

## Cardiac Arrest after Succinylcholine

### Mortality Greater with Rhabdomyolysis Than Receptor Upregulation

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THIS all began during the World Congress of Anaesthesiologists in Holland in June 1992, at an extramural multinational panel convened to prepare an educational videotape.† Speakers from the United States and Germany described pediatric cases of sudden rhabdomyolysis and hyperkalemic cardiac arrest after administration of succinylcholine. Despite prompt and apparently skilled resuscitation, the mortality rate was 40–55%. This surprising and puzzling mortality rate prompted considerable discussion and, over time, repeated reflection on what might be happening.

#### Background

Succinylcholine was introduced into clinical practice in 1951.<sup>1</sup> By 1953, cardiac arrest during induction of anesthesia had been observed in burn patients given succinylcholine,<sup>2</sup> although its mechanism, hyperkalemia, was not reported until 1967.<sup>3</sup> Other conditions resulting in succinylcholine-induced hyperkalemia were soon identified, including direct muscle trauma, denervation phenomena (upper motor neuron lesions, *e.g.*, stroke or cord section, and lower motor neuron lesions, *e.g.*, Guillain-Barré syndrome, motor nerve section, ventral horn disorders), intraabdominal infections (perhaps an intensive care unit [ICU] disorder), and, some years later, patients with prolonged ICU treatment—disuse atrophy and pharmacologic denervation by nondepolarizing neuromuscular blocking drugs.<sup>4</sup> In time, the basis for this hyperkalemia was identified as upregulation of skeletal muscle nicotinic acetylcholine receptors.<sup>4</sup> This upregulation is a manifestation of increased numbers of

altered receptors at and around the endplate, with extension of receptors across the entire muscle membrane when acetylcholine is totally divorced from endplate interactions.

The other primary cause of succinylcholine-induced hyperkalemia and cardiac arrest is acute rapid rhabdomyolysis,<sup>5</sup> first reported just 4 yr after the seminal article by Tolmie *et al.* concerning burn-related hyperkalemia. Reports from the past 40+ yr appear to imply that resuscitation is more difficult and mortality greater when the underlying basis is rhabdomyolysis. That impression prompted examination of these two disorders.

#### Mechanisms of Hyperkalemia

##### Receptor Upregulation

When there is upregulation of skeletal muscle acetylcholine receptors, potassium release after administration of succinylcholine appears to be caused by two factors: a change in subunit type from  $\epsilon$  to  $\gamma$ , and an increase in numbers of acetylcholine receptors, which spread onto the surface membrane outside the endplate area. The altered receptor has a smaller single-channel conductance with a longer mean channel open time.<sup>4</sup> An increase in altered acetylcholine receptors is potentiated by use of steroids.<sup>6</sup>

Efflux of potassium through these altered receptors is magnified: Loss of radioactive potassium from isolated rat diaphragm was increased by acetylcholine 3–4 days after birth (before change of fetal  $\gamma$ -type acetylcholine receptors to adult  $\epsilon$ -type), and 7–14 days after sectioning of the phrenic nerve (when altered types and increased numbers of acetylcholine receptors had developed). Radioactive potassium loss was not altered by acetylcholine in the diaphragm of adult rats and after the denervated diaphragm had become reinnervated.<sup>7</sup> Other reports confirmed increased acetylcholine-induced potassium efflux in denervated muscle, 2.5-fold to fourfold greater than normal.<sup>8,9</sup> These findings from isolated superfused tissue may not be directly applicable to the *in vivo* situation.

Both succinylcholine and acetylcholine are agonists of the acetylcholine receptor.<sup>4</sup> This channel-related agonist-triggered potassium release is magnified by the number of involved muscles, probably a greater factor in

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hyperkalemia than that caused by increased efflux per altered channel.<sup>4</sup> If cardiac arrest has occurred, the challenge of resuscitation is likely reduced once potassium channels close and redistribution of potassium is more effective. During external massage, cardiac output is perhaps 25% of normal, and potassium is distributed primarily into the central circulation, thereby delaying the redistribution of potassium and the associated decrease in plasma potassium concentration.

### *Rhabdomyolysis*

Rhabdomyolysis, or breakdown of muscle surface membrane function, results in loss of cell contents: myoglobin, potassium, and creatine kinase (CK). Increased plasma CK denotes increased muscle membrane permeability, by itself not damaging. Myoglobinuria does not result in renal failure in the absence of overt pigmenturia.<sup>10</sup> A survey of the spectrum of disorders in which rhabdomyolysis occurs indicates that the underlying defects involve abnormal metabolism, ischemia, direct trauma, altered membrane permeability, fuel-exhaustive exercise, abnormal distribution of salts and water across muscle membranes, or exposure to toxins.<sup>10</sup> Although crush injury and pressure ischemia may cause an ongoing rhabdomyolysis, these do not appear to be factors in cases of cardiac arrest related to succinylcholine-induced rhabdomyolysis.

Rhabdomyolysis may occur, in part, as a result of steroid effects on skeletal muscle during ICU care.<sup>4,6,11</sup> Steroids, with additive inhibition of acetylcholine receptors during denervation,<sup>6</sup> can also cause a necrotizing myopathy.<sup>11</sup> Rhabdomyolysis may occur for no apparent reason, without exposure to drugs, anesthesia, or undue muscle stress. Amazingly enough, skeletal muscles can recover from episodes of rhabdomyolysis with minimal permanent damage.<sup>10</sup> In part because of these last two points, the putative mechanism of an episode of rhabdomyolysis may be obscure and challenging. Although the intracellular structure of muscle is well described, its dysfunction in rhabdomyolysis at times defies explanation.<sup>10</sup> In general, when a myopathy is present, succinylcholine is a virtual toxin to the unstable membranes because of its effect in sharply increasing permeability.<sup>4</sup>

If acute rhabdomyolysis occurs rapidly, plasma potassium increases quickly and may exceed the capacity for redistribution. Furthermore, with cardiac arrest and resuscitation, cardiac output is limited to the central circulation. The continued loss of potassium from multiple affected muscles could result in sustained and marked hyperkalemia and difficult resuscitation. Furthermore, generalized effects of a myopathy, involving limited activity or an associated cardiomyopathy, may diminish a patient's cardiac reserve. Theoretically, this situation may be worse than that of resuscitation in a patient with receptor upregulation, and presumably finite opening of acetylcholine receptor channels.

### **Literature Search and Inclusion Criteria**

A review of reports of succinylcholine-induced hyperkalemia and cardiac arrest was undertaken. Sources included an ongoing personal archival reference file system (presently 5,900+ references, including copies of all articles), begun in the 1960s when my interest into succinylcholine-induced hyperkalemia began; Index Medicus (early); citations in published reports; and Medline (late). Bias in this collection is caused by cases not reported because of an unwelcome result, potential legal factors, or articles that may have been missed.

Criteria for inclusion into the study were as follows: (1) use of succinylcholine, including the ICU milieu; (2) sudden immediate unexpected cardiac arrest; and (3) presence of hyperkalemia, verified by measured plasma potassium concentration, typical electrocardiogram pattern, or reasonable proximate cause by context: intravenous induction, use of succinylcholine not specified, immediate intubation, and cardiac arrest (this was seen more often in records from the 1950s and early 1960s).

Excluded from this analysis are temporary bradycardia-a-systole after even a single use of succinylcholine<sup>1</sup> and arrest related to anaphylaxis.<sup>13</sup> The former generally results in brief arrest (< 60 s) and easy resuscitation without the need to discontinue anesthesia.<sup>12</sup> The latter features a slower onset of arrest and signs of an allergic response, e.g., flushed red skin, "goose pimples," and difficulty in ventilation.<sup>13</sup> Myopathies are responsible for many of the episodes of rhabdomyolysis; the silent myopathy malignant hyperthermia is excluded because its rhabdomyolysis is later in onset. Cardiac arrest produces hepatic ischemia-hypoxia, and the related increase in catecholamines results in hepatic potassium release.<sup>14</sup> Although such release could complicate interpretation of postarrest potassium levels, modern resuscitation techniques appear to minimize this response.

### **Cases: Hyperkalemia during Anesthesia without Succinylcholine**

Rapid rhabdomyolysis can occur in the absence of use of succinylcholine, e.g., during or just after the use of a potent volatile agent, because both perturb membranes of skeletal muscle. Four cases illustrate this type of rhabdomyolysis, namely, arrest even though succinylcholine had not been used.

The first case occurred in an 8-yr-old boy who underwent a 35-min procedure, felt sick after 10 min in the recovery room, and experienced cardiac arrest. Becker dystrophy had been diagnosed 4 yr previously, but his condition was mild. Plasma potassium was 12 mEq/l, and resuscitation required 2 h. Recovery was marred by a T7 paraplegia.<sup>15</sup> The second case occurred within 10 min after starting induction, and resuscitation was successful after 90 min.<sup>16</sup> The third case occurred in a 6-yr-old boy,

80 min after induction, with 7.9 mEq/l potassium and CK to 200,000 U/l. Ultimately, brain death occurred. This boy was virtually asymptomatic before surgery, but he had a history of pigmenturia and a resting CK concentration of 13,000 U/l.<sup>17</sup> The fourth case occurred in a 6-yr-old boy with probable Duchenne dystrophy who was scheduled for muscle biopsy. Baseline CK concentration was 15,000 U/l, and potassium concentration was 4.6 mEq/l. Nitrous oxide and halothane were tolerated but with a pulse of 120 beats/min (duration not provided). He was stable in recovery for 15 min and then experienced cardiac arrest; potassium concentration was 7.9 mEq/l. Resuscitation was successful; CK concentration exceeded 25,000 U/l. Although reported as a malignant hyperthermia case, this was a myopathy-related rhabdomyolysis.<sup>18</sup>

### Cases: Anesthesia, Cardiac Arrest, and Succinylcholine

#### *Receptor Upregulation*

**Thermal Trauma.** At one burn center, during 1953–1956, 4 of 5 cardiac arrests occurred during induction, and all survived resuscitation (which until 1960 necessitated thoracotomy).<sup>2</sup> Through the early 1960s, there were 18 reported instances of cardiac arrest in burn patients; 5 patients had 2 arrests each.<sup>19</sup> All but 1 of the 18 survived. In these earlier reports, the use of succinylcholine was not always recorded, especially before 1960, but was assumed for sudden abrupt cardiac arrest after an intravenous induction and immediate intubation. Interestingly, resistance to the competitive antagonist *D*-tubocurarine was noted,<sup>19</sup> which is the parallel accompaniment of the agonist sensitivity of succinylcholine in receptor upregulation.<sup>4</sup> In 1967, the origin of potassium in these cases of cardiac arrests was convincingly identified.<sup>3</sup> The landmark article by Tolmie *et al.*<sup>3</sup> concerned a burned Marine who had had 10 uneventful anesthetics with succinylcholine in the first 26 days. Five additional anesthetics resulted in increased potassium concentrations, 7–8.5 mEq/l, after succinylcholine, and cardiac arrest resulted with 3 of these. He recovered uneventfully.<sup>3</sup> Another patient, a 16-yr-old with 55% burns, tolerated 40 mg succinylcholine on postburn day 15 but suffered cardiac arrest after the same dose on postburn days 34 (thoracotomy required) and 43.<sup>20</sup> He survived. The total number of patients was 20, with 28 cardiac arrests and one death.

**Muscle Trauma.** Muscle trauma alters the muscle surface membrane much like denervation and thermal trauma.<sup>4</sup> A report of 14 trauma patients included 3 succinylcholine-related cardiac arrests, with recovery in all.<sup>21</sup> In patients who did not experience cardiac arrest, peak plasma potassium concentrations (> 6.0 mEq/l) ranged up to 9.6 mEq/l. Values in the 3 patients who experienced cardiac arrest were 9.1, 9.5, and 9.8 mEq/l. An

additional study of 59 patients included one patient who experienced cardiac arrest and survived (peak potassium concentration, 8.6 mEq/l).<sup>22</sup>

The total number of patients was 4, with 4 cardiac arrests and no deaths.

#### **Upper or Lower Motor Neuron Denervation.**

There is an astonishing example of investigation into etiology from 1969. A debilitated patient with a neurologic deficit underwent craniotomy and experienced cardiac arrest at induction after administration of succinylcholine.<sup>23</sup> When the surgery was finished, another 40 mg succinylcholine was administered; cardiac arrest did not recur despite marked increases in potassium concentration: 3.7 mEq/l at baseline, 7.1 mEq/l at 1.5 min, and 9.2 mEq/l at 2 min.

Botulism occurred in a 28-yr-old man who had been injecting “black tar” heroin and noted gradually progressive symmetrical weakness. Because of weakness-related dyspnea, he was given 20 mg etomidate and 80 mg succinylcholine for tracheal intubation. He experienced cardiac arrest within 60 s and was resuscitated in 2 min.<sup>24</sup>

In the study by Cooperman<sup>25</sup> of 37 patients, 1 experienced cardiac arrest and was resuscitated. Peak plasma potassium concentrations in individual patients were 7.2, 7.6, 9.1, and 9.1 mEq/l.<sup>25</sup> There are other individual case reports of 13 patients who experienced cardiac arrest, two of whom died.<sup>26–36</sup> Peak potassium concentrations were 7.3–11.0 in 4 patients.<sup>26</sup> In 4 additional patients, peak concentrations were 11.6,<sup>27</sup> 6.9,<sup>30</sup> 8.3,<sup>35</sup> and 9.2 mEq/l.<sup>34</sup> Five of these patients experienced cardiac arrest despite the use of small pretreatment doses of a nondepolarizing neuromuscular blocking drug.<sup>28–30,33</sup> One patient with coma and ischemic stroke, during electroencephalography to examine brain viability was given succinylcholine to minimize muscle artifacts. Arrest occurred with a potassium concentration of 8.3 mEq/l; he did not survive.<sup>36</sup> The total number of patients was 17, with 17 cardiac arrests and 2 deaths.

**Intensive Care Unit Milieu.** Patients in the ICU undergo upregulation of skeletal muscle nicotinic acetylcholine receptors because of several factors: muscle disuse from lying in bed,<sup>4</sup> pharmacologic denervation in nondepolarizing neuromuscular blocking drugs are used,<sup>4</sup> and steroid potentiation of denervation-type effects.<sup>4,6</sup> Steroid use during ICU care can additionally produce a necrotizing myopathy.<sup>11</sup> My bias is to place these cases under receptor upregulation, although myopathic steroid effects could be a factor in some patients. After a period of ICU care, succinylcholine, used for tracheal suction or reintubation, produced cardiac arrest.<sup>37–43</sup> Peak potassium values were 6.8, 7.1, 7.4, and 8.9,<sup>37</sup> 9.9,<sup>38</sup> 8.7,<sup>39</sup> 8.3,<sup>40</sup> 13.9,<sup>41</sup> and 11.2 mEq/l.<sup>43</sup> The total number of ICU patients was 16, with 16 cardiac arrests and 3 deaths.

**Miscellaneous Receptor Upregulation.** A 1975 survey of pediatric cardiac arrest included three cases of succinylcholine-induced hyperkalemia related to thermal trauma, direct trauma plus renal failure, and serious metabolic acidosis. One of these three patients died, but the specific disorder was not stated.<sup>44</sup>

A 4-yr-old 18-kg boy with anemia, malaise, and fever to 39.6°C for several weeks had widespread osteolytic areas on radiograph. Biopsy diagnosis was embryonal rhabdomyosarcoma. A 20-mg dose of succinylcholine resulted in cardiac arrest; plasma potassium concentration was 7.3 mEq/l 9 min after succinylcholine was given. Resuscitation was successful; later muscle biopsy showed nonspecific small myopathic changes.<sup>45</sup>

A 28-yr-old man recovering from the neuroleptic malignant syndrome (peak CK concentration, 305,000 U/l [now 5,000 U/l]) was given 100 mg succinylcholine for change of his endotracheal tube. Cardiac arrest occurred with a potassium concentration of 8.3 mEq/l. Resuscitation was successful.<sup>46</sup>

A 34-yr-old man recovering from malignant hyperthermia required bronchoscopy for atelectasis. Cardiac arrest occurred after succinylcholine administration, with a potassium concentration of 8.3 mEq/l. Resuscitation was successful. This case was classified as upregulation despite the earlier episode of malignant hyperthermia because the arrest characterized ICU-related upregulation. He returned home after a 5-month hospital stay.<sup>47</sup>

A 15-yr-old 75-kg girl underwent liver transplantation for fulminant Epstein-Barr viral hepatitis. During prolonged ICU care, she developed hyperkalemia (potassium concentration, 9.0 mEq/l) after administration of 110 mg succinylcholine. She did not survive.<sup>48</sup> The total number of patients was 7, with 7 cardiac arrests and 2 deaths.

### *Rhabdomyolysis*

The difficulty with patients who have rhabdomyolysis is that many suffer from serious myopathies, such as Duchenne or Becker dystrophy. These myopathies are usually occult at the time of anesthesia. The patient may superficially appear fit but may not have adequate reserve, and thus may not be able to tolerate additional stresses. The myopathy may, in part, be responsible for the severity of response to acute hyperkalemia. The following division of rhabdomyolysis patients into subgroups was complicated by uncertain diagnoses in some or lack of postevent testing in others.

**Duchenne Dystrophy.** A series of patients collated from emergency telephone contacts (24 h/day sponsored hotline) to the Malignant Hyperthermia Association of the United States included 25 children, 23 of whom were boys. Ten (all male) died after succinylcho-

line-related cardiac arrest.<sup>49</sup> Mean peak group potassium concentration was 7.4 mEq/l, and median peak potassium concentration was 7.5 mEq/l. Eight of these children had Duchenne dystrophy. A German series described 9 children, 8 of whom were boys; 5 patients (all male) died.<sup>50</sup> Peak potassium concentrations were greater than 10, 10.3, 11.2, and 12.0 mEq/l. Two patients had Duchenne dystrophy (patients from references 49 and 50 with other diagnoses are listed under other rhabdomyolysis categories). There are additional patients with Duchenne dystrophy who experienced cardiac arrest after use of succinylcholine.<sup>51-61</sup> An 8-month-old boy with potassium concentration greater than 10 mEq/l required resuscitation for 13 min, and his CK concentration increased to 285,000 U/l.<sup>56</sup> Other cardiac arrest-related potassium values were 8.9,<sup>51</sup> 12.6,<sup>52</sup> 6.8,<sup>54</sup> more than 10,<sup>55,56</sup> 8.7,<sup>57</sup> 5.4 (30 min after resuscitation),<sup>59</sup> and 6.1 mEq/l.<sup>61</sup> The total number of patients was 23, with 23 cardiac arrests and 2 deaths.

**Becker Dystrophy.** Four patients had Becker dystrophy.<sup>50,62-64</sup> In one patient, arrest occurred 30 min after induction.<sup>63</sup> The total number of patients was 4, with 4 cardiac arrests and 2 deaths.

**Other Myopathy.** Ten patients had other myopathies.<sup>49,50,65,66</sup> Arrest-related potassium values were 10.3<sup>65</sup> and 9.5<sup>66</sup> mEq/l. The total number of patients was 10, with 10 cardiac arrests and 7 deaths.

**Unknown Diagnosis.** Twenty patients had unknown diagnosis.<sup>49,50,67-70</sup> One death, in a 15-yr-old boy who experienced cardiac arrest with a potassium concentration of 11.5 mEq/l, was interpreted as malignant hyperthermia associated with hemolysis, when in fact the episode was not likely malignant hyperthermia and the pigmenturia was likely myoglobin.<sup>69</sup> The patient initially had received 80 mg succinylcholine for intubation and was given an additional 40 mg because of inadequate relaxation. Twenty minutes later, he received 40 mg succinylcholine for abdominal relaxation and immediately experienced cardiac arrest.<sup>69</sup>

An 11-yr-old girl given succinylcholine experienced cardiac arrest with a potassium concentration of 10.2 mEq/l. After 2 h of unsuccessful resuscitation, the potassium concentration was 8.7 mEq/l. Complex resuscitation (including bypass) required 4.5 h for restoration of a normal rhythm. CK concentration increased to 800,000 U/l, and she had a normal recovery.<sup>70</sup> Her family has an indeterminate myopathy, as shown by increased CK values in several members. Her muscle biopsy had normal histology-histochemistry, did not exhibit a myopathy, and was normal with regard to the diagnosis of malignant hyperthermia. Another patient's arrest-related potassium value was 5.8 mEq/l (after resuscitation).<sup>67</sup> The total number of patients was 20, with 20 cardiac arrests and 6 deaths.

**Table 1. Patients, Arrests, Deaths, and Mortality**

	Patients (n)	Arrests (n)	Deaths (n)
Receptor upregulation			
Thermal trauma	20	28	1
Muscle trauma	4	4	0
Denervation	17	17	2
ICU milieu	16	16	3
Miscellaneous	7	7	2
Total	64	72	8
Rhabdomyolysis			
Duchenne	23	23	2
Becker	4	4	2
Other myopathy	10	10	7
Unknown diagnosis	20	20	6
Total	57	57	17
	Mortality (deaths/arrests × 100) (%)		
Receptor upregulation	11.1		
Rhabdomyolysis	29.8		

ICU = intensive care unit.

### Plasma Potassium, Muscle Intracellular Stores, and Hyperkalemia

Total plasma potassium (milliequivalents) is small; furthermore, relatively small losses from intracellular potassium stores result in pronounced hyperkalemia if redistribution is limited.<sup>71</sup> For example, a patient with a 5-l blood volume and a hematocrit of 40% has a 3-l plasma volume. This 3-l plasma volume, with a potassium concentration of 4 mEq/l, contains 12 mEq circulating potassium. If cardiac output is low, as in cardiac arrest and external massage, distribution of released or injected potassium may be solely into the central volume, without rapid redistribution. In that case, the rapid release of 12 mEq potassium will double the plasma concentration; a release of 20 mEq potassium will increase plasma potassium to more than 10 mEq/l. During resuscitation of a patient with cardiac arrest, cardiac output is perhaps 25% of normal. A continuing small amount of potassium release might be sufficient to sustain toxic hyperkalemia.

### Discussion

Receptor upregulation-related cardiac arrests totaled 72, with 8 deaths and a mortality rate of 11.1%. Rhabdomyolysis-related arrests totaled 57, with 17 deaths and a mortality rate of 29.8% (table 1). Statistical analysis is not valid because these cases are scattered over almost 50 yr and several countries, with considerable differences in monitoring and therapy related to time and locale. Furthermore, the data are incomplete because some articles were likely missed in the literature search, and some were never published. The apparent lower mortality in cardiac arrest related to receptor upregulation does not remove the contraindication to use of

succinylcholine.<sup>4</sup> In addition, the fact that no cardiac arrests occurred in a group of patients with receptor upregulation who had marked increases in plasma potassium concentration after succinylcholine does not condone its use.<sup>72</sup>

Duchenne and Becker dystrophy, featuring vulnerable muscle membranes and fragile patients, is the pathology underlying many of the patients with rhabdomyolysis reported in the literature. This X-linked disorder is a dystrophinopathy, described in depth in a monograph on skeletal muscle disorders.<sup>73</sup> Cardiac involvement in Becker dystrophy<sup>74</sup> may, in part, explain the numerically increased mortality rate (no statistics possible) compared with Duchenne dystrophy (table 1). The patients with Becker dystrophy were aged 3 months<sup>62</sup> and 5, 8, 50 and 11 yr.<sup>63</sup> Other myopathies, some without a specific diagnosis, also contribute to this collation (11 deaths in 30 patients; table 1) and underscore the need for caution in anesthesia of such patients. Some myopathies, *e.g.*, the myotonias, mandate avoidance of succinylcholine because of development of rigidity.<sup>75</sup>

Anesthesia for a patient with a known or suspected myopathy has a potential risk of rhabdomyolysis, and succinylcholine is contraindicated. Potent volatile agents may be briefly tolerated in myopathic patients, but it seems prudent to switch to intravenous agents and nitrous oxide (if desired) once an intravenous catheter is placed. Four cases (see Cases: Hyperkalemia with Anesthesia but without Succinylcholine) document serious complications from rhabdomyolysis in myopathic patients given volatile agents without use of succinylcholine.

One of these frightening complications occurred within 10 min of induction of anesthesia.<sup>16</sup> Although some might then totally avoid volatile agents, a serious complication in an isolated case should not dictate change in overall practice. There have been safe applications of volatile agents in myopathic patients: 43 patients with Duchenne dystrophy who received a total of 61 general anesthetics without evident problems included 37 who received halothane and 12 who received succinylcholine.<sup>76</sup> The judicious brief use of volatile agents in myopathic patients appears acceptable, but only with great caution and careful monitoring. Any change in vital signs should prompt investigation of urine color, electrolytes, and blood gas tensions.

In conclusion, the evidence supports the position that succinylcholine-induced hyperkalemia during rapid acute rhabdomyolysis is more likely to result in an unsuccessful resuscitation than is the potassium efflux resulting from upregulation of acetylcholine receptors.

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