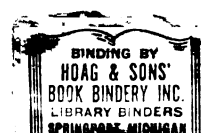
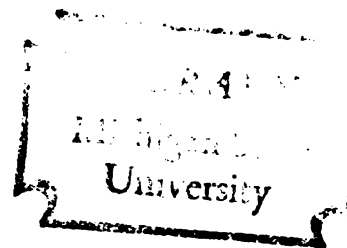


CARDIOVASCULAR EFFECTS OF
GALLAMINE AND SUCCINYLCHOLINE
IN THE DOG

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ABSTRACT

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By

A. Thomas Evans

The use of muscle relaxants in veterinary medicine has been limited to purposes of restraint, specifically restraint of the horse. Small animal practitioners rarely use muscle relaxants in conjunction with anesthesia due in part to a lack of knowledge of the cardiovascular effects of muscle relaxants in the dog.

The purpose of this study was to provide evidence that the use of gallamine or succinylcholine does not adversely affect the cardiovascular system of the dog anesthetized with halothane.

In the current study cardiac output, cardiac index, stroke volume, heart rate, peripheral vascular resistance, arterial pressure and central venous pressure were measured in dogs given either 0.4 mg/kg gallamine or .4 mg/kg succinylcholine intravenously. Eight dogs were used in the study, with each dog receiving each relaxant once. On the day of the study, a cannula was implanted in both the common carotid artery and jugular vein of each animal. The arterial catheter contained a thermistor probe for thermal dilution cardiac output determinations. Muscle relaxation was monitored by recording the

twitch response to electrical stimulation of the peroneal nerve. Anesthesia was induced with a mixture of halothane and oxygen by mask, dogs were intubated with endotracheal catheters, and end-expired halothane concentration was maintained at 1.1%. Cardiovascular variables were recorded prior to injection, one minute after injection, five minutes after injection, and ten minutes after injection of the muscle relaxant. Blood PCO_2 , PO_2 and blood pH were maintained within normal limits by controlling respiration and base excess. The administration of either muscle relaxant resulted in total paralysis as determined by absence of muscle twitch. Mean time from total paralysis to return of one-tenth of total twitch was 26 minutes for gallamine and 22 minutes for succinylcholine. An increase in heart rate and mean arterial pressure at the one minute time period was the only statistically significant finding during the succinylcholine study, while injection of gallamine did not cause significant changes.

The study demonstrated that 0.4 mg/kg of gallamine or succinylcholine does not adversely affect the cardiovascular system of Beagle dogs anesthetized with halothane.

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A. Thomas Evans

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TABLE OF CONTENTS

	Page
INTRODUCTION.	1
REVIEW OF LITERATURE.	5
Cardiovascular Effects of Gallamine.	5
Summary.	9
Cardiovascular Effects of Succinylcholine.	11
Summary.	20
MATERIALS AND METHODS	22
Animals.	22
Materials.	23
Equipment and Calibration.	24
Calculations	26
Procedure.	29
Data Analysis.	31
RESULTS	33
General Considerations	33
Cardiovascular Effects of Gallamine.	36
Cardiovascular Effects of Succinylcholine.	37
DISCUSSION.	40
CONCLUSIONS	51
REFERENCES.	52

LIST OF TABLES

Table		Page
1	Blood evaluations for 8 dogs prior to study.	33
2	Mean temperatures of 8 dogs given either gallamine or succinylcholine	34
3	Duration of paralysis of 8 dogs given either gallamine or succinylcholine	35
4	Mean end tidal halothane concentration of 8 dogs given either gallamine or succinylcholine.	35
5	Mean serum potassium concentrations from 8 dogs given either gallamine or succinylcholine.	36
6	Mean cardiovascular variables from 8 dogs given 0.4 mg/kg gallamine.	38
7	Mean cardiovascular variables of 8 dogs given 0.4 mg/kg succinylcholine.	39

LIST OF FIGURES

Figure	Page
1 Diagrammatic sketch of equipment arrangement	27

INTRODUCTION

The use of muscle relaxants in veterinary medicine has been largely limited to equine restraint. Contrary to the rare use of muscle relaxants in small animal practice, relaxants have been used extensively as an adjunct to anesthesia in man. Benefits realized include profound muscle relaxation, ease of controlling ventilation, and reduced concentrations of anesthetics, allowing utilization of balanced anesthesia techniques.

An understanding of the physiology of the neuromuscular junction is necessary before a discussion of the action of muscle relaxants is begun. A nerve action potential passes from the motor nerve located in the spinal cord to the nerve terminal at the myoneural junction. The nerve action potential causes the release of quanta of acetylcholine from the synaptic vesicles in the nerve terminal adjacent to the synaptic cleft. The released acetylcholine crosses the synaptic cleft where it reacts with endplate receptors to increase permeability of both sodium and potassium. The change in permeability to sodium and potassium ions causes a depolarization of the endplate potential which in turn causes a depolarization of the muscle membrane adjacent to the endplate. This ultimately results in muscle contraction. The acetylcholine then rapidly diffuses away from the endplate or is quickly hydrolyzed by cholinesterase. Muscle relaxants have

been categorized as being either depolarizing or nondepolarizing depending on their action at the myoneural junction. Gallamine, a nondepolarizing muscle relaxant, exerts its action by competing with acetylcholine for endplate receptors (competitive inhibition). Succinylcholine initially mimics the action of acetylcholine at the endplate receptors and may cause depolarization sufficient to cause muscle fasciculations (depolarization block). The muscle is then desensitized to the action of acetylcholine.

Why haven't veterinarians utilized muscle relaxants to a greater extent? One reason might be the required presence of a ventilator, whether human or mechanical, to insure adequate respiratory excursion. This problem is being alleviated by the development of mechanical ventilators by veterinary suppliers and improved educational opportunities for undergraduate and graduate veterinarians in respiratory and anesthesia physiology.

A second issue may be an inadequate understanding of the pharmacology of muscle relaxants and specifically their effects on the cardiovascular system. A comprehensive review of the literature reveals that many studies have been completed but that results are conflicting and confusing.

For example, early studies did not monitor blood gas values or depth of anesthesia. A rise in blood pressure often seen after administration of succinylcholine was usually attributed to the drug. Subsequent studies revealed that the increase in blood pressure could often be explained by a concurrent rise in PCO_2 .

Anesthesia also has profound effects on the cardiovascular system. Early studies in dogs used no anesthesia, while recent studies in man did not monitor depth of anesthesia. Since depth of anesthesia affects cardiovascular function, it would be difficult to separate cardiovascular effects caused by the anesthetic from cardiovascular effects related to the muscle relaxant. Results obtained from these studies should be suspect.

Studies on cardiovascular effects of muscle relaxants have involved the use of many species of animals. Dogs, cats, horses, cattle, guinea pigs, nonhuman primates, and man have each played a role in gathering information on the cardiovascular effects of muscle relaxants. The only reliable information to arise from all of these studies is that each species reacts somewhat differently to the administration of relaxants. One would surmise that, if information was needed on the cardiovascular effects of muscle relaxants in the dog, the dog should be the experimental animal studied. Data from the human extrapolated to the dog would not be acceptable. This is in fact the case, as the human reacts to succinylcholine with a shorter duration of action than the dog. Consequently, the dog was chosen as the experimental subject for the current experiment.

The manner in which muscle relaxation is monitored has been a subject of debate among researchers studying relaxants. A recent review (53) mitigated some of the uncertainty by accepting both mechanical and electrical methods of monitoring muscle relaxation. The current study employs a mechanical method of monitoring duration of paralysis.

The purpose of the study was to determine whether or not muscle relaxants could be safely used in the dog without any serious cardiovascular deviations. The major areas controlled were depth of anesthesia and prevention of severe blood gas abnormalities. This was accomplished by controlling end-tidal concentration of halothane and the serial analysis of arterial samples, respectively.

REVIEW OF LITERATURE

Cardiovascular Effects of Gallamine

In 1951, Marbury *et al.* (69) studied the effects of gallamine in patients anesthetized with ether or cyclopropane and found an increase in pulse rate 35% greater than control values. This was attributed to a vagolytic effect of gallamine.

Doughty and Wylie (31) studied the effects of gallamine the same year and found an increase in pulse rate in 100% of 245 human cases. Patients were anesthetized with thiopentone, nitrous oxide and oxygen. If cyclopropane was used as the anesthetic, the increase in heart rate did not occur. They concluded that the tachycardia was due to a vagal block unaccompanied by a sympathetic block. In further studies involving cats and rabbits, performed by the same investigators, it proved impossible to produce tachycardia either by reflex or by direct action on the heart. By way of explanation, they proposed the possibility of reduced vagal tone in the two species.

Independent clinical studies by Artusio *et al.* (3) and Condon (23) in 1951 confirmed the occurrence of tachycardia in anesthetized man, probably due to a vagolytic action of gallamine. Both investigators found negligible effect on blood pressure as measured by cuff.

Riker and Wescoe (82), in 1951, found that gallamine increased heart rate by an atropine-like effect, that is, reducing the activity

of the vagus at postganglionic nerve endings, but was devoid of other atropine-like effects. Studies were performed by injection of gallamine into intact cats lightly anesthetized with pentobarbital.

Bovet (14), working with dogs in 1951, found no modification of blood pressure by gallamine in an experiment in which the type of anesthetic was not mentioned.

Further evidence of a vagolytic action of gallamine was shown in 1955 by Roberts *et al.* (83) in cats anesthetized with Dial Urethane. In their experiment, gallamine diminished the occurrence of cardiac arrhythmias induced by epinephrine.

Another clinical study (94) was reported in 1963 involving 116 human patients anesthetized with thiopentone, nitrous oxide and oxygen. Ventilation was assisted and blood pressure obtained by auscultating the arm. Gallamine caused a rise in blood pressure in 74% of 116 patients with a mean rise of 12 mm Hg. A fall in blood pressure was also noted in 24% of the patients studied. They explained that factors which could affect changes in blood pressure included increased carbon dioxide tension of the blood, which would increase blood pressure, and controlled ventilation, which would decrease blood pressure.

Conflicting results were reported by Watts and Prescott (98) in 1965, when the effect of gallamine on cardiac rhythm during halothane, nitrous oxide, and oxygen anesthesia in human patients was studied. There was no change in blood pressure in 19 out of 20 patients; however, all patients exhibited at least a 20% increase in heart rate. In 1967, a more complete study of cardiovascular effects of gallamine

was reported by Smith and Whitcher (87). In this study, the hemodynamic effects of gallamine administered during halothane anesthesia were an increase in cardiac output, arterial pressure, left ventricular work with a variable response in stroke volume. The action of gallamine was attributed to cardiovagal block, myocardial stimulation and a slight sympathetic ganglionic block. They proposed that the sympathetic blocking action of gallamine is weaker than the cardiovagal action so the sympathetic system dominates and a tachycardia results.

Kennedy (57) reported similar results the following year during a study of the cardiovascular effects of gallamine in man anesthetized with thiopentone, tubocurarine, nitrous oxide and trichlorethylene. Patients were artificially ventilated. Heart rate and cardiac output increased 40% and 35%, respectively. There was no change in stroke volume, but a slight increase in mean arterial pressure and a slight decrease in total peripheral resistance.

Brown and Crout reported on the ionotropic effect of gallamine on guinea pig heart muscle in 1966 (17). They concluded that gallamine stimulates heart rate and force through a release of norepinephrine. The effect was not seen if propranolol or reserpinized atria were used. Preparations made tachyphylactic to gallamine responded normally to norepinephrine, and if the tissue exposed to norepinephrine was washed, the response to gallamine was restored.

Further studies by Brown and Crout (18) were reported in 1970. The results of studies in open chest cat anesthetized with pentobarbital complemented their earlier work. Cardiac rate and right ventricular contractile force were increased. Reserpine pretreatment

inhibited the response to gallamine almost completely and any residual effect was abolished by propranolol. It was concluded that the positive inotropic effect of gallamine is due mainly to the release of norepinephrine from adrenergic neurons.

In 1970, decorticate rats and cats were given propranolol followed by gallamine in a study by Rathbun and Hamilton (79). Gallamine had an anticholinergic effect on the heart in both species, so a true atropine-like action may complement any sympathomimetic action of gallamine in producing the tachycardia seen in clinical practice. They concluded that the action of gallamine is a competitive antagonism of acetylcholine, but the vagolytic action of gallamine is confined to the heart and possibly vascular system.

Working with open chest dogs maintained with chloralose, Hughes (47) found that gallamine slightly increased stroke volume and cardiac output which he related to cardiovagal block. Blood pressure and total peripheral resistance were slightly reduced.

Finally, in 1973, evidence was found by Reitan *et al.* (81) to show that, at least in humans, there is a lack of cardiac inotropic effect of gallamine. Experiments were carried out in 12 women anesthetized lightly with halothane, nitrous oxide and oxygen. The cardiac pre-ejection period and its quotient with left ventricular ejection time were used to measure the inotropic state. Six patients were given atropine to stabilize their heart rate, followed by two doses of gallamine. There was a significant decrease in both indices (positive inotropy) in this group. When atropine alone without gallamine was given to a second group of 6 patients, a similar significant decrease

in the indices occurred. When this group was immediately reatropinized and given gallamine similar to the protocol sequence of the first group, there was no change in pre-ejection period and its quotient with left ventricular ejection time. It was concluded that there was no positive cardiac inotropic action demonstrated by gallamine in human subjects anesthetized with halothane.

Summary

The cardiovascular effects of gallamine have been studied in many species under a variety of conditions. Investigators have established that gallamine causes a tachycardia, but they do not agree on its origin. Much of the confusion may be due to species variation. Indeed, Wylie and Churchill-Davidson, in discussing the effects of muscle relaxants in man, state "there is no single species that responds to these drugs in exactly the same manner as man." For example, Reitan (81), in his study involving humans, found no positive cardiac inotropic action of gallamine. Conversely, Brown and Crout, working with guinea pigs in 1966 (17) and with cats in 1970 (18), reported a positive inotropic action of gallamine which they explained by a release of norepinephrine from adrenergic neurons.

A second explanation for varying results is related to different investigative techniques. Brown and Crout measured ionotropy by means of a strain gauge sutured to the left ventricle of cats. Reitan's experimental method consisted of clinical evaluation of cardiac function by measuring cardiac pre-injection period and its quotient with left ventricular ejection time. The two completely different methods of measuring ionotropy may have resulted in conflicting results.

The only study which did not report a tachycardia was one performed on cats and rabbits. It was theorized that these particular animals have a reduced vagal tone and consequently do not respond to the vagolytic action of gallamine. However, Riker (82) and Roberts (83), in separate studies, found that cats do indeed respond to gallamine administration with a tachycardia. Part of the discrepancy may be due to choice of anesthetics as Doughty and Wylie (31) anesthetized their cats with nitrous oxide and oxygen.

Other factors which affect the presence of tachycardia and hypertension include: presence of premedication, spontaneous or controlled ventilation, blood PCO_2 , and dose of gallamine. Premedication with atropine may reduce effect of gallamine on cardiac ganglia. Vigorous positive pressure ventilation may reduce cardiac output by reducing venous return. Another possible mechanism in dogs, cats and rabbits involves the effect of various doses of gallamine on sympathetic ganglia. Paralyzing doses of gallamine facilitate transmission through the sympathetic ganglia and potentiate hypertensive reflexes mediated by them and the adrenal medulla. With somewhat larger doses ganglionic transmission returns to normal while very large doses block ganglia (82). Hypertension with small doses could be due to the initial ganglionic stimulation and the decreasing effect of larger doses to the subsequent return of transmission to normal.

Another possible explanation for the confusion surrounding the alleged effects of gallamine on the cardiovascular system involves the amount of vagal tone present. In two separate studies involving dogs, Bovet (14) and Hughes (47) found no increase in blood pressure

after gallamine administration. However, Hughes did find that heart rate was slightly increased, along with small increases in cardiac output and stroke volume. He theorized that atrial contraction increased because of vagal block causing more effective filling of the ventricle which results in increases in stroke volume and cardiac output.

Because gallamine seldom caused tachycardia in dogs, Hughes speculated that vagal influence on heart rate in anesthetized dogs is less than in humans. In general, the cardiovascular effect of gallamine can be summarized as one related to the amount of vagal tone with the possibility of an additional effect from release of norepinephrine from adrenergic neurons. In addition, differences in response can be related to different species, anesthetics, and experimental protocol.

Cardiovascular Effects of Succinylcholine

One of the first studies concerned with the cardiovascular effects of succinylcholine was reported in 1952 by Bourne *et al.* (13), who monitored human patients anesthetized with thiopentone, nitrous oxide, and oxygen anesthesia. There was no effect on blood pressure after a single dose; however, large doses caused blood pressure to rise. Further studies on anesthetized dogs and cats revealed that succinylcholine in large doses has a nicotinic effect on blood pressure. In the dog, a dose greater than 5 mg/kg and in the cat a dose greater than 10 mg/kg is needed to raise blood pressure. This action is abolished by administration of the ganglionic blocking agents

hexamethonium and tetraethylammonium. A hypotensive effect of succinylcholine was not seen in either the cat or the dog.

Thesleff (93) noted in 1952 that the rise in blood pressure after administration of succinylcholine was due to stimulation of autonomic ganglia with resulting mobilization of adrenaline and vasoconstriction. However, ganglionic blocking substances did not entirely prevent the rise in blood pressure, so Thesleff proposed a direct action on blood vessels could not be ruled out. In addition, he thought that a large dose of succinylcholine may cause a ganglionic block.

Adderley and Hamilton (2) found similar results in humans given succinylcholine after thiopentone, namely a rise in blood pressure which could be controlled by blocking autonomic ganglia.

Somers (91) also reported a slight rise in pressure in cats given 2 mg succinylcholine. A 10 mg dose caused a larger rise in blood pressure which was thought to be nicotinic in character. Hexamethonium or tetraethylammonium blocked the blood pressure increase. Somers failed to demonstrate any effect of the drug in cats under chloralase anesthesia and was unable to produce hypotension in either cats or dogs.

In 1954, Calvert and Morgan (21) produced conflicting results in man during thiopentone anesthesia. A small but consistent fall in mean systolic and diastolic blood pressure was noted while pulse rate was virtually unchanged. They attributed reports by other workers, of increased blood pressure, to increased carbon dioxide tension and the stimulus of intubation.

Phillips (77), in the same year, working with human patients, recorded that succinylcholine produced cardiovascular side effects, but

in some patients the relaxant was given prior to barbiturate anesthesia and doubt exists about the adequacy of oxygenation in such cases.

Under these circumstances he found marked muscle fasciculation accompanied by a rise in blood pressure which was maintained during the period of apnea produced by the drug. An initial bradycardia was followed by tachycardia as relaxation of the skeletal muscles occurred.

The following year Beretervide (9) noted that the bradycardia and hypotension following administration of succinylcholine resulted from central nervous system parasympathetic action and that hypertension and tachycardia resulted from stimulation of sympathetic ganglia. Beretervide concluded that the drug had no effect on the heart or circulation, but as many of his experiments were carried out on conscious animals without artificial ventilation, his results must be suspect.

Also in 1955, Johnston (50), investigating the effects of succinylcholine on the cardiovascular system of 100 patients who had been premedicated with atropine and anesthetized with small doses of pentothal, found slight slowing of the pulse in 28 cases and definite bradycardia in 32 cases. There was also pacemaker shift to the atrio-ventricular (AV) node in 7 patients. This bradycardia was usually followed in about two minutes by a brisk tachycardia. The muscarinic effects could be modified by atropine, but not always prevented in the dosage prescribed. In explaining blood pressure changes, Johnstone noted that one often sees a slight transient hypertension after a single dose and prolonged mild hypertension after a continuous drip infusion of succinylcholine. The initial hypertension has been attributed to an asphyxial type of response in the absence of adequate

ventilation, possibly aggravated by muscle activity. The prolonged pressure response is attributed by Paton (76) to the nicotinic effects of succinylcholine and succinyl monocholine, and these are not influenced by atropine.

During studies in 15 horses by Belling and Booth (8) the same year, there was a slight increase or decrease of heart rate but changes were not consistent. Blood pressure was measured in the facial artery by kymograph with horses restrained and anesthetized on a surgery table. Blood pressure measured in 5 horses was not impaired as long as the respiratory muscles were not impaired. As soon as paralysis developed, blood pressure increased, presumably due to hypercapnia.

Bradycardia following intravenous administration of succinylcholine to infants and children was reported by Leigh *et al.* (64) in 1957. They suggested that infants and young children have a low true cholinesterase activity and that acetylcholine derived from succinylcholine accumulates and causes a bradycardia-nodal rhythm.

The same year Elder *et al.* (36), in a clinical study of the cardiovascular effects of muscle relaxants in 6 patients anesthetized with thiopental, nitrous oxide and oxygen, found very little effect of succinylcholine on mean blood pressure, central venous pressure or cardiac output.

In 1958, Heymans and De Vleeschouwer (46) concluded that succinylcholine does not decrease systemic arterial pressure or depress the mechanism of blood pressure homeostasis. Their studies were carried out in dogs anesthetized with chloralase and morphine without benefit of other controls.

Also in 1958, Larsen (62) found only slight changes in heart rate and blood pressure in the horse. Further studies by Larsen *et al.* (63) in 1959 revealed a tachycardia with 4 of 8 horses suffering cardiac muscle necrosis. Blood pressure was not measured.

Hansson (45), in 1958, studied the effects of succinylcholine in horses, calves, pigs and dogs. Injection of succinylcholine caused a pronounced increase in blood pressure in the horse, no change in blood pressure in the calf and inconsistent results in the dog and pig. Changes in blood pressure were thought to be due to a direct effect of succinylcholine on the vasomotor and cardiac center or secondary to reduced ventilation.

Stevenson (92) reported in 1960 a rise in blood pressure in dogs thought to be due to ganglionic stimulation and adrenaline release. He also reported an increased concentration of potassium in plasma after succinylcholine administration.

The same year Wahlin (97), using a drop counting method of blood flow measurement devised by Lindgren (66), observed a fall in superior mesenteric artery blood flow following succinylcholine administration. He felt the fall in blood flow might have been associated with contraction of intestinal musculature.

Lupprian and Churchill-Davidson (67), studying the effect of succinylcholine on cardiac rhythm in human patients, found an increase in heart rate after the first dose, but a slowing of heart rate after subsequent doses. The sinus bradycardia could be prevented in 68% of the patients by atropine. Since atropine is believed to act principally at the sino-atrial node, they thought this was strong evidence of vagal stimulation by succinylcholine.

Conversely, Barreto (6), in 1960, working with patients 4 weeks to 16 years of age, anesthetized with ether or thiobarbiturate followed by nitrous oxide and oxygen, found that the predominant response to intravenously administered succinylcholine was a sinus tachycardia.

Also in 1960, Craythorne *et al.* (28) found a bradycardia following intravenous administration of succinylcholine to infants and children. Patients were studied before operation, premedicated with atropine or scopolamine and anesthetized with cyclopropane, nitrous oxide and oxygen or ethyl ether. They theorized the cause of the bradycardia may be due to stimulation of pulmonary chemoreceptors.

Williams *et al.* (99), in 1961, using halothane anesthesia in man, found that injected succinylcholine was followed by a moderate hypertension and tachycardia while successive doses of succinylcholine caused bradycardia. Administration of trimetaphan prevented the action of succinylcholine on cardiac rhythm. This drug is thought to block vagal transmission principally at the cardiac ganglion, which means that succinylcholine acts at a site on the vagal pathway which is at or proximal to the cardiac ganglion. They concluded that succinylcholine probably stimulates the sympathetic nervous system.

Adams and Hall (1), in 1963, using artificially ventilated spinal cat preparations or cats anesthetized with thiopentone, nitrous oxide, and oxygen, found that succinylcholine has both a nicotine and a muscarine-like effect. In anesthetized cats, there was a sharp fall in blood pressure followed by a rapid rise to above pre-injection levels, with blood pressure stable two to three minutes later. If atropine was given in sufficient quantity to block the vagus nerve,

then the initial sharp fall was abolished. Atropine and hexamethonium completely abolished blood pressure change when given before succinylcholine.

Galindo and Davis (40), in 1962, working with monkeys, explained the slowing of the heart as a secondary reflex effect brought about by a rise in blood pressure after the initial injection.

In 1963, Graf *et al.* (42) injected succinylcholine into anesthetized man and produced a biphasic action. A sudden initial decrease in peripheral blood flow and heart rate was followed by an increase throughout the apnea period. They concluded that succinylcholine seems to be a general vasodilator substance partially caused by a local action on peripheral circulation. That is, the smooth muscle bed of blood vessels may constrict and relax similarly to skeletal muscle.

Dowdy (33), one year later, suggested the initial bradycardia from succinylcholine injection was due to an acetylcholine-like phenomenon at the receptor site of the cholinergic nerves. Acetylcholine and succinylcholine also stimulated autonomic ganglia and this effect could proceed to stimulate the sympathetic ganglia of myocardial nerves releasing catecholamines and resulting in stimulation of beta effectors. Paradise (75) explained that ventricular pacemaker fibers were innervated by sympathetic nerves which contain acetylcholine. The acetylcholine acted on a storage depot of catecholamines effecting their release which resulted in an increased firing rate of ventricular pacemakers. Succinylcholine mimics this acetylcholine action.

Conversely, Mathias and Evans-Prosser (70), in 1968, stated that sympathetic stimulation plays no part in alteration of the cardiac rhythm caused by succinylcholine. In certain circumstances, the action of succinylcholine on cardiac rhythm is exerted reflexly by stimulation of peripheral receptor organs (carotid sinus) and that this effect may be blocked by the prior administration of a non-depolarizing muscle relaxant.

In 1970, Zinn *et al.* (102), studying the effect of succinylcholine on the cardiovascular system of horses, concluded that the hypertension seen is probably due to the combination of adrenaline release, hypoxia and hyperpnea, muscle fasciculations, and ganglionic stimulation.

The following year Leighton (65), using dogs anesthetized with halothane, nitrous oxide and oxygen, studied the effect of succinylcholine on the cardiovascular system. A dose of 4 mg/kg resulted in a fall in arterial pressure with no change in cardiac output. Blood pressure, accompanied by an increase in heart rate, then rose higher than preinjection levels. Bradycardia was not observed. Administration of atropine blocked blood pressure changes. Leighton then conducted experiments showing the effect of alpha and beta adrenergic blockade upon the biphasic response to succinylcholine. Norepinephrine was injected and an increase in blood pressure noted. Then phenoxybenzamine (10 mg/kg) was administered followed by norepinephrine and the absence of pressor action was noted. Then isoprenaline (beta agonist) was given and an increase in heart rate noted. Propranolol was then injected followed by isoprenaline and the response was eliminated. Subsequent succinylcholine administration resulted in

hypertension without an overshoot. Leighton also studied the effect of ganglionic blockade on the action of succinylcholine. After he obtained a succinylcholine response, the right vagus was exposed and stimulated producing cardiac standstill. Subsequent hexamethonium administration followed by vagal stimulation resulted in normal heart action. Succinylcholine given at this time produced a typical response but with a marked overshoot. Leighton theorized that the initial fall in arterial pressure must be due to an action on the peripheral vasculature as cardiac output did not change. Ganglionic vagal blockade and adrenergic receptor blockade failed to prevent this response to succinylcholine indicating that this response is not mediated through the autonomic nervous system, nor is it the reflex result of circulatory change elsewhere. In conclusion, Leighton noted that, since atropine blocks the response completely, it would appear that succinylcholine produces the effects which have been observed by an action upon the muscarinic receptors in the peripheral vasculature.

A new concept explaining cardiovascular changes from succinylcholine injection was reported by Mori *et al.* (73) in 1973. They injected succinylcholine into patients anesthetized with halothane and found an arousal response in the electroencephalogram which was accompanied by increases in heart rate and blood pressure. While gallamine produced no arousal pattern in the electroencephalogram, it did prevent the changes produced by a subsequent injection of suxamethonium. It is postulated that the depolarizing drugs produce an increased activity in the afferent discharge of the muscle spindles which leads to the electroencephalogram arousal pattern. They

concluded that this arousing pattern may have some role in the tachycardia and hypertension produced by these drugs.

Summary

The most debated controversy involving the effects of succinylcholine on the cardiovascular system involves the presence or absence of hypertension. Graf (42), in his exhausting literature review, found 63 references indicating succinylcholine is associated with arterial hypertension, 16 references indicating hypotension, and 5 references indicating a biphasic response. The literature review for the current study found 12 reports of hypertension after succinylcholine administration, 6 in human, 2 in horse, 2 in dog, and 2 in cat. There were also 4 reports of hypotension in the human and one report of hypotension in the cat. A biphasic response was seen 6 times, 4 in human and once each in cat and dog. No response was seen in man, twice in the horse, 3 times in the dog and once in a cat. Explanations for increases in blood pressure include ganglionic stimulation, a direct myocardial effect, stimulation of peripheral receptor organs, a local action on peripheral circulation, a direct effect on the cardiac center, an increase in PCO_2 , and a reflex response from the act of intubation. Bradycardia was thought to be due to a muscarinic effect, stimulation of pulmonary chemoreceptors, or accumulation of acetylcholine derived from succinylcholine.

The convincing experiment by Leighton (65) identified the biphasic cardiovascular effect of succinylcholine in the dog. He proposed that an effect on the peripheral blood vascular system explained the initial hypotension seen after intravenous administration

of succinylcholine. Much of the confusion arising from the reports of earlier workers (9,92,94) is due to their failure to record whether the experimental animals used in their studies were atropinized. Leighton systematically used atropine, ganglionic blockers, and alpha and beta blockers to sort out the effect of succinylcholine from secondary phenomena. In summary, the explanation for the action of succinylcholine on the cardiovascular system is still in doubt.

MATERIALS AND METHODS

Animals

Eight conditioned purebred Beagle dogs, 4 female and 4 male, obtained from a biological supply company,^a were utilized in this study. The animals' ages ranged from 6 months to 1 year, and weights ranged from 7 to 10 kg. Prior to the day of study, dogs were housed separately in concrete kennels in accordance with Public Law 89-544. The dogs were cleaned, watered and fed a balanced ration twice daily. Pooled fecal samples were checked for evidence of internal parasites. In addition to a physical examination, a blood sample was collected so that complete blood counts, blood urea nitrogen determinations, and serum glutamic pyruvic transaminase levels could be evaluated. Dogs were vaccinated against canine distemper, canine infectious hepatitis, and leptospirosis as puppies, and immunity against these diseases was considered adequate. All laboratory tests were performed at the veterinary clinical pathology laboratory, Michigan State University.

^aLaboratory Research Enterprises, Inc., 6251 South Sixth St., Kalamazoo, MI 49009.

Materials

Catheters used in the study included an end hole, 75 cm cardiac catheter^a and a double lumen, 100 cm, 10 French cardiac catheter.^b The end hole catheter was used for collection of pooled venous blood samples, recording of central venous pressure and for injection of room temperature saline for determination of cardiac output. The double lumen catheter was placed in the descending aorta, via the carotid artery, and was used for collection of arterial blood samples and recording of arterial pressure. The side hole position of the double lumen catheter was occupied by a calibrated thermistor^c stabilized with epoxy cement by a local laboratory.^d The thermistor was used to monitor changes in blood temperature for determination of cardiac output by thermal dilation technique.

A polypropylene tube was used for collection of end expiration gas samples in order to monitor anesthetic concentration. The tube was inserted into the lumen of an endotracheal tube near the plastic adaptor and advanced to the tip of the endotracheal tube near the thoracic inlet. A ten milliliter glass syringe with a three-way stopcock was used to collect gas samples.

^aCournand Teflon Catheter #7550, U.S. Catheter and Instrument Co., P.O. Box 787, Glen Falls, NY 12801.

^bCournand Double Lumen Catheter, U.S. Catheter and Instrument Co., P.O. Box 787, Glen Falls, NY 12801.

^cVeco 32A7, Victory Engineering Corp., Victory Road, Springfield, NJ 07081.

^dDept. of Physiology, Michigan State University, East Lansing, MI 48824.

Development of hypothermia during the study was avoided by means of a thermostatically controlled circulating water blanket^a which was used to insulate dogs from the surgery table. In addition, an electronic thermometer^b was used to monitor esophageal temperature.

Equipment and Calibration

An eight channel photorecorder with oscilloscope^c was used to monitor arterial pressure, central venous pressure and cardiac output. Pressure transducers^d used for monitoring arterial and venous pressure were calibrated by means of integrated resistors contained by the photorecorder. The arterial and venous catheters were connected to the transducers and then to the preamplifiers of the photorecorder. Electronic averaging was used to obtain mean values.

A three-channel graphic recorder^e was utilized for monitoring presence of muscle twitch during the period of paralysis. Conversion of the physical twitch to a visual tracing was by means of a force displacement transducer.^f The transducer was calibrated using integrated resistors in the graphic recorder. One of the dog's posterior limbs was stabilized with a modified Thomas splint apparatus which was connected to the force displacement transducer by means of

^aModel K-13, Gorman-Rupp Industries Co., Belleville, OH.

^bModel 41TF, Yellow Springs Instrument Co., Yellow Springs, OH.

^cModel DR-8, Electronics for Medicine, White Plains, NY.

^dModel P23Db, Statham Transducers, Inc., Hato Rey, Puerto Rico.

^eModel 50 Polygraph, Grass Instrument Co., Quincy, MA.

^fModel FT10, Grass Instrument Co., Quincy, MA.

adhesive tape and 2.0 silk suture. The tape was used to form a loop which in turn was taped to the tarsal area of the dog's leg. The silk suture was used to connect the loop to the force displacement transducer. Counter force was applied to the transducer until a stable recording was maintained. To elicit a twitch, the peroneal nerve was stimulated with a single rectangular stimulus of 0.1 milli-second in duration, 15 volts in strength, at a rate of .5 pulses/second.

A gas chromatograph^a was used to monitor alveolar anesthetic concentration. A 15 x 1/8 inch stainless steel screened 60/80 mesh silica gel column was used. Column and detector temperature were maintained at 165°C and 200°C, respectively. Gases used were hydrogen at 50 psi flowing 60 ml/min, air at 50 psi flowing 300 ml/min, and nitrogen at 60 psi flowing at 100 ml/min. Calibration gas tanks were prepared by adding liquid halothane to size E gas cylinders to yield nearly complete saturated concentrations of anesthetic at atmospheric pressure following the procedure of Sawyer *et al.* (84).

A blood gas analyzer^b was used to monitor blood concentrations of oxygen, carbon dioxide and hydrogen ion. Calibration of the blood gas analyzer was checked before each sample, and base excess was computed by means of a nomogram.^c Arterial blood was used for all analyses.

^aGaschromatograph GC-M, 115 Frankfurter Ringer, Munich, Germany.

^bModel 72, EMD-RUPVEJ, Radiometer Copenhagen, Copenhagen, Denmark.

^cSiggaard-Anderson Alignment Nomogram, Radiometer Copenhagen, Copenhagen, Denmark.

A semi-closed circle anesthesia machine^a was used to deliver halothane and oxygen to the experimental subjects. Ventilation was controlled by a mechanical ventilator^b with end tidal carbon dioxide concentration maintained at 5% by means of a carbon dioxide analyzer.^c Figure 1 shows a diagrammatic sketch of equipment arrangement.

Calculations

A thermal dilution technique was used for determination of cardiac output. Room temperature saline was injected into the right atrium and, after flowing through the pulmonary circulation, a fall in temperature was recorded by the thermistor located in the descending aorta. Before each injection, blood temperature, injectate temperature and volume of injectate were recorded.

The change in temperature was visualized as a curve, the area of which was measured as a triangle by planimetry.^d Three separate determinations of area were made with the average used in calculation for cardiac output. Paper speed was verified by counting time lines. Cardiac output was calculated by the following modified Stewart-Hamilton formula (61):

^aModel Rotameter, The Foregger Co., Inc., New York 18, NY.

^bAnesthesia Ventilator Series 300/SO, Ohio Chemical and Surgical Equipment Co., Madison, WI.

^cMedical Gas Analyzer, LB-2, Beckman Instruments, Fullerton, CA 92634.

^dK & E Compensating Polar Planimeter, Keuffel and Esser Co., New York, NY 10017.

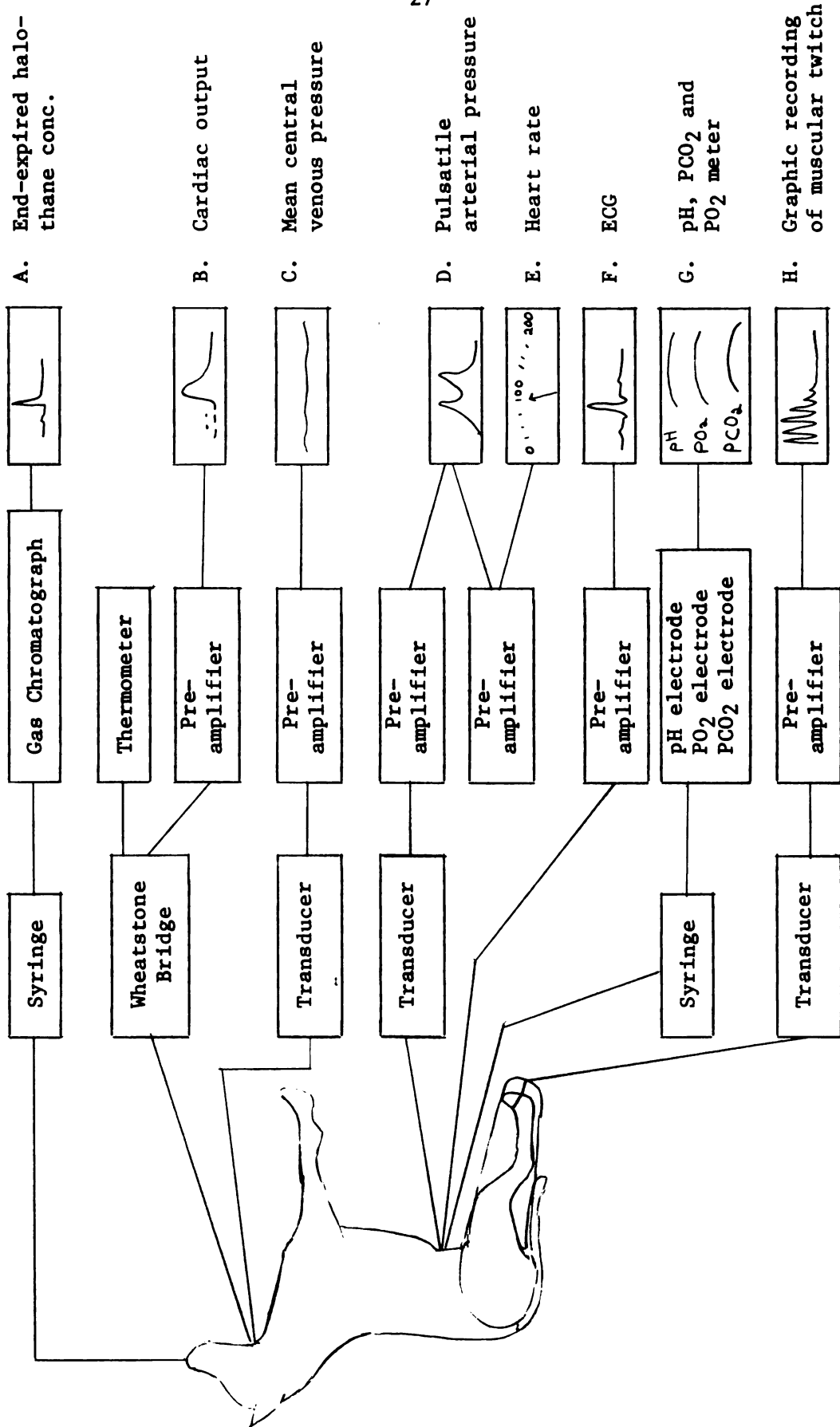


Figure 1. Diagrammatic sketch of equipment arrangement.

$$CO = \frac{V_i (T_b - T_i) (R) (F)}{A}$$

where CO = cardiac output in l/min

V_i = volume of the injectate in ml

T_b = temperature of the blood in degrees centigrade

T_i = temperature of the injectate in degrees centigrade

R = standard deflection due to 3 ohm resistor given in cm/C°

F = paper speed in cm/min

A = area under the curve in cm².

Cardiac index, stroke volume and total peripheral vascular resistance were determined from cardiac output values.

Formulae utilized for these calculations included:

$$CI = \frac{CO}{BSA}$$

$$SV = \frac{CO}{HR} \times 1000$$

$$TPVR = \frac{MAP - MVP}{CO}$$

where CI = cardiac index

CO = cardiac output in l/min

BSA = body surface area in m²

HR = heart rate in beats/min

SV = stroke volume in ml

TPVR = total peripheral vascular resistance in peripheral vascular resistance units (PRU)

MAP = mean arterial pressure in mm Hg

MVP = mean venous pressure in mm Hg.

Body surface area was determined from a nomogram (37).

Calibration of the gas chromatograph involved the injection of a known concentration of halothane (0.80%) and determination of the deflection on a recorder.^a The gas chromatograph was determined to be linear over the span of concentrations used in the study and therefore a proportion was utilized to determine the unknown anesthetic concentration.

$$\frac{\text{unknown anesthetic concentration}}{[\text{standard deflection (mm)}]} = \frac{[\text{halothane standard (\%)}]}{[\text{sample deflection (mm)}]} [\text{sample deflection (mm)}]$$

Procedure

On the day of study a dog was selected at random and was brought to the surgical preparation area. A 3 ml EDTA sample of venous blood was drawn from the cephalic vein and taken to the clinical pathology laboratory for evaluation. Using a gentle manner, the dog was then anesthetized with halothane and oxygen delivered by mask. Preanesthetics were not used. After intubation, anesthesia was maintained by 1 to 1.5% halothane in oxygen delivered by a semi-closed circle anesthesia machine.

After anesthetic stabilization the dog was transported by gurney to the catheterization room. In order to prevent development of accidental hypothermia, the dog was insulated from the gurney and catheterization table by a circulating warm water blanket. After surgical preparation of the lateral cervical area, exposure of the

^aModel 1005, Beckman Instruments, Inc., Fullerton, CA.

jugular vein and common carotid artery was accomplished. A double lumen cardiac catheter was placed in the descending aorta via the carotid artery. Fluoroscopy^a was used to verify correct positioning. The catheter was then double ligated in place to insure that movement would not occur. The end hole cardiac catheter was then introduced to the level of the right atrium via the jugular vein. Position was verified by a 3 ml injection of radiopaque dye^b witnessed by fluoroscopy. In order to prevent development of blood clots within the lumens of catheters, heparinized saline was used as a periodic flushing agent. At the conclusion of 30 minutes of catheterization procedure, the dog was transported to the surgical laboratory.

Catheters were then connected to pressure transducers and control values for arterial pressure and ventral venous pressure were obtained. The arterial thermistor catheter was connected to a Wheatstone bridge which was in turn connected to a pressure preamplifier which allowed visualization of cardiac output curves. The thermal dilution technique was used for determination of cardiac output. The dog's blood temperature was continuously recorded by an electronic thermometer via the Wheatstone bridge. Lead II electrocardiogram was continuously monitored, and heart rate was computed from the arterial pulse tracing on the photographic printout.

In order to provide support and a stable base for the force displacement transducer, a modified Thomas splint apparatus was fitted to

^aModel HRT, General Electric Co., Medical Systems Division, Detroit, MI 48219.

^bHypaque 50%, Winthrop Lab., New York, NY.

a rear leg (16). The force displacement transducer was then connected to the leg via adhesive tape and silk ligature with the resting tension adjusted so that during intermittent electrical stimulation, a stable tracing was obtained. Alveolar concentration of halothane was determined by gas chromatograph and maintained at 1.1 times the minimum alveolar concentration (34) throughout the experimental procedure. Preparation procedure from induction of anesthesia to beginning of experiment averaged 75 minutes in duration.

After control determinations of cardiac output, arterial pressure, central venous pressure, total peripheral resistance, cardiac index and heart rate, the dog was given either succinylcholine or gallamine 0.4 mg/kg intravenously via the lingual vein. Cardiac output determinations were made at 5-minute intervals until the twitch response had returned to 1/10 of control values. Blood pH was monitored from samples drawn from the femoral catheter. If the hydrogen ion concentration expressed in terms of pH was less than 7.30, correction was completed before injection of the muscle relaxant to be tested. Metabolic acidosis was corrected by the administration of 7.5% sodium bicarbonate solution and respiratory acidosis was corrected by adjustment of the rate or volume of the ventilatory pattern. A total of 8 dogs was involved in the study. Each dog served as his own control as the procedure was repeated after 2 weeks with the second relaxant.

Data Analysis

Analysis of data was accomplished through the facilities of the computer laboratory of Michigan State University. An analysis of variance (randomized complete block design) was used to compare

differences due to time. Data collection points analyzed were control, $x + \text{one minute}$, $x + 5 \text{ minutes}$, and $x + 10 \text{ minutes}$. Tukey's w-procedure (89) was used to test for differences between means. The level of probability chosen for this study was 0.05.

RESULTS

General Considerations

Eight dogs were employed in the study. A total of 16 trials was completed with each dog undergoing the experimental procedure twice. Succinylcholine was used in the first trial followed in 2 weeks by the administration of gallamine.

Laboratory examination of each dog included a fecal examination for parasites, a complete blood count, blood urea nitrogen determination and evaluation of serum glutamic pyruvic transaminase levels. All values (Table 1) were within the normal range established for the Beagle (19,27,96).

Table 1. Blood evaluations for 8 dogs prior to study

SGPT (S.F. units)	BUN (mg/100 ml)	WBC (cells/mm ³)	PCV (%)	Hb (gm/100 ml)	Protein (gm/100 ml)
16.2±3.2	15.3±2.6	12,462±3,488	48±2	16.8±1	5.5±0

Mean and standard deviation values from 8 dogs recorded from jugular vein blood samples.

During the experimental procedure, dogs were placed on warm water blankets in order to prevent accidental hypothermia. At each time period the gallamine group averaged 35.4°C while the succinylcholine group was slightly warmer (Table 2). The mean temperature at each time period for either gallamine or succinylcholine was not significantly different from their respective control means.

Table 2. Mean temperatures of 8 dogs given either gallamine or succinylcholine

	Control (°C)	x + 1 min (°C)	x + 5 min (°C)	x + 10 min (°C)
Gallamine	35.4±1.3	35.4±1.3	35.4±1.3	35.4±1.3
Succinylcholine	36.1±0.85	36.2±0.85	36.3±1.0	36.3±1.0

Mean and standard deviation of esophageal temperature values.
X equals time of injection of muscle relaxant.

Within 45 seconds after injection of either relaxant, muscle paralysis was complete. The duration of paralysis was monitored by two criteria: when the twitch response had returned to 1/10 of control values and when the twitch response had returned to maximum. Cardiovascular variables were monitored up to the return of 1/10 of control twitch. Table 3 displays the mean duration of paralysis for succinylcholine and gallamine.

End tidal halothane concentration was monitored to insure parallelism of anesthetic depth among the dogs studied. Table 4 displays mean end tidal anesthetic concentration for the 2 groups of dogs.

Table 3. Duration of paralysis of 8 dogs given either gallamine or succinylcholine

	Return to 1/10 twitch (min)	Return to complete twitch (min)
Gallamine	26±7	40±11
Succinylcholine	22±12	37±19

Mean and standard deviation values for 2 groups of 8 dogs measured at 1/10 and complete return of control twitch.

Table 4. Mean end tidal halothane concentration of 8 dogs given either gallamine or succinylcholine

	% halothane
Gallamine group	1.11±.06
Succinylcholine group	1.14±.11

Mean and standard deviation values for 2 groups of 8 dogs.

Serum potassium levels were monitored from samples drawn before, during, and after administration of a muscle relaxant. Specific times were: 1) preanesthesia, 2) anesthetized but before injection of relaxant, 3) 15 minutes after injection of a relaxant, and 4) 2 weeks after the experimental procedure. Only 6 dogs were included in this phase of the experiment due to incomplete data from 2 of the dogs. In

the gallamine group of dogs, preanesthetic serum potassium levels were not significantly different from any other time periods. However, the mean of the 2 week potassium serum sample was significantly different from the anesthetized preinjection sample mean and the 15 minute postinjection sample mean. In the succinylcholine experiment, the preanesthesia sample was significantly different from the 15 minute postinjection sample and the 2 week sample. All other sample comparisons were homogeneous (Table 5).

Table 5. Mean serum potassium concentrations from 8 dogs given either gallamine or succinylcholine

		<u>Time</u>		
	Preanesthesia (mEq/l)	Preinjection (mEq/l)	15 minutes Postinjection (mEq/l)	2 weeks (mEq/l)
Gallamine	3.8±.42	3.5±.37	3.4±.62	4.2±.37
Succinylcholine	4.2±.45	3.3±.36	4.1±.63	4.3±.24

Mean and standard deviation values for 8 dogs from blood samples taken prior to induction of anesthesia, before injection of muscle relaxant, 15 minutes after injection of muscle relaxant and 2 weeks after the experimental procedure.

Cardiovascular Effects of Gallamine

After intravenous administration of gallamine, cardiac output and heart rate exhibited slight increases. Specifically, cardiac output increased 5% at x + 1, 7% at x + 5, and 7% at x + 10 when compared with control values. Heart rate was increased 7% at x + 1, 4% at x + 5, and

3% at $x + 10$ when compared with control values. Stroke volume decreased 5% at $x + 1$, then slightly increased at the next 2 data points, while mean arterial pressure increased 12% at $x + 1$, then slightly decreased to 8% above control for the next 2 data points.

Cardiac index and central venous pressure exhibited opposite movements as cardiac index increased slightly, while central venous pressure slightly decreased. Total peripheral resistance slightly increased at $x + 1$, but then gradually declined toward control values.

Analysis of variance revealed that the slight variations from control were not significant at the 0.05 level; however, there was a significant difference between values from individual dogs. The identification of the source of variation may explain the occurrence of large standard deviation found with certain variables. Table 6 displays the cardiovascular changes from injection of gallamine.

Cardiovascular Effects of Succinylcholine

Intravenous administration of succinylcholine resulted in a 9% increase in cardiac output at $x + 1$ minute, followed by a gradual reduction to control values over the next 10 minutes.

Heart rate also initially increased and was followed by a slow return to control values. In a manner similar to the change in cardiac output, mean arterial pressure exhibited the greatest increase at $x + 1$ minute (24%), only to return to control values at the 5 minute mark.

Mean central venous pressure, stroke volume and cardiac index exhibited small changes from control values with mean venous pressure and cardiac index increasing slightly and stroke volume decreasing at $x + 1$ minute.

Table 6. Mean cardiovascular variables from 8 dogs given 0.4 mg/kg gallamine

Time (min)	C	x + 1	x + 5	x + 10
CO (l/m)	1.38±27	1.44±.26	1.47±.43	1.48±.38
CI	2.94±.52	3.05±.52	3.12±.50	3.14±.47
HR (beats/min)	94±22	101±15	98±22	97±21
SV (ml)	15±5	15±4	16±6	16±5
TPR (PRU)	42±9	46±10	44±11	44±9
MVP (mean mm Hg)	5±2	4±2	4±1	4±2
MAP (mean mm Hg)	62±9	69±13	67±12	66±11

Mean and standard deviation values for 8 dogs for each variable recorded immediately before and at 1 minute, 5 minutes, and 10 minutes after injection of gallamine.

CO = cardiac output; CI = cardiac index; HR = heart rate; SV = stroke volume; TPR = total peripheral resistance; MVP = mean venous pressure; MAP = mean arterial pressure.

Total peripheral resistance increased 15% at x + 1 minute, returning to control at x + 5 minutes.

At the 0.05 level of significance, analysis of variance (randomized complete block design) revealed that changes observed for heart rate and mean arterial pressure were significant. Changes observed in cardiac output, cardiac index, stroke volume, mean central venous pressure and total peripheral resistance were not significant.

Comparisons of means by Tukey's w-procedure (89) revealed that control and x + 1 minute means for heart rate and mean arterial pressure

were significantly heterogeneous. Other comparisons between means involving these two variables were not significant.

There was significant variation between dogs as shown by analysis of variance ($P < 0.05$). This identifies a source of variation which might be mistakenly attributed to an action of succinylcholine.

Table 7 displays cardiovascular data from injection of succinylcholine.

Table 7. Mean cardiovascular variables of 8 dogs given 0.4 mg/kg succinylcholine

Time (min)	C	x + 1	x + 5	x + 10
CO (l/m)	1.58±.40	1.73±.33	1.71±.32	1.57±.26
CI	3.36±.79	3.67±.74	3.63±.75	3.30±.52
HR (beats/min)	113±22	125±11*	119±13	116±14
SV (ml)	15±4	14±2	15±3	14±3
TPR (PRU)	51±10	59±20	49±11	52±12
MVP (mean mm Hg)	4±3	5±4	4±3	3±3
MAP (mean mm Hg)	82±12	103±24*	85±5	83±12

Mean and standard deviation values for 8 dogs for each variable recorded immediately before and at 1 minute, 5 minutes, and 10 minutes after injection of succinylcholine.

CO = cardiac output; CI = cardiac index; HR = heart rate; SV = stroke volume; TPR = total peripheral resistance; MVP = mean venous pressure; MAP = mean arterial pressure.

* Statistically significant difference when compared with control ($P < 0.05$).

DISCUSSION

This study was undertaken to eliminate some of the doubts veterinary practitioners may have concerning the use of muscle relaxants in conjunction with halothane anesthesia. Muscle relaxants have not been used in veterinary medicine partially due to a lack of information on the cardiovascular effects in the dog. Indeed, the reports of death involving the use of succinylcholine in the horse may have frightened some veterinarians from considering the use of muscle relaxants as an adjunct to anesthesia.

With the present study halothane anesthesia was chosen because it is widely used in veterinary anesthesia. Atropine preanesthesia was not utilized in order to eliminate a possible source of extraneous effect on the autonomic nervous system.

Temperature was controlled by means of circulating water blankets in order to eliminate the possibility of accidental hypothermia. However, even with stringent preventive measures, a moderate degree of hypothermia did develop. Several investigators (10,22,68,101) have reported an effect from hypothermia on the duration and magnitude of neuromuscular blocking drugs. Bigland *et al.* (10) found an increased duration and magnitude at the motor end plate from succinylcholine and a decreased duration of action from the non-depolarizing drug d-tubocurarine. Supporting results were found by Cannard (22) and Zaimis

(101) when studying the effect of lowered muscle temperature on the action of neuromuscular blocking drugs in man. They found that lowering muscle temperature to 26°C increased the magnitude and prolonged the duration of the blockade produced by succinylcholine. Hypothermia for the current study was not less than 36°C and consequently probably played no significant role in the duration of action of succinylcholine or gallamine.

The acid-base status of each dog was monitored by analysis of arterial blood samples collected prior to injection of a muscle relaxant. If blood pH was below 7.30, proper corrective techniques were instituted before injection of the relaxant. In work involving cats, acidosis has been shown to have little effect or even accelerating recovery from the neuromuscular block of gallamine (48). Conversely, respiratory alkalosis has been reported to prolong neuromuscular block from gallamine (56). In cats given succinylcholine (48), respiratory acidosis antagonized the block and speeded recovery, while respiratory alkalosis slightly potentiated the paralysis. Metabolic acidosis and alkalosis did not modify the duration or intensity of neuromuscular paralysis. The possible mechanisms of action for effects from changes in pH include: 1) an increase in PCO_2 will increase blood pressure and blood flow which may reduce blockade and shorten recovery; 2) the activity of the drug is inversely proportional to that fraction bound to protein and alterations in plasma pH modify the ability of plasma proteins to take up certain drugs, 3) finally, a change in ionization could occur at receptors when pH is altered. Although the duration of block from succinylcholine in the dog is variant from the cat, alterations

in duration of paralysis from changes in pH should be similar. In the current study, any deviations in pH and PCO_2 were corrected prior to injection of the muscle relaxant.

The effect of halothane on the heart and circulation is well documented (12,20,41,49,51,52,80,85). In order to maintain the same conditions for each group of dogs, end tidal halothane concentration was closely monitored. Hypotension and muscle relaxation will result from increasing concentrations of halothane. It is not unrealistic to think that early reports of hypotension from muscle relaxants might have been due in part to deep levels of anesthesia. Black (12) recently listed five possible mechanisms to explain the occurrence of hypotension during halothane anesthesia: 1) by suppressing autonomic nervous activity, 2) by causing peripheral vasodilation, 3) by altering the ability of baroreceptor reflexes to compensate for changes in blood pressure, 4) by inhibiting the vasomotor center and, finally, 5) by modifying the contractile force of the heart. Raventos (80), in the initial study of the cardiovascular effects of halothane, proposed that hypotension was due to mesenteric ganglionic blockade. Hughes (49) ventilated closed chest dogs with 1 and 2% halothane and noticed falls of arterial blood pressure similar to those following hexamethonium. This was without comparable reduction in peripheral vascular resistance or comparable impairment of either the cardiac slowing induced by vagal nerve stimulation or the contractions of the nictitating membrane induced by preganglionic cervical sympathetic nerve stimulation. This indicates that ganglionic blockade does not fully explain the hypotension produced by halothane. Burn *et al.* (20)

found little evidence of neural blockade in the superior cervical ganglia of the cat and also demonstrated a blood pressure fall in an eviscerated animal. Thus hypotension may be due to depression of central autonomic centers. The most plausible explanation for the effects of halothane is a combination of factors.

Neuromuscular transmission is also affected by halothane. Karis *et al.* (52) state that even though muscular relaxation is mainly attributable to the central effect of halothane, the peripheral action which involves a reduction in sensitivity of the postjunctional membrane is not negligible and could be significant when neuromuscular transmission is impaired by disease or curare-like agents. When halothane was studied in the amphibian nerve-muscle preparation (41), the blocking concentrations of halothane were found to be 1.5% for the nerve stimulated twitch, 4% for the axonal conduction, and 4% for the directly stimulated muscle. From these results, it was concluded that the peripheral blockade produced by halothane occurs at the neuromuscular junction. By the use of the microelectrode penetration of single fibers, it was demonstrated that, at the neuromuscular junctions, the postjunctional membrane is the synaptic structure most sensitive to the action of halothane. In the current study, halothane concentration was maintained at a mean of 1.11% for the gallamine group and 1.14% for the succinylcholine group, thereby limiting any effect on neuromuscular transmission.

The duration of neuromuscular block was monitored by a mechanical recording of twitch using a method proposed by Bowen (16). There is some controversy involving the ideal method of recording muscle

activity; however, Katz (53) compared electrical and mechanical methods of recording spontaneous and evoked muscle activity and concluded that a mechanical recording of twitch is an acceptable way of monitoring neuromuscular block.

The primary objective of this study was to report on the cardiovascular effects of gallamine and succinylcholine administration to dogs anesthetized with halothane. Ideally, one would like to see a minimal or possibly a slight positive effect on the cardiovascular system from the administration of these two drugs. In general, the administration of the muscle relaxants, as defined in terms of this study, had minimal effect on cardiovascular variables.

Cardiac output increased slightly after administration of gallamine, maintaining the increase throughout the evaluation period, while succinylcholine exhibited a slight increase at the first data point but slowly returned to control values over the next two data points. These changes were not significant at the 0.05 level.

Clinically, a small increase in cardiac output could be beneficial, principally to counteract cardiovascular depression commonly seen during general anesthesia. The changes in cardiac output can be related to small increases in heart rate. After gallamine administration, heart rate increased 7% over control values. This result agrees with other reports in quality but not quantity. Increases as high as 40% have been reported (57) with an average increase of 25% (69,98). Changes in heart rate due to gallamine have been related to a vagal blocking action similar to atropine (23,31,82,83), myocardial stimulation (87), or positive chronotropic effect secondary to local

catecholamine release (18). The lack of marked increases in heart rate during the present study may reflect increased attention to providing a stable animal before and during action of gallamine. Increased levels of CO_2 in the blood may occur during anesthesia and subsequently may increase heart rate. Another possible explanation is that many of the cited studies were performed clinically on human subjects. If the level of anesthesia was not deep and the cerebral cortex active, the sensation of total paralysis may have stimulated the release of epinephrine and subsequently a chronotropic effect on the heart. The current study controlled the blood PCO_2 and anesthetic level in order to mitigate the above effects. As a result, a modest increase in heart rate occurred which was analyzed as being not significant.

In contrast, the small increase in heart rate from succinylcholine was found to be significant. Increases in heart rate have been found by other investigators who have related their findings to: 1) a nicotinic action of succinylcholine (1,13,54), 2) vagal stimulation and reflex stimulation of peripheral receptor organs (70), and 3) an arousal response in the electroencephalogram from afferent discharge of muscle spindles (73). The nicotinic action of succinylcholine has been well documented (91,92,93) by investigators who utilized the ganglionic blockers hexamethonium and tetraethylammonium chloride to prevent increases in heart rate after injection of succinylcholine. Reflex stimulation of the carotid sinus precipitated by a vagal type action would increase heart rate. Indeed, Mathias *et al.* (70) state that "it is generally considered that the action of succinylcholine on the heart is identical to that of vagal stimulation." This would explain

the often seen biphasic nature of succinylcholine's action on cardiac rhythm, i.e., initial slowing followed by tachycardia.

A new explanation for the action of succinylcholine on cardiac rhythm was introduced by Mori *et al.* (73) in 1973. They postulated that the depolarizing drugs produce an increased activity in the afferent discharge of the muscle spindles which leads to the electroencephalogram arousal pattern. This arousing pattern may have some role in the tachycardia produced by succinylcholine. Whatever the effect of succinylcholine, much of the confusion of its effect is probably due to similarity between the succinylcholine and acetylcholine molecules. This similarity makes it difficult to determine the exact mechanism or mechanisms of action, there being a different effect at different sites (the heart cell, the ganglion, the motor end plate). Evidence for postganglionic stimulation is found in the development of hypertension and tachycardia after the administration of large doses of succinylcholine.

The present study did not show a slowing of heart rate followed by an increase in rate to above control levels. Atropine was not used so that any muscarinic effect of succinylcholine should have been apparent. The noted increase in rate could neither be explained in terms of reflex action as an initial bradycardia was not seen. An asphyxial response aggravated by muscular activity can also not be used to explain the tachycardia as blood PCO_2 and PO_2 were closely monitored as the animal was artificially ventilated. In order to achieve ganglion stimulation, doses larger than those used in this experiment would seem to be needed. We are left with the possibility

that muscle fasciculation and resultant afferent discharge of muscle spindles may somehow play a role in the occurrence of tachycardia.

In a manner similar to heart rate, mean arterial pressure increased after injection of gallamine and succinylcholine with the increase in pressure after the latter significant. Increases in mean arterial pressure can be caused by increases in peripheral resistance or increased cardiac output. Succinylcholine is thought to increase mean arterial cardiac output. Succinylcholine is thought to increase mean arterial pressure through stimulation of autonomic ganglia (9,13,54,92, 93,102). However, at least one report (41) points out that ganglionic stimulation should include vasoconstriction of skin and splanchnic areas and this is not the case. Other explanations for the action of succinylcholine on blood pressure include a hypotensive muscarinic effect on receptors in the peripheral vasculature (41,63), a hypertensive response to asphyxia (91,50), and vagal stimulation from an acetylcholine-like action (9,64,67).

The action of gallamine on blood pressure can be related to cardiovagal block (83), myocardial stimulation (17,18) and a slight sympathetic ganglionic block (86,93). A convincing study by Brown *et al.* (18) utilizing cats and guinea pigs enforces the theory of myocardial stimulation to increase blood pressure. They used reserpinized atria and inhibited the response to gallamine almost completely with any residual effect abolished by propranolol. Recently, Reitan (81), working with anesthetized man, could not demonstrate any ionotropic action of gallamine. The current study found only a small nonsignificant increase in blood pressure. One possible explanation

is that experimental technique has improved. Original workers used a kymograph to record changes in pressure with little attention to maintaining a stable environment. Modern experiments utilize accurate pressure transducers with a supporting role from blood-gas monitors, thermistors, and anesthetic concentration analyzers. Another factor which contributed to conflicting results is the number of different species which have been used. Almost all domestic animals plus man have contributed to knowledge about the action of gallamine and succinylcholine. This fact cannot help but introduce an enormous degree of variation. The reason the current study did not produce striking changes in heart rate and arterial pressure may be due to closer monitoring of control variables.

Other cardiovascular variables did not change significantly after injection of succinylcholine or gallamine. Mean central venous pressure, stroke volume, total peripheral resistance and cardiac index were all homogeneous with respect to their control values.

It is interesting to note that a nonsignificant rise in total peripheral resistance did occur during the succinylcholine trial. This might possibly be related to muscle fasciculations during the depolarization stage of paralysis, as the modest increase in resistance (15%) was not present at the 5 minute mark.

Succinylcholine-induced increased serum potassium has been reported by many investigators as a complication of the clinical use of succinylcholine (11,26,95). In order to determine if succinylcholine administration causes a rise in serum concentration, blood samples were collected prior to induction of anesthesia before injection of

the muscle relaxant, 15 minutes after injection, and 2 weeks after the experimental procedure. The interesting result was that the sample collected from the anesthetized dog before injection of succinylcholine was significantly lower than the preanesthesia sample, the postinjection or the 2-week sample. Therefore, injection of succinylcholine raised serum potassium an average 0.8 mEq/l. Administration of gallamine did not produce a similar response. Succinylcholine is thought to change cell membrane permeability for potassium with a resulting loss of potassium from the cell, a decrease in resting membrane potential, and an increase in serum potassium (54). The cat has shown a similar response to succinylcholine (76). Although the increase in the current study was statistically significant, it was not clinically significant.

In the present study the duration of action of succinylcholine was longer than the duration of action seen in man, cat or horse. Possible explanations include decreased plasma pseudocholinesterase, atypical plasma pseudocholinesterase or a phase II (desensitization) block (100).

Decreased plasma pseudocholinesterase may be the result of hepatic disease as plasma pseudocholinesterase is synthesized by the liver. In the current study, there was no evidence of liver necrosis as determined by serum glutamic pyruvic transaminase levels. Atypical plasma cholinesterase is a hereditary defect in man (100) which has not been reported in the dog. The occurrence of a desensitizing or phase II block after one dose of succinylcholine in the dog should be considered (90). This type of block occurs in man after repeated doses of succinylcholine (100).

The rate of elimination of muscle relaxants also has an important role in determining duration of action. The nearly complete ionization of gallamine limits the ability of this relaxant to cross cell membranes resulting in limited distribution. Consequently, renal tubular reabsorption of the relaxant is prevented after being filtered in the glomerulus. In addition, only a small fraction of gallamine molecules are bound to protein and most are free to pass with the plasma filtrate enhancing renal elimination of the drug.

In contrast, elimination of succinylcholine in most species depends on 1) clearance from the active site by diffusion or by local hydrolysis in the capillary and 2) removal by muscle blood flow (100). Factors which affect these points include hepatic disease (100), body temperature (101), preanesthetic medication, and cardiac output.

CONCLUSIONS

The intravenous administration of succinylcholine or gallamine following the criteria defined in this study does not adversely affect cardiac output, mean arterial pressure, heart rate, stroke volume, mean venous pressure, total peripheral resistance, or cardiac index. The use of these agents as an adjunct to anesthesia in the dog should be encouraged in contemporary veterinary practice.

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