Succinylcholine-induced Hyperkalemia:
Effects of Succinylcholine on Resting Potentials and Electrolyte Distributions in Normal and Denervated Muscle

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Ion distributions and resting potential changes in normal and denervated rat gastrocnemius muscle after administration of succinylcholine were compared. A marked increase in potassium concentration was found in blood returning from denervated muscle, compared with that from normal muscle. Sodium content of denervated muscle also increased much more than that of normal muscle. Baseline resting potentials were 80–90 mV in normal muscle and 60–70 mV in denervated muscle. This difference was due to a change in membrane ion permeability rather than to impairment of active sodium transport in denervated muscle. After administration of succinylcholine, normal and denervated muscles appeared to behave similarly in extent of depolarization, agreement between measured and calculated depolarization, and ability to exchange sodium for potassium. The abnormally large net ion transfer which follows application of succinylcholine to denervated muscle appears to be due to the increased area of succinylcholine-sensitive membrane in such muscle, rather than to denervation-induced impairment of active sodium transport. (Key words: Succinylcholine; Electrolytes; Hyperkalemia; Denervated muscle.)

Hyperkalemia sufficient to cause cardiac arrhythmias and ventricular fibrillation after intravenous administration of succinylcholine to patients with burns, massive trauma, and spinal cord transection has been reported.1-3 The syndrome has also been seen in patients who have multiple sclerosis and muscular dystrophy.4 It has been suggested that the increase in serum potassium arises from an increased sensitivity of the injured muscle fibers to succinylcholine,5 a condition paralleling the supersensitivity of denervated muscle to acetylcholine.6 Denervation, which itself can lead to succinylcholine hyperkalemia,6 is accompanied by other changes in skeletal muscle, in addition to the spread of acetylcholine sensitivity, most notably changes in resting-membrane permeability7 and in active ion transport across the cell membrane.8 The latter is of particular interest in view of the possibility that impairment of sodium extrusion (and thus of potassium re-uptake) may contribute to hyperkalemia.

The present experiments were designed to examine the role of denervation phenomena in succinylcholine-induced hyperkalemia, with particular reference to the part played by impairment of active transport.

Methods

Two experimental protocols were followed, one employing a single injection of succinylcholine, the other a slow continuous infusion. In this way the responses of normal and denervated muscle to both transient and sustained stimuli could be compared. Subjects of the experiments were male Sprague-Dawley rats, initial weights 300–350 g, four weeks after denervation of the left gastrocnemius muscle. Denervation was carried out using pentobarbital anesthesia by removal of a 1-cm segment of sciatic nerve through an incision in the posterior surface of the thigh. Aseptic technique and antibiotic protection were used. The gastrocnemius accounts for the bulk of the muscle mass denervated by this procedure; the normal gastrocnemius at sacrifice weighed approximately 1.5 g, the atrophic denervated muscle between 0.7 and 1.0 g. The period between denervation and further experimentation was set at four weeks, for two reasons. Clinically, it is well within the post-injury time span during which patients are
in danger of developing succinylcholine hyperkalemia. Experimentally, post-denervation muscle changes are at their maximum in three to four weeks.6,9

Pentobarbital anesthesia was used for all experiments. Sodium pentobarbital, 60 mg/kg, was administered intraperitoneally, the rats' tracheas were intubated, and the lungs were mechanically ventilated with the aid of a Harvard rodent respirator.

To compare the amounts of potassium released by normal and denervated muscle after succinylcholine, serum and muscle from normal and denervated limbs of four rats were analyzed for Na and K content. Each rat was given 0.2 ml sodium heparin, 1,000 units/ml, through a catheter in the left jugular vein. After a control blood sample had been taken from the right femoral vein, 1 mg succinylcholine was administered through the jugular catheter. Blood samples were obtained from both left and right femoral veins during the 5 minutes following succinylcholine injection. The gastrocnemius muscles were then removed, blotted, and weighed.

A separate series of experiments was designed to estimate the effect of potassium released by the denervated muscle on serum potassium levels in the total circulation. Four normal and four operated rats were prepared as above. A control blood sample was taken from the carotid artery of each rat, 1 mg succinylcholine was injected through the jugular catheter, and a second blood sample was taken from the carotid artery during the 2 minutes following succinylcholine injection.

The following procedure was used to follow the course of the gastrocnemius resting-potential depression and recovery after succinylcholine injection, and to determine muscle Na and K content after recovery of muscle resting potential to normal levels. Resting potentials of normal and denervated gastrocnemius muscle cells were sampled at 2-minute intervals following a 1-mg dose of succinylcholine administered as above. Potentials were measured by a method described previously.9 In most cases 10–20 potentials were averaged for each time interval. Standard deviations for the mean of ten cells were in the vicinity of 6 mV. Both normal and denervated muscles were removed for analysis as described above approximately 30 minutes after the injection, at a time when the resting potential had returned to pre-succinylcholine values.

Gastrocnemius resting potentials during succinylcholine infusion were measured in four normal and four denervated muscles. Control potentials were measured, and an infusion of saline-diluted succinylcholine (0.05 mg/ml infused at a rate of 0.2 ml/min) was begun through a catheter in the jugular vein. Resting potentials were measured at intervals from 0 to 30 minutes after the beginning of the infusion.

Na and K distributions during succinylcholine infusions were determined in a separate group of four normal and four operated rats. Each rat was nephrectomized, then received an injection of approximately 10 μg of Na₂³⁵SO₄ into the vena cava. After an equilibration time of two hours, the rats were heparinized and an infusion of saline-diluted succinylcholine (0.05 mg/ml at 0.2 ml/min through the jugular catheter) was begun. Blood was sampled from the aorta after 15–20 minutes of infusion, and normal and denervated gastrocnemius muscles were removed. Controls were four rats treated identically but given an infusion of saline solution. Previous experiments in this laboratory have shown that in normal nephrectomized rats sulfate space remains constant between one and a half and six hours after injection of Na₂³⁵SO₄. Calculations of muscle transcellular sulfate distribution indicate that the increase in intracellular SO₄³⁻ due to succinylcholine-induced depolarization is very small and results in no significant increase in the error of estimation of muscle extracellular space from sulfate space.

Serum and muscle Na and K were determined photometrically. Activity of serum and muscle samples was assayed by standard methods in a scintillation counter. Extracellular space was estimated by sulfate space and transcellular distributions of Na and K calculated with the assumptions outlined in a previous paper.9 For each variable, differences between experimental values and appropriate controls were evaluated using standard t tests. When possible, each rat served as his own control, and the results were analyzed by paired t tests; when this was not possible, as in the resting-potential measurements, groups of rats
TABLE 1. Extracellular and Intracellular Ion Concentrations Used in Calculating Resting Potential*

<table>
<thead>
<tr>
<th></th>
<th>[K]_s</th>
<th>[K]_i</th>
<th>[Na]_s</th>
<th>[Na]_i</th>
<th>Resting Potential (Calculated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal gastrocnemius</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>4.13</td>
<td>175.50</td>
<td>143.52</td>
<td>15.14</td>
<td>91.45</td>
</tr>
<tr>
<td>After 15 minutes of succinylcholine infusion</td>
<td>5.29</td>
<td>160.70</td>
<td>141.73</td>
<td>20.53</td>
<td>84.18</td>
</tr>
<tr>
<td>Denervated gastrocnemius</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>4.13</td>
<td>159.23</td>
<td>143.52</td>
<td>22.76</td>
<td>88.89</td>
</tr>
<tr>
<td>After 15 minutes of succinylcholine infusion</td>
<td>5.29</td>
<td>145.21</td>
<td>141.73</td>
<td>35.63</td>
<td>81.53</td>
</tr>
</tbody>
</table>

* Four rats were used, with one hind limb denervated in each. The values are those shown graphically at times zero and 15 minutes in figure 2. Electrolyte values are in mEq/l of water; resting potentials in mV. The identical extracellular electrolyte values for normal and denervated sides were determined on arterial samples from the dorsal aorta, on the assumption that the extracellular environment is most accurately represented as an ultrafiltrate of the arterial blood arriving at the muscle.

were compared and the differences analyzed by non-paired t tests.

Resting potentials were calculated from sodium and potassium distributions according to the equation

\[ V_m = \frac{RT}{F} \ln \left( \frac{[K]_o + b[Na]_o}{[K]_i + b[Na]_i} \right) \]

**Fig. 1.** Effects of a single intravenous injection of succinylcholine on serum and muscle electrolytes and resting potentials in normal and denervated muscle. ○, normal side; ●, denervated side. Values represent averages from four rats; brackets indicate ±SE. Muscle sodium and potassium values are in mEq/100 g fat-free dry solids (FFDS); serum potassium in mEq/l. There were no significant changes in muscle K following succinylcholine in either normal or denervated muscle. Muscle Na was significantly increased in denervated muscle 5 and 15 minutes after succinylcholine; in normal muscle the increase in Na was significant at 5 minutes but not at 15 minutes.
where $V_m$ is the potential across the cell membrane and $b$, the membrane sodium–potassium permeability ratio, is arbitrarily assigned a value of 0.01. The values for the ion concentrations are shown in figure 2 and listed in table 1.

**Results**

Administration of a bolus of succinylcholine led to a small, non-significant increase in potassium concentration in blood collected from the normal leg, and an increase from 3.88 to 7.48 mEq/l of serum potassium in femoral vein blood collected from the denervated side, a significant ($P < 0.05$) increase of 3.60 mEq/l (fig. 1a).

In blood collected from the carotid artery, succinylcholine produced no change in serum potassium concentration in normal rats (0.02 mEq/l average increase in serum K, not significant), but a significant ($P < 0.05$) increase of 0.45 mEq/l in rats with unilateral gastrocnemius muscle denervation.

Although resting potentials were considerably lower in denervated than in normal muscles, the magnitudes of depolarization induced by succinylcholine were approximately the same in both. The resting potentials recovered to pre-succinylcholine levels within half an hour in denervated muscle; in normal muscle recovery appeared to be incomplete at that time. There was no difference between maxi-
maximum resting-potential percentage changes in the two sides (fig. 1d). At the time of maximum depolarization after succinylcholine administration there was a slight increase in normal muscle-tissue sodium (Na/100 g fat-free dry solids; P < 0.05) and a large (P < 0.01) increase in the already-high sodium content of denervated muscle (fig. 1c). The tissue sodium in denervated muscle remained at this high level well beyond the half-hour period in which the resting potential had returned to its normal value (fig. 1c, d).

When succinylcholine was given by slow infusion, instead of as a single bolus, both normal and denervated muscle showed maximum depolarization within 5 minutes and then, while infusion continued, returned toward normal resting-potential levels (fig. 2d). Again, the denervated muscle gained more sodium than the normal muscle (fig. 2c).

The baseline resting potential of denervated gastrocnemius muscle was found to be 60–70 mV, compared with the 80–90 mV characteristic of normal muscle. The resting potential measured in denervated muscle is thus much lower than the value calculated from the ion distribution (fig. 2d), while in normal muscle measured and calculated potentials are in good agreement. The depolarization produced by succinylcholine infusion agreed with the calculated change in resting potential in both normal and denervated muscle.

Discussion

It is assumed that succinylcholine-induced hyperkalemia is the result of an excess loss of potassium from abnormal muscle, and that chronic denervation can produce muscle changes responsible for this phenomenon.3,4,6 Our results confirm this hypothesis. In rats with unilateral sciatic nerve section, a procedure which denervates a very small portion of the body muscle mass, succinylcholine was followed by a slight but significant hyperkalemia which was absent in control animals. Others have reported similar results in dogs after bilateral sciatic nerve section.6 Our experiments clearly show that the denervated muscle is the source of the excess serum potassium; serum potassium concentration in blood returning from denervated muscle was almost doubled following succinylcholine, while that from normal muscle showed no significant increase.

Possible explanations for the abnormally large loss of potassium from denervated muscle include: increased area of succinylcholine-sensitive membrane; larger than normal increase in sodium and potassium permeability; impairment of active sodium transport with consequent failure of potassium re-uptake immediately after succinylcholine challenge.

The present results suggest that impairment of active transport plays little part in the abnormal response of denervated muscle to succinylcholine. If it played an important role, one would expect denervated muscle to regain its pre-succinylcholine resting potential more slowly than normal muscle, and to retain an increased sodium content for a longer time. The time course of membrane repolarization, however, was at least as rapid in denervated as in normal muscle, and repolarization was obviously not dependent on restoration of pre-succinylcholine ion concentrations. Furthermore, although denervated muscle gained much more sodium than normal muscle, there were no clear-cut differences between normal and denervated muscle in times of retention of excess sodium after either transient or sustained succinylcholine stimulation. Differences in potassium loss and re-uptake could not be detected, probably because only a small percentage of the mass of intracellular potassium is involved in these exchanges.

The present data are not sufficient to distinguish between the alternative mechanisms of increased succinylcholine-induced permeability change and increased area of succinylcholine-sensitive membrane in denervated muscle, since conductance, the bioelectrical correlate of permeability, has a dimension of area (mhos/cm²). However, the similarities of normal and denervated muscle in the magnitudes of the depolarization induced by succinylcholine, and in the agreement between measured and calculated depolarization, are consistent with the hypothesis that denervated muscle responds to succinylcholine with an increase in ion permeability of the same magnitude as that in normal muscle but over a greater area. This difference corresponds to the well-established spread of acetylcholine sensitivity from its normally restricted sub-
junctional area to the entire surface of the chronically denervated muscle cell. Across this increased surface area more sodium may enter the cell, and more potassium be released to the extracellular compartment, than across the relatively small cholinceptive area of normal muscle.

A further implication of the present results is that the low baseline resting potentials of denervated muscle are not solely a function of the decrease in sodium pump activity, as suggested by some investigators, but require the postulation of a change in membrane permeability to account for the large discrepancy between measured and calculated resting potentials. This discrepancy indicates that the membrane sodium-potassium permeability ratio is greater in denervated than in normal muscle. An increase in membrane resistance, reported by others to follow denervation, suggests that the change consists of a decrease in potassium permeability rather than an increase in sodium permeability.

References

Metabolism

LIDOCAINE CONCENTRATIONS Continuous lumbar epidural anesthesia, utilizing 1 per cent lidocaine with epinephrine, 1:200,000, was administered to 22 patients in labor. Fifty to 60 mg lidocaine were injected every hour, with a maximum of seven injections (mean 4.2 injections). Larger doses of 100 to 120 mg, with epinephrine, were given for delivery. Blood concentrations were measured by gas chromatography. Samples were obtained from a maternal vein, from the fetal scalp 20 minutes after injection, and from clamped sections of the umbilical cord at delivery. At delivery mean blood concentrations of lidocaine were 0.84 mg/ml in the umbilical vein and 0.72 mg/ml in the umbilical artery. The mean maternal vein concentration throughout labor was 0.99 mg/ml, and for fetal scalp blood the mean was 0.43 mg/ml. Maternal and fetal concentrations increased as labor progressed. The mean maternal concentration (scalp) was 0.70 mg/ml after injection. Maternal concentrations were well below the reported toxic values of 5 to 30 mg/ml. Both intrauterine and umbilical concentrations were well below the reported toxic threshold of 3.0 mg/ml. (Fox, G. S., and others: Intrauterine Fetal Lidocaine Concentrations during Continuous Epidural Anesthesia, Am. J. Obstet. Gynec. 110:896, 1971.)