The Effect of Hypothermia on Adductor Pollicis Twitch Tension During Continuous Infusion of Vecuronium in Isoflurane-Anesthetized Humans

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The effect of total body cooling on force of contraction of the adductor pollicis was determined during a constant rate infusion of vecuronium. Anesthesia was induced with thiopental and maintained with isoflurane/nitrous oxide in eight volunteers (study group) and seven surgical patients (control group). After train-of-four (TOF) stimulation of the ulnar nerve, we measured the amplitude of the first response (T1) in the train and the ratio of the fourth-to-first response (TOF ratio). Vecuronium was then administered as an intravenous (IV) bolus, 25 μg·kg⁻¹·h⁻¹, followed by continuous IV infusion, 25 μg·kg⁻¹·h⁻¹; central body (core) temperature was maintained stable for 60 min, at the end of which T1 and TOF responses were constant. In the study group, core temperature was then reduced (using circulating-water blankets) by a mean of 2.6°C, decreasing the T1 and TOF ratio, respectively, by 19% and 18% per °C reduction in adductor pollicis temperature. Normothermia was maintained in the control group for a mean of 111 min, with no significant change in T1 and TOF responses. We conclude that, during a constant-rate infusion of vecuronium, the magnitude of neuromuscular block increases significantly when adductor pollicis temperature decreases secondary to core cooling.

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Intraoperative hypothermia significantly affects the neuromuscular function of the adductor pollicis muscle, independent of muscle paralysis (1–3). In the absence of neuromuscular blocking drugs, adductor pollicis twitch tension decreases 10%–15% per °C reduction in central body (core) temperature, when core temperature is less than 36°C (1,2). Clinically, this effect is important because perioperative administration of muscle relaxants typically is guided by adductor pollicis twitch response (4), and hypothermia can confound the interpretation of this response (5,6).

To quantify the clinically observed effects of hypothermia on the mechanical responses of the adductor pollicis muscle in the presence of neuromuscular block, we studied muscle response during hypothermia and normothermia in volunteers and surgical patients anesthetized with isoflurane and partially paralyzed by a continuous infusion of vecuronium.

Methods

With approval from our committee on human research and written informed consent, we studied eight healthy volunteers and seven surgical patients, ASA class I or II. Anesthesia was induced by sodium thiopental, 1–5 mg/kg, and the inhalation of nitrous oxide, 70%, and isoflurane, 4%–5%. In the volunteers, tracheal intubation was accomplished without the use of a muscle relaxant. In the surgical patients tracheal intubation was facilitated by succinylcholine, 1.0 mg/kg, to assist in expediting the anesthetic induction sequence, and because this dose of succinylcholine does not alter the subsequent neuromuscular response to a vecuronium infusion (7). Anesthesia was maintained with nitrous oxide, 60%–70%, and isoflurane, 0.9%–1.2%, in oxygen (end-tidal concentration as measured by mass spectrometry), supplemented by intravenous (IV) fentanyl as indicated. Mechanical ventilation was adjusted to maintain end-tidal %F<sub>CO</sub>2 between 30 and 35 mm Hg. Airway humidification was provided by a heat-and-moisture exchanging filter (Pall Biomedical Products, Glen Cove, NY). Routine vital function monitoring included pulse oximetry, electrocardiography, and non-invasive blood pressure determinations.

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Adductor pollicis temperature was measured continuously using a 22-gauge, 18-mm-long needle thermocouple (Mon-a-Therm®; Mallinckrodt, Anesthesia Products Inc., St. Louis, MO) inserted directly into the muscle, 1 cm proximal to the metacarpophalangeal joint of the thumb. Core temperature was measured continuously using an esophageal temperature probe (Mon-a-Therm®). Thenar skin, lower arm, and finger temperatures were measured using 1-cm diameter, self-sticking probes (Mon-a-Therm®).

Supramaximal, square-wave stimuli of 0.2 ms duration in a train-of-four (TOF) sequence (2 Hz) were applied every 12 s to the ulnar nerve at the wrist, and the evoked mechanical response of the adductor pollicis muscle (twist tension) was measured by a force-displacement transducer and displayed on a polygraph. The first response in each train (T1) and the ratio of the fourth to the first twist (TOF ratio) were recorded continuously. The control T1 was obtained immediately before administration of vecuronium.

In all subjects, at 30–45 min after induction of anesthesia, when isoflurane concentrations and adductor pollicis twist tensions were constant and unchanged, vecuronium, 25 µg/kg, was administered as an IV bolus, followed immediately by a constant infusion of 25 µg·kg⁻¹·h⁻¹. With this regimen, the twitch tension initially decreases, then recovers and settles at a stable level within 45 min (8). Blood samples were drawn approximately 60 min after the start of the vecuronium infusion, at which time the twitch tension was stable, and again at the completion of the study. Samples were heparinized, placed in ice, centrifuged, and acidified within 1 h. Vecuronium plasma concentrations were measured by capillary gas chromatography; this assay is specific for vecuronium parent compound, has a coefficient of variation of 4%–15%, and is linear over the range 5–5000 ng/mL (9).

The study was divided into two parts. First, the effect of progressively reducing core temperature on adductor pollicis response was studied in eight volunteers (study group). Anesthesia was induced and core temperature was maintained at >36.0°C using a Bair Hugger® forced-air warmer (Augustine Medical Inc., Eden Prairie, MN), while the adductor pollicis monitoring was established (10). End-tidal isoflurane concentration and adductor pollicis twitch tension were observed to be stable for 15 min, after which vecuronium was administered as previously described. Sixty minutes after the vecuronium infusion was started, (at which time twitch tension had been stable for approximately 15 min), hypothermia was induced using circulating water blankets (Blanketrol®; Cincinnati Sub Zero Products, Inc., Cincinnati, OH), and active cooling was continued until core temperature decreased to <34.5°C. The arm being studied was exposed to room air throughout the study. At the end of the study period, the vecuronium infusion was terminated, and the volunteers were rewarmed using forced air.

Adductor pollicis temperature and twitch tension were recorded from both hands in five of the eight volunteers to determine whether active local warming of the hand would influence twitch tension during hypothermia. Local warming was achieved by covering one arm with a Bair Hugger® warming unit (blowing air at 40°C) during the period of active cooling.

In the second part of the study, we excluded hypothermia as a variable, and investigated the effect of continued exposure to isoflurane on adductor pollicis twitch tension (11). Anesthesia was induced in seven surgical patients (control group) as described for the volunteers, but included administration of succinylcholine, 1.0 mg/kg IV, to facilitate tracheal intubation. When isoflurane concentrations and twitch tension were stable (30–45 min after induction of anesthesia), vecuronium was administered using the same bolus dose and infusion regimen as for volunteers. The vecuronium infusion was continued at a constant rate (25 µg·kg⁻¹·h⁻¹) until the end of the surgical procedure. Normothermia was actively maintained throughout the study using forced air warming with a Bair Hugger®.

Duration of vecuronium infusion in the two groups was compared using an unpaired t-test. Adductor pollicis twitch tension, core temperature, and vecuronium plasma concentration at the beginning and end of the study were compared using paired t-test. The relationships between temperatures per se (core, adductor pollicis muscle, and thenar skin), and between temperatures and twitch tension (T1 and TOF ratio) were derived using least-squares linear regression. Differences were considered significant at P < 0.05. Results are expressed as the mean ± SD (unless otherwise specified).

Results
The mean age of volunteers (3 females and 5 males) was 24 ± 3 yr (range = 21–29 yr) and mean weight, 76 ± 14 kg (range = 58–102 kg), compared with 43 ± 16 yr (19–61 yr) and 81 ± 14 kg (67–106 kg) in the control group (1 female and 6 males). The mean durations of vecuronium infusion (including the 60-min period until twitch tension stabilized) in the study group, 210 ± 45 (range 180–300 min), and in the control group, 171 ± 29 min (range 150–210 min), were not different.

Effects of Hypothermia
The core, adductor pollicis, and thenar skin temperatures, and T1 and TOF ratios decreased significantly during hypothermia (Table 1). The decrease in T1 and TOF ratios began immediately upon cooling. Before induction of hypothermia, temperature values for core,
Table 1. Changes in Temperature and Twitch Tension During Total Body Cooling

<table>
<thead>
<tr>
<th>Temperature site</th>
<th>Cold hand&lt;sup&gt;a&lt;/sup&gt; (n = 8)</th>
<th>Warm hand&lt;sup&gt;a&lt;/sup&gt; (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ&lt;sup&gt;b&lt;/sup&gt; temperature (°C)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Core</td>
<td>-2.6 ± 0.9</td>
<td>-2.5 ± 0.8</td>
</tr>
<tr>
<td>Adductor pollicis</td>
<td>-2.7 ± 0.7</td>
<td>-1.3 ± 0.9</td>
</tr>
<tr>
<td>Thenar skin</td>
<td>-3.0 ± 0.6</td>
<td>+2.0 ± 0.9</td>
</tr>
<tr>
<td>Δ T1/Δ temperature, (%/°C)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Core</td>
<td>19 ± 6</td>
<td>18 ± 7</td>
</tr>
<tr>
<td>Adductor pollicis</td>
<td>19 ± 6</td>
<td>NA</td>
</tr>
<tr>
<td>Thenar skin</td>
<td>17 ± 7</td>
<td>NA</td>
</tr>
<tr>
<td>Δ TOF ratio/Δ temperature (%/°C)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Core</td>
<td>18 ± 6</td>
<td>17 ± 8</td>
</tr>
<tr>
<td>Adductor pollicis</td>
<td>18 ± 6</td>
<td>NA</td>
</tr>
<tr>
<td>Thenar skin</td>
<td>16 ± 7</td>
<td>NA</td>
</tr>
</tbody>
</table>

<sup>a</sup> All volunteers had one arm that was uncovered and in which the temperatures were allowed to decrease with central temperature (cold hand). In five of these volunteers, the contralateral arm was warmed with forced air (warm hand).

<sup>b</sup> Δ refers to the change in the variable from the beginning until the end of the period that core temperature was decreasing.

adductor pollicis muscle, and thenar skin were 36.4 ± 0.2°C (range 36.0-36.7), 36.0 ± 0.2°C (range 35.8-36.5), and 34.3 ± 0.6°C (range 33.4-35.2), respectively; T1 and TOF ratios were 60% ± 14% (range = 47%-85%) and 33% ± 14% (range = 18%-55%) of baseline.

For volunteers as a group, there was a significant linear relationship between core and adductor pollicis muscle temperatures (core = 0.98 × [adductor pollicis] + 0.67, r = 0.97), and between adductor pollicis muscle and thenar skin temperatures (adductor pollicis = 0.86 × [thenar skin] + 3.00, r = 0.85). For each volunteer, there was a significant linear relationship between decrease in twitch tension (T1 and TOF ratio) and core (r values of 0.95-0.99), adductor pollicis muscle (r values of 0.95-0.99), and thenar skin (r values of 0.90-0.94) temperatures. The relationships of core temperature to T1 and to TOF responses for all volunteers are shown in Figures 1 and 2. The decrease in T1 and TOF ratio per °C reduction in adductor pollicis temperature was 19% ± 6% and 18% ± 6%, respectively (Table 1). Changes in T1 and temperature at the three sites over time in one volunteer are shown in Figure 3.

Local warming of one hand (n = 5 volunteers) prevented a decrease in the temperature of the thenar skin, and diminished the decrease in adductor pollicis muscle temperature during hypothermia (Table 1). However, warming did not alter the decrease in the T1 and TOF ratios per °C reduction in adductor pollicis temperature (Table 1).

Vecuronium plasma concentrations were measured in seven volunteers and increased significantly from 87 ± 29 ng/mL at the beginning of the cooling phase to 104 ± 40 ng/mL at the end (P < 0.05).

**Effect of Isoflurane**

Sixty minutes after the vecuronium infusion was started, adductor pollicis twitch tension was stable and unchanging in all patients. Thereafter, core, adductor pollicis, and thenar skin temperatures, adductor pollicis twitch tension, and vecuronium plasma concentrations did not change significantly during further continued exposure to isoflurane for 111 ± 29 min (range = 90-150 min) (Table 2, Figure 4).

**Discussion**

We found that as adductor pollicis muscle temperature decreased, vecuronium-induced neuromuscular block increased. That is, for each °C reduction in core temperature, adductor pollicis twitch tension decreased by a mean of 19%. This decrease in muscle twitch tension associated with hypothermia might be due to the direct effects of temperature temperature-induced c or pharmacodynamics study, we observed th
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Warm hand*  
(n = 5)  
-2.5 ± 0.8  
-1.3 ± 0.9  
+2.0 ± 0.9  
18 ± 7  
NA  
NA  
17 ± 8  
NA  
NA  

Figure 2. Relationship between core temperature and adductor pollicis train-of-four (TOF) ratio in eight volunteers undergoing active total body cooling during isoflurane anesthesia. After the start of cooling, there is a significant linear relationship between core temperature and TOF ratio \( r = 0.95-0.99 \) in each volunteer. The TOF response decreased 18% ± 6% (mean ± SE) per °C reduction in core temperature.

Figure 3. Changes in adductor pollicis twitch tension \( (T_1 = \text{amplitude of first response in train-of-four}) \) and core, adductor pollicis muscle, and thenar skin (skin) temperatures over time in one patient undergoing active total body cooling during isoflurane anesthesia. Neuromuscular block was produced by vecuronium, 25 \( \mu \)g/kg, intravenous bolus and constant-rate infusion, 25 \( \mu \)g/kg-h, started at time 0. There is a significant linear relationship between core and adductor pollicis muscle temperatures \( r = 0.99 \), and between adductor pollicis muscle and thenar skin temperatures \( r = 0.85 \). After the start of cooling, a significant linear relationship was found between adductor pollicis twitch tension and core or adductor pollicis temperatures \( r = 0.99 \) and 1.00, respectively. The \( T_1 \) response decreased 28% per °C reduction in both core and adductor pollicis muscle temperatures.

effects of temperature on the muscle (1, 2), and/or to temperature-induced changes in the pharmacokinetics or pharmacodynamics of vecuronium. In an earlier study, we observed that, in the absence of a muscle relaxant, adductor pollicis twitch tension decreases by 13% per °C decrease in core temperature (1). Because the magnitude of that effect is little different from the 19% per °C reduction that we observed in this study, it could be concluded that the present results are due to the same direct effects of hypothermia on the muscle that were observed in the previous study. However, we also observed that, during the period of cooling, the vecuronium plasma concentrations increased by approximately 20%, suggesting that a pharmacokinetic mechanism may be partially responsible for some of the observed decrease in twitch tension.

The increase in vecuronium concentration was apparently due to the decreasing core temperature, an explanation supported by our findings in the control group in which temperature was maintained constant and vecuronium concentrations did not change. For the plasma concentration of a drug to increase during a constant infusion, the drug's volume of distribution or clearance must decrease. For pancuronium, the central and steady-state volumes of distribution, but not clearance, significantly decrease in response to hypothermia to 34°C (12). In contrast, hypothermia to 34°C reduces the plasma clearance of d-tubocurarine without affecting the steady-state volume of distribution (13). Thus, the effect of hypothermia on pharmacokinetics is not the same for all muscle relaxants, and we cannot determine which pharmacokinetic changes most likely contributed to the increase in vecuronium plasma concentrations.

Hypothermia also may alter muscle pharmacodynamics (i.e., the sensitivity of muscle to vecuronium-induced block), but current data on such an effect is inconsistent. In cats, the sensitivity of the neuromuscular junction to pancuronium-induced block is increased by temperature reduction (12), but in humans, hypothermia is not associated with any change in neuromuscular junction sensitivity to the effects of d-tubocurarine (14). If, in our study, plasma vecuronium plasma concentrations had not increased as the core temperature decreased, we could have concluded that the reduction in adductor pollicis response may have been due to a hypothermia-induced increase in neuromuscular junction sensitivity. However, because vecuronium plasma concentrations increased during hypothermia, we cannot estimate the contribution of pharmacodynamic mechanisms to the decrease in adductor pollicis response.

We attempted to overcome the effects of core hypothermia on muscle twitch tension by applying heat locally to the skin over the adductor pollicis muscle. We found that the absolute decrease in twitch tension was unaffected by surface warming. This suggests that, in the situation of mild central hypothermia, muscle temperature is more influenced by core temperature than by local skin temperature (2), and/or that hypothermia...
Table 2. Variables in Patients Maintained Normothermic (n = 7)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>End of study period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (min)</td>
<td>60 (all patients)</td>
<td>171 ± 29 (150–210)</td>
</tr>
<tr>
<td>Core temperature (°C)</td>
<td>36.5 ± 0.7 (35.7–37.2)</td>
<td>36.7 ± 0.7 (35.8–37.8)</td>
</tr>
<tr>
<td>T1 twitch response (%)</td>
<td>67 ± 25 (23–97)</td>
<td>59 ± 27 (18–97)</td>
</tr>
<tr>
<td>Train-of-four ratio (%)</td>
<td>32 ± 25 (0–77)</td>
<td>27 ± 24 (0–77)</td>
</tr>
<tr>
<td>Concentration (ng/mL)</td>
<td>109 ± 36 (54–148)</td>
<td>104 ± 37 (48–155)</td>
</tr>
</tbody>
</table>

Results are mean ± so; range in parentheses.
Baseline = 60 min after start of vecuronium infusion; time = interval since start of vecuronium infusion; T1 = amplitude of first response in train-of-four at the time of the observation expressed as a percentage of the same response obtained before the administration of vecuronium; concentration = vecuronium plasma concentration.

Figure 4. Adductor pollicis twitch tensions (solid lines) and vecuronium plasma concentrations (dashed lines) in all seven patients (control group) at the beginning (Baseline) and end of the study period. Baseline was at 60 min after the start of the vecuronium infusion, when twitch tension had stabilized, and the end-point (End) was an average of 111 min (range 90–130 min) later. Twitch tensions are expressed as a percent of the control value (i.e., the twitch tension immediately preceding the start of the vecuronium infusion). Neither twitch tension nor vecuronium concentration changed significantly over the study period.

induces systemic, not local, changes that alter muscle twitch response. Accordingly, during studies of neuromuscular function alone, temperature must be carefully controlled; specifically, maintenance of core temperature is more important than attempting to maintain adductor pollicis temperature using only local surface warming.

A reduction in core temperature of 2.5°C, which commonly occurs during anesthesia and surgery, results in a 45%–50% increase in neuromuscular block induced by a constant-rate infusion of vecuronium. Therefore, during anesthesia-induced hypothermia, neuromuscular function should be monitored closely to determine whether, and when, the dosage of vecuronium should be reduced as temperature decreases.

We studied the effects of hypothermia on adductor pollicis response using anesthetized volunteers because the techniques of cooling and data collection were complex, time-consuming, and unachievable in surgical patients. However, to investigate the effect of continued exposure to isoflurane alone on adductor pollicis response, we chose to use surgical patients given the same constant-rate infusion of vecuronium as our volunteer group. Continued enflurane exposure increases d-tubocurarine-induced neuromuscular block (i.e., decreases muscle twitch tension), in a time-dependent manner (11). Therefore, we sought to determine whether isoflurane had a similar effect, as this would have confounded our analysis of the effect of hypothermia on muscle twitch tension. However, we found that neither adductor pollicis twitch tension nor vecuronium plasma concentration changed significantly in response to continued exposure to isoflurane. These data indicate that the neuromuscular effects observed in our hypothermic volunteers resulted from thermal perturbations, not to isoflurane anesthesia per se.

There are obvious differences (i.e., age, performance of a surgical procedure), between the patients (control) and volunteers (study group). However, these differences do not invalidate the control group, because the purpose of the control group was to eliminate duration of anesthesia and continued exposure to isoflurane as causes of decreased adductor pollicis twitch tension. Because adductor pollicis twitch tension and vecuronium plasma concentration did not change in the control group it is reasonable to conclude that the changes in these variables which we observed in the study group were secondary to hypothermia.

In summary, we found that the adductor pollicis twitch tension (T1 and TOF ratio) decreases approximately 20% per °C reduction in core temperature during a constant-rate infusion of vecuronium during isoflurane anesthesia. However, when core temperature is maintained normothermic, muscle twitch tension does not change. We postulate that temperature-induced alterations in the pharmacokinetics of vecuronium account, at least in part, for the effects of hypothermia on adductor pollicis twitch tension. Our findings reinforce the need for careful monitoring of neuromuscular function in clinical settings where hypothermia occurs.

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Inc. for donation of the thermocouples; Datex Medical Instrumentation Inc. for the loan of a Capnomac® anesthetic gas monitor; Becton Dickinson & Company for the loan of a Program 2 syringe pump; Hermes Systems Inc. for the loan of an Iddicare® automatic record-keeping system; Cincinnati Sub-Zero Inc. for the loan of a Blanketrol II circulating-water warmer; and Pall Biomedical Products Inc. for donating heat-and-moisture exchanging filters.

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