

## Exaggerated Increase in Serum Potassium Following Succinylcholine in Dogs with Beta Blockade

Richard L. McCammon, M.D.,\* and Robert K. Stoelting, M.D.†

The authors tested in dogs the hypothesis that beta-adrenoceptor blockade might alter the time course or magnitude of serum potassium (K<sup>+</sup>) changes following the administration of succinylcholine (SCh). The results indicate that the normal increase in K<sup>+</sup> induced by SCh (1 mg/kg intravenously) is exaggerated in the presence of propranolol-induced (0.25 mg/kg), beta-adrenoceptor blockade. Specifically, a peak increase of 1.7 mEq/l (43%) over control K<sup>+</sup> was noted in the beta-blocked dogs versus a 0.5 mEq/l (13%) increase in control dogs. The peak increase in K<sup>+</sup> occurred later in the beta-blocked dogs (60-90 min post-SCh) versus control dogs (30 min post-SCh). The authors postulate that these results reflect impairment of intracellular uptake of the SCh-induced acute K<sup>+</sup> load secondary to beta-adrenoceptor blockade. Additionally, in a third group of dogs, diazepam in a dose of 0.5 mg/kg attenuated the K<sup>+</sup> increases (1 mEq/l—24%) following SCh in beta-blocked dogs. Whether these data can be extrapolated to beta-adrenoceptor blocked patients remains a matter for further investigation. In the interim, periodic monitoring of K<sup>+</sup> is warranted in any patient receiving medications known to alter the state of activity of the beta-adrenoceptor. In particular, careful consideration must be given to the potential impact of various interventions (SCh administration, K<sup>+</sup> infusion) on K<sup>+</sup> levels in beta-adrenoceptor blocked patients. (Key words: Ions: potassium. Neuromuscular relaxants: succinylcholine. Sympathetic nervous system: sympatholytic agents, propranolol.)

A GROWING BODY of evidence indicates that the state of activity of the adrenergic nervous system, and in particular the beta 2-adrenoceptor, is important in the acute regulation of serum potassium (K<sup>+</sup>) levels. Studies in both animals and humans have demonstrated that stimulation of the beta adrenoceptor results in a decline in K<sup>+</sup> levels.<sup>1-8</sup> In contrast, beta-adrenoceptor blockade has been shown to augment and prolong the increase in K<sup>+</sup> following acute K<sup>+</sup> loading.<sup>9,10</sup>

Potassium efflux from muscle has been shown to increase after succinylcholine (SCh) in dogs and is particularly pronounced from denervated muscle.<sup>11</sup> This phenomenon also occurs in humans. In normal patients this manifests as a 0.3-0.5 mEq/l increase in K<sup>+</sup> levels occurring within the first 10 min following SCh administration.<sup>12,13</sup> In patients with denervation injuries or burns, however, SCh administration may result in dramatic and potentially life-threatening elevations in K<sup>+</sup> levels.<sup>14</sup> Additionally, it has been reported that pretreat-

ment with diazepam attenuates the magnitude of increase in K<sup>+</sup> following SCh in humans.<sup>12,15</sup>

These results led the authors to question whether coexisting beta-adrenoceptor blockade as produced by propranolol might alter the time course or magnitude of change in K<sup>+</sup> following SCh. This study describes the K<sup>+</sup> changes following the administration of SCh to anesthetized dogs with or without propranolol-induced, beta-adrenoceptor blockade. In addition, the impact of diazepam pretreatment on SCh-induced K<sup>+</sup> changes was evaluated in the presence of beta-adrenoceptor blockade.

### Materials and Methods

This study was approved by the Indiana University Animal Experimentation Committee. Fifteen mongrel dogs (8-20 kg) were divided randomly into three equal groups. Anesthesia was induced with thiopental 15-20 mg/kg iv. The trachea then was intubated, and mechanical ventilation of the lungs was established. Maintenance of anesthesia was provided with halothane 1-1.5% and nitrous oxide 60% in oxygen. All dogs received 100 ml of normal saline in the first 10 min after the induction of anesthesia, followed by 100 ml/h for the remainder of the study. Serum K<sup>+</sup> and arterial blood gases were measured following the initial 100-ml fluid administration to establish control levels.

Dogs in Group 1 then received SCh 1 mg/kg iv and K<sup>+</sup> was measured at 1, 3, 5, 10, 15, 30, 60, 90, 120, 150, and 180 min post-SCh administration. Arterial blood gases were measured at 60 and 120 min post-SCh administration, and ventilator settings were adjusted to maintain the PaCO<sub>2</sub> between 35 and 45 mmHg.

Dogs in Group 2, following the initial 100-ml fluid challenge, received propranolol 0.25 mg/kg iv, followed 10 min later by SCh 1 mg/kg. Serum K<sup>+</sup> and arterial blood gases were measured at the same time intervals post-SCh administration as in Group 1. In addition, to insure persistence of beta-adrenoceptor blockade, additional doses of 0.1 mg/kg of propranolol were administered just after K<sup>+</sup> was measured at 60 and 120 min. This dose of propranolol is similar to the dose used by other investigators to produce beta-adrenoceptor blockade in dogs.<sup>16,17</sup>

Dogs in Group 3 received diazepam 0.5 mg/kg iv at the time of induction of anesthesia in addition to the thiopental. Following the initial 100-ml fluid challenge,

\* Associate Professor of Anesthesiology.

† Professor and Chairman of Anesthesiology.

Received from the Department of Anesthesia, Indiana University School of Medicine, 1120 South Drive, Indianapolis, Indiana 46223. Accepted for publication June 1, 1984.

Address reprints requests to Dr. McCammon.

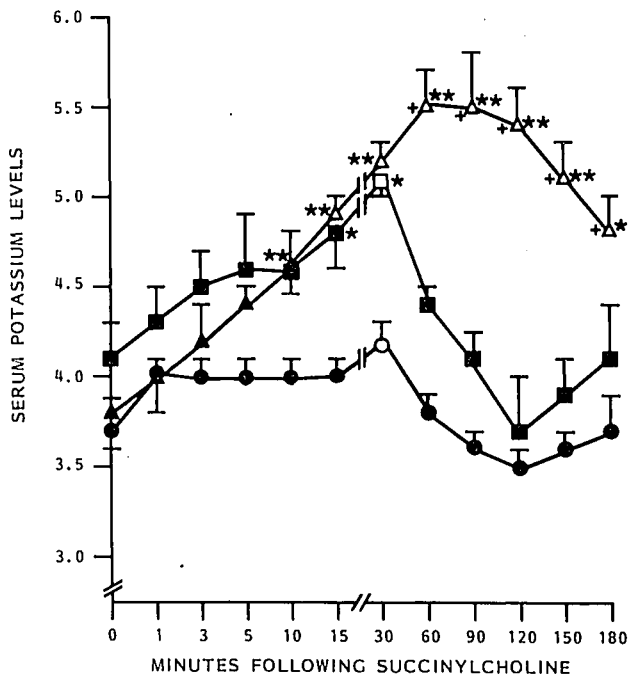


FIG. 1. Absolute changes in K<sup>+</sup> levels for the three groups. Circles denote Group 1 (control); triangles denote Group 2 (propranolol); and squares denote Group 3 (diazepam-propranolol). Values depicted are mean  $\pm$  SEM. Open symbols denote significant ( $P < 0.05$ ) changes from control within an individual group. \*\* $P < 0.05$  Group 2 versus Group 1. \* $P < 0.05$  Group 3 versus Group 1. † $P < 0.05$  Group 2 versus Group 3.

dogs in Group 3 received propranolol 0.25 mg/kg iv and subsequently were managed identically to Group 2.

Changes in serum K<sup>+</sup> from control within each group were analyzed using two-way analysis of variance and Dunnett's test. Comparison of data among the three groups was done using one-way analysis of variance and the Student-Newman-Keuls test.  $P < 0.05$  was considered statistically significant.

### Results

The absolute values for K<sup>+</sup> following SCh for Groups 1, 2, and 3 are depicted in figure 1. There was no statistical difference among the three groups in control K<sup>+</sup>. The only significant change in serum K<sup>+</sup> from control within Groups 1 and 3 occurred at 30 min. In contrast, K<sup>+</sup> levels in Group 2 were significantly different from control from 10 min post-SCh until the end of the study period. Dogs in Group 2 manifested the greatest absolute and per cent increase in K<sup>+</sup> (1.7 mEq/l-43%), and this peak occurred later (60-90 min) than the peak increases in either Groups 1 or 3. Peak increases of 0.5 and 1.0 mEq/l (13 and 24%) occurred at 30 min in Groups 1 and 3.

The absolute values for K<sup>+</sup> in Group 2 differed significantly from those in Group 1 from 10 min post-

SCh until the end of the study period at 180 min. In contrast, although dogs in Group 3 manifested greater absolute increases in K<sup>+</sup> than did dogs in Group 1, only the 15 and 30 min K<sup>+</sup> differed significantly between these two groups. Finally, K<sup>+</sup> was significantly different between Groups 2 and 3 from 60 min post-SCh until the end of the study period.

### Discussion

In light of existing literature, the results of this study are not surprising. For example, early studies in animals demonstrated that epinephrine injection resulted in a marked decrease in K<sup>+</sup>.<sup>1,2</sup> More direct evidence substantiating this phenomenon in humans has been provided by Brown *et al.*<sup>8</sup> These investigators demonstrated a decrease in K<sup>+</sup> of  $0.82 \pm 0.19$  mEq/l following an epinephrine infusion in healthy volunteers in which attained serum epinephrine levels were comparable to those postmyocardial infarction, a time known to be associated frequently with hypokalemia. In addition, this epinephrine-induced hypokalemia was prevented by the prior administration of a new, experimental beta-2-selective blocker—ICI 118551. Likewise, a number of case reports or series have noted hypokalemia complicating the treatment of asthma or premature labor with various beta-adrenoceptor agonists.<sup>3-7</sup>

In contrast, Rosa *et al.* demonstrated that propranolol-induced beta-adrenoceptor blockade augmented and prolonged the increase in K<sup>+</sup> following an infusion of potassium chloride (0.5 mEq/kg over 50 min).<sup>9</sup> Similar findings were noted by Carlsson *et al.*, who demonstrated that exercise-induced increases in K<sup>+</sup> were greater and more prolonged in patients with nonselective, propranolol-induced beta-adrenoceptor blockade than in those patients with beta-1-selective, metoprolol-induced beta blockade.<sup>10</sup>

We speculate that the propranolol-induced, beta-adrenoceptor blockade in this study did not alter the amount of K<sup>+</sup> efflux from muscle but rather resulted in impairment of the intracellular reuptake of the released K<sup>+</sup> by muscle. This manifested as exaggerated and prolonged K<sup>+</sup> increases post-SCh. The authors have no ready explanation to explain why it took so long (60-90 min) for the peak potassium levels to occur. Similarly, we are unaware of any case report in which hyperkalemia following SCh has been a problem in a patient who has been receiving propranolol. Nevertheless, periodic monitoring of K<sup>+</sup> in patients receiving medications known to alter the state of activity of the beta 2 adrenoceptor is warranted. In particular, careful consideration must be given to the potential impact on K<sup>+</sup> following various interventions (SCh administration, K<sup>+</sup> infusions) in beta-adrenoceptor blocked patients.

Fahmy *et al.*<sup>12</sup> and Eisenberg *et al.*<sup>15</sup> have demonstrated that intravenous diazepam (0.05 mg/kg) significantly attenuates the increase in K<sup>+</sup> following SCh (1 mg/kg) in patients. Neither group have been able to explain this protective effect of diazepam, and both central and peripheral mechanisms have been postulated. In this study, diazepam also attenuated the increase in K<sup>+</sup> following SCh in dogs with beta-adrenoceptor blockade. However, until the mechanism of this protective effect is established, it is impossible to predict its possible clinical usefulness.

In summary, the results of this study indicate that in dogs the degree and duration of SCh-induced K<sup>+</sup> increase is exaggerated in the presence of beta-adrenoceptor blockade. In addition, diazepam in a dose of 0.5 mg/kg attenuates the K<sup>+</sup> increase following SCh in dogs with beta-adrenoceptor blockade.

### References

1. D'Silva JL: The action of adrenaline on serum potassium. *J Physiol* 82:393-398, 1934
2. Todd EP, Vick RL: Kalemotropic effect of epinephrine; analysis with adrenergic agonists and antagonists. *Am J Physiol* 220:1964-1969, 1971
3. Hurlbert BJ, Edelman JD, David K: Serum potassium levels during and after terbutaline. *Anesth Analg* 60:723-725, 1981
4. Moravek MA, Hurlbert BJ: Hypokalemia associated with terbutaline administration in obstetrical patients. *Anesth Analg* 59:917-920, 1980
5. Berend N, Marlin GE: Characterization of B-adrenoceptor subtype mediating the metabolic actions of salbutamol. *Br J Clin Pharmacol* 5:107-111, 1978
6. Bengtsson B, Fagerstrom PO: Extrapulmonary effects of terbutaline during prolonged administration. *Clin Pharmacol Ther* 31:726-32, 1982
7. Smith SK, Thompson D: The effect of intravenous salbutamol upon plasma and urinary potassium during premature labor. *Br J Obstet Gynaecol* 84:344-347, 1977
8. Brown MJ, Brown DC, Murphy MG: Hypokalemia from beta 2-receptor stimulation by circulating epinephrine. *N Engl J Med* 309:1414-1419, 1983
9. Rosa RM, Silva P, Young JB, Landsberg L, Brown RS, Rowe JW, Epstein FH: Adrenergic modulation of extrarenal potassium disposal. *N Engl J Med* 302:431-434, 1980
10. Carlsson E, Fellenius E, Lundberg P, Svensson L: B-adrenoceptor blockers, plasma potassium, and exercise. *Lancet* 2:424-425, 1978
11. Gronert GA, Lambert EH, Theye RA: The response of denervated skeletal muscle to succinylcholine. *ANESTHESIOLOGY* 39:13-22, 1973
12. Fahmy NR, Malek NS, Lappas DG: Diazepam prevents some adverse effects of succinylcholine. *Clin Pharmacol Ther* 26:395-398, 1979
13. Stoelting RK, Peterson C: Adverse effects of increased succinylcholine dose following d-tubocurarine pretreatment. *Anesth Analg* 54:282-288, 1975
14. Weintraub HD, Heisterkamp DV, Cooperman LH: Changes in plasma potassium concentration after depolarizing blockers in anesthetized man. *Br J Anaesth* 41:1048-1052, 1969
15. Eisenberg M, Balsley S, Katz RL: Effects of diazepam on succinylcholine-induced myalgia, potassium increase, creatine phosphokinase elevation, and relaxation. *Anesth Analg* 58:314-317, 1979
16. Wagner DL, Moorthy SS, Stoelting RK: Administration of anticholinesterase drugs in the presence of beta-adrenergic blockade. *Anesth Analg* 61:153-154, 1982
17. Horan BF, Prys-Roberts C, Hamilton WK, Roberts JG: Haemodynamic responses to enflurane anaesthesia and hypovolemia in the dog and their modification by propranolol. *Br J Anaesth* 49:1189-1197, 1977