Medical Intelligence

Pathophysiology of Hyperkalemia Induced by Succinylcholine

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INTEREST in hyperkalemia induced by succinylcholine (SCh) stems from reports[3,8,17,18,22,37,38,40,41,62,66,67,70,72,73,75,99] from 1958 onward concerning cardiac arrest in convalescing burned patients immediately after induction of anesthesia and injection of SCh. In 1967, Tolmie, Joyce, and Mitchell[94] demonstrated that such episodes of cardiac arrest were caused by release of potassium (K+), and thus opened a new field of clinical investigation. Because the pattern of response found in burned patients[80] has also been observed to various extents in patients with muscle trauma,[11,71,79,98] neurologic motor deficits,[21,24-26,83,87,91-93] or tetanus,[79] a common mechanism—supersensitivity—has been postulated. This review analyzes the hyperkalemic responses of muscle in subjects with various neuromuscular diseases against a background of the physiology of normal myoneural junction and muscle, and the pharmacologic effects of SCh and acetylcholine (ACh) on these responses.

Definition of Terms

Muscular action is normally a *contraction* and very infrequently a *contracture* (similar to a cramp). A *contraction* is short, reversible, and propagated; it becomes sustained by

tetanic fusion of single twitches. A *contracture*[15,32,90] is prolonged, reversible, and nonpropagated, and may involve only a portion of the muscle. Within the limits of the data of this review, both contraction and contracture are associated with electrical depolarization.

Sensitivity,[6,90] unless otherwise specified, refers to chemosensitivity and is related to the effectiveness of acetylcholine (ACh) in depolarizing a membrane.

Supersenitivity[6,90] means that a dose of ACh much smaller than usual (one thousandth) is effective for depolarization.

Lower motor neuron lesion or denervation is due to either a loss of the motor nucleus (ventral horn cell) or motor nerve section.

Upper motor neuron lesion is isolation of the lower motor neuron from higher centers, produced by either section of the spinal cord (paraplegia) or an intracranial lesion involving motor tracts. Tetanus is apparently a form of upper motor neuron lesion.[14,33]

Neurotropism[48,49] refers to interrelationships between nerve and muscle exclusive of the phenomena of junctional transmission, and includes fibrillation, changes in sensitivity, and effects on metabolism.

Responses to Stimulation in Normal and Abnormal Muscle

Normal skeletal muscle[59] has discrete end-plate areas where the nerve terminal closely approaches the muscle. These end-plate areas contain receptor sites that are supersensitive to the depolarizing action of ACh and are relatively resistant to electrical depolarization.[6,90] The surface of the surrounding muscle membrane has few receptor sites, or none at all, and is electrosensitive;

K^+ FLUX
$\mu Eq/min/100g$

▲ Denervated
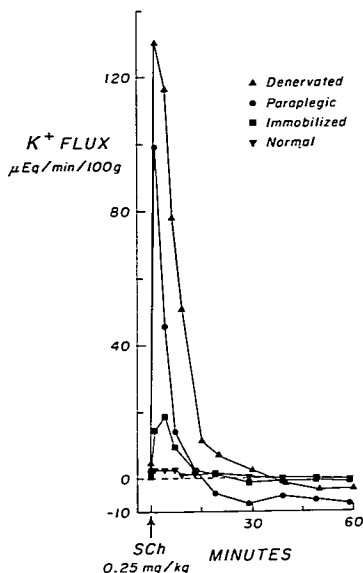● Paraplegic
■ Immobilized
▼ Normal

SCh
0.25 mg/kg   MINUTES

FIG. 1. K^+ fluxes of normal[44,47] (N = 10), immobilized[47] (N = 5), paraplegic[45] (N = 7), and denervated[44] (N = 5) canine skeletal muscle after SCh injection. Efflux indicated by positive values, influx by negative. Unpaired t tests indicate that the first portions of the curves are different from each other.

that is, it is relatively sensitive to electrical stimuli and resistant to the usual depolarizing dose of ACh.[6,90] Overall chemosensitivity of the entire muscle increases when new receptor sites form outside the end-plate area, thus decreasing the threshold to chemical depolarizers. With denervation, the entire muscle membrane becomes a chemoreceptor[6] and is supersensitive, and the depolarizing dose of ACh is smaller by a factor of about 10^{-4} than that for normal muscle.[15,84,90]

When ACh depolarizes the receptor site in normal muscle, the resulting local action currents electrically depolarize the adjacent muscle membrane to produce a propagated action potential.[59] ACh is rapidly hydrolyzed,

the end-plate and muscle membrane repolarize, and the cycle can begin again. The action of SCh is similar to that of ACh,[89] except that its effect lasts longer—possibly due to binding or slower metabolism, or both.[34,35,56,58] Because the initial depolarization of the receptor site persists, the threshold of the adjacent electrosensitive membrane quickly rises, producing an inexcitable membrane and, therefore, paralysis.[97] With repolarization, paralysis continues for a while, depending on the dose.[89,97] The reason is unknown, but it is possibly related to binding on receptor sites.[35,56]

In denervated muscle, ACh produces a contracture[15] resulting from chemical depolarization of the entire supersensitive membrane unaccompanied by conducted responses.[6] The contracture tension produced by a dose about 10^{-4} of that for normal muscle is greater than twitch tension.[15,84] The magnitude of the contracture response in denervated muscle is proportional to the size of the supersensitive membrane; that is, a given dose of ACh produces a greater and greater response as sensitivity continues to increase.[32]

The contracture response also occurs in both human and animal muscle affected by various upper motor neuron lesions (cord section[20,84] or intracranial upper motor neuron lesions[64,86]) following the injection of either strychnine[20] or ACh.[20,64,84,86] Data are insufficient to relate the contractures seen in upper motor neuron lesions directly to supersensitivity, although there is at least a partial increase in sensitivity.[84]

In abnormal muscle, the differing response is best evaluated by measuring the sensitivity to ACh, the naturally occurring transmitter. This is done most effectively by placing a micropipet adjacent to a single fiber, for intermittent release of small amounts of ACh (iontophoresis).[6,59] This technique permits one to detect gradation of sensitivity along a fiber, and is superior both to the intra-arterial injection of ACh,[20,64,84,85] which provides only a crude evaluation of the sensitivity of the entire muscle,[6] and to the intravenous injection of ACh,[86] after which most of the ACh is hydrolyzed before it reaches the muscle. Sensitivity is judged by the magnitude of

contractile response or by measurements of electrical depolarization, or both.

Ionic Fluxes, Oxygen Consumption, and Blood Flow in Normal and Abnormal Muscle

A chemical depolarizer acting at the end-plate receptor site increases ionic permeability and produces depolarization.[27,53] Increased permeability is the primary effect and depolarization is secondary, for studies of denervated muscle indicate that ACh increases permeability even if the muscle is already completely depolarized.[53] In normal muscle, this increase in permeability probably occurs only at the receptor site and not over the remaining electrosensitive membrane.[27,53] The associated ionic fluxes include influx of sodium (Na^+) and efflux of K^+.[53,59] Some of the increased extracellular K^+ is lost to the venous circulation and accounts for the small increase in systemic serum K^+ (0.5 mEq/l) found after the administration of SCh in subjects with normal muscle.[46,71,80]

Denervated skeletal muscle (lower motor neuron lesion) responds to both ACh[15] and SCh[44] with an initial machine-gun-like burst of action potentials, followed immediately by a muscle contracture associated with electrical silence. With SCh,[44] a large muscle K^+ efflux (fig. 1) and Na^+ influx,[61] a fourfold increase in muscle oxygen consumption ($\dot{V}_{O_2}$) (fig. 2), and an associated threefold increase in muscle blood flow (table 1) occur. Muscle $\dot{V}_{O_2}$ increases because of both stimulation of the Na^+/K^+ pump to restore ionic equilibrium[82] and the muscle contracture. The increase in muscle blood flow is probably due to vasodilatation produced by release of ATP[42] during contracture. Hyperkalemia by
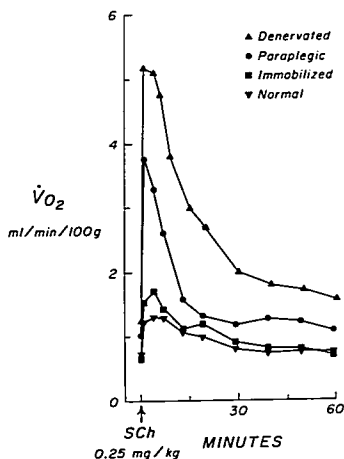

FIG. 2. $\dot{V}_{O_2}$'s of normal[44,47] (N = 10), immobilized[47] (N = 5), paraplegic[45] (N = 7) and denervated[44] (N = 5) canine skeletal muscle after SCh injection. Unpaired t tests indicate that the first portions of the two upper curves are different from each other and from those of the two lower curves.

itself[12] initially produces vasodilatation for several minutes, followed by vasoconstriction.

The dose of SCh required to relax normal muscle greatly exceeds that necessary to depolarize supersensitive muscle,[44] and supersensitivity to SCh can be demonstrated, associated with extraordinary changes in muscle K^+ flux and $\dot{V}_{O_2}$, using doses of SCh one tenth the size of those in figures 1 and 2.[44,45] Similar changes presumably occur also with ACh,[53,63] but are probably less persis-

TABLE 1. Canine Gastrocnemius Muscle Blood Flow (ml/min/100 g Wet Weight) after Administration of Succinylcholine (SCh) (0.25 mg/kg)

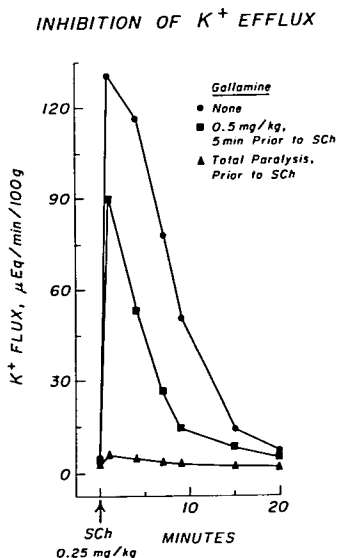| Experimental Condition	Control	Minutes after SCh				
		1	4	7	13	19
Normal[44,47] (N = 10)	11.5	16.4	16.2	14.6	11.2	10.6
Immobilization[47] (N = 5)	12.1	20.8	19.0	15.7	12.1	12.9
Denervation[44] (N = 5)	19.4	53.2*	59.0*	58.5*	46.7*	45.6*
Paraplegia[45] (N = 7)	28.3	62.2*	63.0*	42.9	28.1	23.4

* Different from control, $P < 0.05$.

FIG. 3. K⁺ fluxes of denervated muscle after SCh injection. Gallamine-pretreatment categories are: none; gallamine, 0.5 mg/kg, 5 minutes before SCh; gallamine paralysis (3 mg/kg initial dose plus 4 mg/kg per hour constant infusion begun 15 minutes before SCh). N = 5 in each group. Calculations from data of Gronert et al.[44]

tent, owing to the shorter duration of action of ACh.

Data on the protective effect of a prior small dose of a nondepolarizing relaxant indicate that a small dose attenuates the hyperkalemic response, and that a much larger dose is required to block it completely (fig. 3).[11,24,31,43,44,93,96]

Skeletal muscle developing disuse atrophy as a consequence of tenotomy[30,65] or immobilization[39,85] does not manifest any contracture with ACh or SCh; at most, there is a small increase in sensitivity to ACh. The response of immobilized muscle to SCh[47] is, in general, similar to that of normal muscle, in that there are both muscle relaxation and

an approximate twofold increase in $\dot{V}_{O_2}$ (fig. 2). Its response is different from that of normal muscle in that K⁺ efflux is slightly greater after SCh (fig. 1).

Paraplegic muscle[84] is similar to immobilized muscle in that its increase in sensitivity to ACh is small. Paradoxically, such muscle (and muscle affected by other upper motor neuron lesions) is also similar to denervated muscle. A contracture develops with ACh[64,84,86] or SCh,[45] and muscle blood flow (table 1), K⁺ efflux (fig. 1), and $\dot{V}_{O_2}$ (fig. 2) increase sharply with SCh. K⁺ efflux and $\dot{V}_{O_2}$ of paraplegic muscle do not increase quite as much as in denervated muscle. K⁺ efflux, V_{O_2}, and muscle blood flow are expressed per 100 g muscle and are actually amplified because of the marked muscle atrophy. Thus, the SCh-induced increases in systemic K⁺ following paraplegia are only moderately greater than those following unilateral sciatic-nerve section, even though the initial affected paraplegic muscle mass is perhaps three times that of the denervated muscle mass. With studies made 4 weeks after sciatic denervation or cord section, Stone et al.[88] observed mean peak increases in systemic plasma K⁺ of 1.8 and 2.6 mEq/l, respectively; we found increases of 1.2[44] and 1.7[45] mEq/l.

When denervated muscle atrophies, its K⁺ content decreases (table 2). The intracellular K⁺ content of atrophying individual muscle fibers, expressed as concentration in noncollagenous protein nitrogen, remains constant,[29] whereas fibrous tissue replaces totally atrophied fibers, thus diminishing the K⁺ content of biopsy specimens.[50]

The impressive weight loss of immobilized muscle apparently is not related to total fiber atrophy with connective tissue replacement, because muscle K⁺ content is the same as that of normal muscle (table 2).

We found that paraplegic canine gastrocnemius muscle atrophied in 2 weeks as much as denervated or immobilized muscle had in 1 month (table 2). This more rapid atrophy may have been related to the animals' lack of appetite and their resulting poor nutrition. The early weight loss of paraplegic muscle apparently was not related to connective tissue replacement, as muscle K⁺ content was similar to that of normal muscle (table 2). By

4 weeks, however, muscle atrophy had progressed to 50 per cent, biopsy specimens contained increased amounts of connective tissue, and muscle K^+ content was much decreased. With paraplegia, despite the intact lower motor neurons, reflex activity was virtually nil[45] and the severe atrophy led to fibrosis. This combination of atrophy and fibrosis following cord section in dogs has been reported.[95]

Muscle blood flow rate per 100 g wet weight is highest in paraplegic muscle, compared with denervated, immobilized, or normal muscle (table 1). This is probably accounted for by the combined effects of sympathectomy accompanying cord section and muscle atrophy.

The differences in response between denervated, paraplegic, and immobilized muscle (figs. 1 and 2) are also probably related to neurotropic effects. These tropic changes in muscle become greatest as the end-plate and muscle become most isolated from the nerve.[16,19,48] After denervation, SCh induced the greatest changes in muscle blood flow, K^+ flux, and $\dot{V}_{O_2}$ because of the complete absence of neuronal influence. These changes were not as impressive after cord section, when lower motor neurons were intact but isolated from higher centers and relatively inactive. Immobilization effectively produced muscle atrophy, but, except for a slight increase in K^+ efflux, the minimal motor nerve activity prevented neurotropic changes.

A recurring difficulty in analyzing data pertaining to such considerations as sensitivity and atrophy is the ambiguous use of the term "disuse." For years, this term has been applied to the sequelae of cord section (upper motor neuron lesion), when what is really meant is disuse of nerve,[30,54,95] with consequent disuse atrophy of muscle. Disuse atrophy of muscle by itself is produced by tenotomy[30,65] or immobilization.[39,85] Any study of disuse associated with cord section introduces the tropic effect[48,49] of an upper motor neuron lesion on the anterior horn cell, and subsequently the muscle. Since a portion of the overall effect is apparently the same—neuronal inactivity and muscular atrophy—the differences may be semantic.

TABLE 2. Ratios of Abnormal to Expected Normal Canine Muscle Weights and K^+ Content of Gastrocnemius

Experimental Condition	Ratio. Abnormal Muscle Wt↑ Expected Normal Muscle Wt	K^+ (Mean ± SE) (mEq/100 g)
Normal[44,47] (N = 10)	1.0	8.6 ± 0.3
Immobilization 10 days[45] (N = 1)	0.86	9.2
20 days[47] (N = 1)	0.71	7.5
30–40 days[47] (N = 5)	0.61*	8.4 ± 0.3
Denervation[44] 30–40 days (N = 5)	0.74*	5.1 ± 0.7*
Paraplegia[45] 2 weeks (N = 4)	0.69†	8.3 ± 0.6†
4 weeks (N = 7)	0.51	5.3 ± 0.3

* Different from normal, $P < 0.05$.

† Different from 4-week paraplegic, $P < 0.05$.

‡ Ratio of normal muscle weight (mean, 64.5 g) to body weight (mean, 18.1 kg) = 3.61×10^{-3}.

Changes in Muscle Sensitivity

Sensitivity of muscle is increased in five sets of circumstances.

1) Nerve impulses cease for varying periods after denervation,[15,28,55] cord section,[20,54,84] or other upper motor neuron lesions,[20] prolonged motor nerve blockade by local anesthetics,[65] or blockade of transmitter release by nerve toxins such as botulinum[90] or β-bungarotoxin.[51] Sensitivity in mammals begins to increase within a day or so and is maximal within 10 days, with some species variation.[90]

2) Degenerating nerve is associated with an increase in sensitivity. When one of two nerves to a single muscle is sectioned, sensitivity increases around the denervated end-plate, despite the remaining functional connection from the intact nerve.[74] Similarly, an area of increased sensitivity develops

around an isolated short segment of excised nerve placed on the surface of an innervated muscle.[55]

3) Degeneration of muscle after trauma results in markedly increased sensitivity, though the motor nerve is still intact.[60] Even minor muscle trauma is effective; for example, a thread placed on the surface of an innervated muscle produces a temporary slight increase in sensitivity.[55]

4) Disuse of innervated muscle may increase sensitivity, depending on the type of lesion. After immobilization from external or internal fixation,[39,85] there is a limited increase in sensitivity—limited probably because the nerve was active for maintenance of muscle tone.[65] After tenotomy, which results in continued constant shortening,[30] sensitivity does not increase at all.[65] Thus, the level of conducted neuronal activity affects the sensitivity of the postsynaptic receptors.[1,39] For, after sensitivity has increased (from several different causes),[28,55,65,78] external stimulation to nerve or directly to muscle results in a decrease in sensitivity back toward normal. This is but partially effective, however, in the presence of degenerating nerve[55,74] or muscle.[60]

5) Axoplasmic flow is blocked by the use of drugs such as vinblastine[2] or colchicine[51] (which do not block nerve conduction, transmitter release, or neuromuscular transmission), or by nerve section.[68] Sensitivity increases after either drug treatment or nerve section; however, the increase after the latter is delayed depending on the length of the degenerating fiber—the farther the nerve is sectioned from the muscle, the longer the delay before sensitivity increases.[68]

Clinical Implications

Although SCh-induced hyperkalemia can be related directly to supersensitivity in muscle affected by denervation or direct trauma, the relationship is not clear in regard to upper motor neuron lesions or thermal trauma.

Upper motor neuron lesions include cord section,[45,87,88,92] stroke,[24,91] multiple sclerosis[24] or encephalitis with motor involvement,[26] and tetanus.[14,33,79] Although a slight increase in sensitivity has usually (but not always)[54]

been demonstrated after cord section,[84] this increase is small compared with that for denervated muscle,[84] despite the fact that the hyperkalemic response is almost as great (fig. 1). Our limited data on sensitivity, involving the low dose of SCh, suggest that sensitivity was increased to some extent 4 weeks, but not 2 weeks, after canine cord section. Solandt and Magladery[84] demonstrated (fig. 4) that rat paraplegic muscle showed an increased sensitivity to ACh (albeit less than that of denervated muscle) only during the early period of muscle atrophy (the initial 12 days), when flaccidity was present. Once reflexes returned and the muscle regained weight, sensitivity rapidly returned to normal. Claude Bernard[10] likewise recognized evidence of increased excitability in paraplegic subjects. At that time testing was crude, consisting of injecting small doses of strychnine and comparing the contractile responses of abnormal and normal muscle.

We might infer from Solandt and Magladery's[84] data (fig. 4) that the temporary period of increased ACh sensitivity would mean that the patient would be temporarily at risk to SCh and that the hyperreflexic patient with an upper motor neuron lesion should now respond to SCh normally. However, this may not be true, because the injection of SCh has been followed by the finding in the venous effluent of serum K^+ concentrations of 10 mEq/l from the hyperreflexic arm of a patient with an upper motor neuron lesion secondary to encephalitis.[26] It is not possible to say whether this K^+ was released by atrophic, and presumably supersensitive, muscle or by hyperreflexic, and presumably normally sensitive, muscle. If the K^+ were released by hyperreflexic muscle, then either the return of reflexes could not override the tropic effect of the upper motor neuron lesion and the hyperreflexia is a sign of increased sensitivity, or the K^+ efflux would be related to something other than increased sensitivity by itself. Further investigations should examine the relationship between supersensitivity and SCh-induced K^+ efflux in upper motor neuron lesions.

Assuming hyperactive reflexes are a sign of increased chemosensitivity to ACh, then a period of increased activity of abnormal mus-
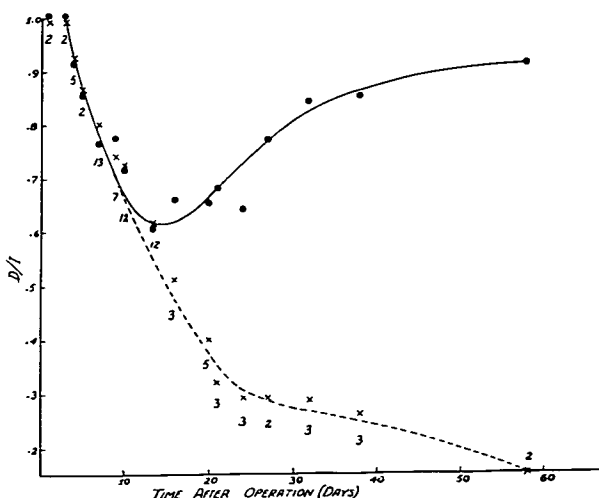
FIG. 4. Gastrocnemius–soleus muscle atrophy[84] in rat after denervation (×) or section at T6 level (●). D/I is $\dfrac{\text{abnormal muscle weight}}{\text{expected normal muscle weight}}$. See text for details. (From Solandt DY, Magladery JW: A comparison of effects of upper and lower motor neurone lesions on skeletal muscle. J Neurophysiol 5:373–380, 1942. By permission of the American Physiological Society.)

cle in a patient with either an upper motor neuron lesion or tetanus should produce a K^+ efflux proportional to the amount of stimulated abnormal muscle. This could account, at least in part, for some of the episodes of cardiovascular instability reported to occur in patients with tetanus.[96] It also implies that the period of risk to SCh in the paraplegic or hemiplegic patient may persist indefinitely; the present data suggest that this period is at least 3 to 6 months.[24,83]

The mechanism of hyperkalemia in burned patients[80] may be due to muscle membrane damage[24,58] or to increased chemical sensitivity related to disuse atrophy,[46] but not to disuse atrophy by itself.[47] Burned patients suffer constant, unrelenting pain greatly aggravated by movement and, in addition, undergo considerable weight loss during convalescence.[4] In a study of immobilization atrophy,[47] animals were in excellent condi-

tion and probably maintained some muscle tone in the plaster cast, despite more than 25 per cent atrophy. Thus, the K^+ efflux with SCh was small. In a recent study of paraplegia,[45] the animals ate poorly, were inactive, and had flaccid paralysis—and no attempt was made to activate the distal reflex apparatus.[5] Yet their gastrocnemius muscles atrophied much faster than did even denervated muscle (table 2), which theoretically should have been undergoing maximum atrophy because of both disuse and loss of the motor nerve. If burned patients move little because of severe pain and maintain poor muscle tone, and if the effect of this relative disuse of nerve and muscle is aggravated by inanition, then atrophy and increased sensitivity may occur, resulting in increased K^+ release by SCh.

In patients in whom SCh produces a massive K^+ efflux, muscle loses compara-

tively little K^+. Muscle K^+ efflux resulting in a decrease in muscle K^+ content of about 1 per cent is sufficient to increase serum K^+ to 10 mEq/l, a value generally associated with cardiac depression severe enough to produce circulatory arrest.[24,71,87,92,94] Muscle K^+ loss is shown by the following calculations: The K^+ content of denervated[44] or paraplegic[45] muscle is about 5 mEq/100 g wet weight, or 50 mEq/kg. The proportion of muscle in a 70–kg man is about 40 per cent[91]; this amount of muscle weighs 28 kg and contains 1,400 mEq K^+ (28×50 mEq). Since 2 per cent of K^+ in muscle is extracellular,[76] the intracellular muscle K^+ content amounts to approximately 1,372 mEq. With a blood volume of 5 liters and a hematocrit of 40 per cent, the plasma volume is 3 liters. The concentration of K^+ in the plasma is normally about 4 mEq/l; the total content of K^+ in the plasma is then 12 mEq. Release of K^+ by SCh produces a peak increase in plasma K^+ in 3 to 5 minutes. If one assumes that all the muscle is abnormal, that it releases K^+, and that the concentration of K^+ in the plasma increases from 4 to 10 mEq/l, there will be 30 mEq K^+ in plasma—a 250 per cent increase; in this patient the intracellular K^+ content has decreased by 18/1,372, or about 1.3 per cent. If the subject is paraplegic, then approximately half of his muscle mass would release K^+ and the K^+ content of muscle would decrease about 2.6 per cent.

After the efflux of K^+, the increase in circulating K^+ is initially and rapidly taken up by the liver and later recirculated to muscle.[36] This is consistent with the patterns in figure 1, which show that, during the hour of observation, K^+ influx only partially replaces the K^+ lost by efflux.

Clinical reports of SCh-induced hyperkalemia do not mention the associated muscle contracture, although this has been reported in animal studies.[44] Such contracture has not been noted, perhaps, because of preoccupation with vital signs, the electrocardiographic picture, and, occasionally, resuscitation. In studies not concerned with hyperkalemia, SCh has been found to produce contracture of the denervated arm[13] and of the ptotic upper eyelid (third-nerve palsy).[69] Other abnormal muscle that is sus-

ceptible (e.g., in cases of myotonia[77] or malignant hyperthermia[57,58]) may respond to SCh with a contracture. Use of SCh in myotonia has, in general, been avoided, but occasional administration has not resulted in cardiovascular collapse[7] or marked increase in serum K^+ when this has been measured.[23] In malignant hyperthermia, the serum K^+ concentration increases greatly when body temperature has risen sharply and acidosis is extreme.[9] The serum K^+ concentration may increase rapidly when the response is triggered by SCh[45] and more slowly when halothane alone initiates the response.[9,45] The SCh-triggered rapid increase, perhaps, is due to muscle membrane efflux, and the later slower increase is attributable to hepatic release[32] secondary to the stress of conditions such as acidosis and hyperthermia.

Summary

SCh is unequivocally contraindicated in the management of patients who have sustained thermal trauma or direct muscle trauma and those who have neurologic disorders involving motor deficits, including tetanus. The mechanism is clear in some, but not all, of these conditions, and is related to increased chemosensitivity of the muscle membrane due to the development of receptor sites in extrajunctional areas. Though SCh induces a small release of K^+ in normal muscle, it produces a potentially lethal efflux in the presence of increased sensitivity. This K^+-releasing action of SCh begins about 5 to 15 days after injury and persists for 2 to 3 months in patients who have sustained burns or trauma, and perhaps 3 to 6 months in patients with upper motor neuron lesions.

References

1. Aguilar CE, Bisby MA, Diamond J: Impulses and the transfer of trophic factors in nerves. J Physiol (Lond) 226:60P–61P, 1972
2. Albuquerque EX, Warnick JE, Tasse JR, et al: Effects of vinblastine and colchicine on neural regulation of the fast and slow skeletal muscles of the rat. Exp Neurol 37:607–634, 1972
3. Allan CM, Cullen WG, Gillies DMM: Ventricular fibrillation in a burned boy. Can Med Assoc J 85:432–434, 1961
4. Artz CP, Moncrief JA: The Treatment of

Burns. Second edition. Philadelphia, W. B. Saunders Company, 1969

5. Asratyan EA: The effect of use and disuse on the morphology and function of spinal neurons, The Effect of Use and Disuse on Neuromuscular Functions. Edited by E Gutmann, P Hnik. New York, Elsevier Publishing Company, 1963, pp 213–218

6. Axelsson J, Thesleff S: A study of supersensitivity in denervated mammalian skeletal muscle. J Physiol (Lond) 147:178–193, 1959

7. Baraka A, Haddad C, Afifi A, et al: Control of succinylcholine-induced myotonia by d-tubocurarine. ANESTHESIOLOGY 33:669–670, 1970

8. Belin RP, Karleen CI: Cardiac arrest in the burned patient following succinylcholine administration. ANESTHESIOLOGY 27:516–518, 1966

9. Berman MC, Kench JE: Biochemical features of malignant hyperthermia in Landrace pigs, International Symposium on Malignant Hyperthermia. Edited by RA Gordon, BA Britt, W Kalow. Springfield, Ill., Charles C Thomas, 1973, pp 287–297

10. Bernard C: Cited by Cannon WB, Haimovici H[20]

11. Birch AA Jr, Mitchell GD, Playford GA, et al: Changes in serum potassium response to succinylcholine following trauma. JAMA 210:490–493, 1969

12. Brace RA: Time course and mechanisms of the acute effects of hypokalemia and hyperkalemia on vascular resistance. Proc Soc Exp Biol Med 145:1389–1394, 1974

13. Brim VD: Denervation supersensitivity: The response to depolarizing muscle relaxants. Br J Anaesth 45:222–226, 1973

14. Brooks VB, Curtis DR, Eccles JC: The action of tetanus toxin on the inhibition of motoneurones. J Physiol (Lond) 135:655–672, 1957

15. Brown GL: Actions of acetylcholine on denervated mammalian and frog's muscle. J Physiol (Lond) 89:438–461, 1937

16. Buller AJ, Eccles JC, Eccles RM: Interactions between motoneurones and muscles in respect of the characteristic speeds of their responses. J Physiol (Lond) 150:417–439, 1960

17. Bush GH: The use of muscle relaxants in burnt children. Anaesthesia 19:231–238, 1964

18. Bush GH, Graham HAP, Littlewood AHM, et al: Danger of suxamethonium and endotracheal intubation in anaesthesia for burns. Br Med J 2:1081–1085, 1962

19. Cannon WB: A law of denervation. Am J Med Sci 198:737–750, 1939

20. Cannon WB, Haimovici H: The sensitization of motoneurones by partial "denervation." Am J Physiol 126:731–740, 1939

21. Case History Number 62: Circulatory collapse following succinylcholine: Report of a patient with diffuse lower motor neuron disease. Anesth Analg (Cleve) 50:431–437, 1971

22. Clinical Anesthesia Conference: Burns and the airway: a challenge in anesthesia. NY State J Med 62:2023–2024, 1962

23. Cody JR: Muscle rigidity following administration of succinylcholine. ANESTHESIOLOGY 29:159–162, 1968

24. Cooperman LH: Succinylcholine-induced hyperkalemia in neuromuscular disease. JAMA 213:1867–1871, 1970

25. Cooperman LH, Strobel GE Jr, Kennell EM: Massive hyperkalemia after administration of succinylcholine. ANESTHESIOLOGY 32:161–164, 1970

26. Cowgill DB, Mostello LA, Shapiro HM: Encephalitis and a hyperkalemic response to succinylcholine. ANESTHESIOLOGY 40:409–411, 1974

27. del Castillo J, Katz B: Local activity at a depolarized nerve–muscle junction. J Physiol (Lond) 128:396–411, 1955

28. Drachman DB, Witzke F: Trophic regulation of acetylcholine sensitivity of muscle: Effect of electrical stimulation. Science 176:514–516, 1972

29. Drahota Z, Gutmann E: Long-term regulatory influences of the nervous system on some metabolic differences in muscles of different function, The Effect of Use and Disuse on Neuromuscular Functions. Edited by E Gutmann, P Hnik. New York, Elsevier Publishing Company, 1963, pp 143–148

30. Eccles JC: Investigations on muscle atrophies arising from disuse and tenotomy. J Physiol (Lond) 103:253–266, 1944

31. Editorial: Succinylcholine and trauma. JAMA 210:549–550, 1969

32. Elmqvist D, Thesleff S: A study of acetylcholine induced contractures in denervated mammalian muscle. Acta Pharmacol Toxicol (Kbh) 17:84–93, 1960

33. Eyrich K, Agostini B, Schulz A, et al: Klinische und morphologische Beobachtungen von Skelettmuskelveränderungen beim Tetanus. Dtsch Med Wochenschr 92:530–540, 1967

34. Feldman SA: Muscle Relaxants. Volume 1. London, W.B. Saunders, 1973, p 25

35. Feldman SA: Muscle Relaxants. Volume 1. London, W.B. Saunders, 1973, pp 62–63

36. Fenn WO: The role of potassium in physiological processes. Physiol Rev 20:377–415, 1940

37. Finer BL, Nylén BO: Double cardiac arrest with survival. Br Med J 1:624–625, 1959

38. Finer BL, Nylén BO: Cardiac arrest in the treatment of burns, and report on hypnosis as a substitute for anesthesia. Plast Reconstr Surg 27:49–55, 1961

39. Fischbach GD, Robbins N: Effect of chronic disuse of rat soleus neuromuscular junctions on postsynaptic membrane. J Neurophysiol 34:562–569, 1971

40. Fleming WB, Hueston JT, Stubbe JL, et al:

Two episodes of cardiac arrest in one week: Full recovery after cardiac massage. Br Med J 1:157–160, 1960

41. Forrest T: A report on two cases of cardiac arrest. Br J Anaesth 31:277–279, 1959

42. Forrester T: An estimate of adenosine triphosphate release into the venous effluent from exercising human forearm muscle. J Physiol (Lond) 224:611–628, 1972

43. Gronert GA: Potassium response to succinylcholine (letter to the editor). JAMA 211:300, 1970

44. Gronert GA, Lambert EH, Theye RA: The response of denervated skeletal muscle to succinylcholine. ANESTHESIOLOGY 39:13–22, 1973

45. Gronert GA, Milde J, Theye RA: Unpublished data

46. Gronert GA, Theye RA: Serum potassium changes after succinylcholine in swine with thermal trauma or sciatic nerve section. Can Anaesth Soc J 18:558–562, 1971

47. Gronert GA, Theye RA: Effect of succinylcholine on skeletal muscle with immobilization atrophy. ANESTHESIOLOGY 40:268–271, 1974

48. Guth L: "Trophic" influence of nerve on muscle. Physiol Rev 48:645–687, 1968

49. Gutmann E, Hník P: Denervation studies in research of neurotrophic relationships, The Denervated Muscle. Edited by E Gutmann. Prague, Publishing House of the Czechoslovak Academy of Sciences, 1962, pp 13–56

50. Hines HM, Knowlton GC: Changes in the skeletal muscle of the rat following denervation. Am J Physiol 104:379–391, 1933

51. Hofmann WW, Thesleff S: Studies on the trophic influence of nerve on skeletal muscle. Eur J Pharmacol 20:256–260, 1972

52. Houssay BA, Marenzi AD, Gerschman R: Mechanismo simpatico-adrenalino-hepático y potasio sanguineo. Rev Soc Argent Biol 12:434–453, 1936

53. Jenkinson DH, Nicholls JG: Contractures and permeability changes produced by acetylcholine in depolarized denervated muscle. J Physiol (Lond) 159:111–127, 1961

54. Johns TR, Thesleff S: Effects of motor inactivation on the chemical sensitivity of skeletal muscle. Acta Physiol Scand 51:136–141, 1961

55. Jones R, Vrbová G: Two factors responsible for the development of denervation hypersensitivity. J Physiol (Lond) 236:517–538, 1974

56. Kalow W: Relaxants, Uptake and Distribution of Anesthetic Agents. Edited by EM Papper, RJ Kitz. New York, Blakiston Division, McGraw-Hill, 1963, pp 302–313

57. Kalow W: Succinylcholine and malignant hyperthermia. Fed Proc 31:1270–1275, 1972

58. Kalow W: Some aspects of the pharmacology of muscle relaxants, International Symposium on Malignant Hyperthermia. Edited by RA Gordon, BA Britt, W Kalow. Springfield, Ill., Charles C Thomas, 1973, pp 166–178

59. Katz B: Nerve, Muscle, and Synapse. New York, McGraw-Hill, 1966

60. Katz B, Miledi R: The development of acetylcholine sensitivity in nerve-free segments of skeletal muscle. J Physiol (Lond) 170:389–396, 1964

61. Kendig JJ, Bunker JP, Endow S: Succinylcholine-induced hyperkalemia: Effects of succinylcholine on resting potentials and electrolyte distribution in normal and denervated muscle. ANESTHESIOLOGY 36:132–137, 1972

62. Kern ER: Role of the anesthesiologist in the treatment of severe burns. Int Anesthesiol Clin 3:829–841, 1965

63. Klaus W, Lüllmann H, Muscholl E: Die Wirkung von Acetylcholin auf den K- und Na-Flux und ihre pharmakologische Beeinflussung am denervierten Rattenzwerchfell. Naunyn-Schmiedebergs Arch Pharmacol 241:281–292, 1961

64. Lanari A: Action de l'acetylcholine intra-artérielle dans certaines affections du système nerveux et des muscles. C R Soc Biol (Paris) 123:1090–1091, 1936

65. Lømo T, Rosenthal J: Control of ACh sensitivity by muscle activity in the rat. J Physiol (Lond) 221:493–513, 1972

66. Lowenstein E: Succinylcholine administration in the burned patient. ANESTHESIOLOGY 27:494–496, 1966

67. Lowenstein E: Use of succinylcholine in burned patients (letter to the editor). ANESTHESIOLOGY 28:234–235, 1967

68. Luco JV, Eyzaguirre C: Fibrillation and hypersensitivity to ACh in denervated muscle: Effect of length of degenerating nerve fibers. J Neurophysiol 18:65–73, 1955

69. Marshall M: Action of suxamethonium on ptosis due to third-nerve palsy. Br Med J 2:1116–1117, 1964

70. Masters FW, Hansen JM, Robinson DW: Anesthetic complications in plastic surgery. Plast Reconstr Surg 24:472–480, 1959

71. Mazze RI, Escue HM, Houston JB: Hyperkalemia and cardiovascular collapse following administration of succinylcholine to the traumatized patient. ANESTHESIOLOGY 31:540–547, 1969

72. McCaughey TJ: Hazards of anaesthesia for the burned child. Can Anaesth Soc J 9:220–233, 1962

73. McCaughey TJ: Use of succinylcholine in burned patients (letter to the editor). ANESTHESIOLOGY 28:234, 1967

74. Miledi R: The acetylcholine sensitivity of frog muscle fibres after complete or partial denervation. J Physiol (Lond) 151:1–23, 1960

75. Moncrief JA: Complications of burns. Ann Surg 147:443–475, 1958

76. Moore FD: Metabolic Care of the Surgical Patient. Philadelphia, W.B. Saunders, 1959, p 7

77. Örndahl G: Myotonic human musculature: Stimulation with depolarizing agents. II. A

clinico-pharmacological study. Acta Med Scand 172:753–765, 1962

78. Purves D, Sakmann B: The effect of contractile activity on fibrillation and extrajunctional acetylcholine-sensitivity in rat muscle maintained in organ culture. J Physiol (Lond) 237:157–182, 1974

79. Roth F, Wüthrich H: The clinical importance of hyperkalaemia following suxamethonium administration. Br J Anaesth 41:311–316, 1969

80. Schaner PJ, Brown RL, Kirksey TD, et al: Succinylcholine-induced hyperkalemia in burned patients—1. Anesth Analg (Cleve) 48:764–770, 1969

81. Skelton H: The storage of water by various tissues of the body. Arch Intern Med 40:140–152, 1927

82. Skou JC: Enzymatic basis for active transport of Na^+ and K^+ across cell membrane. Physiol Rev 45:596–617, 1965

83. Smith RB, Grenvik A: Cardiac arrest following succinylcholine in patients with central nervous system injuries. ANESTHESIOLOGY 33:558–560, 1970

84. Solandt DY, Magladery JW: A comparison of effects of upper and lower motor neurone lesions on skeletal muscle. J Neurophysiol 5:373–380, 1942

85. Solandt DY, Partridge RC, Hunter J: The effect of skeletal fixation on skeletal muscle. J Neurophysiol 6:17–22, 1943

86. Stavraky GW: Some aspects of the effects of intravenous injections of acetylcholine on the central nervous system. Proc Trans Roy Soc Can 37 (Section V):127–139, 1943

87. Stone WA, Beach TP, Hamelberg W: Succinylcholine—danger in the spinalcord-injured patient. ANESTHESIOLOGY 32:168–169, 1970

88. Stone WA, Beach TP, Hamelberg W: Succinylcholine-induced hyperkalemia in dogs with transected sciatic nerves or spinal cords. ANESTHESIOLOGY 32:515–520, 1970

89. Thesleff S: The effects of acetylcholine, decamethonium and succinylcholine on neuromuscular transmission in the rat. Acta Physiol Scand 34:386–392, 1955

90. Thesleff S: Effects of motor innervation on the chemical sensitivity of skeletal muscle. Physiol Rev 40:734–752, 1960

91. Thomas ET: Circulatory collapse following succinylcholine: Report of a case. Anesth Analg (Cleve) 48:333–337, 1969

92. Tobey RE: Paraplegia, succinylcholine and cardiac arrest. ANESTHESIOLOGY 32:359–364, 1970

93. Tobey RE, Jacobsen PM, Kahle CT, et al: The serum potassium response to muscle relaxants in neural injury. ANESTHESIOLOGY 37:332–337, 1972

94. Tolmie JD, Joyce TH, Mitchell GD: Succinylcholine danger in the burned patient. ANESTHESIOLOGY 28:467–470, 1967

95. Tower SS: Trophic control of non-nervous tissues by the nervous system: A study of muscle and bone innervated from an isolated and quiescent region of spinal cord. J Comp Neurol 67:241–267, 1937

96. Tseuda K, Oliver PB, Richter RW: Cardiovascular manifestations of tetanus. ANESTHESIOLOGY 40:588–592, 1974

97. Waud DR: The nature of "depolarization block." ANESTHESIOLOGY 29:1014–1024, 1968

98. Weintraub HD, Heisterkamp DV, Cooperman LH: Changes in plasma potassium concentration after depolarizing blockers in anaesthetized man. Br J Anaesth 41:1048–1052, 1969

99. Wilde NJ, Tur JJ: Cardiac arrest in plastic surgery. Plast Reconstr Surg 35:401–408, 1965

Burns

SERUM PROTEINS IN BURNS Serum proteins were measured for 60 days after an acute burn in children. Albumin concentration fell by almost half and remained low for the entire 60 days. Alpha-2 globulins rose during the first two weeks due to increasing haptoglobulin concentration. Gamma globulin concentration fell to about 0.8 g/100 ml during the first week: most of the fall was due to reduction in IgG. Patients who died had even lower values of gamma globulins. *(Ritzmann, S. E., Daniels, J. C., and Larson, D. L.: Diagnostic interpretation of serum protein abnormalities in thermal burns, Am J Clin Pathol 60:135–144, 1973.)* ABSTRACTER'S COMMENT: The authors recommend repeated measurement by electrophoresis and treatment with albumin or gamma globulin as indicated. They do not present convincing clinical correlation and have not attempted to measure results of the recommended treatment.