CONTROL OF VAGAL CARDIOVASCULAR REFLEXES DURING SURGERY EMPLOYING β-DIETHYLAMINOETHYL XANTHENE-9-CARBOXYLATE METHOBROMIDE * † ‡

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Instances of vagal cardiac inhibition have appeared in the literature since 1850, when Weber and Weber (1) showed the inhibitory effect of the vagus nerve on the heart. Review of the subsequent literature dealing with increased vagal tone has shown that irritation of the olfactory nerve of the rabbit produced bradycardia and cardiac arrest (2), pressure on the larynx produced bradycardia which disappeared after atropinization (3), stimulation of peribronchial, vascular or pleural nerve plexuses produced vagal cardiovascular reactions (4), congestion and edema of the lungs resulted in bradycardia and rapid shallow breathing (5), bronchial constriction produced severe cardiac inhibition and death (6–8), and cardiac damage was a precipitating factor in those reactions occurring during endotracheal intubation under anesthesia. As these reactions have in common an increased vagal tone it was anticipated that methantheline bromide * because of its parasympatholytic and ganglionic blocking properties might be useful for inhibiting these reactions and for correcting those cardiovascular disorders which are associated with an increased vagal tone.

The purpose of this paper is fourfold: (1) to determine the frequency of vagal cardiovascular reflexes among normotensive and hypertensive subjects undergoing surgical procedures; (2) to establish the value of methantheline bromide in the prophylaxis of vagal cardiovascular reflexes occurring during surgery; (3) to evaluate the combined use of digitalis and methantheline bromide in the prophylaxis of this reaction, and (4) to decide whether or not the ganglionic blockade produced by methantheline bromide significantly inhibits sympathetic as well as parasympathetic activity.

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METHODS AND MATERIALS

Two hundred and ninety individuals were studied. Of these, 202 were surgical patients who were studied before, during and after surgery and 88 were nonsurgical patients who were studied medically (table 1).

TABLE 1

PATIENTS STUDIED

Surgical Patients

Type of Operation	Number of Patients	Percentage*
1. Pulmonary resections	80	39.6
2. Extrapleural chest operations	14	6.9
3. Intrapleural operations other than resections including thoracotomies, mediastinal tumors, decortications, hamartoma, thoracolumbar sympathectomy, diaphragmatic hernias	46	22.7
4. Esophagectomy and esophagogastrostomy	7	3.4
5. Coarctation of aorta	17	8.4
6. Mitral commissurotomies	13	6.4
7. Patent ductus arteriosus	12	5.9
8. Pericardial operations	3	1.5
9. Bone flap	1	.5
10. Substernal thyroidectomy	1	.5
11. Abdominal	8	4.0
	202	99.8

Medical Patients

Type of Disease	Number of Patients	Percentage
1. Normal subjects	13	14.8
2. Hypertension and arteriosclerosis	51	57.9
3. Arteriosclerosis obliterans and thromboangiitis obliterans	24	27.2
	88	99.9

Of the surgical patients, 194 had operations on or within the chest and 8 had operations within the abdomen. The average age for the surgical group was 45 years (range 12 to 78), and 51 per cent were males. Fifty-two per cent of the group undergoing a surgical procedure were poor operative risks because of the presence of cardiac disease.

For purposes of comparison the surgical patients were divided into four groups. All patients of all four groups received morphine, scopolamine and seconal® preoperatively. Group I consisted of 79 patients who received no additional medication; group II, 55 patients who received digitoxin®, 0.8 or 1.2 mg., orally, twelve hours before surgery; group III, 27 patients who received methantheline bromide, 50 to 100 mg. orally, one to two hours preoperatively, and group IV, 41 patients who received digitoxin® and methantheline bromide in the doses prescribed.

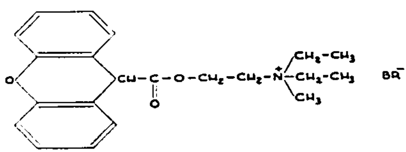
Anesthesia consisted of pentothal® and curare for intubation and ether and oxygen or nitrous oxide and oxygen for maintenance. Intermittent direct-writing electrocardiographic tracings with a Sanborn visocardiette and continuous cathode-ray oscilloscopic visualizations were made throughout anesthesia on 152 patients.

The 88 medical patients consisted of patients with hypertension and peripheral vascular disease. The average age was 44 years (range 30 to 65). Forty-eight per cent were males. The medical studies were carried out before and after administration of 50 to 150 mg. of methantheline bromide orally, or 5 to 8 mg. intravenously. In all instances the last dose was given one hour before testing. Medical studies were made in an air-conditioned room with a room temperature of 25 C., ±1.5. Measurements of relative blood flow through the finger or toe were made with a digital pneumoplethysmograph (12). Blood pressures were recorded by auscultation or with the sphygmotonograph (13). Hypertension was considered to be present when the blood pressure was greater than 150 mm. of mercury systolic or 90 mm. diastolic.

Chemically, methantheline bromide is a quaternary amine which is readily soluble in ordinary solvents and in gastric and intestinal secretions (14–16). Its empiric and descriptive formulas are shown in figure 1.

RESULTS

The frequency of vagal cardiovascular reactions was determined in 202 surgical patients (fig. 2). Eighty-three of these patients were hypertensive and 119 normotensive. In the total group the frequency of reactions among patients of groups II and III was less than those of group I and was significant statistically in both groups at the 5 per cent level. Group IV as compared with group I showed a highly significant reduction in frequency which was significant at the 1 per cent level. That this is due to the drug rather than to the presence or absence of hypertension is shown by the essentially equal distribution of hypertensive patients in the four groups. In groups I, II, III and IV the



β-DIETHYLAMINOETHYL XANTHENE-9-CARBOXYLATE METHOBROMIDE (BANTHINE)

FIG. 1.

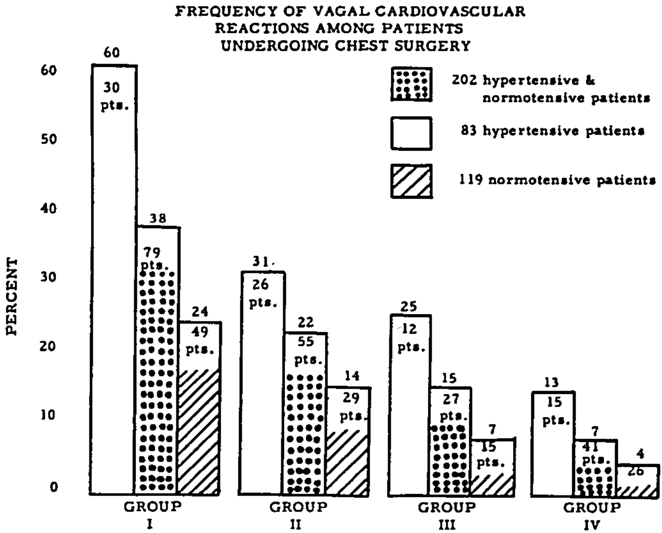


FIG. 2.

percentage of hypertensive patients was 38, 47, 44 and 37 per cent, respectively. Among the 83 hypertensive patients there was a significant reduction in the frequency of reactions among those in groups II and III as compared with group I. This occurred in both groups at the 5 per cent level. A still further reduction was seen in patients in group IV as compared with patients of group I and here there was a highly significant reduction at the 1 per cent level. Among the 119 normotensive subjects, comparisons of groups II, III and IV with group I showed a reduction in each case which was significant at the 5 per cent level. Thus it is concluded that the preoperative use of digitalis and methantheline bromide resulted in a significantly low incidence of vagal cardiovascular reactions among normotensive patients undergoing operation. Among hypertensive patients the incidence was still lower.

A high incidence of vagal cardiovascular reactions among patients undergoing operation for correction of hiatus hernia and carcinoma of the esophagus was encountered. Of 17 patients undergoing these operations 80 per cent showed vagal cardiovascular reactions. These reactions occurred during incision of the chest or abdominal wall and were not specifically associated with manipulation of the diaphragm or esophagus. This is a higher incidence of reactions than among any of the other types of surgical procedures in this series.

The time of occurrence and severity of vagal reactions was studied in 49 patients. The time was measured from a rapid intubation to the onset of hypotension and bradycardia. The average time was thirty-two minutes, the range 0 to ninety minutes. In two instances the reaction occurred during intubation and it was thought that this was the etiology of the reaction. In most instances, however, the reaction occurred during incision of the chest wall before periosteal scraping had begun. Three reactions occurred ninety minutes after intubation and were associated with traction on the hilum of the lung, retraction of the heart and vagotomy. In half of the patients a precipitous fall in blood pressure and pulse rate occurred with little warning. In the remainder, a gradual decrease in the pulse rate for twenty to thirty minutes preceded the onset of hypotension. The severity of the reaction is shown in table 2.

The effect of methantheline bromide on increased vagal tone due to digitalis intoxication was studied to determine whether methantheline bromide could reduce the toxicity of digitalis, thereby making this drug more suitable for preoperative preparation of surgical patients with cardiac disease. The patient studied was a 58 year old woman with arteriosclerotic coronary artery disease who reentered the hospital on two occasions because of digitalis intoxication. On the first admission an electrocardiogram showed the presence of sino-auricular block, occasional nodal escape beats and a definite digitalis effect. At this time she gave a history of taking 0.4 Gm. of digitalis leaf daily for six weeks. Eight milligrams of methantheline bromide was given intravenously. One minute later the pulse became regular with the establishment of sinus tachycardia with a rate of 120 beats per minute. The patient was discharged with normal sinus rhythm. She returned six months later, after having taken 0.4 Gm. of digitalis daily for one month. The electrocardiogram showed a 2:1 auriculoventricular block which reverted to a sinus tachycardia after the intravenous injection of 5 mg. of methantheline bromide (fig. 3). She returned two months later after having taken 0.3 Gm. of digitalis daily for eight weeks (fig. 4A and B). An electrocardiogram showed the presence of a sino-auricular block which was treated with 5 mg. of methantheline bromide intravenously. Three minutes after the drug was taken a normal sinus rhythm was established (fig. 4C). One hundred minutes later sino-auricular block with nodal beats was seen (fig. 4D). One hundred minutes later a normal sinus rhythm was again observed (fig. 4E). The drug was given every four hours orally which maintained a normal sinus rhythm for at least sixteen hours (fig. 4G). Similar restoration of sino-auricular and auriculoventricular block to sinus rhythm or sinus tachycardia has been observed in 3 other subjects with digitalis intoxication.

Tests of the effect of methantheline bromide on the sympathetic nervous system were carried out to determine whether a significant

TABLE 2

TOTAL NUMBER OF PATIENTS HAVING VAGAL SHOCK

Group I—No specific prophylactic treatment

Patient number	Age, years	Diagnosis	Operation	Minutes after intubation	Blood pressure before, during, after atropine therapy	Pulse rate before, during, after atropine therapy
1	26	Coarctation of aorta	Aortectomy	90	240/90—125/80—150/75	126—72—80
2	31	Pulmonary tuberculosis	Pneumonectomy	60	124/80—50/35—110/80	76—60—100
3	47	Carcinoma of esophagus	Esophagectomy	45	140/82—85/60—130/80	96—72—120
4	70	Hamartoma of lung	Lobectomy	35	140/80—110/70—160/90	80—60—115
5	27	Patent ductus arteriosus	Division and suture	35	150/90—110/65—135/80	100—66—100
6	63	Hiatus hernia	Transthoracic repair	20	160/90—90/60—120/70	60—60—64
7	56	Bronchogenic carcinoma	Lobectomy	15	140/80—100/55—120/60	72—72—72
8	66	Bronchogenic carcinoma	Lobectomy	60	200/100—100/80—160/100	90—60—120
9	51	Bronchiectasis	Lobectomy	25	150/105—100/60—120/80	92—74—100
11	22	Neoplasm of lung	Pneumonectomy	50	120/90—90/55—140/80	80—60—120
12	33	Coarctation of aorta	Aortectomy	17	210/105—95/65—140/90	100—68—100
13	46	Hiatus hernia	Transthoracic repair	30	130/80—90/55—115/70	105—68—104
14	31	Pulmonary tuberculosis	Lobectomy	30	118/90—90/65—130/85	115—68—132
15	55	Granuloma of lung	Lobectomy	55	120/80—60/40—125/80	74—54—112
16	60	Bronchogenic carcinoma	Lobectomy	30	130/85—115/80—130/90	80—65—92
17	31	Pericardial cyst	Excision	60	120/80—75/50—110/70	105—66—120
18	64	Bronchogenic carcinoma	Pneumonectomy	40	140/82—70/50—120/70	100—58—120
20	27	Coarctation of aorta	Aortectomy	30	168/80—100/55—130/85	84—75—120
21	71	Bronchiectasis	Pneumonectomy	90	132/80—0/0—110/80	80—60—120
22	64	Diaphragmatic hernia	Transthoracic repair	20	150/100—130/90—150/100	88—78—120
29	36	Coarctation of aorta	Aortectomy	25	188/80—90/60—100/60	80—64—80
37	33	Coarctation of aorta	Aortectomy	25	190/120—110/70—140/80	110—72—110
40	27	Mediastinal tumor	Excision	30	120/80—75/50—120/75	105—60—130
42	29	Pulmonary tuberculosis	Lobectomy	20	105/70—80/60—100/70	100—60—120
43	38	Bronchiectasis	Lobectomy	20	142/92—90/70—120/70	90—64—90
47	30	Pulmonary tuberculosis	Lobectomy and thoracoplasty	20	120/70—80/60—118/80	85—72—135
48	65	Carcinoma of esophagus	Esophagectomy	0	155/70—70/? —105/65	85—72—90
49	37	Pulmonary tuberculosis	Lobectomy and thoracoplasty	30	112/78—55/40—95/60	110—84—120
Mean	44			36	147/86—87/56—125/77	92—67—107
Maximum	71			90	240/120—130/90—160/100	126—78—135
Minimum	22			0	105/70—0/0—95/60	60—54—64

TABLE 2—*Continued*

Group II—Digitalis preoperatively

Patient number	Age, years	Diagnosis	Operation	Minutes after intubation	Blood pressure before, during, after atropine therapy	Pulse rate before, during, after atropine therapy
10	69	Mediastinal tumor	Resection	30	190/110—130/80—200/110	80—54—104
26	22	Coarctation of aorta	Aortectomy	20	180/105—120/75—175/90	140—86—140
33	68	Bronchogenic carcinoma	Thoracotomy	17	110/70—70/50—130/80	80—75—82
34	68	Carcinoma of esophagus	Esophagectomy	40	180/90—115/85—180/100	90—60—115
35	69	Carcinoma of esophagus	Esophagectomy	45	150/90—70/55—120/80	60—60—100
36	69	Bronchogenic carcinoma	Pneumonectomy	15	145/80—80/60—125/85	76—66—100
38	71	Duodenal ulcer	Vagotomy and gastroenterostomy	90	138/84—35/20—130/80	125—50—120
39	56	Pulmonary tuberculosis	Lobectomy	25	135/70—80/55—120/80	100—60—100
41	38	Pulmonary tuberculosis	Lobectomy	25	130/80—80/55—115/70	85—60—120
44	23	Coarctation of aorta	Aortectomy	22	180/80—110/75—160/80	85—64—85
45	24	Coarctation of aorta	Aortectomy	23	170/90—85/60—135/80	115—66—125
46	58	Pulmonary tuberculosis	Thoracoplasty	0	175/90—110/70—170/110	64—64—85
Mean	53			29	157/86—90/61—147/87	92—64—105
Maximum	71			90	190/110—130/85—200/110	140—86—125
Minimum					110/70—35/20—115/70	60—54—82
Group III—Methantheline Bromide preoperatively						
19	46	Pulmonary tuberculosis	Lobectomy	35	140/90—90/65—135/90	94—68—86
23	57	Diaphragmatic hernia	Transthoracic repair	30	130/80—95/60—120/75	74—60—85
24	60	Bronchogenic carcinoma	Thoracotomy	30	135/70—90/55—110/60	84—68—84
25	63	Bronchogenic carcinoma	Lobectomy	30	170/80—90/50—120/70	85—76—90
27	62	Diaphragmatic hernia	Transthoracic repair	5	140/85—90/55—120/80	80—60—74
Mean	58			26	143/81—91/57—121/75	83—67—84
Maximum	63			35	170/90—95/65—135/90	94—76—90
Minimum	46			5	130/70—90/50—110/60	74—60—74
Group IV—Digitalis and Methantheline Bromide preoperatively						
28	53	Bronchogenic carcinoma	Lobectomy	45	180/100—140/90—160/95	128—74—130
30	52	Diaphragmatic hernia	Transthoracic repair	35	150/94—95/70—110/75	100—84—95
31	66	Carcinoma of esophagus	Esophagectomy	45	125/75—75/50—120/80	80—64—85
32	71	Carcinoma of esophagus	Esophagectomy	20	110/70—60/40—120/85	72—72—96
Mean	61			36	142/85—93/62—127/84	95—74—102
Maximum	71			45	180/100—140/90—160/95	128—84—130
Minimum	52			20	110/70—60/40—110/75	72—64—85

EFFECT OF METHANTHELINE BROMIDE
ON A V BLOCK IN A PATIENT WITH
DIGITALIS INTOXICATION

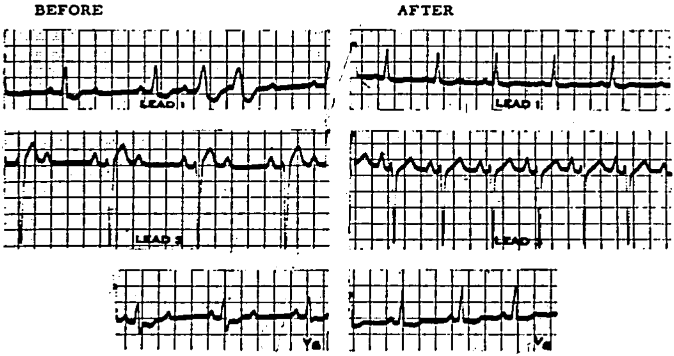


FIG. 3.

degree of blocking of the sympathetic nervous system at the level of the sympathetic ganglions occurred when therapeutic doses of methantheline bromide were administered.

A. Posture Test: The pulse rate and blood pressures were studied in 30 patients in the supine and standing positions before and one hour after administration of 150 mg. of methantheline bromide to determine the effect of the drug on the pulse rate and blood pressure. With the subject in the horizontal position, the pulse rate after methantheline bromide increased an average of 10 beats and the systolic and diastolic blood pressure increased an average of 5 per cent and 3 per cent, respectively. When the patient assumed the upright position, there was an additional 10 per cent increase in pulse rate and a 5 per cent increase in systolic and diastolic blood pressures, respectively. Thus methantheline bromide in these doses did not produce postural hypotension and had no sympatholytic effect.

B. Flack Test: The blood pressure was determined in 30 subjects before and after blowing against a resistance of 30 mm. of mercury for twenty seconds and before and one hour after administration of 100 mg. of methantheline bromide orally, in order to determine the effect of the drug on the normal pressor reaction to blowing. Before administration of methantheline bromide the average rise in systolic pressure after blowing was 8 mm. of mercury, while after the drug it was 10 mm. of mercury. Thus this reflex was not blocked with this dose of the drug, indicating no sympatholytic effect.

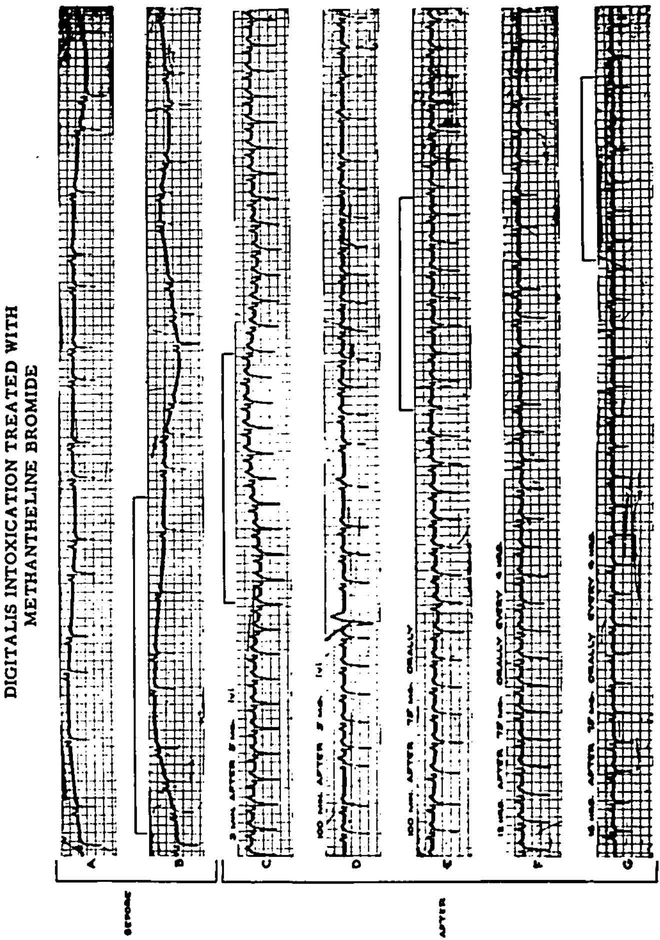

DIGITALIS INTOXICATION TREATED WITH
METHANTHELINE BROMIDE
BEFORE
AFTER

FIG. 4.

C. Cold Pressor Test: This test was carried out on 20 subjects before and one hour after oral administration of methantheline bromide to determine the effect on the pressor response to cold. Before methantheline bromide the average rise in blood pressure was 21 mm. of mercury, while after the drug it was 25 mm. of mercury. Thus methantheline bromide failed to interrupt this sympathetic reflex.

D. Digital Vasoconstrictor Reflexes: Vasoconstrictor reflexes were recorded plethysmographically from the finger and toe of 7 patients following startle and painful stimuli before and one hour after administration of 100 mg. of methantheline bromide. The reflex was inhibited to a moderate degree in 4 of the patients, indicating an inconsistent inhibition of the motor nerves.

DISCUSSION

The syndrome of bradycardia and arterial hypotension is commonly referred to as the "vagovagal reflex," which is a term indicating that both the afferent and efferent limbs of the vagus nerve are involved. This term has been correctly used in relation to tracheal intubation and traction on the hilum of the lung where afferent and efferent impulses travel in the vagus nerve. However, this term has been avoided in this paper, as it emphasizes only one of the afferent pathways for this reflex mechanism. As there are many such pathways (intercostal nerves, trigeminal nerves, and so forth), the term "vagal cardiovascular reflex" is used (11). The vagal cardiovascular reflex may be defined as a parasympathetic reaction in which there is increased vagal tone resulting in bradycardia and arterial hypotension.

Certain terms used in this report are described for the purpose of this study as follows: (1) An anticholinergic agent is one which inhibits the action of acetylcholine and which therefore may inhibit impulse transmission across sympathetic and parasympathetic ganglions and parasympathetic impulse transmission at the neuro-effector organ of sweat glands, blood vessels and muscles. Methantheline bromide is classified as such an agent. (2) A ganglionolytic agent is one which inhibits transmission of impulses across parasympathetic and sympathetic ganglions. Hexamethonium chloride is an example. (3) A parasympatholytic agent is one which inhibits parasympathetic impulses at any site along the parasympathetic system. Atropine, which blocks at the neuro-effector organ, is an example. (4) A sympatholytic agent is one which inhibits sympathetic impulses at any site in the sympathetic system. The hydrogenated alkaloids of ergot are such agents. (5) An adrenolytic agent is one which reverses the pressor action of epinephrine. Dibenamine® is an example. It is recognized that the drugs mentioned as examples have other functions and actions in addition to those mentioned.

From these definitions it is apparent that all anticholinergic agents are sympatholytic and parasympatholytic. However, all sympatholytic and parasympatholytic agents are not necessarily anticholinergic. Also all ganglionolytic agents are sympatholytic and parasympatholytic. However, all sympatholytic and parasympatholytic agents are not ganglionolytic. Likewise an adrenolytic agent is necessarily sympatholytic, but a sympatholytic agent is not necessarily adrenolytic.

The data indicate that the frequency and severity of vagal cardiovascular reactions may be intensified by: (1) the presence of underlying disease, especially hypertension or arteriosclerosis, (2) mechanical manipulation of body structures such as the chest wall, carotid sinus, hilum of the lung, diaphragm, trachea, or bronchi, (3) the anesthetic agent itself, such as pentothal® and cyclopropane, or (4) drugs used preoperatively, such as morphine or digitalis. Digitalis is known to be vagotonic in its action and may produce vagal cardiovascular reactions (17–24). The slowing of the cardiac rate among patients with cardiac failure is evidence of its vagotonic effect and the increased duration of asystole following carotid sinus pressure in the digitialized patient is evidence of sensitization to this reaction (25–28). That sensitization is of importance particularly in the overdigitalized patient is well illustrated by figures 2, 3 and 4, where sensitization occurred to such an extent that deep breathing resulted in paroxysmal sinus arrest.

A highly significant reduction in the frequency and severity of the reaction occurred with methantheline bromide combined with digitalis and a significant reduction was seen with methantheline bromide alone. The reduction showed greatest significance among the hypertensive patients. In these studies 50 to 100 mg. of methantheline bromide with an average dose of 75 mg. was effective prophylactic therapy. The larger doses were used among hypertensive patients, among patients receiving digitalis and among those patients undergoing operations for diseases of the chest. With these dosages the heart rate increased slightly but not sufficiently to complicate the surgical procedure.

The time of occurrence of the vagal reaction averaged thirty-two minutes after intubation and was associated most commonly with incision of the chest wall rather than with intubation or hilar traction. This is due presumably to stimulation of the afferent fibers of the intercostal nerves. This is in keeping with the work of Weiss (27), who has shown that the vagal cardiovascular reaction is brought about by stimulation of various afferent pathways and could not be produced by stimulation or irritation of the efferent pathways of the vagus nerve.

These data seem to indicate that severe vagal reactions and sudden death may in certain instances occur from a combination of these vagotonic states and that these reactions may be prevented by the careful consideration of the factors involved and the prophylactic use of parasympatholytic agents.

SUMMARY

The frequency and severity of vagal cardiovascular reactions were studied in 202 patients undergoing chest operations and 88 patients being treated for medical diseases. Four groups of patients were studied. Group I received only the routine preoperative medication of morphine, scopolamine and seconal®. Group II received digitalis in addition. Group III received methantheline bromide, and group IV received digitalis and methantheline combined. The frequency of the vagal reaction among the entire group was highest among those not receiving digitalis or methantheline bromide and lowest among those receiving both of these drugs. Usually, the reaction occurred thirty-two minutes after intubation. Studies on the influence of methantheline bromide upon the medical patients with increased vagal tone due to digitalis intoxication indicate that the former is a powerful antagonist to the vagotonic effect of digitalis. Thus the combined use of these drugs makes possible the utilization of the advantages of digitalis without the fear of increasing vagal reactions which has been for many years a contraindication to the use of digitalis in the preoperative preparation of patients for operation.

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