating pressure continue until the patient's carbon dioxide concentration matches the setting of the "servo."

This system of regulation closely mimics the normal control of breathing (fig. 2). The end-tidal gas sample is analogous to the arterial blood; the carbon dioxide analyzer and the servo amplifier to the respiratory center which is sensitive to the arterial carbon dioxide tension and which determines the sequence and degree of activation

TABLE 5

DRUGS USED FOR PREMEDICATION AND INDUCTION

	Induction Agents		Premedication Agents					
	Thiopental	N_2O-O_2	None	Morphine	Meperidine	Pentobarbital	Atropine	Scopolmine
Number of cases	109	—	7	25	20	16	0	102
Number of cases	—	62	15	3	2	4	16	31
Total			22	28	22	20	16	133

of the respiratory muscles. The electrical connection between this amplifier and the servo-motor adjusting the variable pressure regulator may be compared to the spinal cord and phrenic nerve. Finally the variable pressure regulator resembles the diaphragm.

RESULTS

Analysis of Cases.—The extensive clinical applicability of the nitrous oxide-succinylcholine combination in general and of this automatic apparatus in particular can be appreciated from the summaries in tables 1 to 5. The apparatus was used for 171 operations. The servo-control of the carbon dioxide concentration was used in approximately half of the cases.

Table 1 shows the age distribution by decades with a range from 5 to 85 years and a median of 51 years. The risk of anesthesia is shown in table 2. It reflects the restriction of the use of the apparatus to elective cases during the developmental phases. The types of operations are summarized according to region in table 3. The duration of anesthesia is indicated in table 4. In 30 cases, investigations were carried out for periods up to five hours either before or after operation, in order to assess the performance of the apparatus and the response of the patients without surgical intervention.

The Concentration of Nitrous Oxide and the Amnesic-Analgesic State.—The concentration of nitrous oxide in the inspired mixture was usually between 65 and 80 per cent. With an early experimental mixer system, the concentration fluctuated as much as 10 per cent from the desired value. The mixer system now in use over six months has maintained the concentration within 1 per cent of the desired level for as long a period as desired. The concentration was deliberately maintained between 81 and 87 per cent in 20 patients to determine its effect on arterial oxygen saturation.

It was essential to determine what was the lowest concentration of nitrous oxide (and reciprocally the highest oxygen concentration) which would regularly obliterate memory for the operation. In order to evaluate this effect of nitrous oxide, other central nervous system depressants were either omitted entirely or given in minimal doses (table 5). The median doses of morphine, meperidine, and pentobarbital are 10, 75, and 100 mg. respectively. In the last 100 cases, premedication was usually restricted to 0.4 mg. of scopolamine. The contribution of this drug in producing amnesia is now being studied. In 109 cases, thiopental was used for induction and in doses rarely exceeding 0.3 Gm. The remaining 62 cases were induced with an 80 per cent nitrous oxide-20 per cent oxygen mixture which was respired for about 5 minutes with a conventional mask and rebreathing apparatus.

The amnesia was complete in all but 9 patients. In 8 of these, the inspired nitrous oxide concentration was at times between 50 and 61 per cent. The recollections usually consisted of "picking" and "scratching" during superficial operations or "tugging" during intra-abdominal procedures. Three felt distinct but tolerable pain of a minor nature for brief periods. All 9 remembered hearing conversations or other operating room sounds.

As a result of this experience at the beginning of the series, concentrations of 65 per cent or more were used in almost all of the remainder of the cases. However, one patient who received 71 per cent nitrous oxide did recollect some of the events occurring during an orthopedic operation. He remembered hearing surgeons discussing the procedure, manipulating his leg and hammering. However, he declared that he did not experience pain at any time and could not recall the skin incision or closure.

The amnesic property of nitrous oxide was explored further in approximately 50 patients by attempting to obtain motor responses to verbal commands during the "anesthesia." Operating conditions remained adequate for intraabdominal surgery even though the intensity of the neuromuscular blockade was deliberately reduced to permit such voluntary responses. These patients, on request, opened their eyes, squeezed their hands and shook their heads "yes" or "no." These responses could almost invariably be elicited with 65 per cent nitrous oxide, occasionally with 80 per cent nitrous oxide, and even in one instance with 86 per cent nitrous oxide. Postoperatively, none recalled being asked such questions or giving these responses. Clearly, they were not "anesthetized" in the usual sense of being asleep. Rather

TABLE 6

Total Dosage of Succinylcholine

Grams of Succinyl-choline	<0.5	0.5–0.9	1.0–1.4	1.5–1.9	2.0–2.4	>2.5	Unrecorded	Total
Number of cases	8	31	32	27	15	22	36	171

they were amnesic and analgesic, and resembled closely patients rendered analgesic with ether (5). Many patients described vivid dreams, some of which were distinctly pleasurable while others were unpleasant. In a few, the dream content was related to the operation. Most of the patients who remembered events or unpleasant dreams were not, apparently, disturbed by these recollections. However, no precise information is yet available regarding any deeper psychological or psychiatric repercussions of these experiences.

TABLE 7

Rate of Administration of Succinylcholine

	Duration of Anesthesia	Succinylcholine Grams/hour						Unrecorded	Total
		0–0.2	0.3–0.4	0.5–0.6	0.7–0.8	0.9–1.0	>1.0		
Number of Cases	more than 2 hrs.	3	8	8	6	5	9	16	55
Number of Cases	less than 2 hrs.	4	4	63	18	5	2	20	116
Total		7	12	71	24	10	11	36	171

The electroencephalographic changes during such anesthesias were recorded in a further effort to explore this amnesic state. A preliminary report of these findings has already been presented (6). When the inspiratory mixture contained 65 per cent nitrous oxide, the electroencephalogram was at times indistinguishable from the control tracing. More frequently however, the fronto-occipital tracings showed a slightly slower dominant rhythm than the control and small amounts of low voltage fast activity. At 80 per cent nitrous oxide, the dominant rhythm slowed still further and low voltage fast activity became more prominent, and at times, dominant. It is important to recognize that even when fixed concentrations of nitrous oxide were respired.

Succinylcholine and Immobility.—An excellent surgical field was usually produced by the intravenous administration of succinylcholine. Table 6 shows the total doses of succinylcholine and table 7 the rates of administration when the anesthesia lasted more or less than two hours. In general, the higher infusion rates were employed when the operations were relatively short. The median rate of administration in the longer cases was 0.5 Gm. per hour. Adequate spontaneous respiratory efforts usually were resumed at the end of operation, especially if gross over-dosage was avoided earlier. The prompt reappearance postoperatively of muscular activity and consciousness when succinylcholine and nitrous oxide were discontinued lessened the postoperative problems of maintenance of the airway.

The rate of administration was regulated by manually varying the degree of constriction of the tubing of a gravity infusion. The flow rate was increased when spontaneous respiratory or extraneous reflex movements occurred and was decreased when they disappeared. Although this technique is very widely employed, it was not considered satisfactory. The degree of neuromuscular block was not kept constant. Spontaneous movements, respiratory or otherwise, recurred irregularly during the operation and prevented its continuation until more of the relaxant was given. Conversely, gross overdosage was easily produced if close attention was not paid to the management of the infusion rate and led to apnea which could outlast the operation, a complication which occurred five times in this series. More commonly however, spontaneous but inadequate respiratory efforts were found postoperatively. This complication was usually the consequence of the higher infusion rates. Serious hypoventilation occurred in one patient suffering from preexisting asthma and emphysema and was an imminent threat to life from asphyxia. Severe bouts of asphyxia due to hypoventilation and partial respiratory obstruction occurred in 6 other patients. This difficulty, therefore, remains a problem of major clinical importance.

Two types of treatment were used in managing postoperative hypoventilation and partial neuromuscular block. The first, and most important, consisted of manual assistance to respiration by intermittent positive pressure usually through the endotracheal tube. This was continued until adequate spontaneous breathing resumed and oxygenation was well maintained while breathing room air. The other remedy which proved valuable was the intravenous administration of edrophonium (Tensilon®), a known anticurare agent which probably acts through its anticholinesterase activity (7, 8). Dr. J. S. Schweiss suggested this treatment since there is evidence that the depolarizing drugs appear to produce a curariform type of block upon prolonged administration (9, 10). The intravenous injection of 10–20 mg. of edrophonium in 16 patients effectively increased the tidal volume of respiration. Spontaneous respirations began within one minute after the administration of 10 milligrams of edrophonium in 2 apneic patients. These spontaneous respirations, however, were inadequate to maintain oxygenation and additional manual assistance was required.

Respiration.—The ventilatory efficiency of a respirator should be judged by how it carries out the two main functions of breathing—the addition of oxygen and the removal of carbon dioxide from the body. These functions have been assessed by measurements of the arterial oxygen saturations and carbon dioxide tensions. These studies have been carried out with Dr. Duncan A. Holaday and will be reported later in detail. In general, inflating pressures between 5 and 10 mm. of Hg produced arterial carbon dioxide tensions between 30 and 40 mm. of Hg. The apparatus was capable of maintaining the arterial carbon dioxide tension at approximately the desired level for long periods of time. For example, the arterial carbon dioxide tension of one subject did not vary by more than 1.5 mm. of Hg from the preset value over a three hour period. Arterial oxygen saturations were carried out on 22 samples obtained from 8 individuals while the inspiratory oxygen concentration was between 21 and 45 per cent and the arterial carbon dioxide tension was maintained between 30 and 42 mm. of Hg. The average oxygen saturation was 96 per cent with a range of 89 to 100 per cent. Two of these 7 less well saturated samples were obtained from a 78-year-old emphysematous man with known pulmonary disease.

Circulation.—Under the specific conditions of these studies, there appeared to be no obvious depression of the circulation. The systolic pressure rose more than 25 per cent in 18 patients. Lesser degrees of arterial hypertension were observed quite commonly. The systolic pressure rose above 200 mm. of Hg in 11 patients, 6 of whom had preoperative pressures of 170 mm. of Hg or more. The cause of this hypertension has not been determined. It may be the result of surgical stimulation during light anesthesia. Succinylcholine causes an intense stimulation of the carotid body in experimental animals (11), and may produce hypertension reflexly through widespread sympathetic discharge. This mechanism may also be responsible for the tachycardias exceeding 100 beats per minute seen in 8 individuals in whom no other cause was apparent. A systolic arterial hypotension of 25 per cent was seen in 9 patients. In three instances, this was attributed to hemorrhage or bone trauma, and in four others it was associated with abdominal exploration and visceral traction.

Discussion

It is difficult to decide on purely clinical grounds just how artificial respiration should be carried out. The goal of this work was an attempt to mimic clinically the system of control which the body ordinarily uses. This system possesses the important advantage of producing an immediate response to the frequently changing situation occurring in the operating room in much the same way that the body functions in other situations. Such a system may have application in other fields where artificial respiration is required. Saxton and Myers devised such a control mechanism for a Drinker respirator in treating poliomyelitic patients (12). They described their apparatus as an "electromechanical substitute for the normal respiratory mechanism."

This system of gas mixing and respiratory control requires apparatus which cannot be considered simply as an improved version of existing anesthesia machines. In order to carry out these two functions reliably, some principles relatively new in anesthesia were employed. (1) The mixing system was controlled mechanically and was monitored continuously and objectively. (2) The gas mixture was administered through a mechanically actuated nonrebreathing valve. (3) The patient's expired gas was sampled to determine the immediate past performance of the respirator in order to provide for proper respirations in the immediate future.

The monitoring system which verifies accurately the composition of the mixture, provides information which is not available in standard anesthesia machines. It is possible to determine from a single dial reading exactly what mixture the patient is receiving. This is difficult to do with the rebreathing systems in common use because of the variable combination of the exhaled and fresh gases, the variable degree of blow off, and other factors. The valves and gauges of conventional machines are not designed for accurate mixing of gases at the flow rates adults require in nonrebreathing systems. The end-exhalation carbon dioxide concentration which here is measured accurately cannot be appreciated at all by the unaided five senses.

The design of this apparatus also illustrates the principle of combining objective measurements and mechanization to create a self-regulating device. With each breath, the apparatus carries out four processes—sampling, analysis, comparison, and readjustment. In only a few seconds, a readjustment is made for discrepancies between the setting of the machine and that required by the changing clinical situation. Manually actuated and subjectively controlled apparatus generally available to the anesthesiologist does not respond as promptly and regularly as do self-regulating machines of this general type. The degree of neuromuscular blockade ought to be regulated in a similar fashion and studies are in progress toward this end.

The use of the nonpotent anesthetic agents or very low (amnesic) concentrations of the more potent ones, in combination with muscle relaxants, is a practice which is currently gaining favor and apparently growing in popularity. It is believed that the low incidence of hypotension tends to support the thesis that the lighter the depth of anesthesia the less frequently will circulatory depression occur. When the hypotension was associated with traction or intestinal manipulation, it was untreated and disappeared without any further therapy. There are, however, three notes of caution regarding this approach which this study has emphasized. First, the patient may be conscious, experience pain or remember events occurring during the operation if the concentration of nitrous oxide is reduced below 65 per cent. Secondly, the widespread use of controlled respiration associated with the use of muscle relaxants may be safer and more reliable if mechanical rather than manual methods are used. Finally, the administration of relatively large doses of the muscle relaxants may cause prolonged apnea or hypoventilation postoperatively. The central problem here is the avoidance of overdose by the relaxant. The degree of neuromuscular block of the patient ought to be assessed objectively before more of the relaxant drug is given.

Summary

An apparatus has been devised for the maintenance of nitrous oxide-oxygen anesthesia in 171 patients immobilized with the muscle relaxant, succinylcholine. The inflating pressure and hence also the depth of respiration was controlled by a self-regulating system utilizing measurements of the carbon dioxide concentration at the end of exhalation. Light anesthesia combined with relaxants administered in this fashion was found useful in many clinical circumstances. The inspiratory oxygen concentration, the inflating pressure and the end-exhalation carbon dioxide concentration were objectively measured in determining the performance of the machine and the respiratory responses of the patient.

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