

Impact of Hypothermia on the Response to Neuromuscular Blocking Drugs

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Muscle strength is reduced during hypothermia, both in the presence and in the absence of neuromuscular blocking drugs. A 2°C reduction in body temperature may double the duration of neuromuscular blockade. Central body and muscle temperatures decline in parallel, as long as peripheral vasoconstriction does not occur. A reduction in muscle strength must be expected at a body temperature less than 36°C (corresponding to a muscle temperature of approximately 35°C). Local cooling of the hand may make adductor pollicis twitch tension monitoring less useful during clinical anesthesia. The efficacy of neostigmine is maintained during mild hypothermia. The use of a nerve stimulator is strongly recommended to monitor the effect of neuromuscular blocking drugs during intraoperative hypothermia.

INTRAOPERATIVE hypothermia due to decreased metabolic heat production, increased heat loss, and reduced compensatory responses is common.¹ A body temperature less than 35°C is frequently encountered.² The influence of temperature change on the effect of drugs used in anesthetic practice is clinically important. During the past 10-15 yr, several investigations have shown that changes in body temperature influence the effect of neuromuscular blocking drugs. Despite the introduction of nerve stimulators that monitor neuromuscular function during surgery, residual paralysis at the end of anesthesia still occurs not infrequently,³⁻⁶ and intraoperative hypothermia is a contributing factor to this adverse effect.⁷ The aim of this presentation is to review available literature regarding the influence of hypothermia on neuromuscular function in the presence and absence of muscle relaxants.

Temperature-Muscle Twitch Tension Relation in the Absence of Muscle Relaxants

In Vitro Studies

The Muscle Fiber. The maximum tension elicited in a muscle is dependent on the result of two opposing

processes, the internal shortening and relaxation of the contractile component.⁸⁻¹⁰ The rate of the chemical and enzymatic reactions fueling the process of shortening is reduced with decreasing temperature.^{11,12} The time provided for the actin and myosin filaments to be interdigitated (internal shortening) at lower temperatures is prolonged because of a higher temperature coefficient of the velocity of relaxation than that of muscle shortening. This has been demonstrated *in vitro*, using the frog sartorius muscle and rat diaphragm.⁸⁻¹⁰ Therefore, it is generally believed that the twitch response elicited upon direct muscle stimulation is increased at hypothermia.¹³

Neuromuscular Function. If the twitch tension is evoked indirectly by nerve stimulation, this basic change in contractility caused by cooling may be masked because of a temperature effect on nerve conduction and/or chemical and physiologic processes related to the neuromuscular junction. The velocity of nerve conduction in human volunteers is delayed approximately $2 \text{ m} \cdot \text{s}^{-1} \cdot ^\circ\text{C}^{-1}$ reduction in temperature in the temperature range 36°-26°C, but block of nerve impulses does not occur.¹⁴ The endplate membrane sensitivity to agonist drugs is significantly increased at 20°C compared with 37°C in a rat nerve-diaphragm preparation.¹⁵ Indirectly evoked release of transmitter from the readily available presynaptic store by nerve stimulation is a temperature-dependent process in the rat nerve-diaphragm preparation, with maximum transmitter output at approximately 20°-25°C, and decreasing output at either lower or higher temperatures.¹⁶ A similar biphasic pattern of spontaneous transmitter release is also observed in the same type of preparation. Numerous processes are involved when transmitter is released from the nerve terminal. The biphasic pattern is explained by the observation that these processes are influenced by temperature at a varying degree and at varying temperature levels. The maximum transmitter release at approximately 20°-25°C is related to a temperature-dependent rate of Ca removal from its intracellular active site.^{16,17} Consistent with these *in vitro* observations, the indirectly elicited muscle twitch response in the intact nerve-muscle preparation (rat diaphragm, avian biventer cervicis muscle) increased with hypothermia in the temperature range 37°C to 25°C.^{18,19} Unfortunately, data from human neu-

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romuscular junctions and nerve-muscle preparations are not available.

The resting membrane potential,^{20,21} endplate membrane threshold for initiation of a propagated action potential,^{14,22} endplate sensitivity to antagonists,²³ and acetyl cholinesterase activity^{15,18} are not significantly influenced by hypothermia.

In Vivo Animal Studies

The effect of hypothermia is mostly studied in cats. Dependent on muscle type, either an increase (2.5%/°C in flexor hallucis longus, a fast twitch muscle), or a decrease (2%/°C in soleus, a slow twitch muscle) has been recorded.²⁴ Even when studies are performed in the same muscle (tibialis anterior), results differ. Either a 5%/°C reduction,²⁵ unchanged,^{26,27} or a 6%/°C increase in twitch tension has been reported.²⁸ A study in dogs showed a 5% decrease in twitch tension/°C decrease in muscle temperature.²⁹ There are no obvious reasons for the described discrepancies from *in vivo* animal studies, because similar anesthetic regimens, cooling procedures, twitch tension monitoring, and modes of nerve stimulation were applied.

Human Studies

The results from human studies are consistent. The adductor pollicis twitch response is reduced when muscle temperature is decreased.³⁰⁻³⁷ This finding is independent of the cooling method (total body or local cooling), the anesthetic used (intravenous or inhalational), or the temperature range studied. A twitch response depression of 2-10%/°C reduction in muscle temperature has been reported.

Clinically, the most relevant temperature range is 34°-37°C, because central body temperature will normally stabilize within these limits during most surgical procedures. In a study of patients anesthetized with isoflurane-nitrous oxide, body temperature was decreased by total body cooling within this temperature range, whereas temperature and twitch response were re-

corded simultaneously and continuously from the adductor pollicis.³⁶ A close relation between central body and adductor pollicis temperatures was found, with a temperature difference of 0.5°-1.0°C between them (fig. 1). The adductor pollicis twitch tension decreases approximately 10%/°C reduction in central body or adductor pollicis muscle temperature (fig. 2). A temperature threshold was also determined (central body temperature 36°C, adductor pollicis 35.2°C), above which the adductor pollicis twitch tension remained stable despite decreasing temperature (fig. 2). In a control group of patients anesthetized for more than 3 h (central body temperature > 36.5°C), the twitch response did not change. The reason for the observed temperature threshold is unclear, but a gradual decrease of the safety margin (less available neurotransmitter) at the neuromuscular junction when the temperature is decreasing may be the mechanism.³⁸

Halogenated inhaled anesthetics influence neuromuscular transmission by reducing the acetylcholine receptor opening time.³⁹ Net charge transfer across the endplate membrane is reduced, which results in decreased endplate potential and impaired neuromuscular transmission. These effects will decrease the safety margin at the neuromuscular junction but will normally not be observed, unless combined with other factors that diminish neuromuscular function. This is consistent with the observation that the twitch tension does not change with time during isoflurane anesthesia in humans, as long as central body temperature is maintained constant.³⁶ Isoflurane reduces the margin of safety at the neuromuscular junction, and it may make the neuromuscular junction more susceptible to dysfunction when temperature decreases. The uptake of isoflurane in muscles may increase with hypothermia, because the solubility of isoflurane in blood increases approximately 5%/°C decrease in temperature.⁴⁰ It is necessary to separate the effect of temperature from that of isoflurane on neuromuscular function during mild hypothermia.

This can be achieved by studying the effect of hypo-

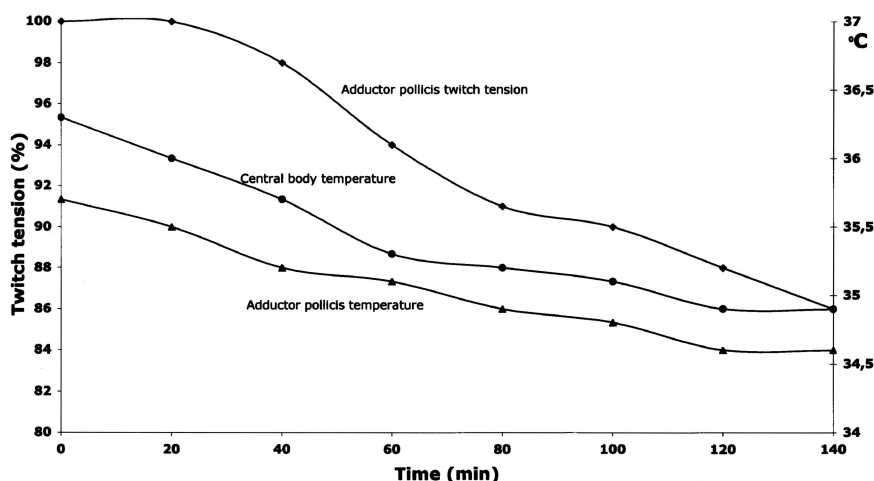


Fig. 1. Simultaneous recording of the changes in central body and adductor pollicis muscle temperatures, and adductor pollicis twitch tension during central body cooling of a patient anesthetized with nitrous oxide-isoflurane in the absence of neuromuscular blocking agents. From Heier *et al.*³⁶; used with permission.

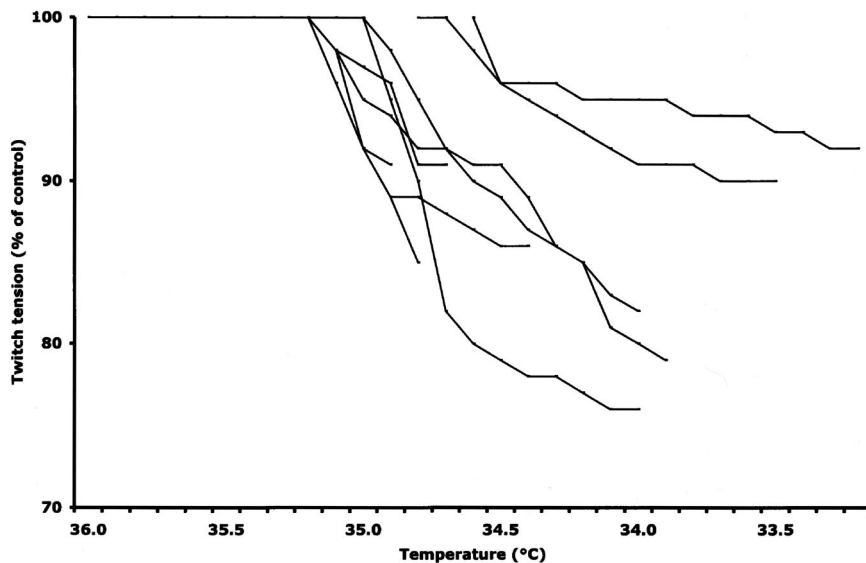


Fig. 2. Recording of the changes in adductor pollicis muscle temperature and twitch tension in 10 patients during nitrous oxide-isoflurane anesthesia in the absence of neuromuscular blocking drugs. A temperature threshold (35.2°C) was detected. From Heier T *et al.*³⁷; used with permission.

thermia on adductor pollicis twitch tension obtained in patients anesthetized with nitrous oxide-fentanyl anesthesia.³⁷ This latter technique of anesthesia has been shown to have minimal depressant effect on neuromuscular function.^{41,42} The decrease in the adductor pollicis twitch tension during mild hypothermia was similar during nitrous oxide-fentanyl (10% per °C) and nitrous oxide-isoflurane anesthesia,³⁷ which suggests that the hypothermic effect on twitch tension is mainly caused by the reduction in muscle temperature. However, a difference between groups may have been obscured by the small numbers of patients included and the large variability in response (5–20%/°C). A summary of the effects of hypothermia on muscle strength in the absence of neuromuscular blocking drugs is shown in table 1.

Influence of Hypothermia on the Action of Muscle Relaxants

The study of the effect of muscle relaxants during hypothermia is complex for two reasons: (1) The effect of hypothermia on the twitch tension itself (see previous section) must be separated from that on the action of the muscle relaxant. (2) Pharmacokinetic (what the body does to the muscle relaxant) and pharmacodynamic

(what the muscle relaxant does to the body) factors must be distinguished.

In Vitro Studies

In vitro studies have the advantage that the influence of pharmacokinetic factors is eliminated. The influence of temperature on the potency of muscle relaxants has been studied *in vitro*.^{18,20,22,23,43–47} Inconsistent results have been obtained, which may be explained by differences in experimental conditions. In some studies, the direct effect of temperature on the twitch response could not be differentiated from that on the action of the muscle relaxant, because cooling occurred in the presence of the drug being investigated.^{20,23} The temperatures at which experiments take place also differ to a great extent, and therefore, the biphasic pattern of transmitter release¹⁷ cannot adequately be accounted for. The results may be influenced by differing amounts of calcium and magnesium added to the organ bath.⁴⁸ The solubility of carbon dioxide increases during hypothermia, and the concomitant decrease in pH influences the potency of muscle relaxants.⁴⁹ Not all studies have compensated for this effect.⁵⁰

Recently, however, a few studies have been published that account for these confounders.^{45–47} The results from these studies are more consistent, showing a gradually increasing potency of pancuronium and vecuronium with decreasing temperature, whereas that of *d*-tubocurarine shows a biphasic pattern with peaks at 17° and 32°C, and troughs at 27° and 37°C. This biphasic pattern of *d*-tubocurarine effect was first demonstrated in 1951, when Holmes *et al.*⁴³ found that the dose of *d*-tubocurarine required to maintain a stable 50% block was greater at 26°C than at either higher or lower temperatures. It is not known what causes the potency difference of steroidal and isoquinolinium drugs at hypothermia, but the differing results between drug

Table 1. Effect of Hypothermia on Muscle Twitch Tension in the Absence of Neuromuscular Blocking Drugs

| | Effect on Twitch Response | References |
|-------------------------|---------------------------|------------|
| <i>In vitro</i> studies | Increased 4–5%/°C | 18,19 |
| Animal studies | Unchanged | 28,29 |
| | Increased 3–12%/°C | 24,29,30 |
| | Decreased 2–6%/°C | 25,26,31 |
| Human studies | Decreased 2–10%/°C | 32–39 |

groups suggest that the biphasic potency pattern of *d*-tubocurarine with temperature changes is not solely dependent on varying transmitter output from the nerve terminal.

A study using rat diaphragm suggests that the effect of hypothermia on the potency of muscle relaxants is accentuated in the presence of isoflurane, but the magnitude of this effect is higher at 37°C than at 27°C.⁴⁷

In Vivo Animal Studies

In 1958, Bigland *et al.*,²⁵ in both cats and dogs, showed a decreased effect of small bolus doses of *d*-tubocurarine administered intravenously or intraarterially in the femoral artery after the leg muscle temperature was reduced to 33°C to 26°C, compared with the contralateral leg, which was maintained at normal temperature. Because the central body temperature was maintained constant and the drug doses administered were small and of short duration, apparently pharmacokinetic factors did not confound the results. Reduced blood flow to the cold limb, implying that delivery of drug was reduced, could not explain the observation, because the opposite effect on muscle twitch response was found when suxamethonium or decamethonium was administered. Therefore, the observed effect of hypothermia on the twitch response was probable caused by pharmacodynamic factors. However, the reduced effect on the twitch response was reversed when a bigger dose of *d*-tubocurarine was administered.²⁵ This inconsistency may be explained by *in vitro* results showing that transmitter mobilization decreases with hypothermia.^{17,20} In addition, the prejunctional inhibition of acetylcholine release by *d*-tubocurarine may not be apparent at low concentrations of the drug.⁵¹ Consequently, a small dose of *d*-tubocurarine, which affects prejunctional acetylcholine receptors (and consequently transmitter mobilization) to a limited extent, may be antagonized by hypothermia because of increased release of transmitter from the readily available stores.¹⁷ A larger dose of drug will result in decreased twitch response, presumably because prejunctional acetylcholine receptors are influenced to a greater extent and for a longer time, thereby inhibiting transmitter mobilization.^{17,20} This may also explain the results obtained by Zink and Bose.¹⁸ They found a transient initial increase in twitch tension during hypothermia in the intact nerve-muscle preparation (avian biventer cervicis) partially blocked by *d*-tubocurarine. However, the effect was not sustained, and the degree of block increased over time to a level deeper than precooling.¹⁸ Therefore, these findings are not inconsistent with the *in vitro* results showing increased potency of muscle relaxants at temperatures less than 33°C.

The duration of action of muscle relaxants is significantly increased in cats during total body cooling, and the infusion rate needed to obtain a given degree of block decreased at a body temperature of 29°C compared with that at normothermia, for *d*-tubocurarine^{52,53} and pancuronium.^{26,27} Because the central body temperature is allowed to change

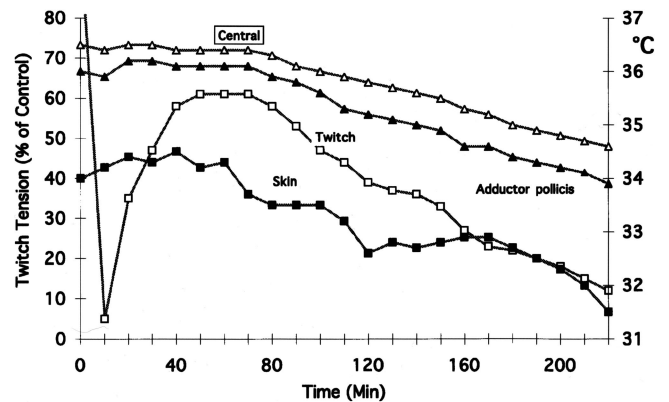


Fig. 3. Simultaneous recording of the changes in central body, adductor pollicis muscle and thenar skin temperatures, and adductor pollicis twitch tension during a constant-rate infusion of vecuronium in a patient anesthetized with nitrous oxide-isoflurane. Adductor pollicis twitch tension decreased 20%/°C reduction in central body and adductor pollicis temperatures. From Heier *et al.*⁵⁸; used with permission.

during this type of experiment, both pharmacokinetic and pharmacodynamic factors may be involved. However, *in vivo* animal studies are consistent, demonstrating that muscle relaxants have a prolonged duration of action at temperatures less than 30°C.

Human Studies

Human studies are consistent and show results similar to those obtained in animals. However, results of a study using the isolated forearm technique on awake humans suggest that the effect of hypothermia may be less on depolarizing than nondepolarizing block.⁵⁴

When the central body temperature is maintained constant, the recovery of neuromuscular block is significantly prolonged in an artificially cooled arm, as compared with a normothermic arm in the same individual.⁵⁵⁻⁵⁷ The duration of action of a vecuronium bolus dose of 0.05 mg/kg was 34 min in the cold arm (estimated muscle temperature < 32°C), as compared with 21 min in the contralateral normothermic arm.⁵⁶

In a study where the central body temperature was allowed to decrease gradually from 36.5°C to 34°C, the twitch response decreased 20%/°C reduction in muscle temperature during a constant infusion rate of vecuronium (fig. 3).⁵⁸ The plasma concentrations of vecuronium increased gradually with time, suggesting that pharmacokinetic factors were involved. In a control group of patients where the central body temperature was maintained above 36.5°C, the neuromuscular block and the plasma concentrations of vecuronium remained stable for the duration of a 3-h infusion.

A decrease in body temperature from 36.5°C to 34.4°C increased the duration of action of 0.1 mg/kg vecuronium (from injection to 10% recovery) from 28 to 62 min and the spontaneous recovery time (from 10% T1 recovery to train-of-four ratio = 75%) from 37 min to 80 min, respectively, in a group of oral surgery patients.⁵⁹ Similar

Table 2. Effect of Hypothermia on Duration and Effect of Neuromuscular Blocking Drugs

| | Effect on Neuromuscular Blocking | References |
|-------------------------|---|-------------|
| <i>In vitro</i> studies | IC ₅₀ increased 3–6%/°C (steroidal drugs); biphasic change with isoquinolinium drugs | 47–49 |
| Animal studies | Magnitude of twitch depression decreased 50% after administration of small <i>d</i> -tubocurarine boluses at 28°–31°C | 26 |
| | Duration of action increased 2–3 times after administration of clinical doses of all neuromuscular blocking drugs at 28°–30°C | 26–28,54,55 |
| Human studies | Duration of action and recovery times increased 60–100% at body temperature 34°–35°C (central cooling) | 60–63 |
| | Duration of action and recovery times increased 60–100% at peripheral skin temperature < 27°C (peripheral cooling) | 57 |
| | 40–80% decrease in infusion requirements during CPB | 64,65,68,69 |

CPB = cardiopulmonary bypass; IC₅₀ = drug concentration needed to depress twitch tension 50% of control.

findings have been reported for atracurium and rocuronium^{60,61}

Cardiopulmonary bypass frequently involves moderate to deep hypothermia (27°–32°C), and plasma volume and blood flow to kidney and liver may change significantly during the procedure. Despite markedly different physiologic circumstances, the influence of temperature on the action of muscle relaxants seems to follow the same pattern as in the absence of bypass with mild hypothermia. This is shown for *d*-tubocurarine,^{62,63} pancuronium,^{64–66} atracurium,^{67,68} and vecuronium.^{65,68} Changes in plasma protein binding capacity during cardiopulmonary bypass are not considered to influence the action of muscle relaxants significantly, because most of these drugs are less than 50% protein bound.^{69,70}

In summary, *in vivo* animal and human studies consistently show that the duration of action of muscle relaxants is significantly prolonged with hypothermia, even within the temperature range of 34°–37°C commonly encountered during routine surgery.

In humans, almost all information on the influence of hypothermia comes from studies where neuromuscular function has been recorded from the adductor pollicis muscle. The status of the adductor pollicis may not reflect that of the diaphragm or the laryngeal muscles. These airway muscles are much more resistant to the effect of muscle relaxants than the adductor pollicis.^{71,72} However, in a study on cardiac surgery patients, the electromyographic signal from the diaphragm was significantly reduced when body temperature was reduced 5°C.⁷³ No study has simultaneously compared the effect of hypothermia on different muscle groups.

A summary of the influence of hypothermia on the effects of neuromuscular blocking drugs is shown in table 2.

Influence of Hypothermia on the Pharmacokinetics and Pharmacodynamics of Muscle Relaxants

The reduced requirements for and increased duration of action of muscle relaxants at hypothermia may be

caused by changes in pharmacokinetics, pharmacodynamics, or both.

Pharmacokinetics

Hypothermia may influence the action of muscle relaxants by changing the distribution and/or the rate of metabolism and excretion of the drug. In the intact animal or in humans, reduced rate of elimination of the drug will result in a slower decline of the plasma concentration with time and, consequently, an increased amount of drug delivered to the neuromuscular junctions. This is shown to be the case for pancuronium and *d*-tubocurarine in cats, when the body temperature was decreased to below 30°C.^{27,52} The plasma clearance was 60% lower for both drugs at 29°C, compared with normothermia. This was associated with a 50% reduction in the cumulative combined renal and biliary excretion 8 h after drug administration.

In 1981, Ham *et al.*³⁵ studied the pharmacokinetics of *d*-tubocurarine at body temperatures of 35.8° and 31.9°C in neurosurgical patients. Despite markedly prolonged duration of action of the drug in some hypothermic patients, the pharmacokinetic variables did not differ between the groups. Differences may have been obscured by large variability of the results. The results are also difficult to interpret, because factors known to influence the neuromuscular transmission may have been involved. Several patients used drugs, *e.g.*, anticonvulsants, that influence neuromuscular transmission; the patients may have had neurologic diseases; and hyperventilation was sometimes used during the surgery.^{74–77}

In healthy human volunteers, Caldwell *et al.*⁷⁸ studied the pharmacokinetics of vecuronium and its metabolite 3-desacetylvecuronium over a range of temperatures (34°–37.5°C). Clearance of vecuronium decreased 10%/°C reduction in central body temperature, which may partly explain the increased duration of action observed in hypothermic patients (fig. 4).⁵⁹ Clearance of 3-desacetylvecuronium did not change with temperature.

A similar relationship between central body temperature and plasma clearance occurs with rocuronium.⁶¹

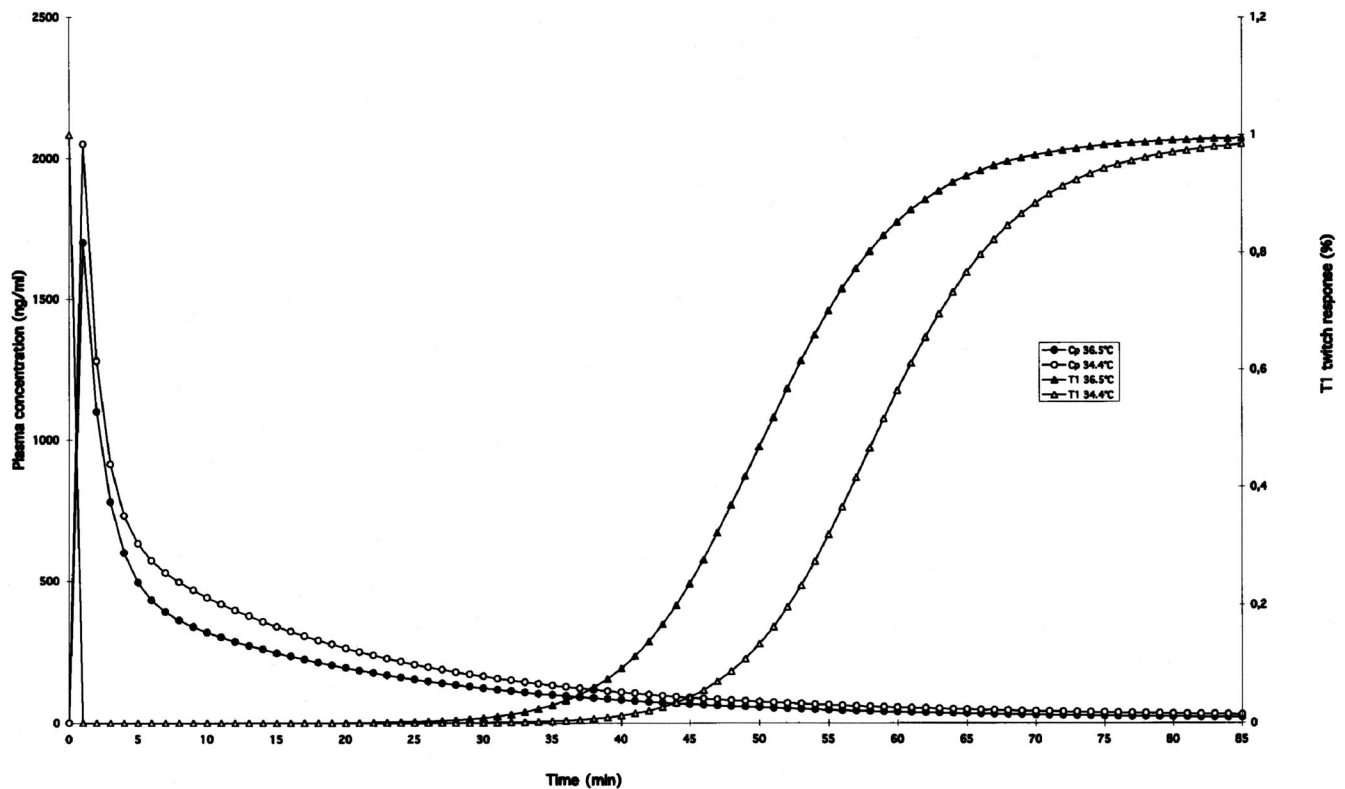


Fig. 4. Simulation of plasma concentration (C_p) and adductor pollicis twitch tension (T_1) after a bolus injection of vecuronium 0.1 mg/kg during isoflurane anesthesia in a 75-kg healthy volunteer. The figure shows the difference in effect of vecuronium when administered either at central body temperature 36.5°C or 34.4°C. The plasma concentration of vecuronium declines more slowly and the duration of vecuronium block is prolonged at 34.4°C. From Caldwell *et al.*⁷⁸; used with permission.

Pharmacodynamics

In vitro studies⁴⁵⁻⁴⁷ and local cooling experiments in humans at a constant body temperature⁵⁵⁻⁵⁷ suggest that the potency of muscle relaxants is significantly increased at muscle temperatures below 32°C. However, central body temperatures below 33°C are only rarely encountered during routine surgery. Therefore, the results from these studies may not be applicable to the typical clinical situation.

Pharmacodynamics describe the relation between drug concentration and effect, and therefore, $C_{p_{ss50}}$ (steady state drug concentration associated with 50% of maximum effect) can be used to define drug potency.⁷⁹⁻⁸² The $C_{p_{ss50}}$ can be estimated after injection of a bolus dose, despite not obtaining steady state conditions, by use of an integrated pharmacokinetic-pharmacodynamic model.⁸² With use of this model, the pharmacodynamics of vecuronium were determined in human volunteers in the temperature range 34°-37.5°C.^{78,83} In these studies where partial paralysis was obtained with vecuronium at varying but constant body temperatures, the effect of cooling on the muscle fiber itself was not a confounding factor, because the muscle strength recorded at the time of vecuronium injection was used as the control twitch tension. The $C_{p_{ss50}}$ (potency) of vecuronium did not change with temperature in either study. This finding was unexpected, because a temperature threshold (central body temperature 36°C) is ob-

served, below which the twitch response decreases with decreasing temperature in the absence of muscle relaxants.^{36,37} This temperature threshold suggests that a reduced safety margin exists at the neuromuscular junction with hypothermia, which should have become apparent during partial paralysis in the temperature range studied (34°-37.5°C). Therefore, the effect of temperature reduction on the muscle twitch response observed in the absence of muscle relaxants may be related to changes occurring in the contractile apparatus of the muscle, rather than at the neuromuscular junction. Alternatively, a combined effect of a reduction in potency and metabolism of vecuronium at hypothermia could explain why $C_{p_{ss50}}$ (potency) was similar at 34° and 37.5°C.^{78,83} This explanation is unlikely for two reasons. First, *in vitro* studies suggest increased potency of nondepolarizing steroidal drugs during hypothermia.^{45,46} Second, the duration of the experiments studying changes in $C_{p_{ss50}}$ (potency) with hypothermia was short,^{78,83} suggesting that the influence of temperature-related reduction in vecuronium metabolism was insignificant. Experimental studies suggest that hypothermia reduces the sensitivity of the myofilaments to Ca^{2+} , which may explain the altered contractility of cooled muscles.⁸⁴⁻⁸⁶ A change in the contractile apparatus during hypothermia may also explain the reduced dose requirements of vecuronium or atracurium to maintain the adductor pollicis twitch tension during local cooling of the ipsi-

lateral arm in the presence of stable body temperature.⁵⁵⁻⁵⁷ However, a temperature threshold ($< 34^{\circ}\text{C}$) below which the potency of muscle relaxants increases cannot be ruled out, because pharmacodynamic studies have not been performed at temperatures below 34°C in humans. Therefore, it may be concluded that at central body temperatures above 34°C , only pharmacokinetic factors seem to be involved when the duration of action of muscle relaxants increases with decreasing temperatures.

K_{e0} , the plasma-effect site equilibration rate constant, decreases with reduced central body temperature,⁷⁸ suggesting slightly delayed equilibration of drug between the circulation and the neuromuscular junction during hypothermia. The clinical implication is that the onset time of the muscle relaxant is delayed in hypothermic patients, and the recovery time may be slightly prolonged.

The function γ defines the steepness of the drug concentration-effect curve and is therefore a pharmacodynamic variable. During vecuronium block, γ increased $8\%/^{\circ}\text{C}$ reduction in central temperature.⁷⁸ If γ increases, the steepness of the concentration-effect curves increases, and the upper part of the curve shifts to the left. Therefore, the observed increase in γ provides a pharmacodynamic explanation why the plasma concentration needed to establish a steady state 95% vecuronium block is less at a central body temperature of 34.3°C than 36.8°C .⁷⁸

Hypothermia and Reversal of Neuromuscular Block

It has been reported that adequate reversal of vecuronium block (*i.e.*, train-of-four ratio $> 75\%$) can be significantly delayed by hypothermia (> 30 min), even when neostigmine is administered at 10% spontaneous recovery.⁵⁹ This could be caused by the prolonged duration of action of vecuronium at hypothermia, but also by a decreased efficacy of neostigmine when the central body temperature is reduced. The pharmacokinetics, efficacy, and duration of action of neostigmine have been studied in human volunteers during hypothermia.⁸⁷ The central volume of distribution of neostigmine decreased by 38% during hypothermia. The onset time of maximum effect increased (4.6 *vs.* 5.6 min), probably because of reduced muscle blood flow to hypothermic muscles. However, hypothermia did not change the clearance (696 ml/min), maximum effect, or duration of action of neostigmine. Consequently, it is likely that delayed reversal of neuromuscular block in hypothermic patients occurs because the plasma concentration of the neuromuscular blocking drug decreases more slowly during hypothermia.

Local Surface *versus* Total Body Cooling

The temperature of the adductor pollicis muscle, the muscle normally used for twitch response monitoring,

may be reduced either by local surface or central body cooling during clinical anesthesia. Local surface cooling of the adductor pollicis muscle occurs when the surrounding tissues are cooled by application of external cold, *i.e.*, by cold intravenous fluids or vasoconstriction in the skin of the hands. This may make twitch tension monitoring during clinical anesthesia less useful, because the response of the adductor pollicis to ulnar nerve stimulation may change without being accompanied by similar changes in other muscle groups. In contrast, during central body cooling, the adductor pollicis muscle temperature is reduced by the cooled blood perfusing the muscle, which will reduce the temperature of all muscle groups to a similar extent. Therefore, during central body cooling, changes in the adductor pollicis twitch response probably reflect the status of other muscle groups in the body.

In humans, the effect of local cooling on the adductor pollicis twitch response has been studied in the absence^{30,33,37} and presence^{55-57,88} of a neuromuscular blocking drug. The results are consistent, showing a 2-4% decrease in twitch response/ $^{\circ}\text{C}$ reduction in muscle temperature in the absence and approximately 5%/ $^{\circ}\text{C}$ in the presence of neuromuscular blocking drugs. Because the twitch response decreased 10%/ $^{\circ}\text{C}$ in the absence^{36,37} and 20%/ $^{\circ}\text{C}$ in the presence⁵⁸ of a neuromuscular blocking drug during central body cooling, the two ways of cooling seem to affect the adductor pollicis twitch response to a different extent.

This discrepancy may be explained by how the temperature of the adductor pollicis is measured. When a needle thermocouple is inserted in the adductor pollicis muscle, it penetrates only the superficial part of the muscle.^{37,89} The thermocouple cannot reach the deeper segment of the muscle. During total body cooling, the entire adductor pollicis muscle is perfused by cooled blood, and the temperature is uniform throughout the muscle. Therefore, during total body cooling, the temperature recorded with the needle thermocouple in the superficial part of muscle will be the same as that in the deeper part.

In contrast, during local surface cooling, the effect of the applied cold is counteracted by the warmer blood perfusing the muscle. Therefore, there exists a significant temperature gradient between the skin and the adductor pollicis muscle,³⁷ which is the deepest muscle in the thenar eminence, largely covered by other muscles in this region.⁸⁹ Therefore, during local surface cooling, the deeper parts of the muscle are likely to remain warmer than the superficial portion into which the thermocouple is inserted. Consequently, the measured adductor pollicis temperatures recorded in the local cooling experiments reflect the skin rather than the average muscle temperature. It is reasonable to assume that the effect of hypothermia on the adductor pollicis twitch response would be similar during local and cen-

tral body cooling, if the temperature in the deep part of the muscle could be measured.

The skin temperature of the hands gradually approaches room temperature during thermoregulatory peripheral vasoconstriction.^{37,78,90-92} If the patient cools spontaneously, central body temperature does not change after vasoconstriction has occurred. The effect of vasoconstriction on the adductor pollicis twitch response is apparently time dependent.⁸⁸ The adductor pollicis twitch response did not change during the first 2 h of vasoconstriction but then gradually decreased approximately 10% over the next 2 h.

Although local cooling may cause a reduction of the muscle twitch response, the clinical significance of this finding is not obvious. In all but one investigation,⁸⁸ local cooling has been achieved by artificial external application of intense cold. It is unlikely that intense local cooling of the adductor pollicis muscle occurs clinically, even when rapid infusions of cold fluids are running through veins in the dorsum of the hand. Therefore, the results from these local cooling experiments may not be clinically applicable. Furthermore, studies suggest that the adductor pollicis muscle temperature is determined by central body/blood temperature during anesthesia, not by local changes in skin temperature. The adductor pollicis muscle temperature does not change, even when the arms are exposed to room air temperature, as long as the central body temperature does not change.^{36,37,58}

When the central body temperature declines spontaneously, there is a close relation between central body and adductor pollicis temperatures but not between adductor pollicis muscle and skin temperatures.³⁶ The importance of the central body temperature as the determinant of the adductor pollicis muscle temperature was further emphasized in a human study where the temperature reduction of the adductor pollicis muscle during central body cooling was counteracted by application of external heat to the hand (a forced-air warmer blowing air of 40°C). The contralateral hand was used for comparison and was exposed to room air temperature.⁵⁸ The application of local heat increased the skin temperature more than 5°C compared with the cold hand but did not influence adductor pollicis muscle temperature significantly, as illustrated by the fact that the reduction in twitch response secondary to central body cooling was similar in both hands.

Peripheral vasoconstriction has the potential of influencing the muscle twitch response.⁸⁸ However, if adequate anesthesia is administered, thermoregulatory vasoconstriction will not occur until central body temperature is 34°–34.5°C.^{37,78,90-92} Therefore, peripheral vasoconstriction will only rarely contribute to the reduction of the adductor pollicis twitch response that may occur during clinical anesthesia.

It must be concluded that the influence of local cooling on the adductor pollicis twitch response during

clinical anesthesia is insignificant. The adductor pollicis muscle temperature is determined by the blood temperature, and consequently, the effect of cooling on the muscle twitch response can be judged by the changes in central body temperature.

Further, based on the above observations, in human studies of neuromuscular function, we would suggest that normothermia of the adductor pollicis is better obtained by maintaining central temperature than by attempting local warming of the hand or arm.

Electromyographic Recording of Neuromuscular Transmission during Hypothermia

Electromyography monitors the muscle action potentials from a large number of cells in the vicinity of a suitable recording electrode and is therefore described as a compound action potential.⁹³ Both T1 response and train-of-four ratio can be recorded in this way. Clinically, electromyography is most often recorded from the hypothenar region of the hand, in response to supramaximal ulnar nerve stimulation at the wrist. Electromyographic monitoring does not require immobilization of the arm or a force-displacement transducer, in contrast to twitch tension monitoring (mechanomyography), and is therefore suitable in the clinical situation.

Mechanomyography obtained from the adductor pollicis frequently shows significantly more pronounced paralysis than the simultaneously recorded electromyography from the hypothenar region.⁹⁴ During a nondepolarizing block when mechanomyography and electromyography are recorded from the same muscle (adductor pollicis) simultaneously and a resting tension is applied, the difference in measurements diminishes greatly and becomes clinically insignificant.⁹⁵

The evoked electromyography response during hypothermia has been studied only a few times. In the absence of a muscle relaxant, Engbæk *et al.*²⁸ observed in cats an inverse linear relation between the tibialis anterior muscle temperature and electromyographic amplitude. Electromyographic amplitude increased by 2%/°C decrease in temperature during central body cooling when the muscle temperature decreased from 36.6°C to 28.8°C. Simultaneously, the mechanical twitch response increased by 6%/°C decrease in temperature. Similar electromyographic findings (3.6%/°C) were reported by Ricker *et al.*³⁰ during local cooling of the adductor pollicis muscle in awake humans from 36°C to 18°C, but in this study, the mechanical twitch response decreased with hypothermia (3%/°C). In contrast, in awake humans, Bigland-Ritchie *et al.*³¹ observed a decrease of both electromyographic amplitude (4%/°C) and the twitch tension (8%/°C) of the first dorsal interosseous muscle when muscle temperature was decreased by

local cooling from 30°C to 25°C. A reduced electromyographic amplitude was also reported by Young *et al.*⁵⁵ upon artificial local cooling of the hand in neurosurgical patients. Buzello *et al.*³⁴ reported either a small increase or unchanged electromyographic amplitudes, and a decrease in the twitch tension (2%/°C), in patients anesthetized without use of muscle relaxants during cardiopulmonary bypass surgery when the body temperature was reduced from 35°C to 26°C.

Buzello *et al.*⁶⁵ monitored neuromuscular transmission using electromyographic amplitude and the mechanical twitch response simultaneously in patients undergoing hypothermic cardiopulmonary bypass. A constant-rate infusion with alcuronium, *d*-tubocurarine, pancuronium, or vecuronium was started before cooling and stopped after rewarming was completed. In patients paralyzed with alcuronium, *d*-tubocurarine, or pancuronium, electromyographic amplitude increased 40–60% during hypothermic cardiopulmonary bypass, while the adductor pollicis twitch response did not change significantly. In contrast, during vecuronium infusion, both electromyographic amplitudes and twitch tension decreased significantly (20–30%). The effects on electromyographic amplitude and the twitch tension normalized upon rewarming.⁷³

Because these studies show conflicting results, it is not possible to conclude that information obtained by electromyography and mechanomyographic monitoring can be used interchangeably to assess the neuromuscular function during hypothermia.

Conclusions and Clinical Implications

During clinical anesthesia and in the temperature range of 34°–37°C, the adductor pollicis muscle temperature is primarily determined by the temperature of the blood perfusing the muscle (central temperature) and insignificantly influenced by surface cooling effects (*i.e.*, peripheral vasoconstriction). The muscle twitch response will therefore mainly be influenced by central body cooling. The muscle temperature can be estimated by recording central body temperature, because the difference between the two is 0.5°–1.0°C.

In the absence of muscle relaxants, the adductor pollicis twitch response decreases approximately 10%/°C reduction in central body temperature below 36°C. The twitch response decreases approximately 20%/°C in the presence of a vecuronium-induced block. Patients who need complete restoration of muscle strength postoperatively should have their ventilation assisted until central body temperature is greater than 36°C.

The duration of action (time until T1 response recovery = 10%) and recovery time (time until train-of-four ratio = 75%) of muscle relaxants are significantly increased by hypothermia during anesthesia, mainly be-

cause of reduced elimination rate. Duration of action may increase as much as 100% when the central body temperature is reduced by as little as 2°C. Peripheral nerve stimulation and conservative dosing is therefore mandatory in hypothermic patients to prevent the administration of an overdose of muscle relaxants.

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