THE EFFECT OF ANTICHOLINERGIC DRUGS ON THE CARDIAC VAGUS:[1] II, THE CARDIOVASCULAR RESPONSE OF ANIMALS TO ELECTROCONVULSIVE THERAPY[2]

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THE EFFECT of electroconvulsive therapy (ECT) in man poses a number of questions which cannot be answered unequivocally, because the convulsion interferes with the clinical observation of physical signs (palpation of the pulse and auscultation of the heart), and the current generated by the electrical stimulator produces a disturbance in the electrocardiograph recorder. The electrocardiograph tracing is obscured further by action currents from skeletal muscles, particularly during the clonic phase of the convulsion

The following experiments were carried out on animals in order to observe directly the effect of unmodified ECT on the heart and circulatory dynamics. The effect of modifying ECT with thiopental or with succinylcholine and the role which the vagus nerves and anticholinergic drugs may play in modifying cardiac action during such therapy were also studied This information was sought to supplement observations made during clinical investigations on mental patients undergoing ECT (1).

MATERIALS AND METHODS

Direct observations were made first on two rabbits under pentobarbital anaesthesia. Respiration was controlled with an intermittent positive pressure (I.P.P.) pump connected to a tracheotomy tube in order to eliminate the effects of hypoxia and hypercarbia The heart was viewed through a bilateral thoracotomy. After removing the pericardium, silver–silver chloride electrodes were applied to the anterior and posterior aspects of the heart The ECG was recorded on a direct-writing Sanborn Visocardiette Electric shocks of various intensities and durations were applied to the head and to other regions of the body of the rabbit through needle electrodes.

Multiple experiments were carried out then on fifteen mongrel dogs weighing 14 to 44 lb.: before and after cold blocking and electrical stimulation of the vagus nerves, before and after the intravenous administration of thiopental or succinylcholine; and before and after the intravenous administration of anticholinergic drugs (atropine, scopolamine, oxyphenonium, and hexocyclium) or

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sectioning of the vagus nerves. The following animals and preparations were used (Fig. 1):

In four dogs under pentobarbital anaesthesia, respiration was controlled by an I.P.P. ventilator with compressed air or oxygen delivered through an endotracheal tube. Bilateral thoracotomy and pericardectomy were performed to expose the heart and

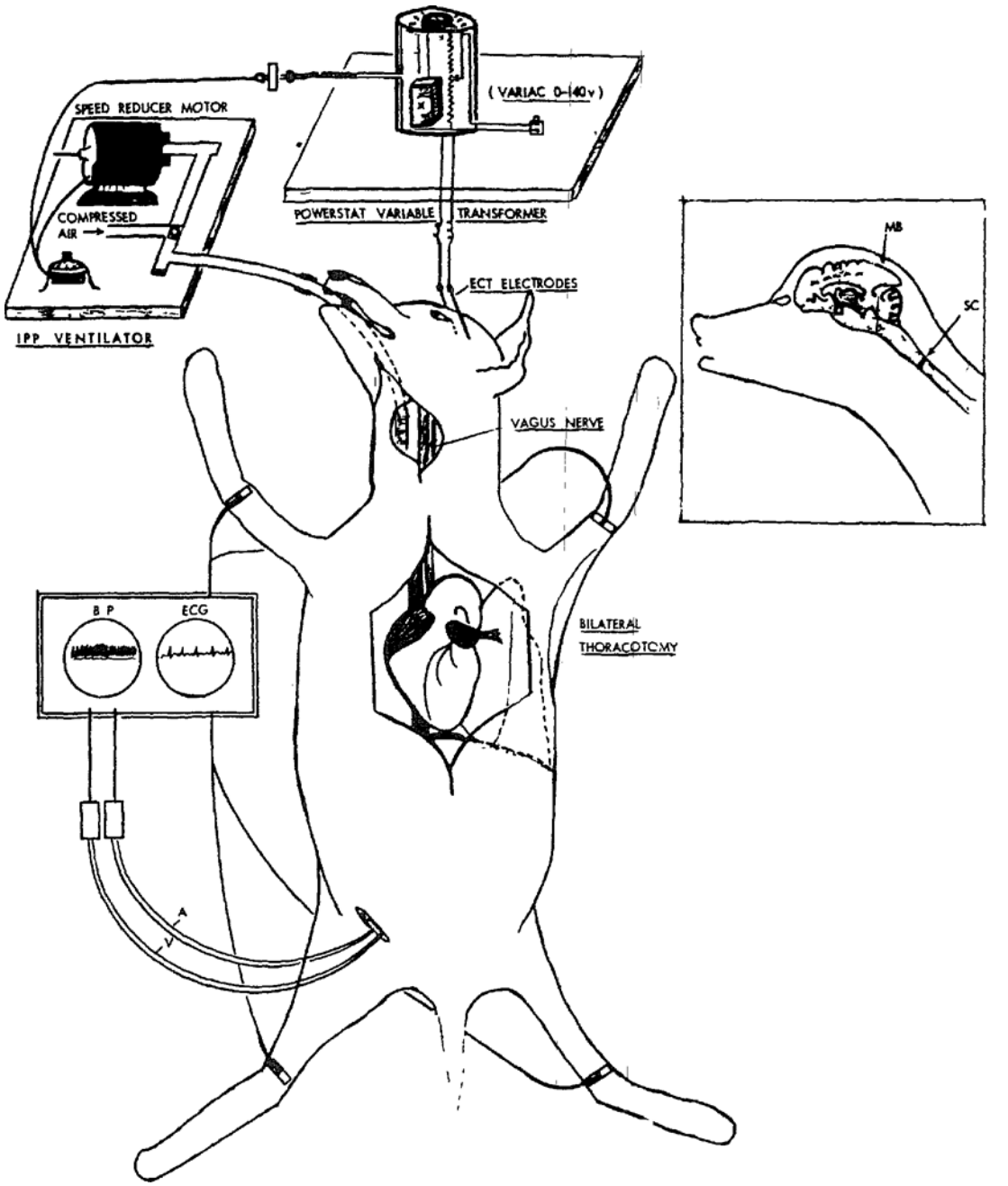


FIGURE 1. Experimental arrangement for observation of the effect of ECT and vagal stimulation on the heart, the blood pressures (aorta and inferior vena cava), and the electrocardiogram Insert shows where central nervous system was interrupted in order to remove non-specific ascending and descending motor and sensory impulses which would complicate the visceral response to ECT when no chemical anaesthesia was desired. A signal light joined the shocking switch to the margin of the thoracotomy to indicate the time when current was flowing (not shown in diagram).

great vessels Blood pressures in the aorta and the inferior vena cava were recorded through eighteen-gauge plastic catheters inserted through the femoral artery and vein and attached to Statham strain gauges, or to a rotating drum kymograph ECG lead 2 and blood pressures were recorded simultaneously on a multi-channel oscilloscope and photographic recorder. The ECG was recorded also on a Sanborn direct-writing Visocardiette. ECT was provided by a powerstat variable transformer (variac 0–140 volts) through needle electrodes.

In three dogs under ether anaesthesia the spinal cord was divided at the level of the second cervical vertebra by a laminectomy and the dog was allowed to recover The cervical vagi were then exposed to study the effect of direct stimulation and the effect of ECT after cold block and section of the vagi. Otherwise the preparations, experiments, and recordings were the same as above

In eight dogs under ether anaesthesia, a mid-brain section was made through burr-holes in the skull. The dog was then allowed to recover The cervical vagi were exposed and bilateral thoracotomy and pericardectomy operations were done in six of these In the other two dogs, the same experiments were carried out, but the thorax was not opened

Observations

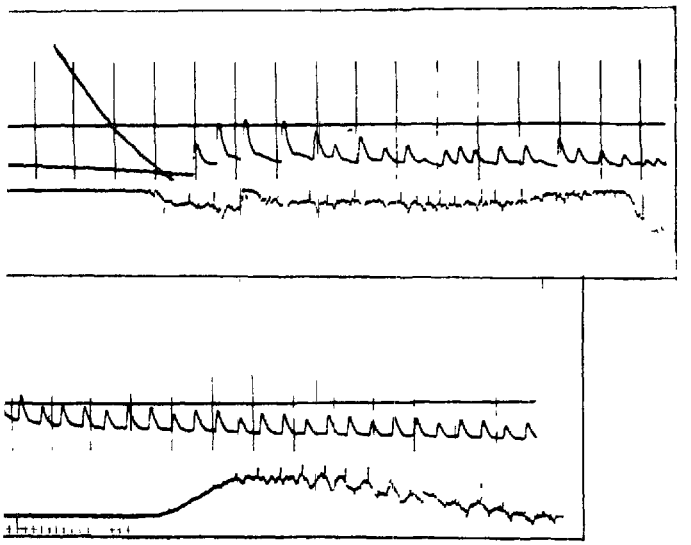
The effect of ECT on the rabbit's heart and ECG was difficult to interpret, even with direct visual observation, because the rapid rate and gross movement of the heart during ECT disturbed the cardiac electrodes and interfered with the action currents on the electrocardiogram When ECT was applied to the head, very marked tachycardia (250+) was produced, with predominant ventricular arrhythmias When the rabbit was shocked through the extremities, the heart went into ventricular fibrillation.

In the dogs under pentobarbital anaesthesia, ECT caused generalized muscle spasms with a brief convulsion When the spinal cord was cut, ECT caused only gross muscle-twitching of the face. When the mid-brain was cut, only very slight extension of the paws was observed.

Cardiovascular Responses to Unmodified Shock

In the absence of drug-induced general anaesthesia or muscle relaxation with succinylcholine in the three preparations with spinal cord transection (C_2) and in the eight preparations with mid-brain transection, shocks applied at 100 to 140 volts for one to three seconds invariably caused cardiac asystole. This was observed visually in the chest, and on the arterial blood pressure tracings The recordings of aortic blood pressure showed a sharp spike upward when the current was applied at the end of diastole followed by a precipitous fall. When the current was applied at the end of systole, the aortic blood pressure fell directly (Figs. 2 and 3). At the same time the venous pressure rose sharply to at least double the resting level.

During these experiments coloured fast-speed motion pictures were taken of the heart so that the effects of ECT during six shocks without premedication and during seven shocks after 1 mg. of atropine could be reviewed in slow motion. Whenever cardiac asystole occurred, first the auricles, and then the ventricles, were seen to distend, and the vascular markings as well as the myocardium became dark. The asystole was usually of brief duration (three to eight



ınd ECG (lead 2) tracings of a male dog, 27 lb. The
under ether anaesthesia and the dog was allowed to
encardectomy was performed Respiration was controlled

.20 v for 2 2 sec , observe immediate fall in aortic blood
ıpanied the flow of electric current (applied in diastole),
r two beats
ravenous administration of 0 5 mg Antrenyl, shock 120 v
ıes to beat after the shock

ırength and duration of the shock. The heart then
ly at first, and then rapidly. Normal cardiac rate
ıeously after several minutes. In one dog the
conds, at which time intermittent manual systole
onded after a few manual compressions, then
rate and rhythm.
.brupt onset of ventricular fibrillation after more
asystole (Fig. 4). In a third dog (mid-brain tran-
G and blood pressures did not alter significantly
shock, and again ventricular fibrillation began
normal rhythm by manual systole and electrical
in these animals.
ıransection electrodes were placed directly on the
liac asystole followed by tachycardia was observed
n when the needle electrodes were placed in the

the neck caused brief asystole when the current
volts). Cutting both vagi in the neck, or cutting
right vagus, invariably prevented cardiac asystole
ıances (twenty-one experiments in six dogs).
atropine (eight dogs, forty-eight experiments),
ogs, eleven experiments), 0 5 mg. of oxyphenonium
r 1 mg. of hexocyclium (one dog, five experiments)

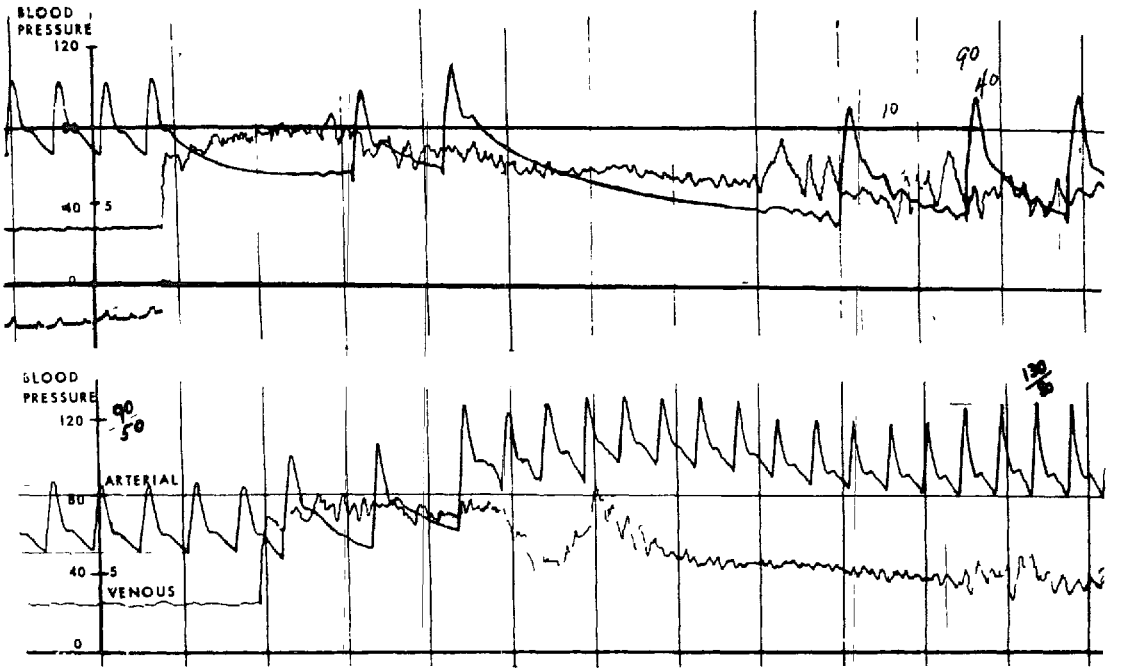


FIGURE 3 Aortic blood pressure, IVC pressure tracings of a male dog, weight 19 lb. The spinal cord was transected at C2 under ether anaesthesia, then the dog was allowed to recover. Bilateral thoracotomy and pericardectomy were performed. Respiration was controlled with oxygen

Upper. No premedication; electroshock 120 v for 1.0 sec.; observe the immediate fall in aortic blood pressure when current was applied early in diastole, asystole lasted 8 sec., except for two beats, then the arterial blood pressure returned to the resting level promptly; the venous pressure rose immediately from 3.5 mm. Hg to 10 mm Hg and then gradually returned to the resting level during the succeeding 54 sec.

Lower: Same dog 15 min after intravenous administration of 1 mg. atropine; observe the slight slowing of heart rate as the aortic blood pressure was rising, and then the slight acceleration in rate, the elevated blood pressure persisted for 140 sec., venous pressure rose immediately as in the unpremedicated state, and returned to resting level slowly (120 v. for 1 0 sec.).

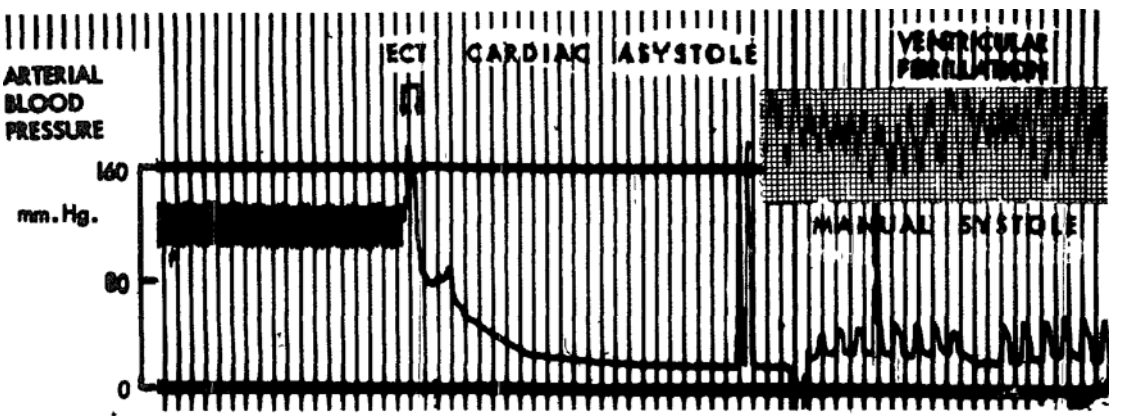


FIGURE 4. Aortic blood pressure of a male dog, 31 lb. The mid-brain was previously transected under ether anaesthesia and it was allowed to recover Bilateral thoracotomy and pericardectomy were then performed, and respiration was controlled with compressed air. Electroshock, 120 v. for 1 sec Observe sharp spike in aortic blood pressure when current applied at the end of systole, then the precipitous fall with absence of pulse waves for more than 20 sec This was followed by two strong contractions and a fall to zero, at which time the heart went into ventricular fibrillation (ECG insert). Manual systole and attempts at electrical defibrillation were unsuccessful This response occurred in two dogs.

prevented cardiac asystole when currents of 100 to 140 volts were applied for two to five seconds. In these experiments, both the arterial and the venous blood pressures rose sharply, and then gradually returned to normal after the convulsion subsided. The venous pressure always remained elevated for a longer period than did the arterial pressure.

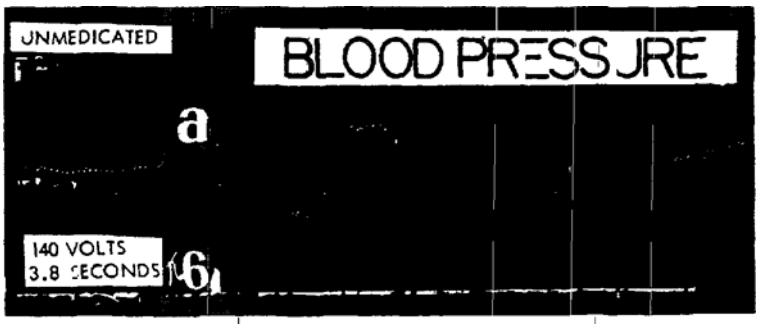


FIGURE 5 Mean aortic pressure tracing on a smoked drum kymograph from a male dog, weight 44 lb The mid-brain was previously transected under ether anaesthesia and the dog was allowed to recover Bilateral thoracotomy and pericardectomy were then performed Respiration was controlled with compressed air No premedication was given Electroshock, 140 v for 3 8 sec Observe marked fall in mean aortic blood pressure and almost complete absence of pulse wave oscillations for over 25 sec followed by slow recovery

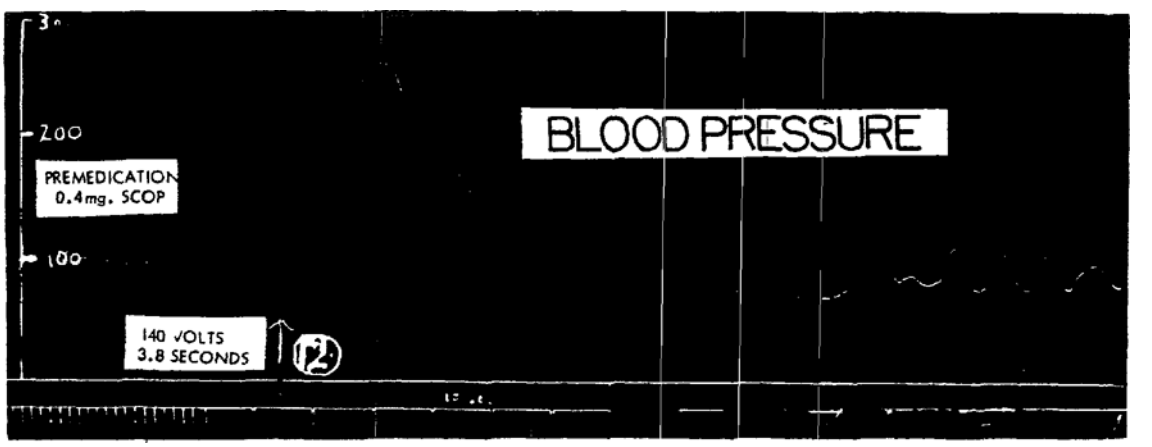


FIGURE 6. Same dog as in Figure 5, 20 min. after premedication with 0 4 mg scopolamine Electroshock, 140 v. for 3.8 sec. Observe very marked rise in mean aortic blood pressure which took 40 sec. to return to resting level. Regular pulse wave oscillations were present throughout the hypertensive episode.

Cardiovascular Response to Modified Shock

The cardiovascular response to ECT appeared to be modified in the four dogs under pentobarbital anaesthesia, in that a greater voltage or duration of shock was required to arrest the heart or cause disturbance of cardiac rate and rhythm

The intravenous injection of 20 to 45 mg. of succinylcholine one to two minutes preceding the application of electroshock eliminated the muscle twitching but

did not cause any significant alteration in the cardiac response, nor was there any alteration in circulatory dynamics, either before or after the administration of atropine. Dogs with mid-brain transection that were given 100 mg. thiopental intravenously immediately before shocking also showed no significant alteration in the cardiovascular response.

When a sufficiently strong electric shock was applied to the extremities or any part of the body (including the head) ventricular-fibrillation was produced. It was then very difficult to restore normal rhythm. The voltage at which ventricular fibrillation occurred was very much higher when the current passed through the head only (> 120 volts, for at least two seconds).

Discussion

Under physiological conditions afferent impulses arising from nervous sinuses on the great vessels of the neck modify the respiration, heart rate, and blood pressure. Stimulation of the central end of the aortic nerve or the central end of the vagus nerve usually slows and weakens the heart and lowers the blood pressure The slowing of the heart is probably due mainly to stimulation of the vagal nucleus, causing an increased discharge along the efferent vagal fibres, which are cardio-inhibitory The fall in blood pressure following stimulation of these nerves may be due to decreased cardiac output and inhibition of vasomotor tone, leading to generalized vasodilatation and decreased peripheral resistance. Increasing the frequency of electrical stimulation applied to the central end of the vagus increases the rate of onset and degree of hypotension, and may delay recovery by causing brief cardiac asystole Similar effects are produced by increasing the strength or duration of stimulation. Electrical stimulation of the sinus nerve produces similar results Vagal section (bilateral) or injection of atropine eliminates this effect (2).

The same cardiovascular effects were observed when ECT was applied to the head of a dog in the manner used clinically for the treatment of mental disorders. These have also been reported when the cerebral cortex is stimulated directly (3, 4)

It has been postulated that vagal hyperactivity is responsible for the arrhythmias seen immediately *after* unmodified ECT. These arrhythmias were thought to be caused by reflexes activated when a large amount of blood was trapped in the periphery during the seizure and was then sucked into the great veins and right auricle as the seizure subsided. Altschule pointed out that this mechanism could not account for the early vagal activation seen immediately after ECT in the absence of a Grand Mal seizure response (5). However, our observations revealed a sharp rise in right auricular pressure (blood pressure in the inferior vena cava), corresponding in time with the tonic phase of the convulsion, so that the blood was evidently not trapped in the periphery, but seemed to be trapped or driven centrally on the venous side of the circulation. This effect was produced immediately by muscle contraction caused by the electric current and induced a sufficiently strong stimulation of the vagus to arrest the heart Similar effects have been seen in man (6, 7). This certainly implicates

vagal hyperactivity as the main cause of cardiac asystole and subsequent cardiac arrhythmias.

Other possibilities have been suggested also. Direct stimulation of intracranial areas occurs, and may affect the cardiac rate through the vagus nerves (8). Stimulation of the hypothalamic centres may occur also during ECT and release posterior pituitary secretion into the spinal fluid causing cutaneous vasodilatation, lacrimation, salivation, and pilo-erection (9, 10, 11) However, it is unlikely that the latter is important in this situation because the clinical response is much too rapid to be explained by a reaction to a hormone secreted into the cerebral spinal fluid.

Another possibility has arisen since succinylcholine came into widespread use for modified ECT It was shown in cats that although succinylcholine closely resembles acetylcholine, only the nicotinic actions and not the muscarinic actions of acetylcholine can be demonstrated on the circulation (12) It has also been demonstrated clinically that the single administration of 60 mg. of succinylcholine produces changes in circulatory dynamics in about 30 per cent of premedicated patients during induction of general anaesthesia Initially a response similar to the muscarinic effect of acetylcholine was seen (bradycardia and hypotension), followed by a nicotinic response (tachycardia and hypertension). This effect could be blocked by atropine Concurrently, changes in the ECG were observed, consisting of flattening of the T wave associated with a depression or "coving" of the ST segment These changes in the ECG were unaffected by atropine (13)

It is possible that the above cardiovascular changes seen with succinylcholine were due to the hypoxia and hypercarbia associated with the muscle twitching that accompanies the depolarizing effect of the drug on skeletal muscle, together with the effect of the sudden arrest of breathing (14, 15, 16)

When smaller doses of succinylcholine were used (10–30 mg.) and the patient's lungs were well ventilated with oxygen, T-wave depression was observed only six times after 365 administrations of modified ECT (1). Alterations in the pulse rate and cardiac rhythm in these patients appeared to be related more to the convulsive reaction to ECT than to the thiopental and succinylcholine administered. Moreover, similar responses of the blood pressure, pulse rate, and ECG were observed during the presently reported experiments, even when succinylcholine was not given, and the cardiovascular response was not altered significantly when succinylcholine was added.

However, one should not rule out the possibility that in an occasional patient the administration of larger doses of succinylcholine (40–100 mg.) might potentiate the vagal stimulation produced by ECT. This effect must be guarded against also by adequate premedication with an anticholinergic drug and by ensuring adequate pulmonary ventilation until full spontaneous breathing returns

Summary

The acute effects of electroconvulsive therapy have been reinvestigated on animals. Our experiments have shown that the effects of ECT on circulatory dynamics were due mainly to stimuli which reached the heart through the vagus

nerves. If these nerves were not blocked, electroshock with a current of duration employed clinically caused a brief period of asystole in almost every experiment, and occasionally caused death, either because of prolonged asystole, or by asystole followed by ventricular fibrillation. The previous administration of an anticholinergic drug in sufficient dosage to block the vagus nerves effectively eliminated the major cardiac reaction to electroshock. The intravenous injection of a moderate dose of thiopental did not appear to alter grossly the cardiovascular response, but did seem to reduce the physical reaction to the electric shock. A small dose of succinylcholine intravenously reduced the reaction of skeletal muscle to the electric shock but did not appear to affect the cardiovascular response to ECT.

Conclusions

Unmodified ECT usually causes cardiac arrhythmias, which are preceded by a brief period of cardiac asystole This cardiac asystole frequently lasts long enough to cause cyanosis even with efficient pulmonary ventilation although no sequelae of a serious nature may be evident. Occasionally it may last long enough to cause cerebral or myocardial ischaemia (with myocardial infarction) which may result in a delayed death In the rare case this cardiac asystole may persist until death.

As a result of the observations made in this study, one must assert that the indications for premedication with anticholinergic drugs far outweigh any objections to their use in patients requiring ECT. In the elderly patient with obvious cardiovascular disease, it is wise to administer at least 1 mg. of atropine intravenously a few minutes before treatment In patients without evidence of circulatory disorders, the authors recommend the intramuscular administration of 2 mg. of atropine about thirty minutes before treatment

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Résumé

Dans le but de préciser leurs effets sur la dynamique circulatoire, nous avons étudié, chez des animaux, la réponse spontanée aux traitements électroconvulsifs Nous avons fait cette étude pour compléter notre observation clinique de malades mentaux soumis à des électrochocs, car il est difficile de recueillir des données précises et fiables au cours des convulsions. Cette étude s'imposait également pour nous aider à trouver les meilleurs moyens de diminuer les réactions cardio-

vasculaires sérieuses que l'on observe et pour prévenir les morts occasionnelles à la suite d'électrochocs.

Nous avons fait nos observations sur des lapins et des chiens soumis à des électrochocs avant et après des blocages des vagues par le froid, l'administration intraveineuse de pentothal et de succinylcholine et l'administration intraveineuse de médicaments anticholinergiques.

Pour chacun des animaux, nous avons contrôlé la respiration en employant un ventilateur à pression positive intermittente et un gros débit d'air et d'oxygène pour être assurés qu'il n'y aurait pas de réinspiration dans le système Nous avons produit les chocs électriques en employant des électrodes ressemblant à des aiguilles placées dans le scalpe et un transformateur à pouvoir contrôlable. Nous avions exposé le cœur et les gros vaisseaux en pratiquant une thoracotomie bilatérale et une péricardectomie partielle. Les pressions sanguines étaient prises dans l'aorte et la veine cave inférieure en employant des cathéters rattachés à des manomètres, la lecture simultanée des pressions et de l'électrocardiogramme était rendue possible grâce à l'usage d'un oscilloscope à plusieurs canaux. Les tracés étaient enrégistrés par photographies. Pour quelques animaux, nous avons employé l'anesthésie générale et pour d'autres, nous avons sectionné la moelle ou le cerveau Au cours des expériences, nous avons fait de la cinématographie rapide du cœur pour pouvoir ensuite, en ralenti, étudier ses réponses ou ses réactions

Ces expériences ont démontré que les effets de l'électrochoc sur le cœur sont attribuables principalement à des influx nerveux atteignant le cœur par les vagues Si l'on ne fait pas le blocage de ces nerfs, l'électrochoc, avec les courants de force et de durée employés en clinique, produit, dans presque tous les cas, une brève période d'asystolie A l'occasion, il peut survenir une mort par asystolie prolongée ou l'installation soudaine d'une fibrillation ventriculaire à la suite d'une brève asystolie Les médicaments anticholinergiques éliminent efficacement la principale réaction cardiaque à l'électrochoc

A la suite de ces études, nous en venons à la conclusion qu'il est dangereux, particulièrement chez les vieillards, de donner des électrochocs sans atténuation L'asystolie cardiaque que produisent ces traitements peut souvent durer assez longtemps pour entraîner de la cyanose, même si la ventilation pulmonaire est adéquate. Habituellement des séquelles sérieuses peuvent passer inaperçues Mais, à l'occasion, l'asystolie peut être assez prolongée pour produire une ischémie cérébrale ou myocardique et entraîner ultérieurement la mort. Plus rarement, l'asystolie persiste et c'est la mort immédiate En conséquence, nous conseillons d'administrer de l'atropine, par voie intramusculaire, avant tout électrochoc, chez les vieillards, à la dose de 1 mg et chez les plus jeunes, à la dose de 2 mg

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