Succinylcholine and Cardiac Excitability

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The medical literature reveals little information and much confusion concerning the cardiovascular effect of succinylcholine. Clinical associations support this idea.

Succinylcholine was first described by Hunt and Traveau in 1906. They observed its effect on blood pressure, but did not acknowledge any neuromuscular effects. Bovet in 1949 reported that succinylcholine had both a muscarinic and a nicotinic effect on the blood pressure, and possibly for this reason did not recommend clinical use of the drug.

In 1952 Thesleff reported that the rise in blood pressure seen following succinylcholine in rats was explainable on the basis of a stimulation of autonomic ganglia, with mobilization of adrenaline and vasoconstriction. He could not rule out a direct action on the blood vessels.

Two years later, Beretervide reported profound bradycardia following succinylcholine administration to dogs and rabbits and stated that this was the result of central vagal stimulation. He also presented evidence that the rise in blood pressure observed after large doses was secondary to sympathetic stimulation. Van Den Brek, in 1956, found both constriction and dilation of arteries and arterioles in rabbit ears following succinylcholine injections. He pointed out that the anesthetic employed was important.

A dual action on the circulation following succinylcholine was also reported by Purpura. He stated that large doses (up to 50 mg/kg.) of succinylcholine in cats and rabbits, resulted first in a parasympathetic paralysis and then a sympathetic block. The effect seen depended on a dose and time relationship.

Wahlin reported that succinylcholine caused sympathetic stimulation on the nictitating membrane of the cat’s eye. In 1960, the same author demonstrated a constricting effect of succinylcholine on the cat’s splanchnic bed and a dilatation of the femoral artery.

In an early clinical report of the circulatory effects of succinylcholine, Martin reported bradycardia, hypertension, and cardiac arrhythmia. Other clinical reports have shown bradycardia and short periods of asystole occurring after intravenous succinylcholine. These effects were most commonly seen in infants and children, were related to the dose of succinylcholine, and were usually seen after the first, second, or third administration of the drug.

We believe that succinylcholine has a definite cardiovascular effect other than bradycardia, and that this effect is most evident when an intravenous drip of succinylcholine was employed for an hour or more. The effect we noted most often was an increased cardiac excitability with resultant arrhythmias and an elevation in the systolic blood pressure.

The present study was designed to test the effects of succinylcholine on cardiac rhythm. The Macacus rhesus monkey was chosen as the experimental animal because its response to succinylcholine on a mg/kg basis is similar to that of man. This is not true of dogs and many other animals.

Most studies were done with a driving electrode as an artificial pacemaker, and a testing electrode placed in different areas in the heart. Other methods have employed a free testing electrode into the right atrium, or testing directly with solutions of epinephrine or employing the QRS complex to trigger a second stimulator.

Methods

The excitability of the heart is expressed as the strength and duration of the electric cur-
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Fig. 1. Schematic correlation made between the electrocardiogram, "strength interval curve" and electrical current pulse, in which the vulnerable period is located in the relative refractory period (peak of the T wave).

rent pulse able to produce an extrasystole; and when this is made at various intervals during the cardiac cycle, the plot of data thus obtained is called the "strength-interval curve." The curve shows that the excitability of the heart does not remain constant. There are an absolute refractory period, a relative refractory period and a period of normal diastolic excitability. Adrian found a period of supernormality, when lower thresholds are needed to produce a premature ventricular contraction than during the diastolic period. Oriaia denied the supernormality period and instead refers to "dips" or periods of relative supernormality. Wegrz and co-workers studying the vulnerable period, that is, the period most likely to induce ventricular fibrillation, located it during one of the "dips." Covino gave importance to this period during hypothermic ventricular fibrillation; he also found lower thresholds during it.

We leave the natural pacemaker unchanged. Theoretically if there are periods of "supernormality," we should be able to elicit them with sub-diastolic stimuli in the form of a rectangular electric pulse (fig. 1).

The experiment was carried out in 20 monkeys of the rhesus Macacus species, 17 of which weighed 2–4 kg. and two older ones weighing 13–16 kg. No premedication was given and anesthesia was induced by open-drop diethyl ether. Intubation via a tracheotomy was quickly performed and maintenance anesthesia was provided by halothane vaporized with room air. An intermittent positive pressure apparatus delivered 24 respirations per minute with tidal volumes of 80–200 cc providing hyperventilation. The plane of anesthesia was controlled by the arterial pressure and the electroencephalogram.

Two electrodes, a positive testing electrode, and a negative indifferent electrode were implanted into the wall of the left ventricle with 0.4 mm. distance between them. In 18 ex-
experiments, continuous recordings of intraarterial and intravenous blood pressures, electrocardiogram and electroencephalogram were made on a Sanborn Recorder Model 150 by standard methods. In two experiments the above systems were monitored plus intrapulmonary artery pressures and cerebral spinal fluid pressure. Simultaneous blood samples from a catheter placed in the coronary sinus and the femoral artery were taken for micro-potassium studies periodically throughout these two experiments. One had a Walton-Brodie strain gauge arch placed on the right ventricle wall, and continuous recordings of myocardial contractility were made.

By means of a Grass stimulator, model S4F, the left ventricle was stimulated for periods of 15 seconds by a rectangular electric current with a frequency of 10 times/second and a duration of 10 milliseconds with a subdiastolic strength. This current was recognized by a response of scattered extrasystoles. A response was defined as five or more extrasystoles occurring during the 15 seconds of stimulation. Each time this response was elicited, the strength of the stimulus was decreased until a negative response was found. This was expressed as the “threshold” (fig. 1).

Only after a period exceeding one hour allowing complete stabilization of anesthesia, were the thresholds determined. A solution of 10 mg./cc. of succinylcholine was employed with the “paralyzing dose” of 2 mg./kg. given every six minutes, so the animal would receive 10 times the “paralyzing dose” in one hour.

The experiments were divided into the following groups: (1) the effect of anesthesia on the threshold; (2) the effect of succinylcholine on the threshold; (3) the effect of bilateral vagotomies and total spinal anesthesia on the threshold, and the response to different doses of succinylcholine.

Results

The Effects of Anesthesia on the Cardiac Excitability Threshold: Six monkeys
were studied under halothane-air anesthesia to elicit the effects various levels of anesthesia had on the threshold. The levels of anesthesia were varied by administering more or less halothane from the Fluotec Mark II vaporizer. The effects of anesthesia alone were determined for at least two hours.

(1) It was evident from all 6 animals that very light anesthesia provided a continually changing threshold, and thus could not be used.

(2) Very deep anesthesia with systolic arterial pressures below 70 mm. of mercury produced a stable low threshold with a heart more susceptible to arrhythmias in all animals.

(3) When anesthesia was maintained at a moderate level for one hour or more, the threshold remained constant and relatively high in 3 monkeys tested. The variation in the threshold during one hour at this level was no more than 3 per cent at any time, so this was the level which we employed.

Effects of Succinylcholine on the Threshold: This series was divided into three groups. In one we were studied the effects of a single large dose (5 to 10 times the “paralyzing”) on the threshold. In another group, 10 times the paralyzing dose was given in one hour. The third group was handled in the same manner as the second group except at the end of one hour the large dose (5 times the “paralyzing dose”) of succinylcholine was given and the effects on the threshold and cardiac rhythm noted.

(1) In the first group 4 monkeys were studied with doses of 5 and 10 times the paralyzing dose of succinylcholine. All animals showed a transient rise in the threshold in the first two minutes and then returned to control values. There was an initial bradycardia of several seconds duration coincident with a rise in the blood pressure. The bradycardia lasted only 10-15 seconds and the blood pressure elevation persisted 2-10 minutes, depending on the dose given (fig. 2).

(2) In the second series 7 monkeys were studied. In 5 animals there was an average fall in threshold of 19.4 per cent after one hour (fig. 3). The range of fall was from 12.2 to 31.4 per cent. In one monkey there was no change in threshold after one hour of succinylcholine doses, and in another monkey there was a 20 per cent rise in threshold at one hour.

The 5 monkeys showed a rise in threshold in the first twenty minutes with an average maximum rise of 5.0 per cent. After the twenty minute mark there was a gradual fall in threshold in all. In 2 animals spontaneous premature contractions were occurring at this time.

(3) In the third series of studies all 7 monkeys, when given a single large dose (5 times “paralyzing dose”) following the one hour period of continuous doses of succinylcholine, the response was invariably a marked lowering of the threshold, and in 5 animals severe spontaneous ventricular arrhythmias occurred.

If lidocaine (Xylocaine) 2 mg./kg. were given at this time, the arrhythmia would revert to normal sinus rhythm, and in the 4 animals studied there was an average increase in the threshold of 43 per cent from the original controls. Dihydroergotamine (DCI) given to 2 monkeys in doses of 2 mg./kg. elevated the threshold an average of 10 per cent over control values.

The Effects of Bilateral Vagotomies and Total Spinal Anesthesia on the Cardiac Excitability Threshold: In an attempt to elucidate the mode of action of succinyl-
choline in causing the threshold changes, 3 animals were subjected to bilateral vagectomies and two monkeys received total spinal anesthesia, by injection of lidocaine 20 mg., 1 per cent, into the cisterna magna producing total paralyzis and anesthesia without any other anesthetic drug. There were no changes in threshold following the vagectomies.

In two animals a correlation was made before and after total spinal anesthesia between the threshold changes with succinylcholine administration and changes occurring simultaneously in different parameters. Figures 2, 4, 5, 6, and 7 demonstrate typical results in one of these animals.

There was a steady increase in the serum potassium levels during the administration of succinylcholine as seen in figure 7, which is correlated with changes in threshold.

Discussion

Our data demonstrate the cardiovascular effects of succinylcholine as measured by changes in the threshold of cardiac excitability and other parameters. These changes are related to the dose. The threshold changes of cardiac excitability are related primarily to time and secondarily to dose.

This drug has a great similarity to acetylcholine, which 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). Our present study was carried out to determine any specific action of succinylcholine on the excitability of the myocardium, and to correlate this with other cardiovascular effects.

Our principle finding, working with doses
Fig. 5. Demonstrates changes produced by 10 times paralyzing dose of succinylcholine given after total spinal anesthesia. The H.R. began to rise in 15 seconds and reached maximum increase of 79 per cent in 30 seconds, followed by a rise in A.B.P. after 15 seconds, and in 30 seconds maximum increase of 331 per cent occurred and lasted 15½ minutes. The M.C.F. started to rise in 15 seconds and in 30 seconds was elevated 308 per cent, and this lasted 15½ minutes. In comparison with Fig. 2, the ventricular beats were regular and uniform in strength after spinal anesthesia. The nature of arrhythmia was also different, being complete A.V. block with regular nodal rhythm. C.S.F.P. (cerebrospinal fluid pressure); P.A.P. (pulmonary arterial pressure); M.C.F. (myocardial contractile force); V.P. (venous pressure); F.A.B.P. (femoral artery blood pressure).

Fig. 6. Demonstrates changes occurring after 10 times the paralyzing dose of succinylcholine given following total spinal anesthesia and bilateral vagotomies. H.R. rose 50 per cent after the succinylcholine dose. A.B.P. started to rise in 15 seconds and in 30 seconds reached a maximum of 56 per cent which lasted 10 minutes. M.C.F. began to rise in 15 seconds and reached 100 per cent at 32 seconds, lasting 11 minutes. The nature of arrhythmia was the same as described under spinal anesthesia alone. C.S.F.P. (cerebrospinal fluid pressure); P.A.P. (pulmonary arterial pressure); M.C.F. (myocardial contractile force); V.P. (venous pressure); F.A.B.P. (femoral artery blood pressure).
in the clinical range, was a fall in the threshold after one hour of continuous administration of succinylcholine.

This can be best explained on the basis of a sympathetic postganglionic stimulation by succinylcholine combined with a direct effect on the myocardium. Evidence for postganglionic stimulation is found in the development of hypertension and tachycardia after administration of a large dose of succinylcholine (fig. 2). These findings were especially marked after blocking the preganglionic efferents (total spinal anesthesia) (figs. 5 and 6). The potentiation of the pressor responses of sympathetic drugs by a prior ganglionic block is well established and was first expressed as Cannon’s Law.22

Evidence for a direct myocardial effect is found in myocardial contractile force changes independent of blood pressure modifications under any circumstances or doses studied (figs. 2, 4, 5, and 6).

The changes in rhythm after one hour of continuous administration are the result of sympathetic stimulation and direct myocardial effects by succinylcholine. There is a transient bradycardia coincident with the initial rise in blood pressure mediated through the baroreceptors and the vagus nerves (fig. 2) and we agree with Becetrevide4 in the presence of a reflex. The following arrhythmia close to ventricular fibrillation (fig. 2), is similar to that produced by epinephrine. The fact that total preganglionic blockade resulted in a regular nodal rhythm (figs. 5 and 6) with A-V block instead of the previous disorganized arrhythmia (fig. 2) is further evidence of a combined effect of succinylcholine.

As a depolarizing muscle relaxant, its principle effect as described by Foldes,24 is related to a disturbance of the repolarization process at the myoneural junction. Essentially, this means there is a change in permeability in the cell membrane for potassium, with a loss of it from the cell and a decrease in the resting membrane potential. This process will increase the serum potassium25 (fig. 7).

These changes in potassium could explain the threshold change in figure 7. A moderate increase in serum potassium coincides with a moderate rise in threshold during the first minutes, but further increase of it (fig. 7) will disequilibrate the relationship between intra and extracellular potassium, dropping the resting membrane potential and threshold and producing arrhythmias.

These three factors: increase in serum potassium, post ganglionic sympathetic stimulation and direct myocardial effect would account for the incidence of arrhythmia found with succinylcholine administration. We cannot rule out a direct stimulation of the adrenal glands by succinylcholine. The fact that the majority of clinicians in anesthesia do not experience cardiovascular changes following succinylcholine in the average healthy patient undergoing anesthesia means that circumstances necessary to elicit cardiovascular effects do not occur relatively often. However, given the proper circumstances that have been discussed, they do occur and have been reported.

It is important to know that arrhythmias can be attributed to succinylcholine administration.

Certain patients with certain disease processes ought to be considered from the point of view of whether succinylcholine is the drug of choice for any given anesthetic procedure. Some of those that we can mention at this time are:

1. Certain cardiac patients, especially those already demonstrating arrhythmias.
2. Patients with potassium problems.
Perhaps under these circumstances the security that some clinicians get from light anesthesia and succinylcholine is not always justified. More studies are being done at the present in an attempt to elucidate more about threshold changes following succinylcholine in relationship to potassium changes and digitalized patients.

Summary

Effects of succinylcholine on cardiac excitability threshold was studied in 20 rhesus Macacus monkeys. A time and dose relationship was demonstrated as important in causing a lowering of the cardiac excitability threshold and arrhythmias. A 19.4 per cent drop in threshold was observed after one hour of continuous administration of succinylcholine. Changes in pulmonary artery pressure, aortic pressure, venous pressure, cerebral spinal fluid pressure, electrocardiogram, electroencephalogram and myocardial contractility were correlated in two monkeys. Serial potassium from the coronary sinus and aorta were studied before and after succinylcholine injections and correlated with the threshold changes. Independent changes in myocardial contractile force and blood pressure is indicative of a direct myocardium action of succinylcholine.

Marked elevation of the threshold and the ability to revert arrhythmias with lidocaine (Xylocaine) and some threshold elevation with dichlorosoproterenol were reported. Bilateral vagotomies and total spinal anesthesia were performed in an attempt to show a direct effect of succinylcholine on the heart. Bilateral vagotomies will not change the threshold. Spinal anesthesia prevents the reflex bradycardia and changes the nature of ventricular arrhythmia, supporting also direct myocardium action of the drug.

A discussion of clinical applications was made and its possible limitations for heart patients.

References


POST SURGICAL IPPB Alternate post upper abdominal surgical patients were subjected to intermittent positive pressure breathing (IPPB) with oxygen and Tergestim. No other medications were used. Postoperative pulmonary complications were determined by roentgenogram and physical examination. IPPB did not prevent the postoperative pulmonary complications in patients subjected to upper abdominal surgery. The IPPB machine cannot replace the bedside work of the postoperative surgical team. (Sands, J. H., and others: Controlled Study Using Routine Intermittent Positive Pressure Breathing in the Post Surgical Patient, Dis. Chest 40: 128 (Aug.) 1961.)

TRACHEOTOMY COMPLICATIONS The over-all mortality in the series of 212 consecutive unsellected tracheotomies was 64 per cent, but in only 2.8 per cent could death be directly attributed to the tracheotomy. There was an incidence of 33 per cent complications attributed to the tracheotomy. These complications included emphysema, pneumothorax, endotracheitis, cannula difficulties, carbon dioxide retention, wound sepsis, stenosis and keloid formation. The deaths were due to accidental dislodge ment of the cannula with airway obstruction, postoperative pneumonia and a misplaced operative incision. (Meade, J. W.: Tracheotomy—Its Complications and Their Management, Study of 212 Cases, New Engl. J. Med. 265: 519 (Sept. 14) 1961.)