CARDIAC EFFECTS OF SUCCINYLDICHOLINE AND SUCCINYLMONOCHOLINE

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ALTHOUGH THE NEUROMUSCULAR BLOCKING EFFECT of succinylcholine is reasonably understood, its cardiac effects are varied and still require clarification. Clinically, hypertension and hypotension, bradycardia and tachycardia as well as dysrhythmia are not infrequently seen during continuous infusion or during repeated intravenous injection of succinylcholine.¹⁻⁴

Succinylcholine and its first step hydrolyzed product succinylmonocholine are structurally similar to acetylcholine.

Several mechanisms of action have been postulated for the cardiac effects of succinylcholine. These are:

1. Direct action on atrial muscarinic receptors and possibly multiple muscarinic and nicotinic receptors in the ventricle.^{5,6}
2. Stimulation of postganglionic parasympathetic fibres to autonomic effector cells.⁷
3. Stimulation of preganglionic autonomic fibres to sympathetic and parasympathetic ganglion cells and to the adrenal medulla.⁷
4. Stimulation of vagal centres or through sensory receptors of carotid or aortic body and carotid sinus.^{8,9}

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The present study evaluates the possible role of succinylmonocholine in the production of some of these cardiac effects. The rabbit was chosen as the experimental animal because it has a low level of plasma cholinesterase,¹⁰ thus allowing greater ease of interpretation of *in vivo* responses to repeated injections of succinylcholine and comparative studies could be done in isolated rabbit hearts where extra-cardiac effects were eliminated.

METHODS

In Vitro Study

Isolated hearts of albino rabbits were perfused through the aorta in a modified Langendorff preparation as previously described.¹¹ A constant column of perfusate of 50 cm H₂O over the aortic valve was maintained with the use of a run-off arm. The perfusate was Chenoweth solution, containing NaCl 119.8 mM, KCl 5.63 mM, CaCl₂ 2.16 mM, MgCl₂ 2.10 mM, dextrose 10 mM and NaHCO₃ 25.0 mM at pH 7.4. This was gassed with 95 per cent O₂ and 5 per cent CO₂ at constant temperature 37° C regulated with a Lauda Thermo-regulator. Left ventricular pressure (LVP) and LV dp/dt were recorded from a 14 gauge needle inserted through the left ventricular muscle, with the needle attached to a high frequency Microdot pressure transducer. The cardiac electrogram was monitored with platinum electrodes in the right atrial appendage and the left ventricular wall one centimetre from the apex.

When the preparation was stabilized it was perfused for 15 minutes with a freshly prepared drug solution, during which time observations were made. After perfusion with one solution, the heart was perfused for 15 minutes with control solution before changing to the next drug solution. The perfusate was not recirculated. Twenty-six hearts were perfused in four groups.

- Group 1 (7) were perfused with 20, 50, and 100 mg/l succinylcholine solution;
- Group 2 (7) were perfused with 20, 50 and 100 mg/l succinyl monocholine solution;
- Group 3 (7) were perfused with mixed solutions of succinyl dicholine and succinyl monocholine equivalent to above concentration;
- Group 4 (5) were pretreated with intraperitoneal reserpine 5 mg/kg 24 hours before the isolation of the hearts and perfused with succinylcholine and/or succinylmonocholine.

In Vivo Study

Seven untreated rabbits and five rabbits pretreated with reserpine were anaesthetized with intravenous alpha-chloralose (150 mg/kg) and ventilated through a tracheostomy with 100 per cent O₂ maintaining slightly hypocapnic arterial blood gas tensions. A cannula was introduced through the carotid artery into the left ventricle for blood sampling and pressure monitoring. Left ventricular pressure, LV dp/dt and ECG were continuously monitored with frequent checking of arterial blood gas and plasma Na and K.

When these parameters became stable, repeated intravenous injections of succinylcholine and succinyl monocholine were done through an external jugular vein.

RESULTS

In vitro data are summarized in Table I.

1. Perfusion with succinylcholine (20, 50, and 100 mg/l) produced more than 10 per cent to 15 per cent decrease in heart rate, left ventricular pressure and dp/dt in five of seven preparations, without cardiac dysrhythmia.
2. Succinyl monocholine decreased the same parameters in four of seven preparations. However, there was a transient increase in LVP and LV dp/dt .
3. The mixture of succinyl dicholine (10–25–50 mg/l) and succinyl monocholine produced positive and negative chronotropic as well as inotropic responses with a significant number of ventricular extrasystoles in three of seven preparations.
4. Intraperitoneal pretreatment of rabbits with reserpine (5 mg/kg) 24 hours before study produced an increased number of spontaneous nodal beats and ventricular extrasystoles in the isolated hearts. These dysrhythmias were further potentiated by succinylcholine and succinylmonocholine, which produced negative inotropic and chronotropic responses.
5. Single bolus injections of succinylcholine or succinylmonocholine 2 mg or 4 mg through the side arm, close to the perfused heart, produced a diphasic response with initial increase of LVP and LV dp/dt and subsequent decrease of the same parameters plus bradycardia.
6. Atropine sulphate (1–2 mg) abolished the negative chronotropic responses described, but not the cardiac dysrhythmias.

In vivo data are summarized in Table II.

1. Repeated intravenous injections of succinylcholine (1–2 mg/kg) at five-minute intervals produced bradycardia within five seconds followed by 10 per cent to 20 per cent increase in LVP and LV dp/dt in all seven rabbits.
2. Repeated intravenous injection of succinylmonocholine (1–2 mg/kg) produced the same but less profound results as succinylcholine in six of seven rabbits.
3. When succinylcholine (0.5 mg–2 mg/kg) and succinylmonocholine (0.5–2 mg/kg) were injected together, there was marked increase in nodal and ventricular ectopic beats as well as positive inotropic responses in all seven rabbits. The latency time to onset of dysrhythmias was 30 seconds to one minute. Plasma potassium and sodium were within normal limits during these dysrhythmic episodes.
4. Atropine sulphate (0.5 mg/kg) intravenously abolished the bradycardia effect of succinylcholine and succinylmonocholine and reduced, but did not abolish the dysrhythmic beats.

The following three groups in Table II consist of the reserpinized animals, animals with cord trans-sections at the level of the foramen magnum and animals with cord trans-section titrated with intravenous trimethaphan to obtain a steady state of LV dp/dt 80 per cent of control. In all three groups there was a transient immediate bradycardia, but without any effect on LVP or LV dp/dt . Animals with trans-section of the cord responded with transient cardiac dysrhythmias following injections of a mixture of succinylcholine and succinylmonocholine, but these ceased spontaneously in less than two minutes.

TABLE I
In Vitro EXPERIMENTS

	N	Heart rate	LVP and LV dp/dt	Nodal and/or ventricular ectopic beats
No Reserpine				
Pre-treatment				
Succinylcholine (20-100 mg/l)	7	↓ (5/7)	↓ (5/7)	None
Succinylmonocholine (20-100 mg/l)	7	↓ (4/7)	↑ (4/7) followed by ↓ (4/7)	None
Succinylcholine (10-50 mg/l) plus Succinylmonocholine (10-50 mg/l)	7	↑ (3/7) followed by ↓ (3/7)	↑ (3/7) followed by ↓ (3/7)	↑ (3/7)
Reserpine Pre-treatment (5mg/kg)	5	↓ (5/5)	↓ (5/5)	↑↑ (5/5)
Succinylmonocholine				

TABLE II
In Vivo EXPERIMENTS

I.V. Dose	N	Heart rate	LVP and LV dp/dt	Nodal and/or ventricular ectopic beats
No reserpine	7	Immediate ↓ (7/7)	↓ (2/7) followed by ↑ (7/7) ↓ (3/7) followed by ↑ (6/7) ↓ (3/7) followed by ↑ (7/7)	None None ↑↑ (4/7) Abolished by cord trans-section or trimethaphan
Reserpinized (5 mg/kg)	5	Immediate ↓ (5/5)	No change	None
Cord Trans-section	5	Immediate ↓ (5/5)	No change	None None ↑ (4/5) Spontaneously abolished in 2 minutes
Trimethaphan	5	Immediate ↓ (5/5)	No change	None

SD = Succinylcholine.
SM = Succinylmonocholine.

DISCUSSION

Acetylcholine has been known to have a diphasic effect on the isolated papillary muscle of the rabbit in a dose related manner. Low doses produced negative chronotropic or inotropic effects, while large doses produced positive chronotropic and inotropic responses. The negative responses were abolished by atropine and non-depolarizing muscle relaxants. Goat¹² found that succinylcholine also has a diphasic action on the isolated rabbit heart. These results suggest two possible types of receptors, muscarinic and nicotinic, in the heart.

In our *in vitro* study, perfusion with succinylmonocholine produced a diphasic response, an initial increase in LVP and dp/dt being followed by a negative inotropic response. Positive response occurred in 1 to 5 minutes and the negative response followed in 5 to 12 minutes. Succinylcholine produced only a negative chronotropic and inotropic response. Single bolus injection of succinylcholine or succinylmonocholine (2–4 mg) through a side arm, close to the perfused hearts, produced immediate positive inotropic response followed by negative chronotropic and inotropic response. These negative cardiac responses were abolished by atropine.

These responses support the hypothesis that muscarinic and nicotinic receptors exist in the heart. Succinylcholine may have a more potent direct muscarinic effect on the myocardium than succinylmonocholine.

The observation that a greater number of dysrhythmias occurred in reserpinized hearts *in vitro* and that these dysrhythmias were further potentiated by succinylcholine and succinylmonocholine is not easy to interpret. The data suggest that the combination of the two drugs was more arrhythmogenic on the isolated heart. The arrhythmogenic effect was potentiated by a reduction in catecholamine stores in the heart. This dysrhythmia may possibly be mediated through type II receptors described by Buccino and Sonnenblick.⁵ They observed in the isolated cat papillary muscle preparation that denervation and reserpine did not abolish the positive inotropic response to acetylcholine and nicotine. They postulated the existence of type II receptors in the ventricular muscle which, unlike classical nicotinic receptors, do not require norepinephrine to exert the positive inotropic effect of acetylcholine.

In several of the untreated animals *in vivo* succinylcholine and/or succinylmonocholine produced a negative inotropic response which was abolished by atropine. There was a sustained positive inotropic response in almost all animals which lasted more than one minute. These diphasic responses were abolished by trimethaphan, cord trans-section and reserpine, suggesting a centrally mediated as well as a peripheral effect. This could be a direct action on the vagal centre in the medulla or an indirect action of sensory receptors such as chemoreceptors or baroreceptors mediated through reflexes. Acetylcholine can increase frequency of impulses from the carotid sinus or carotid body.^{8,9}

The arrhythmogenic effect of a mixture of succinylcholine and succinylmonocholine was significant *in vitro* as well as *in vivo*. The latency time of onset of dysrhythmias *in vivo* was about 30 seconds to one minute. This was abolished by cord trans-section and trimethaphan, suggesting possible contribution from reflex mechanisms. Dysrhythmia was also produced when succinylcholine was injected

one minute after intravenous succinylmonocholine. When succinylcholine was given at intervals greater than 5 minutes following succinylmonocholine there was no dysrhythmia produced, suggesting that some critical balance of the drugs is required *in vivo* to produce dysrhythmias. In one patient anaesthetized with cyclopropane, succinylmonocholine 40 mg intravenously produced no change in heart rate or arterial pressure.⁴ Succinylcholine 40 mg intravenously 1½ minutes following succinylmonocholine produced increased heart rate and arterial pressure. Subsequent injection of succinylcholine produced bradycardia, but no obvious effect was observed with succinylmonocholine.⁴

In summary succinylmonocholine and succinylcholine administered separately or together, produced bradycardia in experiments *in vivo* as well as *in vitro*. The combination of the two drugs has a direct arrhythmogenic effect as well as an indirect reflexly mediated cardiac effect. Acetylcholine has potent muscarinic and nicotinic effects. Because of structural similarities between acetylcholine, succinylcholine, and succinylmonocholine, they could disturb the balance between the sympathetic and the parasympathetic systems. If muscarinic activity predominates, the sino-auricular node would be suppressed as the principal pacemaker. Since ventricular muscle is devoid of cholinergic fibers, simultaneous nicotinic stimulation could enhance other potential pacemakers of the heart, creating extrasystoles and cardiac dysrhythmias.

Since hydrolysis of succinylcholine is a first-order reaction in plasma, the larger the dose given, the more succinylmonocholine will be produced in the blood.¹³ There may be a critical balance of the two drugs which could produce serious dysrhythmia especially in patients whose autonomic balance is already disturbed such as elderly patients, infants, digitalized patients, and patients in shock.

In our study, succinylmonocholine but not succinylcholine produced positive inotropic and chronotropic responses in the isolated heart, but there was no evidence that succinylmonocholine itself produces more serious bradycardia, dysrhythmia or hypotension than succinylcholine *in vivo*.

SUMMARY

The present study evaluated possible contribution of succinylmonocholine in producing serious cardiovascular effects with or without succinylcholine, using albino rabbits as the experimental animal. Forty-eight experiments were performed, 22 *in vivo* and 26 *in vitro* (Langendorf heart).

Succinylcholine and succinylmonocholine administered separately or together, produced an immediate bradycardia *in vivo* as well as *in vitro*. The combination of these drugs had a direct arrhythmogenic effect as well as an indirect reflex mediated cardiac effect. When succinylcholine was given within five minutes following a dose of succinylmonocholine there was significant nodal and ventricular ectopic beats, but no bradycardia. Dysrhythmias in *in vivo* hearts were abolished by cord trans-section, trimethaphan and reserpine pretreatment. There was no evidence *in vivo* that succinylmonocholine produced more serious bradycardia, dysrhythmias or hypotension than succinylcholine.

RÉSUMÉ

Nous avons étudié les effets cardiovasculaires de la succinylmonocholine employée isolément ou en association à la succinyldicholine, ceci chez le lapin albinos.

En tout 48 expériences ont été faites, soit 24 *in vivo* et 24 *in vitro* (cœur de Langendorf).

In vivo et *in vitro*, la succinyldicholine et la succinylmonocholine utilisées séparément ou en association produisaient une bradycardie immédiate. L'association des deux agents, en plus des effets indirects réflexes, était suivie fréquemment d'extrasystoles. Une injection de succinyldicholine donnée en dedans de cinq minutes après une dose de succinylmonocholine était fréquemment suivie d'extrasystoles ventriculaires ou de rythme jonctionnel mais ne produisait pas de bradycardie.

L'on pouvait abolir les troubles du rythme *in vivo*, soit par une section médullaire, soit par l'administration préalable de trimethapan ou de réserpine. *In vivo*, la succinyldicholine ne semblait pas produire plus de troubles du rythme, d'hypotension ou de bradycardie que le succinylmonocholine.

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