

# Succinylcholine-induced Hyperkalemia in Dogs with Transected Sciatic Nerves or Spinal Cords

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Hyperkalemia followed the intravenous injection of succinylcholine (0.25 mg/kg) in dogs with bilaterally-sectioned sciatic nerves or transected spinal cords. The hyperkalemia was significant beginning after the fourteenth day, and became highly significant at 28 days ( $P < 0.001$ ). Mean serum potassium elevation at 28 days was 2.7 mEq/l in cord-transected dogs and 1.8 mEq/l in the sciatic nerve-transected dogs. The results of the animal studies correlate with the clinical observation of hyperkalemia in patients with central nervous system injury with subsequent paralysis. (Key words: Succinylcholine; Hyperkalemia; Sciatic-nerve transection; Spinal-cord transection.)

HYPERKALEMIA following intravenous injection of succinylcholine, with varying degrees of cardiovascular disturbance, has been reported in patients with massive trauma, extensive burns and war injuries.<sup>1-4</sup> Apparently massive trauma is not necessary for this effect, since one of us (W. A. S.) has seen similar phenomena in patients who have had spinal-cord injury without other trauma. At this institution, the serum potassium in the superior vena cava of a quadriplegic patient rose from a control value of 4.3 mEq/l to 11.6 mEq/l within two minutes after injection of succinylcholine. At this time ventricular fibrillation was observed and treated, with successful resuscitation.<sup>5</sup> Since this episode of hyperkalemia seemed to represent a clinical entity different from those previously reported, further study was indicated. Because of the danger involved in clinical investigation, a laboratory study using the dog was designed. In addition to a group of dogs with severed spinal cords, a

group with bilaterally sectioned sciatic nerves was included to study the effects of peripheral nerve injury. The investigation was also designed to establish a relationship between time of injury and occurrence of hyperkalemia.

## Methods

### PREPARATION OF THE EXPERIMENTAL MODEL

Ten healthy, well-fed dogs were premedicated with pentobarbital (Nembutal), 2 mg/kg, meperidine (Demerol), 1 mg/kg, and atropine, 0.008 mg/kg, intramuscularly. An hour later, anesthesia was induced intravenously with thiopental sodium (Pentothal) in a dose sufficient to produce loss of the eyelid reflex, with additional small doses repeated as necessary to maintain light anesthesia. The tracheas were intubated without neuromuscular blocking agents and the lungs manually hyperventilated with 100 per cent oxygen to prevent respiratory acidemia. Slow intravenous infusion of lactated Ringer's solution provided an avenue for drug administration.

A sampling catheter was placed in the right ventricle via the jugular vein and its position confirmed by pressure tracings. The catheter then was withdrawn into the superior vena cava to avoid electrocardiographic changes which it might produce. Continuous tracings of electrocardiographic lead II were recorded.

Baseline blood samples were drawn for arterial pH,  $PCO_2$  and  $PO_2$  and mixed venous blood was drawn for determination of serum potassium. Fifteen to 30 minutes after induction of anesthesia, succinylcholine, 0.25 mg/kg, was administered intravenously and blood drawn at one-minute intervals for seven minutes and analyzed for serum potassium. Potassium analysis was done on a Technicon AutoAnalyzer flame photometer and blood gas analysis on an Astrup radiometer with appropriate electrodes.

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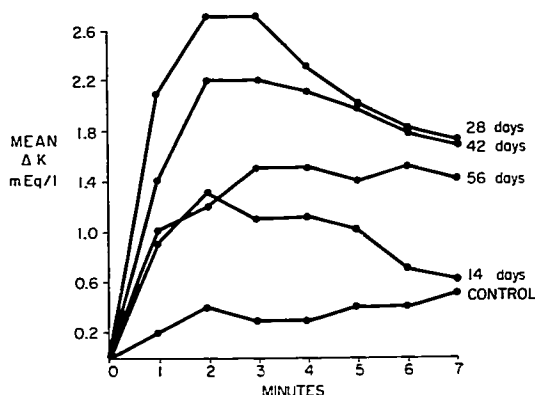


FIG. 1. Mean responses of serum potassium to succinylcholine in dogs with transected spinal cords.

After the preliminary studies, the sciatic nerves were ligated and transected bilaterally in five dogs. Laminectomy was performed in each of the remaining five dogs and the spinal cord ligated and transected at  $D_8$ - $D_{10}$ . The dogs were anesthetized for definitive operative procedure with halothane-nitrous oxide-oxygen. Neurologic examination and electromyography confirmed the neurologic defects in both groups.

#### POSTOPERATIVE CARE

All animals were under the supervision of a veterinarian and dog handlers experienced in the care of paraplegic and quadriplegic dogs. The animals initially were force-fed, and intravenous fluids, electrolyte solutions and glucose were infused as indicated. A high-protein diet with vitamin and iron supplements was provided throughout. This prevented excessive weight loss. Based on the condition of the dogs' coats, wound healing, daily temperatures, appetites, general behavior and frequent laboratory profiles, their general metabolic status was considered good. In the spinal cord-transected dogs, urine was expressed manually until spontaneous urination returned. The cages were padded and the animals were turned frequently.

#### EXPERIMENTAL PERIOD

Following a period of seven days for recovery from the surgical operation for the dogs

with sectioned sciatic nerves and a period of 14 days for the spinal cord-transected dogs, the animals were challenged at weekly intervals with intravenous injection of succinylcholine, 0.25 mg/kg. Within this interval, all surgical wounds were clean, healing satisfactory, and the animals were afebrile. Preoperative medication, anesthesia, ventilation, placement of catheters and blood sampling techniques for the experimental period were the same as described in the preceding section. Since the experimental period was short (less than 30 minutes), nitrous oxide and halothane were not used. Body temperature was not monitored.

The changes in serum potassium were analyzed by the three-way analysis of variance,<sup>6</sup> followed by Student's *t* test.

#### Results

Succinylcholine, 0.25 mg/kg, produced elevations of serum potassium (0.1-0.4 mEq/l) during the control periods in both groups. These elevations were not significant. Prior to injection of succinylcholine during the challenge periods, the baseline levels of serum potassium were within physiologic limits (3.4-5.4 mEq/l) in both groups.

#### DOGS WITH SECTIONED SPINAL CORDS

Beginning with the first challenge at 14 days, mean serum potassium elevations ranged from 1.3 mEq/l to a peak of 2.7 mEq/l at 28

days (fig. 1). Thereafter, the elevation declined, but serum potassium did not return to control values during the experimental period. The results were significant throughout the experiments,  $P < 0.001$  at the first challenge and  $P < 0.05$  at the fifty-sixth day. During the twenty-eighth day's challenge actual serum potassium values ranged from 4.6 to 9.8 mEq/l at one to three minutes, with increases peaking at two minutes with a mean value of 2.7 mEq/l ( $P < 0.001$ , range 0.7–4.7 mEq/l).

The two-minute potassium elevation of the individual dogs are presented in figure 2. Two animals on each of three occasions had serum potassium values greater than 9.0 mEq/l (9.4–9.8 mEq/l). Differential catheterization of the venae cavae of four dogs 56 days after spinal cord section demonstrated a peak mean elevation in the inferior vena cava of 4.6 mEq/l at two minutes, in contrast to a peak of 1.5 mEq/l at three minutes (fig. 3).

#### DOGS WITH SECTIONED SCIATIC NERVES

A mean elevation of serum potassium greater than 1.0 mEq/l at 14 days became highly significant at 28 days ( $P < 0.001$ , fig. 4). Actual potassium values ranged from 3.7 to 7.5 mEq/l. Results of studies not included in the statistical data, carried to 56 days after nerve transection, demonstrated no further elevation. The two-minute potassium elevation of a typical dog is presented in figure 5.

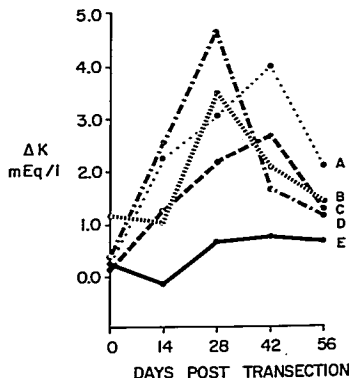


FIG. 2. Two-minute potassium responses of individual dogs with transected spinal cords.

In both groups of dogs, peaking of the T waves, elevation of the S-T segments, premature ventricular or atrial contractions, prolongation of QRS complexes, and short runs of bigeminy or trigeminy were noted on the electrocardiograms. However, no instances of ventricular fibrillation or asystole occurred.

#### Discussion

Significant increases in serum potassium following intravenously-injected succinylcholine

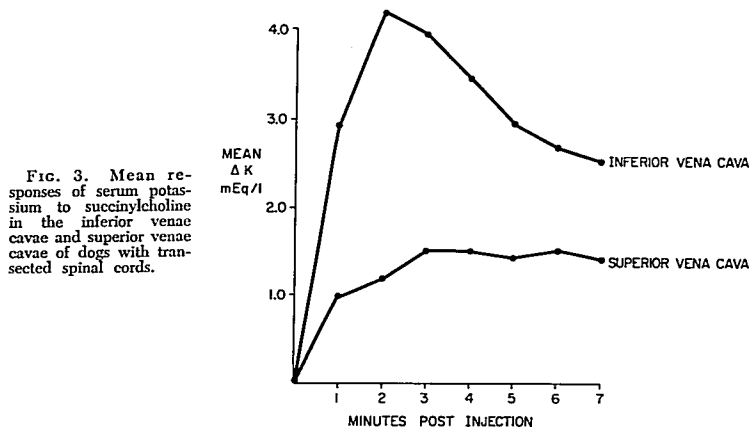


FIG. 3. Mean responses of serum potassium to succinylcholine in the inferior venae cavae and superior venae cavae of dogs with transected spinal cords.

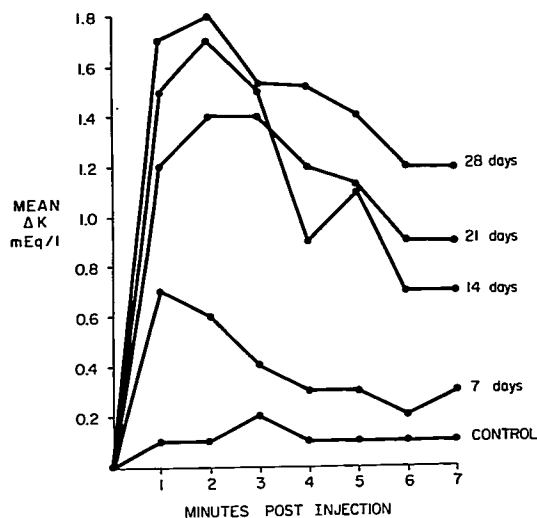


FIG. 4. Mean responses of serum potassium to succinylcholine in dogs with transected sciatic nerves.

were clearly demonstrated in both groups of dogs. The increases, although they began with the first challenge, were time-related, being most significant at 28 days and slowly decreasing during the remainder of the experiment. These findings confirm those in clinical

reports on massive trauma<sup>1-4</sup> and the few reports of patients who have had neurologic injury with subsequent paralysis.<sup>5, 7-10</sup>

Whether the hyperkalemia observed in this study was the result of direct deterioration of the dog's general metabolic status, the surgical

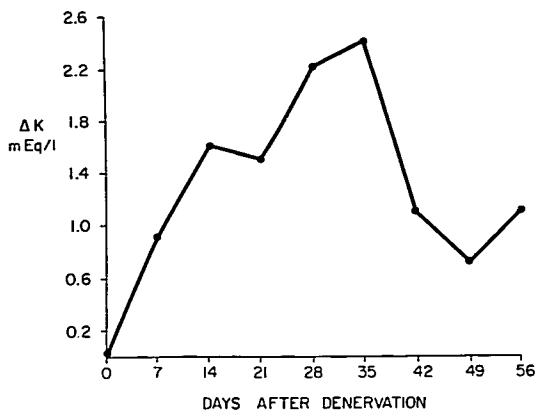


FIG. 5. Two-minute potassium responses to succinylcholine in a typical sciatic nerve-transected dog.

procedure, or increased sensitivity of denervated muscle to succinylcholine, is not clear. However, every effort was made to maintain good nutrition, the surgical wound was closed and clean, and the animals were afebrile. The surgical trauma produced was minimal compared with that reported in human studies.<sup>1-4</sup> The animals were intentionally hyperventilated ( $pH_a$  7.5-7.6,  $P_{aCO_2}$  18-25 torr) to prevent the augmented increases in serum potassium noted during hypercarbia and acidosis.<sup>11-13</sup> Further, the differential results of catheterization of the venae cavae at the termination of the experiment indicate that the source of the potassium was the animal's hindquarter.

A likely explanation for the increase in serum potassium would be that the denervated muscle cell membrane was altered, resulting in an atypical response to the depolarization produced by succinylcholine. Supporting this thought is the work of Axelsson and Thesleff.<sup>14</sup> The authors concluded that with the passage of time the entire denervated muscle membrane, in contrast to the motor end-plate, becomes sensitive to acetylcholine. This sensitivity is characterized by a nonselective increase in permeability of the cell membrane to sodium and potassium. In addition, earlier investigators, using the twitch response, demonstrated in denervated skeletal muscle an augmented response to intra-arterial injection of acetylcholine.<sup>15</sup> This increased sensitivity began on sixth or seventh day and persisted for 56 days. However, in rats with sectioned spinal cords the increased sensitivity began on the third day and persisted for only 21 days. We cannot offer an explanation, other than species differences, for the difference between their findings and ours in which the elevation of serum potassium persisted for the entire experimental period. Since the initial depolarizing phases (Phase I) of neuromuscular blockade with succinylcholine and acetylcholine are similar,<sup>16</sup> each resulting in efflux of potassium ion,<sup>17</sup> it might be expected that in denervation hypersensitivity a large efflux of potassium ion occurs, resulting in significant hyperkalemia.

Since other techniques for endotracheal intubation which do not require succinylcholine

are available, the results of this study and the reported clinical cases suggest that this agent should not be used during the vulnerable period in patients who have had central nervous system injury with subsequent paralysis. The vulnerable period appears to commence about seven days after injury and extend for 90 days.<sup>5, 7-10, 18</sup>

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## Drugs

**THYROTOXICOSIS** In a double-blind trial, the effect of oral propranolol (40 mg four times a day for a week) was assessed in 16 patients with mild to moderate thyrotoxicosis. Propranolol reduced pulse rate and other manifestations of thyrotoxicosis, such as palpitations, sweating, tremor nervousness and peripheral vasodilation. It was of value in conjunction with radioactive iodine in the treatment of thyrotoxicosis to relieve symptoms until the radioactive iodine had suppressed thyroid function. It has also been used with iodine in the preparation of patients for surgical operations on the thyroid, with the result that less time is needed to prepare the patient for the procedure, the gland is less vascular, and the operation is technically easier. (Shanks, R. G., and others: *Controlled Trial of Propranolol in Thyrotoxicosis*, *Lancet* 1: 993 (May) 1969.)

**POTASSIUM POISONING** A depressed elderly woman under treatment for heart failure died about 90 minutes after drinking a liquid medication containing at least 540 mEq of potassium. There were convulsions but no vomiting or diarrhea. ECG showed nodal rhythm with QRS and T wave changes characteristic of hyperkalemia. There were progressive changes of increasing hyperkalemia, terminating in ventricular fibrillation and death. (Kaplan, M.: *Suicide by Oral Ingestion of a Potassium Preparation*, *Ann. Intern. Med.* 71: 363 (Aug.) 1969.)

**TETANUS** Severely-ill tetanus patients presented a characteristic clinical picture which has not been observed in other patients requiring similar treatment. The records of many of the patients with severe tetanus showed hypertension, which started a few days after IPPV commenced and disappeared by the time the patient left the hospital. Pulse rates also tended to increase, and irregularities of cardiac rhythm, including supraventricular tachycardia and ectopic beats of both supraventricular and ventricular origin, were observed in several patients. Since many of the clinical features resembled those seen in the "fight or flight" reaction and in patients with pheochromocytoma, it was suggested that the clinical syndrome present in severe tetanus was due to continuous but fluctuating overactivity of the sympathetic nervous system. Intensive cardiovascular monitoring for periods which have exceeded two weeks in some patients has confirmed our retrospective survey, and shown that many features present in severe tetanus are caused by an increase in the activity and irritability of the sympathetic nervous system. (Kerr, J. H., and others: *Sympathetic Overactivity in Severe Tetanus*, *Proc. Roy. Soc. Med.* 62: 659 (July) 1969.)