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Onset of Succinylcholine-induced Hyperkalemia Following Denervation

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Denervation injuries in baboons were used to define the time course of the hyperkalemic response to succinylcholine. Half-peak increase in serum potassium (2.78 mEq/l) occurred 8.4 days following injury. Peak increase (5.5 mEq/l) appeared 14 days after injury. However, changes in potassium levels begin as early as four days after injury. Succinylcholine or other depolarizing muscle relaxants should not be used after the fourth day following an injury or denervation that involves two or more limbs. (Key words: Neuromuscular relaxants, succinylcholine; Ions, potassium; Nerve, denervation sensitivity.)

CLINICAL REPORTS and experimental studies have demonstrated that certain patients have exaggerated potassium release in response to succinylcholine, occasionally of such magnitude as to result in cardiac arrest. Patients who have denervation injuries, spinal-cord injuries, severe burns, massive trauma, and certain central nervous system and neuromuscular disorders are among those known to manifest this phenomenon.[1-6]

In general, clinical reports have indicated that this hyperkalemic response occurs between approximately three weeks and one year after the onset of the injury or disease process, but neither the onset nor the duration has been well defined.[1,3,6] Because of two unpublished reports of three cases of cardiac arrest in man following succinylcholine occurring seven to ten days after paralyzing spinal cord injury, we decided to examine the early time course of the "sensitive" period in denervation.*,†

The baboon was chosen as our experimental model since as a primate it is closer to man phylogenetically than other laboratory models and it has been observed by us to respond to succinylcholine in a fashion similar to man.‡

Methods

During anesthesia with phencyclidine hydrochloride (Sernalyn®, 1 mg/kg, im), the trachea was intubated and 1.5–2-cm segments of the sciatic nerve (at the level of the inferior margin of the gluteus maximus muscle) and the femoral nerve (in the area of the inguinal ligament) were excised from one leg of each of six baboons (*Papio cynocephalus*) weighing between 25 and 30 kg. Blood loss from the denervation was minimal.

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‡ In a separate experiment we measured the duration of neuromuscular blockade in the baboon after 2 mg/kg succinylcholine given intravenously in 1 minute by observing the time to 90 per cent loss of twitch response to a nerve stimulator, time to return of tidal volume to baseline, and time for twitch to return to 90 per cent of baseline. In addition, pseudocholinesterase levels were determined. Mean time for 90 per cent decrease of twitch was 1.53 ± 0.10 minutes from the start of the 1-minute injection of succinylcholine. Mean time for return of tidal volume to baseline was 8.03 ± 0.18 minutes, with return of twitch to 90 per cent of control in 9.05 ± 0.54 minutes. The mean pseudocholinesterase activity was 5.8 U/ml (±0.99), compared with a mean of 8.44 ± 1.78 U/ml in normal man. All values were greater than 4.0 U/ml, which has been established as the level above which prolonged apnea secondary to abnormalities of pseudocholinesterase does not occur.[22]

The femoral veins of both legs were cannulated percutaneously with 18-gauge catheters for blood sampling and the positions of the catheters were confirmed using a pressure transducer, in addition to measuring blood gases with the animal breathing 100 per cent oxygen. An upper-extremity vein was cannulated for drug administration and maintained with an infusion of 5 per cent dextrose in water. Succinylcholine (2 mg/kg) was administered intravenously over a 1-minute period starting at time zero, and venous blood samples were collected from the denervated and normal limbs at 0, 2, 4, 6, 12 and 15 minutes. After injection of succinylcholine, the animal was manually ventilated for approximately 5 to 10 minutes until adequate spontaneous respiration had resumed. The collected blood samples were analyzed in duplicate for sodium, potassium, serum glutamic oxaloacetic transaminase (SGOT) and creatine phosphokinase (CPK). Activities were measured kinetically at 300 nm and 30 C on a centrifugal analyzer. Reagents were obtained from Worthington Biochemical Corporation, Freehold, N.J. 07728. Duplicate sodium determinations were done with a flame photometer (Instrumentation Laboratories, Boston, Mass., Model #143). Free serum hemoglobin was measured and specimens with values greater than 15 mg/100 ml were discarded as having excessive hemolysis. At approximately three- to four-day intervals following denervation, for as long as 30 days, the test procedure was repeated. In several randomly selected collection periods, simultaneous with the venous sampling, arterial blood samples were obtained from either a femoral-artery or a radial-artery catheter and analyzed in the same way as the venous blood.

The least-squares fit of the data with 95 per cent confidence intervals was calculated for the potassium changes with time following denervation. In addition, the slope of the line fitted to the data for potassium increase versus sodium decrease was determined and compared with a slope of 1 by t test.

Results

Hyperkalemia in the venous drainage of the denervated limb developed in every animal. The time to peak potassium increase in the venous blood from the denervated limb was approximately 14 days, with a mean increase of 5.5 mEq/l. The time to half-peak increase in potassium was 8.4 days, with a mean increase of 2.78 mEq/l at that time. The highest potassium concentration observed in blood from a denervated limb was 15.8 mEq/l, occurring on day 19 following denervation. Time to half-peak potassium increase in blood from the intact limb was 10.3 days, which was not significantly different from the corresponding half-time for the denervated limb. Mean potassium increase in the intact limb at the half-time was approximately 0.5 mEq/l. The least-squares fit of the data for serum potassium versus time from denervation with 95% confidence intervals for the 2-minute samples is shown in figure 1. All results and calculations are for the 2-minute samples, the results with which were very similar to the 4-minute results.

Serum potassium levels in the arterial blood samples were approximately 0.5 mEq/l higher than those in venous blood from the intact limb once potassium elevation had occurred.

To determine whether there was a relationship between sodium and potassium ionic shifts in venous blood, sodium decrease was plotted against potassium increase for the 2- and 4-minute samples (fig. 2). The slopes of the lines fitted to the data were 1.04 ± 0.032 and 0.998 ± 0.038, respectively, neither being significantly different from a slope of 1.

We found no relationship between succinylcholine injection and CPK or SGOT. The 6-, 12-, and 15-minute samples showed similar results but with progressively lower potassium elevations, although even at 15 minutes, once potassium elevation in response to succinylcholine had occurred, peak potassium was still above baseline.

Discussion

Our finding that the time to half-peak potassium increase is 8.4 days indicated that the danger period in "sensitized" patients begins earlier than previously reported. This is consistent with results of a study in the

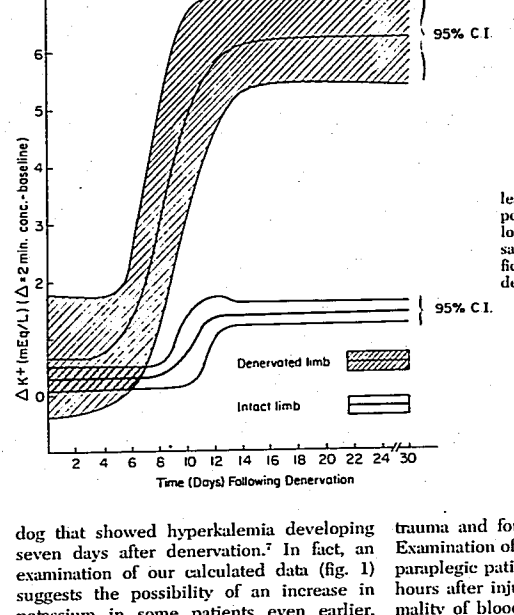

FIG. 1. Representation of the least-squares fit of the data for potassium changes with time following denervation in the 2-minute samples with 95 per cent confidence intervals, comparing the denervated and intact limbs.

dog that showed hyperkalemia developing seven days after denervation.[7] In fact, an examination of our calculated data (fig. 1) suggests the possibility of an increase in potassium in some patients even earlier, perhaps at four days.

We are aware of three paraplegic patients in whom cardiac arrest after succinylcholine occurred seven, eight, and ten days, respectively, following injury. In each of the cases, induction of anesthesia with intravenous administration of thiopental and 60 to 80 mg succinylcholine was followed by tachycardia, profuse diaphoresis, and cardiovascular collapse within 2 minutes. In one of these three patients a venous blood sample obtained after resuscitation had a serum potassium concentration of 11.8 mEq/l. The temporal relationship of events and the markedly elevated serum potassium in one patient strongly suggest hyperkalemia as the cause of these cardiac arrests.

Clinically significant hyperkalemia has not been reported to occur before three weeks after injury. Kopriva *et al.* determined venous serum potassium after succinylcholine in patients within three hours after massive trauma and found no potassium elevation.[8] Examination of the anesthetic records of four paraplegic patients given succinylcholine 24 hours after injury did not reveal any abnormality of blood pressure or pulse, although each patient subsequently had hyperkalemic cardiac arrest.[2] Close scrutiny of the information reported by Birch *et al.* indicates that an exaggerated potassium response to succinylcholine occurred as early as three to five days in two of eight traumatized patients.[4] Weintraub and co-workers documented an increase in potassium in one patient seven days after trauma despite precurarization, which has been shown to attenuate hyperkalemia following succinylcholine.[1,9]

Skeletal muscle hypersensitivity, which can follow not only denervation but decentralization and chronic inhibition of transmitter release by pharmacologic means as well, is presumably caused by a spread of acetylcholine receptors from the motor end-plate to include eventually the entire muscle membrane, a process that starts as early as one to two days after injury, depending on the species and muscle.[10–12] Enlargement of the

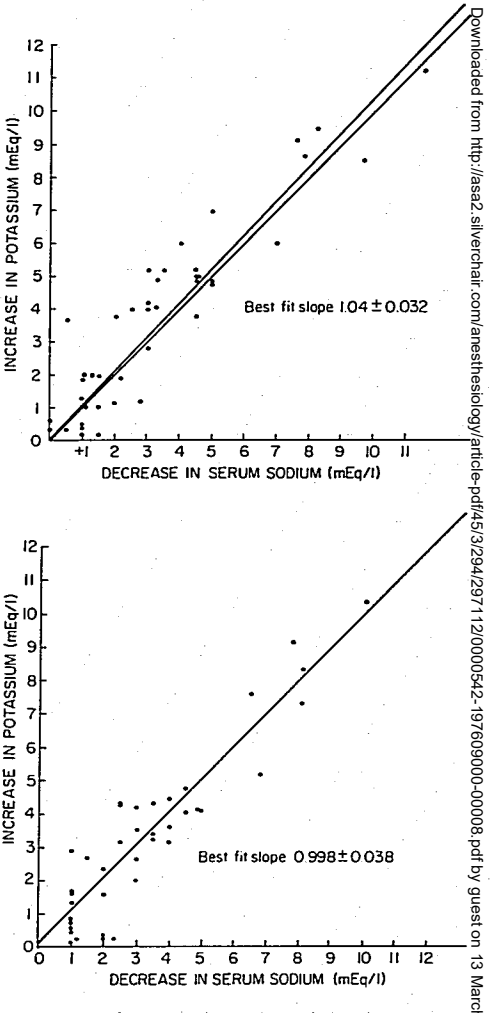

FIG. 2. Slopes of the lines fitted to the data for potassium increase versus sodium decrease in the venous effluent from the denervated limb in the 2-minute samples (A, *above*), and the 4-minute samples (*B, below*). Each slope is not different from a slope of 1 when compared by t test.

receptor area may also be the basis for the hyperkalemic response to succinylcholine.

Kendig *et al.* have found that resting denervated muscle has a higher sodium content than normal muscle, and that following depolarization with succinylcholine, a marked increase in intracellular sodium content occurs, without, however, a measurable change

in intracellular potassium.[13] Potassium content of resting denervated muscle of the dog was found to be lower than that of normal muscle by Gronert *et al.*, but did not significantly decrease following succinylcholine.[14] It is possible that in both of these studies the lack of measurable change in intracellular potassium of denervated muscle following succinylcholine reflects the technical difficulty involved in the measurement and the method of analysis rather than the lack of change of intracellular potassium. Gronert *et al.* have further reported that following denervation, succinylcholine induces a prolonged contraction that is usually associated with a sustained depolarization (for as long as 20 minutes), with potassium efflux continuing as long as depolarization is present.

Our finding of a 1-for-1 sodium-for-potassium exchange in the venous effluent of the denervated limb indicates that the increase in sodium content in denervated muscle is accompanied by a proportional decrease in potassium during depolarization. Although this has been assumed, it has not previously been demonstrated. We were able to detect this relationship by the use of paired values in a model (denervation) that maximized the ionic fluxes of sodium and potassium.

The tendency, once potassium elevation has occurred, for arterial potassium to remain slightly higher than the potassium in the venous effluent of the normal limb may indicate that normal muscle acts as a sink, at least transiently, to store some of the excess potassium released by the denervated muscle. This is in agreement with early reports showing that when an elevated potassium level is present in arterial blood, the venous blood from the resting muscle has a lower potassium concentration than the arterial blood, suggesting deposition of potassium in the muscle.[15–18] Other tissues (for example, the liver) may also serve as potassium sinks, especially in instances of marked diminution in the mass of normal muscle, as in quadriplegia.[18]

The lack of effect of succinylcholine on SGOT and CPK, and electron microscopic studies by Hegab showing no disruption of muscle membranes in denervated muscle following succinylcholine,[19] support the concept that the excess potassium released is due to an enlarged area of muscle membrane that is highly permeable to potassium rather than disruption of the muscle membrane.

We conclude on the basis of clinical observations and laboratory data that the danger period for hyperkalemic cardiac arrest induced by succinylcholine may begin a week following injury, and possibly earlier. We recommend avoidance of depolarizing muscle relaxants and the use of nondepolarizing relaxants in such patients starting four days after the onset of their injury or denervation.

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Oxygen Toxicity

OXYGEN AND MUCOCILIARY CLEARANCE The authors showed previously that an early sign of pulmonary oxygen toxicity in man is suppression of tracheal mucous velocity. This paper reports the effects of oxygen concentration and time in altering mucociliary clearance. Dogs were anesthetized with pentobarbital. Control animals breathed air (100 per cent humidity, 38 C) for as long as 30 hours. Three different groups of dogs received 50, 75, and 100 per cent oxygen (100 per cent humidity, 38 C) for 6–30 hours. Respiration was assisted by transvenous phrenic-nerve stimulation so as to maintain adequate alveolar ventilation while avoiding positive pressure to the airway. Tracheal mucous velocity was decreased significantly by 45, 66, and 84 per cent in dogs breathing 100 per cent oxygen for 2, 4, and 6 hours, respectively. Significant changes in mucous velocity were not observed in animals breathing 75 per cent oxygen until 9 hours had elapsed. Decreases of 42 and 78 per cent were observed at 9 and 12 hours. Dogs breathing 50 per cent oxygen showed an initial increase in tracheal mucous velocity of 66 per cent at the end of 6 hours. An increase of 49 per cent was observed at 12 hours. After 24 and 30 hours of exposure, significant decreases of 20 and 51 per cent were measured. In dogs breathing 100 per cent oxygen for six hours or 75 per cent oxygen for 12 hours, acute inflammation of the trachea and bronchi was seen. Histologically, necrosis and desquamation of epithelium could be observed. Minor changes were seen in both the control group and dogs breathing 50 per cent oxygen for 30 hours. The data again call attention to the potential hazard of oxygen administration. (*Sackner MA, and others: Effect of oxygen in graded concentrations upon tracheal mucus velocity: A study in anesthetized dogs. Chest 69:164–167, 1976.*) ABSTRACTER'S COMMENT: A definite explanation for the increase in mucociliary clearance during the early hours of inhaling 50 per cent oxygen is not given. It is not clear whether this represents potential harm. The data again suggest that except in the neonate, inhalation of less than 50 per cent oxygen is largely devoid of risk.