

Chronotropic Effects of Succinylcholine and Succinylmonocholine on the Sinoatrial Node

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The mechanism of bradycardia caused by the administration of succinylcholine has not been fully elucidated. Accordingly, the effects of succinylcholine and succinylmonocholine on the sinoatrial node were studied in 35 mongrel dogs. The sinus node artery was selectively perfused with autologous blood from a femoral artery at a constant pressure of 100 mmHg, and 30 to 1,000 μ g of succinylcholine or succinylmonocholine was administered directly into the artery.

Succinylcholine caused a transient (63–600 s) dose-related positive chronotropic effect. The heart rate was increased to $14.4 \pm 2.1\%$ (mean \pm SE) above the control value after the administration of 1,000 μ g of succinylcholine. This positive chronotropic effect was inhibited by pretreatment with pindolol or reserpine. By contrast, succinylmonocholine produced a transient (30–248 s) dose-related negative chronotropic effect. The heart rate was decreased to $17.5 \pm 1.4\%$ below the control value after administration of 1,000 μ g of succinylmonocholine. The negative chronotropic effect was blocked partially by atropine.

It was concluded that the positive chronotropic effect of succinylcholine may be mediated through beta-adrenergic receptor stimulation by catecholamine released from the adrenergic nerve endings in the sinoatrial node, and that the negative chronotropic effect of succinylmonocholine may be the result of excitation of cholinergic receptors in the sinus node. However, a direct effect of succinylmonocholine on the sinus node could not be ruled out. (Key words: Neuromuscular relaxants: succinylcholine; succinylmonocholine. Heart: sinoatrial node; arrhythmia.)

SUCCINYLCHOLINE is known to produce a pronounced decrease of the heart rate both in children and adults. In adults, this most frequently occurs with a second or subsequent dose of succinylcholine. Clinical observation offered two explanations for the bradycardia: 1) succinylcholine stimulates the afferent vagal receptors,¹ and 2) choline, produced by hydrolysis of succinylcholine, sensitizes the patient to subsequent doses of succinyl-

choline.² Experimental studies suggest that succinylcholine produces bradycardia by central vagal stimulation,³ and in the isolated heart,⁴ a biphasic change in the heart rate was reported. Moreover, prolonged exposure to succinylcholine, initially increases the threshold of excitability of the heart and later decreases it by sympathetic postganglionic stimulation and a direct myocardial effect.⁵ The effect of succinylcholine on the sinoatrial node has not been established. It has been postulated that small doses of succinylcholine stimulate the activity of the sinoatrial node, while larger doses depress it.⁶

In an attempt to further elucidate the possible mechanism of bradycardia associated with the administration of succinylcholine, we studied the effects of succinylcholine and its metabolite, succinylmonocholine, on the sinoatrial node, using a direct perfusion method via the sinus node artery as originally devised by James and Nadeau,⁷ and modified by Hashimoto *et al.*^{8,9}

Methods

Thirty-five mongrel dogs, weighing 12–22 kg, were anesthetized by intravenous injections of 30 mg/kg pentobarbital sodium, and ventilated with room air and supplemental oxygen through an endotracheal tube, using an animals respirator. The mean value of pH was 7.314 ± 0.02 (mean \pm SE), and the mean values of PaO₂ and PaCO₂ were 125.6 ± 14 mmHg and 39 ± 2 mmHg, respectively. End-tidal CO₂ concentration was also monitored (Morgan 901MK2).

A right-sided thoracotomy was performed, and the heart was suspended in a pericardial cradle. The sinus node artery or the right coronary artery was separated from the heart, and a tapered polyethylene catheter (tip diameter, 0.6 to 1.2 mm) was inserted into the artery. When the sinus node artery was too small for direct cannulation, the catheter tip was left in the main right coronary artery just proximal to the origin of the sinus node artery (fig. 1). The catheter was connected to the perfusion system and the sinoatrial node was perfused with autologous blood obtained from a femoral artery canula and routed through a pulsatile pump (Taiyo). Perfusion pressure was maintained at 100 mmHg by pneumatic resistance (fig. 1). The animals were heparinized initially with 500 units/kg heparin sodium administered intravenously, and thereafter supplemented with 100 units at one-hour intervals. Systemic pressure

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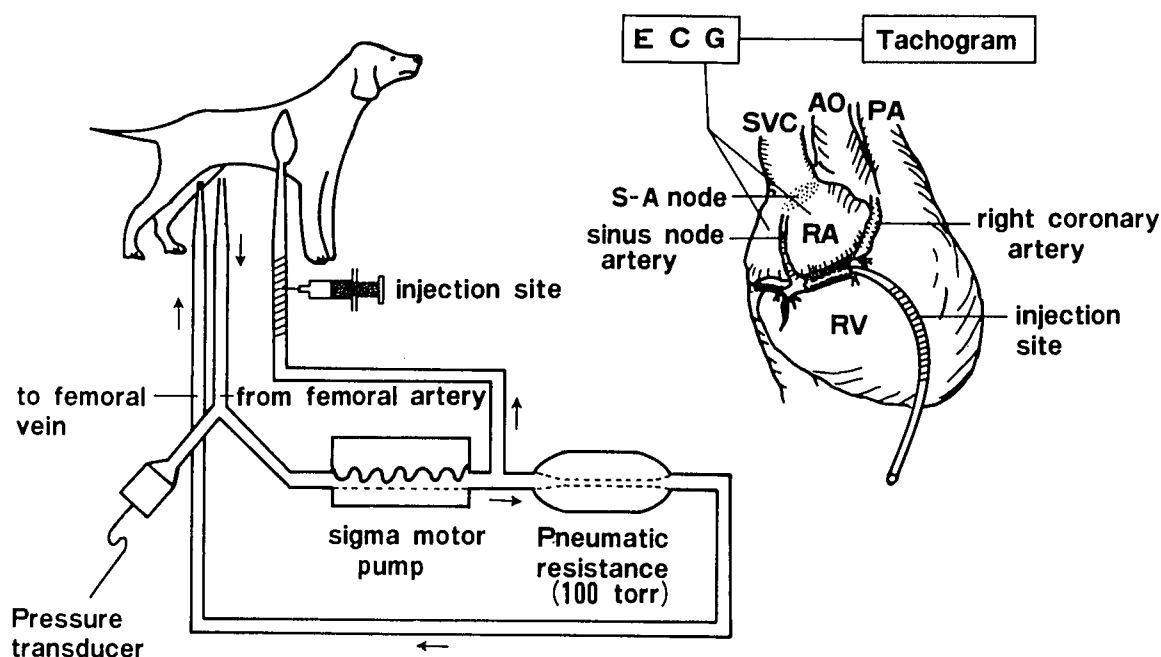


FIG. 1. Diagram of the sinoatrial node perfusion system. (Left) Diagram of the perfusion circuit. Arrows indicate the direction of the blood flow. (Right) Canulation of the right coronary artery.

(Nihonkoden MPV-05) was monitored via a T connector inserted between the arterial canula and pump. For recording (Nihonkoden RM-85) the rate response of the sinoatrial node, a tripolar electrode was placed around the sinus node, and connected to the electrocardiogram (Nihonkoden RD-5) and cardi tachometer (Nihonkoden RT-5).

Drugs were administered into the sinus node artery with a 50- μ l Hamilton microsyringe over a four-second period. The doses of succinylcholine or succinylmonocholine were varied between 30 μ g and 1,000 μ g. In the group given succinylcholine, six dogs were pretreated with 1 μ g pindolol given into the sinus node artery, and two dogs were given 0.1 mg/kg reserpine intramuscularly for three consecutive days prior to the study. In the group given succinylmonocholine, eight dogs were pretreated with 30 μ g atropine given into the sinus node artery.

Changes in heart rate after injection of drugs were analyzed statistically using the Student's *t* test for paired data. The differences were considered significant when *P* values were less than 0.05.

Results

Selective injection of succinylcholine into the sinus node artery caused a transient dose-related increase of the heart rate in 22 dogs. A small dose of succinylcholine (30 μ g) caused an insignificant increase in the heart rate, but large doses such as 100 μ g, 300 μ g, and 1,000 μ g,

caused consistent and significant increases of the heart rate. The mean control value for the heart rate was 141 ± 5 beats/min, and 1,000 μ g of succinylcholine increased the heart rate 14.4 ± 2.1 %. Furthermore, three repeated injections of succinylcholine (1,000 μ g) showed a consistent significant ($P < 0.01$) increase of the heart rate in six dogs from the mean control heart rate of 138 ± 11 beats/min, to 156 ± 13 , 154 ± 12 , and 154 ± 12 beats/min, respectively, after the first, second, and third injections. The mean duration of the increased heart rate was 221 ± 27 s. In six other dogs, the response to succinylcholine was blocked by pretreatment with 1 μ g pindolol. Reserpine pretreatment also inhibited the response to succinylcholine in two additional dogs (fig. 2).

The administration of succinylmonocholine resulted in a dose-related transient decrease in the heart rate in 19 dogs (fig. 3). The mean control value for the heart rate was 141 ± 7 beats/min, and 1,000 μ g of succinylmonocholine decreased the heart rate 17.5 ± 1.4 %. The mean duration of the decrease was 109 ± 25 s. Pretreatment with 30 μ g atropine partially blocked the response to succinylmonocholine in eight dogs and also shifted the dose-response curve upward (fig. 3).

Discussion

Selective perfusion of the sinoatrial node in dogs provides a method to observe the isolated response of the sinoatrial node from small to large doses of drugs while maintaining the blood supply and innervation.¹⁰ By uti-

lizing this approach, James *et al.*¹⁰ and Hashimoto *et al.*^{8,9} have reported the chronotropic effect of various drugs. The present study reveals that direct infusion of the sinoatrial node with succinylcholine produces a positive chronotropic effect. By contrast, succinylmonocholine, a metabolite of succinylcholine, produces a negative chronotropic effect.

Studies of the isolated heart perfused with a physiologic solution showed that succinylcholine had a biphasic action: first, a negative chronotropic effect at small doses, and then a positive chronotropic effect at large doses.⁴ Beretervide³ reported that small doses of succinylcholine, such as 0.12 mg/kg, in conscious dogs caused profound bradycardia by central vagal stimulation. Bradycardia, however, was not seen in dogs anesthetized with pentobarbital; the response to large doses of succinylcholine in anesthetized dogs suggested excitation of the sympathetic nervous system and adrenal glands.³ In our study using pentobarbital anesthesia, a 30- μ g bolus injection of succinylcholine into the artery supplying the sinoatrial node, caused a slight increase in the heart rate. This dose is considered to be comparable to that achieved at the level of the sinoatrial node following a standard intravenous dose as used clinically. We observed no bradycardia; thus, our results are not consistent with these earlier reports. Differences in species and methodology may explain these differences.

Galindo and Davis⁵ suggested that large doses of succinylcholine produced tachycardia in the rhesus monkey by sympathetic postganglionic stimulation. Clinically, Stoelting and Peterson¹¹ also observed an increase in the heart rate following the first dose of succinylcholine. In the present study, the positive chronotropic effect of succinylcholine was blocked by both pindolol and reserpine pretreatment. We therefore postulate that the positive chronotropic effect produced by succinylcholine in this preparation may be due to the release of catecholamine from adrenergic nerve endings and the stimulation of beta-adrenergic receptors in the sinoatrial node.

Ohmura *et al.*¹² reported that succinylmonocholine produced a slight bradycardia in rabbits. This result supports our finding of a negative chronotropic effect for succinylmonocholine. Since atropine partially blocked the negative chronotropic effect of succinylmonocholine, we assume that this effect may be due to stimulation of cholinergic receptors or enhanced vagal activity in the sinoatrial node. However, a direct action of succinylmonocholine on the sinoatrial node cannot be ruled out.

Shoenstadt and Whitcher² suggested that metabolites of the initial dose of succinylcholine sensitize the patient to successive administration of succinylcholine; however, in our study, repeated administration of large doses of succinylcholine caused almost the same increment in the heart rate. This suggests that metabolites of succinyl-

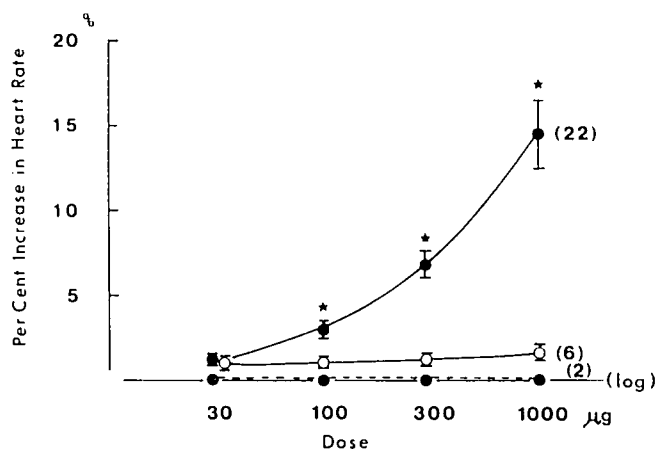


FIG. 2. Dose-response curves of heart rate produced by succinylcholine alone, and succinylcholine with pretreatment by pindolol or reserpine. Number in parentheses indicates the number of dogs. (—●—) = succinylcholine. (—○—) = pindolol-pretreated. (---●---) = reserpine. Values are means \pm SE. * P < 0.01.

choline may not sensitize the sinoatrial node to subsequent doses of succinylcholine. Furthermore, Shoenstadt and Whitcher² suggested that hexaflorinium slowed the hydrolysis of succinylcholine to succinylmonocholine and choline and prevented bradycardia. Takahashi *et al.*¹³ reported that bradycardia with an atrioventricular block was induced by succinylmonocholine after pretreatment with acetylcholine. Based upon these results, it is conceivable that succinylmonocholine may be the major determinant of the effect of repeated injections of succinylcholine. However, the effect of choline on the sinoatrial node cannot be excluded. Williams *et al.*¹⁴ proposed that the cause of bradycardia following repeat doses of

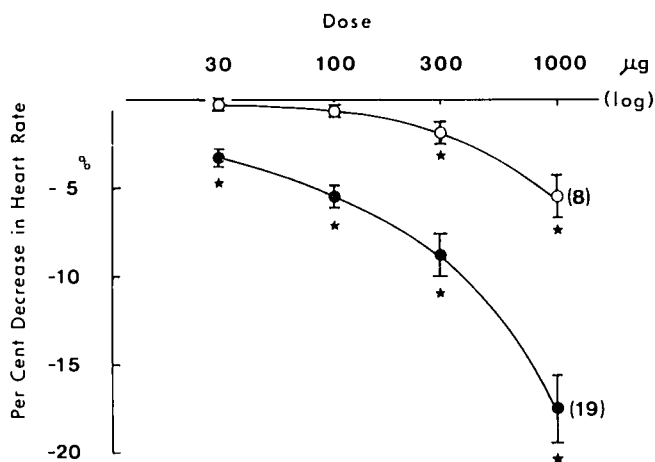


FIG. 3. Dose-response curves of heart rate to succinylmonocholine alone and succinylmonocholine with 30 μ g atropine. Number in parentheses indicates the number of dogs. (—●—) = succinylmonocholine. (—○—) = atropine-pretreated. Values are means \pm SE. * P < 0.01.

succinylcholine in humans was not the accumulation of succinylmonocholine but rather choline.

In summary, the present study showed that succinylcholine produced a dose-related positive chronotropic effect through an indirect stimulation of the sinoatrial node by catecholamine released from nerve endings. On the other hand, succinylmonocholine caused a decrease in the heart rate. This negative chronotropic effect may be caused by cholinergic receptor stimulation, but a direct effect cannot be ruled out.

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