Effects of Intravenous Atropine and Scopolamine During Cyclopropane-Succinylcholine Anesthesia

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WE have noted a high incidence of slow cardiac rhythms during the administration of cyclopropane-succinylcholine chloride anesthesia to adult patients. To counteract these effects, atropine sulphate (0.2 mg.) was injected intravenously in over 300 cases. The clinical results were generally gratifying with conversion of the slow rates to normal or near normal and simultaneous restoration of the systolic blood pressure to preoperative levels. Irregularities of a transient nature were occassionally noted by radial pulse palpation.

To ascertain the nature of the initial bradycardia and the arrhythmias which followed the injection of parasympathetic blocking agents, the following study was undertaken.

Material and Methods

One hundred and fifteen unselected surgical patients, with an age range of 17 to 79 years, were used as subjects. All of the patients studied were given pentobarbital one and one-half hours before operation, and meperidine and atropine or scopolamine one hour before operation, except the patients in group E, who received only pentobarbital and meperidine on the wards and to whom the belladonna alkaloids were administered intravenously 20 minutes before anesthesia as previously described.

All patients underwent major surgical procedures and were anesthetized with 200 to 250 mg. of thiopental intravenously after which oxygen by face mask and bag was given for about one minute. During this period, 40 to 50 mg. of succinylcholine chloride were injected rapidly intravenously while oxygenation was continued for 30–45 seconds. Orotracheal

or nasotracheal intubation was then performed under direct vision, and anesthesia was continued by a closed to-and-fro technique with a 30 to 40 per cent cyclopropane and oxygen mixture delivered from the machine. A solution of succinylcholine, 1 mg./ml., was started as a continuous intravenous infusion, and respirations were controlled or assisted as judged necessary for adequate pulmonary ventilation.

A large number of patients had electrocardiographic lead 2 recorded preoperatively and intermittently during anesthesia, using a Cambridge Simpli-Scribe Model direct writing electrocardiograph. Only those patients who developed bradycardia of 60 beats or less per minute during the course of the anesthesia were thought suitable for our study. As soon as bradycardia became established, continuous electrocardiographic tracings of lead 2 were started, and atropine sulphate 0.2 mg., administered rapidly intravenously to 25 patients (group A). Scopolamine hydrobromide 0.2 mg. was given intravenously to another 25 patients (group B), and atropine or scopolamine 0.1 mg. was given intravenously to a third group of 20 patients (Group C). Twenty patients (group D) received either scopolamine or atropine 0.08 mg. intravenously. A group of 25 unanesthetized adult male and female patients (group E) of comparable age and physical status received atropine or scopolamine 0.2 mg. intravenously twenty minutes before the induction of anesthesia while lead 2 of the electrocardiogram was recorded continuously during the injection and for four to five minutes afterwards.

Results

Group A. The 25 patients in this group received atropine 0.2 mg. intravenously during the period of bradycardia produced by cyclopropane-succinylcholine anesthesia (table 1).

TABLE 1. Sixteen of 25 Patients Showing Early or Late Arrhythmias after Atropine (0.2 mg. Intravenously) During Cyclopropane–Succinylcholine Anesthesia

Age	Systolic Decrease, mm. Hg	Pressor Effect, mm. Hg Systolic	Decrease in Pulse Rate	Early Arrhythmias	Late Arrhythmias	Cardiac Rhythm at Height of Bradycardia
60	30	40	13	Upper nodal rhythm middle nodal rhythm	No	Sinus bradycardia
32	10	25	30	Interference dissociation with synchronization lower nodal rhythm	No	Sinus bradycardia
23	20	25	40	Interference dissociation	No	Sinus bradycardia
27	30	40	12	Middle nodal rhythm	No	Nodal rhythm
44	20	40	20	Upper nodal rhythm	No	Sinus bradycardia
53	10	15	10	Interference dissociation with synchronization	No	Sinus bradycardia
40	15	15	45	Interference dissociation	Ventricular extrasystoles	Sinus bradycardia
50	10	30	28	Interference dissociation with synchronization	No	Sinus bradycardia
38	10	30	18	Interference dissociation ventricular parasystoles	Ventricular extrasystoles	Nodal rhythm
74	20	20	40	Upper nodal rhythm	No	Sinus bradycardia
64	0	0	24	Interference dissociation	No	Sinus bradycardia
74	0	10	60	Interference dissociation with synchronization	No	Sinus bradycardia
45	0	0	20	Auricular extrasystoles	No	Sinus bradycardia
38	20	25	24	Interference dissociation	No	Sinus bradycardia
53	0	0	14	Upper nodal rhythm interference dissociation	Ventricular extrasystoles	Sinus bradycardia
52	0	0	45	Lower nodal rhythm interference dissociation	No	Sinus bradycardia

None had electrocardiographic evidence of cardiac arrhythmias in the control tracings. In 22 patients, sinus bradycardia at a rate of 60 or less per minute was the prevailing rhythm before the injection of atropine. The other three cases showed middle nodal rhythm. Sixty per cent had systolic hypotension of no less than 20 per cent decrease from the preoperative systolic level.

The injection of atropine produced a pressor response in all the patients with hypotension, the systolic increase being usually of equal or greater magnitude than the original decrease from preoperative levels. Sixteen patients (64 per cent) showed cardiac arrhythmias usually within 30 to 50 seconds after the intravenous administration of atropine. All of these early arrhythmias were of supra-

ventricular origin. Interference dissociation, with and without synchronization (fig. 1), was seen in 11 patients (40 per cent); seven patients had upper, middle or lower nodal rhythms; auricular extrasystoles were recorded in one case (4 per cent). Several patients had more than one type of arrhythmia.

One patient developed nodal tachycardia at a rate of 120 per minute. Careful inspection of the tracings failed to reveal any instances in which the bradycardia was intensified after the injection of atropine.

Usually, within 90 to 120 seconds after the atropine injection, late arrhythmias became evident, all of them being of ventricular origin (fig. 2). Three patients had ventricular extrasystoles. One of these patients had simultaneously a ventricular parasystolic rhythm and interference dissociation. All three patients had also shown the earlier type arrhythmias.

Average pulse increase was 30 beats per minute.

Group B. The 25 patients in this group (table 2) received scopolamine 0.2 mg. intravenously during the period of bradycardia. None had cardiac arrhythmias prior to the sinus bradycardia evident in all the tracings at the time of the scopolamine injection. Fifty-six per cent also had systolic hypotension during the period of bradycardia.

The intravenous injection of 0.2 mg. of scopolamine produced a pressor effect similar to that seen in the patients of group A.

Eleven patients (44 per cent) showed early cardiac arrhythmias of supraventricular origin usually within 20 to 30 seconds after the injection of scopolamine. Interference dissociation, with and without synchronization, was the most common arrhythmia (36 per cent of patients); two cases showed atrial pre-
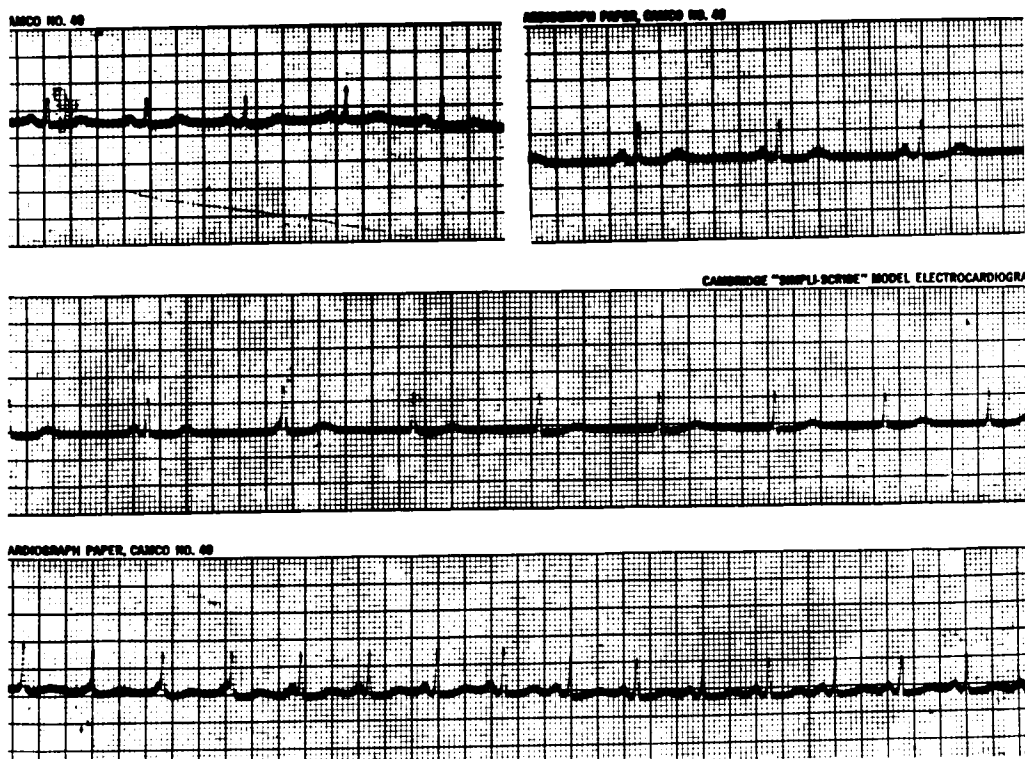

FIG. 1. Interference dissociation after 0.2 mg. of atropine sulphate, intravenously, during cyclopropane-succinylcholine anesthesia. *Top left*—Preoperative, heart rate 80 per minute. *Top right*—Bradycardia during cyclopropane-succinylcholine, 52 per minute. *Middle*—Onset of interference dissociation with synchronization, after intravenous atropine sulphate, 0.2 mg. *Bottom*—Transition from interference dissociation to normal sinus rhythm, 95 per minute.

mature systoles; three cases had slow nodal rhythms and one case had multifocal ventricular extrasystoles.

Late arrhythmias were recorded from two to four minutes after the injection of scopolamine. Eight patients (32 per cent) showed occasional ventricular extrasystoles or extrasystolic coupling. Five of these eight patients also had shown the earlier arrhythmias, and one of the five also had ventricular parasystolic rhythm during an episode of interference dissociation. The average pulse increase was 36 beats per minute.

Group C. Of the 20 patients in this group, ten received intravenous atropine 0.1 mg. and ten received intravenous scopolamine 0.1 mg. during the period of bradycardia. Among the ten patients who received atropine, five developed supraventricular arrhythmias (interference dissociation); one case showed ventricular extrasystoles and one had ventricular parasystolic rhythm during interference dissociation. The average increase in pulse rate was 17 beats per minute for the atropine group.
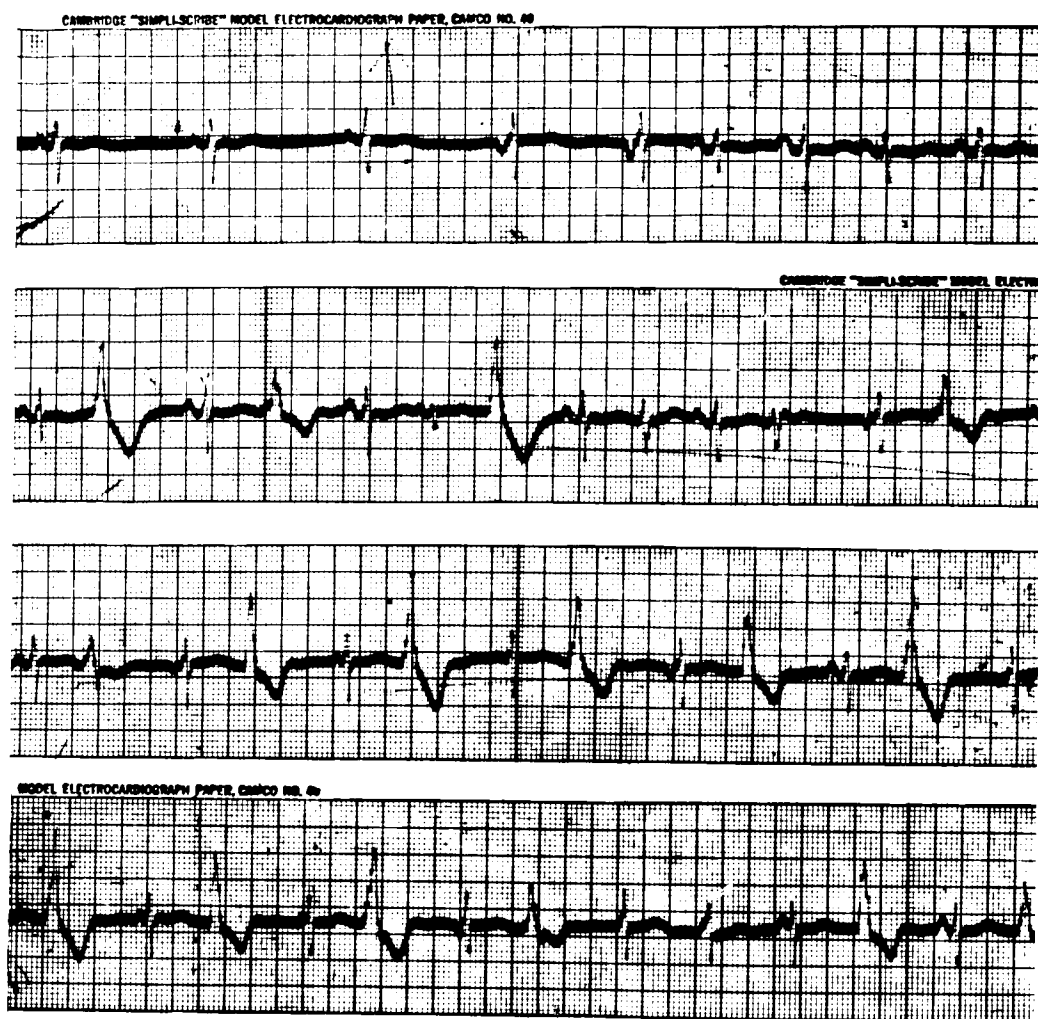
The chronotropic effect took an average of

Fig. 2. Serious alteration of cardiac rhythm following intravenous administration of 0.2 mg. of scopolamine hydrobromide during cyclopropane-succinylcholine anesthesia. Parasystolic focus activating the ventricle with simultaneous interference dissociation; atrioventricular node also stimulating the ventricles.

TABLE 2. Fourteen of 25 Patients Showing Early or Late Arrhythmias after Scopolamine (0.2 mg. Intravenously) During Cyclopropane-Succinylcholine Anesthesia

Age	Systolic Decrease, mm. Hg	Pressor Effect, mm. Hg Systolic	Decrease in Pulse Rate	Early Arrhythmias	Late Arrhythmias	Cardiac Rhythm at Height of Bradycardia
46	0	5	25	Interference dissociation atrial extrasystoles nodal tachycardia	Ventricular extrasystoles	Sinus bradycardia
47	0	0	17	Interference dissociation upper nodal rhythm	No	Sinus bradycardia
53	0	0	15	Interference dissociation ventricular parasystoles	Ventricular extrasystoles	Sinus bradycardia
32	0	10	25	Interference dissociation	Ventricular extrasystoles auricular extrasystoles	Sinus bradycardia
34	15	25	22	Upper nodal rhythm	No	Sinus bradycardia
46	20	15	24	Interference dissociation	Nodal tachycardia	Sinus bradycardia
38	10	15	12	Interference dissociation and synchronization nodal tachycardia	No	Sinus bradycardia
65	15	15	25	Auricular extrasystoles	Ventricular extrasystoles	Sinus bradycardia
33	10	15	5	Interference dissociation lower nodal rhythm	Ventricular extrasystoles	Sinus bradycardia
24	10	15	20	No	Ventricular extrasystoles	Sinus bradycardia
51	20	20	15	No	Ventricular extrasystoles	Sinus bradycardia
40	20	40	23	No	Ventricular extrasystoles	Sinus bradycardia
33	0	10	26	Interference dissociation	No	Sinus bradycardia
51	20	30	20	Interference dissociation lower nodal rhythm	No	Sinus bradycardia

80 seconds to become noticeable in the electrocardiographic tracing. There was no further slowing of the pulse after the injection of atropine.

Of the ten patients who received intravenous scopolamine (0.1 mg.), six (60 per cent) developed interference dissociation, and four patients showed ventricular extrasystoles. The pulse increase averaged 25 beats per minute, and this increase became evident after an average of 34 seconds.

The pressor response in this group was similar to that previously described for groups A and B.

TABLE 3.   Summary of Intravenous Atropine and Scopolamine Effects
During Cyclopropane–Succinylcholine Anesthesia

Group		Pressor Effect (Per Cent)	Supraventricular Arrhythmias (Per Cent)	Ventricular Arrhythmias (Per Cent)	Average Pulse Increase (Beats/Minute)
A	Atropine sulphate 25 cases, 0.2 mg.	100	64	12	30 (100%)
B	Scopolamine hydrobromide 25 cases, 0.2 mg.	100	44	32	36 (100%)
C	Atropine sulphate 10 cases, 0.1 mg.	100	50	20	17 (100%)
	Scopolamine hydrobromide 10 cases, 0.1 mg.	100	60	40	25 (100%)
D	Atropine sulphate 10 cases, 0.08 mg.	75	30	0	26 (50%)
	Scopolamine hydrobromide 10 cases, 0.08 mg.	100	0	0	26 (100%)

Group D. In this group of 20 patients, ten received atropine 0.08 mg. intravenously during the period of bradycardia, and ten received 0.08 of scopolamine.

Only three patients in the atropine group showed interference dissociation. Ventricular arrhythmias were not noted. The pulse increase averaged 20 beats per minute in the five patients showing a pulse rate increase and it took an average of 120 seconds for the pulse increase to become manifest. In five patients, no effect was noted on rate or rhythm. Hypotension was corrected in three of four patients.

In the ten patients who received scopolamine, supraventricular or ventricular arrhythmias were not registered. The average pulse increase was 26 beats per minute, and this increase was evident after an average of 65 seconds. A favorable pressor response was observed in the patients having hypotension, and acceleration of the pulse was noted in all cases.

Group E. This group of 25 patients, received pentobarbital and meperidine for premedication. They were given either atropine or scopolamine, 0.2 mg. intravenously, about 20 minutes before induction of anesthesia. In none of these patients was there electrocardiographic evidence of early or late arrhythmias after the injection of the drugs. Cardiac acceleration was evident in all the cases; sinus tachycardia was seen in seven patients.

A definite slowing of the pulse rate was registered in ten of the 12 patients receiving intravenous atropine, and in 11 of the 13 patients who received intravenous scopolamine. After the initial slowing effect of the drugs, cardiac acceleration followed.

Table 3 gives a summary of our results in groups A, B, C and D.

Discussion

During cyclopropane anesthesia and also after the administration of succinylcholine chloride, bradycardia, varying degrees of cardiac rate slowing and arrythmias have been reported.

Leigh *et al.*[1] noted bradycardia in infants and children following the intravenous use of succinylcholine, and offered the possible explanation that the accumulation of acetylcholine derived from succinylcholine in infants and children who have a low true cholinesterase activity may be responsible for the bradycardia. More recently Craythorne, Turndorf and Dripps[2] reported their observations on cardiac arrhythmias and bradycardia following the intravenous administration of succinylcholine to infants and children during

anesthesia. These changes were not evident when the drug was used intramuscularly. They suggested the possibility that a dual sympathetic and parasympathetic stimulation can be produced by succinylcholine.

Cyclopropane, which seems capable of sensitizing the myocardium to the action of catecholamines,[3] has also been considered to have cholinergic effect on the heart.[4,5]

It is thus likely that in our patients the heart was under the cholinergic effects of both cyclopropane and succinylcholine. Cholinergic activity or vagal stimulation is known to slow sinoatrial nodal pacemaker activity by decreasing the slope of diastolic depolarization. Prepotential action currents are eliminated by acetylcholine and areas like the sinoatrial node lose their rhythmic activity.[6] Under these conditions the rhythmicity of the atrioventricular node remains the same or increases somewhat.[7]

According to Morton and Thomas[8] rapid intravenous atropine administration up to 0.6 mg. causes initial slowing of the heart before producing cardiac acceleration. This was clearly demonstrated in our group of unanesthetized patients who received 0.2 mg. of atropine or scopolamine intravenously. We did not observe this effect on the heart rate in the anesthetized subjects probably because moderate to intense cardiac slowing and sinoatrial depression was already evident as a result of the combined cholinergic effects of cyclopropane and succinylcholine.

The supraventricular arrhythmias exhibited by our patients after atropine or scopolamine administration could be explained by their early vagotonic effect on the sinoatrial node or they could also be the result of the early unmasking of sympathetic activity during the initial weak blockade of vagal fibers produced by atropine and scopolamine, since it is known that sympathetic stimulation, epinephrine and norepinephrine tend to depress sinoatrial node dominance and to institute atrioventricular node dominance of the heart.[9]

The vagal stimulating effect of atropine and scopolamine on the sinoatrial node which was already under intense cholinergic influence, favors the onset of nodal rhythms through downward displacement of the pacemaker. The effect of the early unopposed sympathetic

activity initiated by the partial vagal blockade of atropine and scopolamine, on the atrioventricular node, more readily explains the onset of interference dissociation and rapid impulse formation at the atrioventricular node, instead of the slow nodal rhythms that would be expected if the inherent rhythmicity of the atrioventricular node were not increased by the early preferential unmasking of sympathetic activity at the atrioventricular node.

Later, with the establishment of a more intense partial vagal blockade, stronger sympathetic predominance becomes evident as indicated by the onset of ventricular arrhythmias in our patients.

The appearance of interference dissociation followed a general pattern of sudden increased rhythmicity and firing of the atrioventricular node. This rapid activity is able to capture the ventricles while the atrias are still responding to the impulses originating from the sinoatrial pacemaker. This, in fact, is a true parasystolic rhythm. This observation is in general agreement with Wilson's concept [10] of the origin of interference dissociation. He explained the susceptibility of the heart to atrioventricular dissociation during the early action of atropine by proposing a selective action of the drug in blocking the vagal fibers of the atrioventricular node before it paralyzes those of the sinoatrial node.

In our second group of patients (group B) scopolamine 0.2 mg. was given intravenously instead of atropine. It has been stated that the action of atropine is more pronounced and more prolonged on the heart, intestines and bronchial musculature than that of scopolamine.[11] According to our results, the early or supraventricular arrhythmias appeared sooner after scopolamine than after atropine, but the number of patients with the early type of arrhythmias was higher in the atropine group. The late or ventricular arrhythmias were found to be about three times as frequent after scopolamine than after atropine administration, suggesting a slower but more intense partial vagal blockade by scopolamine.

The results in the group of unanesthetized patients (group E) indicate that in the absence of the sensitizing effect of cyclopropane on the heart, the intravenous injection of 0.2 mg. of atropine or scopolamine, produces an

early negative chronotropic effect in the great majority of cases without apparent disturbances in rhythm, followed by cardiac acceleration.

To those patients in group *C*, we administered smaller amounts of atropine and scopolamine (0.1 mg.) under otherwise the same conditions of anesthesia with cyclopropane and succinylcholine. Our results clearly indicate that during cyclopropane succinylcholine anesthesia, the intravenous use of 0.2 or 0.1 mg. of atropine or scopolamine will produce clinically unimportant supraventricular arrhythmias but also potentially dangerous ventricular arrhythmias.

By further reducing the dose of atropine and scopolamine to 0.08 mg., we found in group *D* that it is possible to achieve a favorable pressor response and also reverse the slow heart rhythms without provoking the potentially dangerous sympathetic dominance which became manifest in the other group of patients receiving larger intravenous quantities of the drugs .

It has recently been shown[12] that the response to atropine injected intravenously during cyclopropane anesthesia is dependent upon the anesthetic concentration of cyclopropane, deeply anesthetized patients showing a higher incidence of ventricular arrhythmias.

It is also probable, in view of the above findings, that patients lightly anesthetized with cyclopropane, will tolerate larger doses of atropine and scopolamine intravenously before ventricular arrhythmias becoming evident.

At the low dosage level of 0.08 mg., intravenous atropine is too weak to produce consistent favorable pressor or chronotropic effects. Scopolamine in this dose is capable of eliciting a constant favorable pressor response as well as a definite increase in the pulse rate without producing arrhythmias.

The fact that ventricular arrhythmias can be readily produced after a relatively small dose of atropine and scopolamine during cyclopropane-succinylcholine anesthesia should warn against the indiscriminate intravenous use of these drugs under these conditions, or when using hydrocarbon anesthetics which may sensitize the myocardium to the action of catecholamines.

Ventricular extrasystoles are potential precursors of more serious types of cardiac arrhythmias. Since a premature systole has a shorter refractory period than the previous cycle beat and its latency is shortened relatively more than its refractory period, a single extrasystole occuring in a heart cycle, makes the heart muscle susceptible to rapid rhythms. Extending this concept to drug action, di Palma[9] stated that if a drug is capable of producing premature systoles, it will also cause more serious arrhythmias.

The decision to use these drugs intravenously during cyclopropane-succinylcholine anesthesia should be based upon a sound appraisal of the clinical situation, especially since we are unable to measure routinely cyclopropane concentrations in every-day clinical practice. Only if critically low heart rates threaten the stability of cardiovascular dynamics in adult patients, may we feel justified in cautiously administering a single intravenous dose of atropine or preferably scopolamine (0.08 mg.). This minimal amount in the majority of instances, will be helpful in restoring blood pressures and heart rates to normal or near normal without triggering arrhythmias of ventricular origin.

Summary

The intravenous injection of 0.2, and 0.1 mg. of atropine or scopolamine during the bradycardia produced by cyclopropane-succinylcholine anesthesia, produced supraventricular and ventricular arrhythmias in a large percentage of cases. Arrhythmias were not noted when 0.2 mg. was administered intravenously to unanesthetized patients.

When smaller doses of atropine and scopolamine were used (0.08 mg.), ventricular arrhythmias were not recorded, and a favorable pressor effect and positive chronotropic effect was noted in the majority of the patients. Scopolamine seems to be more reliable than atropine in producing these effects.

According to our results, the intravenous use of atropine or scopolamine during cyclopropane succinylcholine anesthesia is a hazardous procedure which may produce dangerous ventricular arrhythmias unless small single doses of 0.08 mg. are used.

References

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BURN THERAPY Respiratory tract damage was found to be the essential factor in the death of 106 consecutive burn cases in a series of 1,140 burned patients treated at the Massachusetts General Hospital from 1939 to 1958. About 42 per cent of the fatal cases expired without complicating respiratory tract sepsis. Such sepsis, as a rule, occurs if a patient survived 72 hours. Shock, accounting for 20 per cent of all fatal burn cases in the past, has become a relatively insignificant factor. Increased survival time in burn cases in recent years has resulted in an increase in wound sepsis and incidence of uremic death. Pulmonary embolism and adrenal hemorrhage were relatively uncommon occurrences. (*Phillips, A. W., and Cope, O.: Burn Therapy. II. The Revelation of Respiratory Tract Damage as a Principal Killer of the Burned Patient, Ann. Surg. 155: 1 (Jan.) 1962.*)

FRESH WATER DROWNING In a previous animal study designed to simulate clinical conditions occurring in human fresh water drowning ventricular fibrillation occurred within three minutes after flooding the lungs with fresh water following an episode of obstructive asphyxia. The present study demonstrates the efficacy of positive pressure breathing with 100 per cent oxygen, closed chest cardiac massage, and external electrical defibrillation in resuscitating dogs subjected to simulated fresh water drowning. Although 100 per cent oxygen was superior to air as the inflating gas, resuscitation was not impossible with air. All dogs died within 24 hours with massive hemolysis and myocardial failure. (*Redding, J. S., and Cozine, R. A.: Restoration of Circulation after Fresh Water Drowning. J. Appl. Physiol. 16: 1071 (Nov.) 1961.*)