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Anesthesiology 2009; 111:1372-7

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Succinylcholine-induced Hyperkalemia and Beyond

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Pathophysiology of Hyperkalemia Induced by Succinylcholine. By Gerald A. Gronert and Richard A. Theye. *ANESTHESIOLOGY* 1975; 43:89-99.

The mechanism of succinylcholine-induced hyperkalemia was studied in three lesions affecting canine gastrocnemius muscle. Dogs were treated for 1 month before study: 10 with normal activity, 5 with unilateral sciatic nerve section, active on 3 legs, 5 with unilateral cast immobilization of a hind limb and pelvis, active on 3 legs, and 7 inactive with T6 section of the spinal cord. Succinylcholine responses were determined during thiopental-halothane (mean expired halothane $1.0 \pm 0.2\%$) endotracheal anesthesia with arterial carbon dioxide tension of 38-42 mmHg, arterial oxygen tension of

100-120 mmHg, and muscle and body temperatures maintained at $37^\circ \pm 0.2^\circ\text{C}$. The investigators isolated and collected the venous drainage of gastrocnemius muscle and measured its total blood flow. Muscle potassium release and oxygen consumption were calculated as blood flow \times (arterial content - venous content). Succinylcholine-induced gastrocnemius potassium release was greatest after both sciatic and cord section; oxygen consumption was increased in parallel. Disuse atrophy of one leg slightly increased both values but was insufficient to produce systemic hyperkalemia. Reuptake of potassium followed succinylcholine-induced release. Given before succinylcholine, modest doses of gallamine slightly modified the release of potassium, and total paralysis by gallamine blocked it.

ALTHOUGH the realization was years in coming, serendipity—the gift of finding things of value not sought for—shaped my career on several occasions, and led to the 1975 article with my mentor, Richard A. Theye, M.D. (Professor and Chair, Department of Anesthesiology, Mayo Medical School, Rochester, Minnesota, 1922-1977).¹ And that resulted from my being drafted during the Vietnam conflict and unexpectedly stationed at the U.S. Army Burn Unit at Fort Sam Houston in San Antonio, Texas. I will revisit serendipity later in this article.

Cardiac arrest with succinylcholine in burn patients had been casually rumored during my anesthesia residency (1959-1961), but no one really believed it, and we saw few burn patients at our Denver, Colorado hospitals. In fall 1960, I gave succinylcholine to a seriously burned 5-yr-old girl during my rotation at Los Angeles Children's Hospital, Los Angeles, California. The rumor was again mentioned, but there were no problems. By then, there had been a few reported cases.²⁻⁴

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Submitted for publication August 5, 2009. Accepted for publication August 20, 2009. The research for and preparation of this article was supported solely by the author's personal funds.

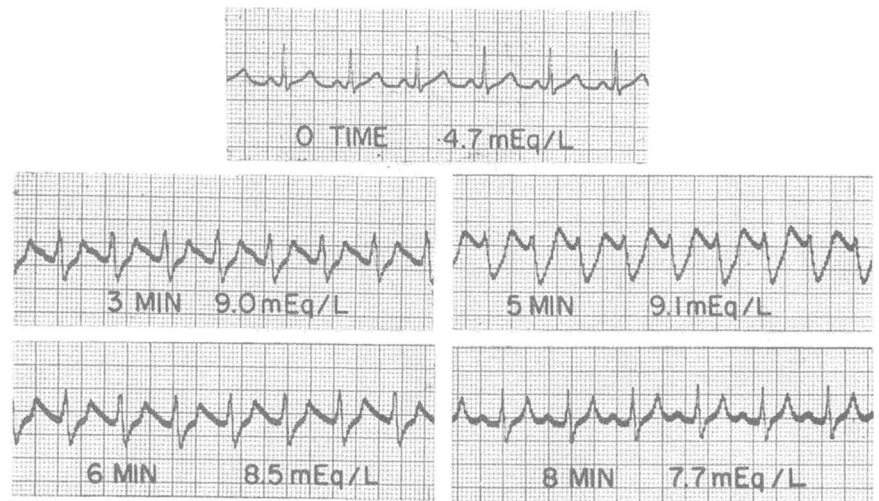
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Private practice anesthesia for 5 yr in Denver satisfied me, but on a visit to Mayo, Rochester, Minnesota, in 1966 to attend a meeting, I was offered and accepted a position focused on neuroanesthesia, teaching, and, I hoped, research. In spring 1967, the seminal article by Tolmie *et al.*⁵ identified and explained hyperkalemia with succinylcholine in a burn patient. This work opened a new field in abnormal physiology, but did not stimulate me at that time.

In April 1967, I received my draft notice and in time 50 copies of my orders. I was to be in San Antonio at Fort

Fig. 1. Continuous tracing of lead II in a patient with burn involving 25% of body surface area, normal sinus rhythm. **3 min:** Widened QRS, peaked widened T waves; P wave no longer evident. **5 min:** Further widening of QRS and T waves; pattern similar to ventricular tachycardia. **6 min:** Slight narrowing of QRS and T waves; QRS more recognizable. **8 min:** Normal sinus rhythm with slight widening of QRS, and marked peaking of T wave. (This is the usual pattern in an electroencephalographic diagnostic of hyperkalemia; it progresses into the above patterns with serum potassium above approximately 8.5 mEq/L.) From Gronert *et al.*⁷; used with permission.



Sam Houston in September for 6 weeks of basic training, spend 1 yr in Vietnam, and then spend 1 yr at a station of my choice. During basic training, my orders were changed. I was the oldest and most experienced drafted anesthesiologist in the group, as many were Berry Plan doctors just out of residency. I was reassigned to the burn unit, as seriously burned casualties were now far more numerous.

I then remembered the single-patient case report of Tolmie *et al.*⁵ It needed to be confirmed in a multiple patient study. The burn unit research committee agreed, and we began it. We used our routine induction, nitrous oxide-halothane. Burn patients have constant severe pain and recognize anesthesia as their only pain-free period, so they readily accepted the facemask, or whatever we offered. Once an arterial line was placed, we gave succinylcholine and measured plasma potassium just before succinylcholine and for some minutes thereafter. We studied 16 normal control patients undergoing elective surgery and 89 burn patients given 147 anesthetics. Peak potassium occurred within 3–5 min and then began to diminish. No patients arrested, despite some potassium levels greater than 8 mEq/L. Figure 1 compellingly explains why an impending arrest could be missed if an electrocardiograph was not used, for there was virtually no change in pulse rate (note the tracing in fig. 1) or blood pressure in this patient. His electrocardiograph gradually returned to normal. Our studies resulted in two articles, with doses of succinylcholine of 0.4, 0.7, and 1.4 mg/kg.^{6,7} All doses resulted in hyperkalemia. Observation of other burn patients provided similar findings.⁸

I returned to Mayo after my 2-yr hitch and wanted to further examine the hyperkalemic response in an animal model. After literature review, I decided on a study in burned swine, as they are similar to humans. The Mayo Research Committee approved the study, despite the plan to dip anesthetized swine into hot water. On our first day, a group of concerned researchers gathered in the hall outside the laboratory to protest and perhaps

halt our destructive and ghastly treatment. The technicians and I in the laboratory tried to ignore the group and began the study. Richard Theye went out into the hall and, in his usual direct profane insulting manner, dispersed the group. I was initially astonished at the gathering, and as usual was impressed with him; he didn't suffer fools.

With endotracheal anesthesia established, we held each of three pigs by the legs, upside down, and dipped the back into 95°C water for 20 s. This established a full-thickness deep second-degree burn just into fat but not affecting muscle. The advantage of the burn was that it destroyed all pain endings in the burned tissue so the pigs had minimal discomfort, in large part because of its sharp border with adjacent normal skin. Three other pigs were controls. I cared for the burned pigs, washed them twice daily in their pens, and applied mafenide acetate. They seemed comfortable, ate well, had no infections, and gained weight. All pigs were anesthetized between 2 and 6 weeks after the burn and given succinylcholine. No pig developed hyperkalemia. We worried that swine may be a species that did not develop a hyperkalemic response, so we sectioned the sciatic nerve in six swine; they showed the hyperkalemic response to succinylcholine.⁹ It is likely that our burn wound was insufficient for our cause.

Serendipity: One pig given succinylcholine developed a rapid increase in temperature. One of our technicians noted this on the esophageal temperature probe, with concomitant signs consistent with malignant hyperthermia (MH). We cooled the pig, hyperventilated it, and used bicarbonate to counteract the acidosis—we had our own blood gas machine in the laboratory, and it was easy to follow changes. The MH episode was controlled, and we congratulated ourselves on our success, and our chance to study MH. We had discovered a laboratory animal suitable for MH study.

Dr. Theye and I had to decide on our next study. He had developed a series of animal preparations that per-

mitted measurement of metabolism in the whole body as well as in individual organ systems.¹⁰ This was perfect for defining abnormal responses in MH. As he put it, this was a new field and we could use a porcine model to determine the role of various organ systems in the MH response. But I said that succinylcholine-related hyperkalemia was equally new and deserved an in-depth study of mechanism. Dr. Theye relented, because, as he said, this was my laboratory time, and both disorders merited study.

We decided on a canine model of skeletal muscle disorders, and investigated peripheral motor nerve denervation (lower motor neuron lesion), muscle disuse atrophy *via* cast immobilization of hind limb and pelvis, and section of the spinal cord well above any nerve supply to the legs (upper motor neuron lesion). See the abstract at the beginning of this article for control conditions. Other reports aided in the design of our study.¹¹⁻¹⁴

We first examined denervation, and demonstrated the hyperkalemic response to succinylcholine¹⁵ and the accompanying muscle contracture. Dr. Edward Lambert, M.D., Ph.D. (Professor, Mayo Medical School, Rochester, Minnesota, 1915-2003), the electromyographic pioneer, personally brought equipment to our laboratory and performed the electromyography: The baseline electromyograph in denervated muscle showed frequent spontaneous action potentials (fibrillation potentials); after succinylcholine, there was a 15-s explosive burst of action potentials, followed by a 30-min period of electrical silence, during which the muscle was not excitable. Electrical activity remained diminished after 60 min. The contracture induced by succinylcholine increased rapidly to a tension exceeding 225 g (off scale) and was still 155 g at 60 min. I cannot directly explain why this response should be prolonged. We thought that we had discovered something rare and wonderful until I found the article by G. L. Brown,¹⁶ who had made the same observation with acetylcholine in 1937. Humbled, I realized that few things are new.

We next studied muscle disuse atrophy due to cast immobilization.¹⁷ Succinylcholine produced a modest increase in potassium efflux and no muscle contracture. Disuse muscle changes and conditioning exercise seemed like opposites, and in time we compared both in greater depth. We used a standardized laboratory protocol so that various studies might be compared, and used the relaxant metocurine. Our findings are presented later in this article.

Finally, we produced an upper motor neuron lesion with T6 cord section. We combined the data from these studies¹ and compared the responses as regards potassium efflux and muscle oxygen consumption (figs. 2 and 3). Oxygen consumption also increased in normal muscle during paralysis with succinylcholine.

The results indicate the risks of succinylcholine in major neurologic deficits. Based on human findings, the sensitivity to succinylcholine seems to begin by 4-5 days

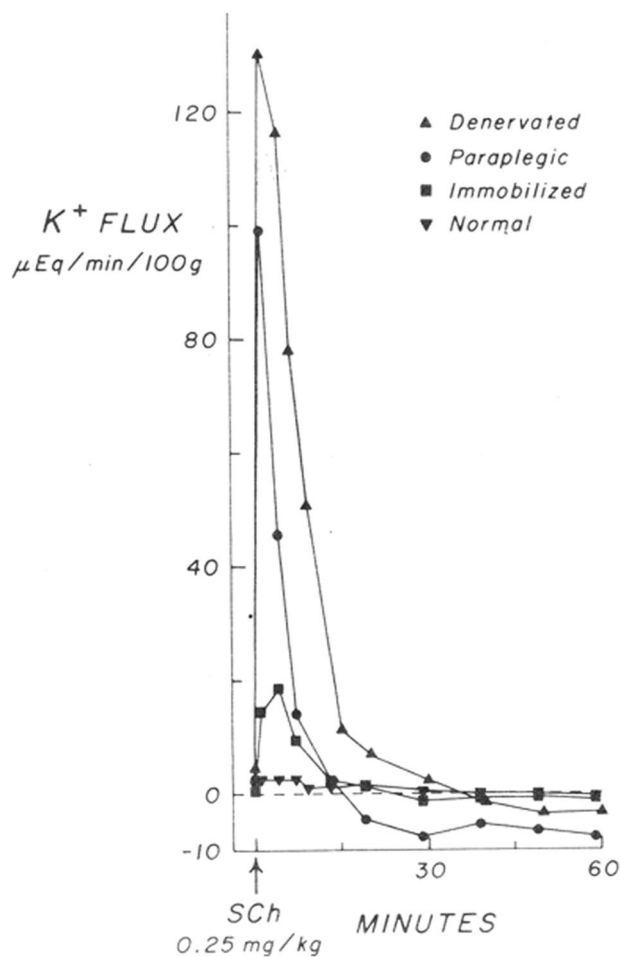


Fig. 2. Potassium fluxes of normal, immobilized, paraplegic, and denervated gastrocnemius muscle after succinylcholine (Sch). Efflux: positive values; influx: negative values. From Gronert and Theye¹; used with permission.

after denervation injury and to persist as long as the lesion remains, or until the affected muscle has withered. Extrajunctional acetylcholine receptors (AChRs) seem to be responsible, a type of receptor up-regulation, as these are depolarized by succinylcholine delivered to the entire muscle by the circulation and undergo prolonged depolarization with a sustained release of potassium. After thermal injury, the onset seems to be approximately a week to 10 days and persists until skin is covered, and there is good overall healing, decent appetite, and weight gain. Remember that a patient with up-regulation of his or her muscle AChRs is both sensitive to succinylcholine and resistant to nondepolarizers. Therefore, a larger dose of the latter is needed for adequate relaxation.

But succinylcholine-hyperkalemia also involves other factors. Until the late 1980s, we thought that anesthetic-related episodes of rhabdomyolysis were part of an aberrant MH reaction. It then dawned on us that these cases involved a primary hereditary muscle disorder, especially in children, and that it was unrelated to MH. Dr. Henry Rosenberg and I published a letter in *ANESTHESIOLOGY* to

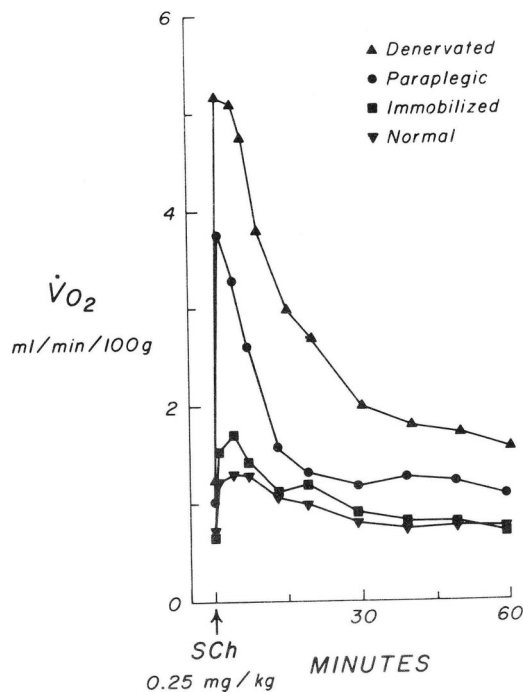


Fig. 3. Gastrocnemius oxygen consumption ($\dot{V}O_2$) of normal, immobilized, paraplegic, and denervated muscle after succinylcholine (Sch). From Gronert and Theye¹; used with permission.

introduce this concept and to suggest great care in administering succinylcholine to young children.¹⁸ It is now evident that there are two separate risks to the use of succinylcholine and a resultant hyperkalemia: an acquired up-regulation of AChRs and several varied inherited myopathies. The mortality after succinylcholine-hyperkalemia-cardiac arrest seems greater when related to a primary hereditary muscle disorder than cardiac arrest due to acquired up-regulation.¹⁹ Certain types of muscular dystrophy or other muscle factors render the surface muscle membrane fragile, with increased permeability to shed intracellular contents. When exposed to succinylcholine, the membrane breaks down, *i.e.*, rhabdomyolysis, with release of potassium, creatine kinase, and myoglobin. This rhabdomyolysis can be prolonged, and even prompt resuscitation of the cardiac arrest may not prevent the apparent greater fatality rate.¹⁹ In addition, potent volatile agents produce this congenital myopathy-related rhabdomyolysis even in the absence of succinylcholine.¹⁹ The onset of hyperkalemia related to volatile agents in myopathies is not the 3- to 5-min response related to succinylcholine, but is slower, occurring some minutes later. The different pathophysiologic processes seem to explain the pure hyperkalemia seen with up-regulation of AChRs and the more complex hyperkalemia-increased creatine kinase myoglobinemia seen in myopathies.

Finally, prolonged intensive care involves three factors that can result in succinylcholine-hyperkalemia: immobilization-related disuse atrophy of skeletal muscle, use of nondepolarizing skeletal muscle relaxants, and possi-

bly inflammation.²⁰ Prolonged exposure to these relaxants, even in small doses, is essentially a blockade of nerve impulses to the muscle. Atrophy of disuse and use of relaxant separately increase the number of extrajunctional AChRs, resulting in hyperkalemia with use of succinylcholine.²¹

Muscle relaxants have a long history: In 1811, Sir Benjamin Collins Brodie (the elder, 1783-1862) applied crude curare as a powder to a wound in the side of a guinea pig; the guinea pig appeared insensible, respiration ceased, and it was apparently dead; upon opening the thorax, the heart was still beating. He found that ventilation would prevent death.²² Succinylcholine was first used in research in approximately 1900, but its action was masked because the animals were paralyzed with curare.²³ Succinylcholine was introduced into clinical care in approximately 1950, due to many efforts: design: Daniel Bovet, D.Sc., Professor (1907-1992); the British group of James Walker, B.Sc., Ph.D., Chemist (1908-1993), Gladwyn Albert Hurst Buttle, O.B.E., M.A., M.B., F.R.C.P. (1899-1983), and Eleanor Zaimis, M.D., M.R.C.P. (1915-1982); the American group of Arthur P. Phillips, II, B.S., M.S., Ph.D. (1917-2000), Julio C. Castillo (born 1905), and Edwin J. de Beer (1902-1959); clinical introduction: Francis Foldes (1910-1997), Stephen Thesleff, M.D., Ph.D., (born 1924), H. G. von Brücke (born 1905), Otto Mayrhofer, Professor of Anesthesiology at Universität Wien (born 1920), Martina Hasfurther, M.D. (born 1924), Cyril F. Scurr, C.B.E., L.V.O. (born 1920), and Wesley Bourne (1886-1965).²⁴ Nobel Prizes were awarded related to drug effects upon ion channels: Daniel Bovet, D.Sc., in 1957 for discoveries relating to synthetic compounds that inhibit the action of substances reacting on skeletal muscle. The Nobel Prize was awarded for research into humoral transmitter function in nerve terminals in 1970 to Sir Bernard Katz, M.D., Ph.D., D.Sc. (1911-2003), Ulf von Euler, Ph.D. (1905-1983), and Julius Axelrod, B.S., M.S., Ph.D. (1912-2004). That of Erwin Neher (b1944), Prof. Dr., Department Membranbiophysik, Max Planck Institute for Biophysical Chemistry Göttingen, Göttingen, Germany, and Bert Sakmann, Prof. Dr., Ph.D. Physics, Max Planck Institute of Neurobiology, Martinsried, Germany (born 1944), in 1991 was for discoveries regarding single ion channels in cells, including AChRs.

Back to skeletal muscle disuse atrophy: Our earlier study¹⁷ of the response of a casted hind limb demonstrated a nonrisky increase in potassium after succinylcholine. That was after 4 weeks of immobilization, and we wondered what duration of disuse-related atrophy would result in this. Dennis L. Fung, M.D., Professor of Anesthesiology at the University of California, Davis, California, showed that this required approximately 20-40 days.²⁵ He next studied the onset and offset of resistance to metocurine with cast immobilization for 3 weeks in dogs.²⁶ Resistance to metocurine began within

4 days, increased during the 3-week period, and steadily recovered. However, we continued to be concerned regarding volitional movement within the cast that might limit the extent of disuse atrophy.

We considered a long-term study with no muscle activity, an approach with formidable challenges. I then participated in a U.S. Department of Agriculture Advisory Committee Meeting in Bethesda, Maryland, in 1992, in which most decided that long-term intensive care animal studies could not be accomplished in a laboratory. I thought differently, although I convinced no one at the meeting.

So we at University of California, Davis, planned a 3-week intensive care experiment (24-h/day monitoring and care) in which dogs were deeply sedated, ventilated *via* an endotracheal tube, and provided special care: fluids, normal body temperature, and regular supportive care to airway, secretions, nutrition, and urine and feces collection.²⁷ This was a complex study and involved experienced laboratory technicians, and a variety of persons from the veterinary and medical schools. We measured the response to metocurine each week, and at the end of the 3-week period saw huge increases in the half-maximal inhibitory concentration (IC_{50}) response to metocurine, *i.e.*, resistance. We gathered the results from our various canine studies, as the protocols had been similar, and observed that the metocurine IC_{50} with exercise was lowest, that normal dogs had a slightly greater IC_{50} , that IC_{50} in dogs with casted immobilization was increased further, and that IC_{50} in intensive care unit immobilized dogs had greater than 10 times the normal IC_{50} .²⁷ The latter finding, likely indicating the presence of many extrajunctional AChRs, seems to be the basis for succinylcholine-induced hyperkalemia in some intensive care unit-related responses to succinylcholine.^{20,21}

Now, the finish: To me, conditioning exercise seemed the opposite of disuse atrophy, and I wondered whether the response to a nondepolarizing relaxant might be the opposite of that to disuse, *i.e.*, sensitivity rather than resistance. I first studied this at the Mayo Clinic, in dogs, and demonstrated that metocurine was more potent in chronically exercised dogs.²⁸ Later, I studied exercise in galloping horses, using the huge treadmill of James Jones, Ph.D., D.V.M., Department of Surgical and Radiologic Sciences, School of Veterinary Medicine, at the University of California, Davis; the room was as loud as a boiler factory. Unfortunately, we could not totally match controls and exercised horses to the same group. Although there was a numerical decrease in IC_{50} for metocurine, it was not significant.²⁹

My last study regarding function of AChRs was to use this same protocol in a variety of species to measure metocurine potency. If there were no marked differences in receptor density and structure, I theorized that the response to metocurine might be proportional to weight. This held for most of the species: rat, cat, fox,

Metocurine Pharmacodynamics

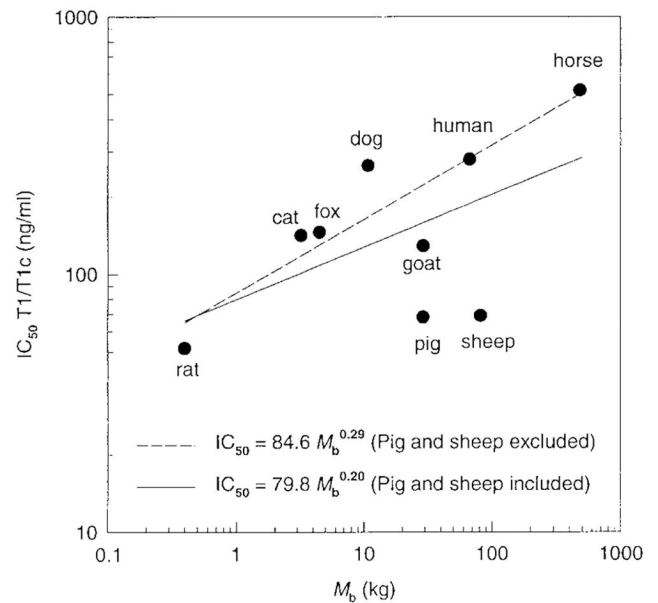


Fig. 4. Multispecies study of metocurine showing a relation among various species differing in size. Data points reproduced from Gronert *et al.*³⁰; used with permission.

dog, goat, pig, sheep, human, and horse (fig. 4). The larger species were healthy and were studied during elective surgery at the veterinary school.³⁰ Antognini *et al.*³¹ provided the data point for goats. These responses may in part be due to the number of acetylcholine receptors per cross-sectional area.³²

In summary, based on our findings and collated data of others, succinylcholine is unequivocally contraindicated in patients with burns, direct muscle trauma, and neurologic disorders involving motor muscle deficits. The resulting hyperkalemia relates to extrajunctional AChRs spread across the muscle membrane and which undergo prolonged depolarization in response to succinylcholine, with release of potassium. In addition, myopathies that weaken skeletal muscle membranes are subject to rhabdomyolysis with stress. Succinylcholine can produce this muscle breakdown almost instantly, and potent volatile agents can do so more slowly, within a number of minutes. A release of relatively small amounts of potassium can produce cardiac arrest, as normal plasma levels approximate 4 mEq/L, and adult plasma volume is roughly 3 l, with a normal circulating total plasma level of 12 mEq. Rapid release of 12 mEq of potassium from a mass of abnormal muscle would double plasma concentration, as redistribution is not rapid. Potassium levels in some patient reports exceeded 10 mEq/L.

Serendipity, energy, inquisitiveness, and aid from others shaped this part of my research career.

The author thanks Dr. J. A. Jeevendra Martyn, M.D., F.R.C.A. (Professor, Department of Anesthesiology and Critical Care, Harvard Medical School, Massachusetts General Hospital, Boston, Massachusetts), and Brian Gronert, M.D. (Anesthesiologist, Anesthesia Associate of New Mexico PC, Albuquerque, New

Mexico), for advice in preparing this article. The author credits Dr. Theye's superb technicians in facilitating our research: James Milde, Richard Koenig, Marilyn Oeltjen, Rebecca Wilson, and William Gallagher.

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