Localized hypothermia influences assessment of recovery from vecuronium neuromuscular blockade

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The purpose of this study was to determine the extent to which localized hypothermia of a monitored extremity alters the assessment of recovery from vecuronium-induced neuromuscular blockade. Bilateral integrated evoked electromyographic (IEMG) responses were measured in the ulnar distribution of 14 anaesthetized patients who had differing upper extremity temperatures as measured at the adductor pollicis to determine whether localized hypothermia alters the clinical assessment of spontaneous recovery from vecuronium-induced neuromuscular blockade. All patients received general anaesthesia with thiopentone, N₂O/O₂ and opioid; 11/14 patients received isoflurane for blood pressure control. Bilateral adductor pollicis, oesophageal and ambient temperatures, and IEMG evoked response (t_1) expressed as percent unparalyzed control were recorded during the anaesthetic. The difference in evoked response between the warmer and the colder upper extremity was calculated at 25%, 50% and 75% spontaneous recovery from neuromuscular blockade in the warm extremity. Differences in temperature between extremities ranged from 0.2–11° C. The difference in IEMG-evoked response between extremities was proportional to the difference in temperature, and there was a direct correlation ($r = 0.78$) between IEMG response and extremity temperature; IEMG response was absent when extremity temper-

ature was less than 25° C. We concluded that localized hypothermia in the monitored extremity decreases the IEMG-evoked response to vecuronium neuromuscular blockade; the greater the temperature decrease, the less the evoked response. Thus, the administration of nondepolarizing relaxants may be inappropriately influenced by monitoring neuromuscular blockade in a cold extremity, especially if its temperature is <25° C.

Cette étude vise à déterminer jusqu'à quel point l'hypothermie locale mesurée sur une extrémité modifie l'évaluation au moniteur de la récupération du bloc neuromusculaire induit par le vécuronium. La réponse électromyographique intégrée (EIMG) bilatérale est mesurée dans la distribution cubitale chez 14 patients anesthésiés qui présentent des températures différentes au membre supérieur mesurées à l'adducteur du pouce pour déterminer si l'hypothermie locale modifie l'évaluation de la récupération spontanée du bloc neuromusculaire produit par le vécuronium. Tous les patients sont anesthésiés au thiopentone, N₂O/O₂ et morphiniques, 11 patients sur 14 recevant de l'isoflurane pour contrôler la pression artérielle. La température de l'adducteur du pouce mesurée bilatéralement, la température oesophagienne et ambiante, et la réponse évoquée à l'EIMG (t_1) exprimée en pourcentage de la température de l'extrémité d'un contrôle non paralysé sont enregistrés pendant l'anesthésie. La différence de réponse évoquée entre l'extrémité chaude et l'extrémité froide est calculée à 25%, 50% et 75% de la récupération spontanée de l'extrémité chaude. La différence entre les extrémités varie entre 0,2 et 11° C. La différence de la réponse évoquée à l'EIMG entre les extrémités est proportionnelle à la différence de température, et on trouve une corrélation directe ($r = 0,78$) entre la réponse à l'EIMG et la température de l'extrémité; la réponse à l'EIMG est absente quand la température de l'extrémité est inférieure à 25° C. Nous en concluons que l'hypothermie de l'extrémité monitorée diminue la réponse évoquée du bloc neuromusculaire provoqué par le vécuronium; plus la baisse de température est importante, moindre est la réponse évoquée. Ainsi, l'administration de myorelaxants non dépolarisants peut être influencée faussement par le monitoring du bloc neuromusculaire d'une extrémité froide, surtout si la température est plus basse que 25° C.

Key words

MEASUREMENT TECHNIQUES: neuromuscular blockade;
MONITORING: neuromuscular function;
NEUROMUSCULAR RELAXANTS: vecuronium;
TEMPERATURE: cooling, hypothermia.

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Depression of the evoked response to nondepolarizing neuromuscular blockade during hypothermia has been demonstrated in animals and in patients subjected to mild to moderate generalized hypothermia.¹⁻⁶ Our clinical observations suggested that in patients receiving vecuronium for maintenance of muscle relaxation, the magnitude of the neuromuscular-evoked response in an exposed cold extremity was smaller than that observed in the extremity that was kept warm. Hypothermia of an exposed monitored body part in an otherwise normothermic patient is not uncommon in the operating room, thus the effect of low temperature in the monitored extremity may alter the management of neuromuscular blockade. The purpose of this study was to measure and compare integrated evoked electromyographic (IEMG) responses between upper extremities of differing temperatures in patients receiving vecuronium to determine the extent to which localized hypothermia alters the assessment of recovery from neuromuscular blockade.

Methods

After receiving approval from the institution's Committee on Studies Involving Human Beings, we studied 14 ASA physical status I-III neurosurgical patients, aged 20-65 yr, with non-lateralizing neurological examination scheduled for elective craniotomy or laminectomy. The arm into which the intravenous catheter was inserted was maintained warm, and intravenous fluids were warmed to body temperature with a blood warmer. The blood pressure cuff was also placed on the warm arm. The skin over the ulnar aspect of each arm was prepared with isopropyl alcohol, and surface electrodes (3M Red Dot) were placed at least 15 min before IEMG data collection to maximize conductance. Temperature was measured with surface thermistors applied over the adductor pollicis in each hand and shielded from ambient thermal effects with YSI 4009 heat-reflecting shields (Yellow Springs Instrument).

Anaesthesia was induced with thiopentone, 70% N₂O in 30% O₂, intravenous or intratracheal lidocaine, fentanyl 5-7 µg · kg⁻¹ or meperidine 1-3 mg · kg⁻¹. Supramaximal train-of-four (0.5 Hz) stimuli of 0.1 msec duration were delivered to the ulnar nerve at the wrist of both arms during induction and at 20 sec intervals thereafter for the remainder of surgery. The signal was generated and the evoked responses processed by Datex NMT 221 (Puritan-Bennett) IEMG monitors, one attached to each arm. The IEMG activity was measured over the ulnar distribution of each hand. Evoked response (*t*₁) was expressed as a percent of unparalyzed control-evoked response.

After control IEMG data were obtained, vecuronium was administered for muscle relaxation in a bolus of

0.05-0.08 mg · kg⁻¹, followed by an infusion adjusted to keep the evoked response of the warmer arm at 10% of unparalyzed control. Isoflurane was administered (0.1-0.6% inspired) in 11 patients as needed for control of blood pressure. The contralateral arm was deliberately cooled to a surface temperature no lower than 22°C by exposure to ambient temperature or by combinations of ice and air convection. Direct contact of ice and skin covering the ulnar nerve was avoided. Bilateral adductor pollicis, oesophageal and ambient temperatures, as well as the evoked response in each arm, were recorded throughout surgery.

The evoked response (*t*₁) in the warm extremity was measured in each patient at 25%, 50% and 75% spontaneous recovery. Simultaneously, the *t*₁ was measured in the cold extremity, then the difference in spontaneous recovery between cold and warm extremity was calculated for each patient. Analysis of these differences was made using the Mann-Whitney U test, rank sum difference in temperature versus evoked twitch height and linear regression analysis. Absolute temperature in each extremity was also compared at each recovery point, with the cold extremity evoked response expressed as a percentage of the warm extremity evoked response for each patient. This relationship was correlated with absolute cold extremity temperature. A *P* value of < 0.05 was used as a criterion of statistical significance.

Results

Mean oesophageal temperature for all patients studied was 35.8 ± 0.62°C. Mean warm arm temperature was 32.9 ± 1.3°C (SD), and cold arm temperature as measured at the adductor pollicis ranged between 22 and 33.5°C. Mean ambient temperature was 21.8 ± 0.9°C.

The evoked response (*t*₁) at 25%, 50% and 75% spontaneous recovery from neuromuscular blockade as well as the temperature difference between extremities for each patient are presented in the Table. The difference in temperature between the upper extremities of each patient ranged from 0.2-11°C, and the difference in *t*₁ increased with decreasing cold extremity temperature. Figure 1 shows the magnitude of the evoked response in the cold extremity as a percentage of the measured response in the warm extremity during recovery. Each data point represents the average *t*_{1,cold}/*t*_{1,warm} of an individual ± SD, since the values were similar at each of the measured recovery points. Linear regression analysis at 25%, 50% and 75% spontaneous recovery also showed a positive correlation between cold extremity temperature and the magnitude of the IEMG response (*r* = 0.78). All patients with cold extremity temperatures < 25°C showed no clinical evidence of spontaneous recovery in the cold arm despite steady recovery in the warm extremity. The

TABLE Comparison of evoked response at 25%, 50% & 75% recovery from neuromuscular blockade

Patient	t_1 -warm 25%	t_1 -cold 25%	t_1 -warm 50%	t_1 -cold 50%	t_1 -warm 75%	t_1 -cold 75%	$T_{\text{warm}} - T_{\text{cold}} (^{\circ}\text{C})$
1	25	12.5	50	37.5	75	50	2.00
2	25	0	50	0	75	0	8.00
3	25	6.25	50	10	75	25	7.00
4	25	6.25	50	18.5	75	25	6.50
5	25	25	50	50	75	75	3.00
6	25	6.25	50	25	75	50	4.00
7	25	8	50	18.5	75	37.5	4.00
8*	25	0	50	0	75	5	10.00
9	25	12.5	50	33	75	65	8.50
10	25	0	50	0	75	0	6.50
11	25	12.5	50	18	75	30	2.20
12*	25	0	50	0	75	0	11.00
13*	25	18	50	30	75	50	0.20
14	25	12.5	50	37.5	75	62.5	2.00

Unit values for evoked response (t_1) are measured height.

*Patients who received isoflurane.

FIGURE 1 Relationship between cold arm temperature ($^{\circ}\text{C}$) and the magnitude of its IEMG evoked response, expressed as a percentage of the warm arm evoked response ($t_{1\text{cold}}/t_{1\text{warm}}$); t_1 values and cold extremity temperatures are the averages $\pm$ SD of the measurements at 25%, 50% and 75% spontaneous recovery from neuromuscular blockade for each patient. Dotted lines represent 95% confidence intervals; $r = 0.78$.

evoked responses in the 11 patients who received isoflurane in addition to $\text{N}_2\text{O}/\text{O}_2$, narcotic and relaxant were similar to the three patients who did not. The correlation between increased disparity in cold and warm extremity t_1 and increased temperature difference is also demonstrated in Figure 2 ($r = 0.71$).

Figure 3 illustrates IEMG recordings from two patients, one in whom the extremity temperatures were 35.1 and 33.0 $^{\circ}\text{C}$ ($\Delta T_{\text{temp}} = 2.1^{\circ}\text{C}$), and the other in whom the temperatures were 29.6 and 23.0 $^{\circ}\text{C}$ ($\Delta T_{\text{temp}} = 6.6^{\circ}\text{C}$). Differences in the magnitude of the t_1 to neuromuscular blockade were directly related to extremity

FIGURE 2 Average $t_{1\text{cold}}/t_{1\text{warm}}$ $\pm$ SD (at 25%, 50% and 75% spontaneous recovery) for each patient as a function of increasing difference in temperature between extremities. Dotted lines represent 95% confidence intervals; $r = 0.71$.

temperature. The rate of spontaneous recovery of observed t_1 was similar in the extremities of patients with a small temperature difference; disparity in rate of recovery between extremities increased as difference in temperature increased. The decrease in measured t_1 paralleled the decrease in extremity temperature.

Discussion

Our findings demonstrate a temperature-dependent decrease in evoked response to vecuronium included neuromuscular blockade if the monitored extremity is cold. Hypothermia in the absence of muscle relaxants has been demonstrated to affect nerve conduction as well as motor

FIGURE 3 Differences in IEMG recordings during spontaneous recovery from neuromuscular blockade in (a) a patient with arm temperatures of 35.1°C (top) and 33.0°C (bottom) ($\Delta T = 2.1^\circ\text{C}$), and (b) a patient with arm temperatures of 29.6°C (top) and 23.0°C (bottom) ($\Delta T = 6.6^\circ\text{C}$). Dashed lines represent 25%, 50% and 75% recovery points.

response to neural stimulation through various mechanisms. Lowering temperature from 39°C to 27°C decreased the rate of acetylcholine hydrolysis to 83% of control in an *in vitro* model.⁷ Decreases in temperature decrease the speed of neural conduction, as shown in human studies of peroneal motor nerve conduction velocity, where a decrease in muscle temperature from 35 to 23.5°C resulted in a 50% reduction in nerve conduction velocity.⁸ Effects on the motor response to electrical stimulation may involve slowing of impulse propagation over muscle fibre or a direct effect on muscle fibre membranes.⁹ While localized cooling of an extremity in animal models and unanaesthetized humans increases muscle action potentials, decreased muscle contractility also occurs, presumably due to the effect of low temperature on the contractile apparatus.^{10,11} Peripheral cooling to 27–32°C in anaesthetized humans produces a linear relationship between skin temperature, twitch tension and train-of-four measurements.¹²

A number of studies have reported augmentation or prolongation of nondepolarizing neuromuscular blockade with hypothermia using a variety of agents.^{1–6} Studies of cardiopulmonary bypass-induced hypothermia reported attenuation of neuromuscular blockade with alcuronium, d-tubocurarine and pacuronium and enhancement of blockade with atracurium and vecuronium.^{13,14} Differences in response to measurement

of neuromuscular blockade proportional to temperature differences between extremities in patients receiving atracurium have also been described.¹⁵ An apparent “recurarisation,” or decreased response to integrated electromyogram stimulation, has been observed in patients following hypothermic cardiopulmonary bypass, which was presumably due to the decrease in extremity temperature as the core and peripheral temperatures equilibrated after discontinuation of rewarming.¹⁶

Several mechanisms have been proposed for both potentiation and antagonism, including changes in biliary and renal excretion, changing drug volumes of distribution, altered local diffusion receptor affinity, changes in pH at the neuromuscular junction,¹⁷ and the net effect of cooling on the various components of neuromuscular transmission.^{3,5,7,10,18–20} Whether the increase in neuromuscular blockade in the presence of both hypothermia and nondepolarizing muscle relaxants is additive or due to hypothermia alone remains to be determined.

Another potential mechanism for apparent delayed recovery from neuromuscular blockade in a cold monitored extremity is the alteration of the pharmacodynamics of muscle relaxants due to vasoconstriction and local haemodynamic changes. Localized hypothermia of the monitored extremity may affect the distribution of blood flow such that elimination of the muscle relaxant is delayed. However, determination of the possible influence of this phenomenon was beyond the scope of this clinical investigation.

We did not detect a difference in recovery from neuromuscular blockade between the 11 patients who received isoflurane and the three patients who did not. However, the number of patients studied is too small to test this observation statistically. Isoflurane has been reported to prolong recovery from vecuronium blockade when given in inspired concentrations greater than 0.9%.¹⁹ Other investigators have shown no effect of isoflurane on the duration of and recovery from neuromuscular blockade when the inspired concentration was 0.5%,²¹ findings similar to ours.

The effect of temperature on skin impedance has been suggested as a causal factor in “apparent” neuromuscular blockade when surface electrodes are used.^{16,22} In our investigation, skin electrodes were applied at least 15 min before control IEMG data were obtained and the arms were carefully wrapped and immobilized to permit satisfactory electrical contact and IEMG signal. These manoeuvres stabilize baseline measurements and decrease motion artifact.²³

Evaluation of the relationship between measurements of muscle and skin temperatures has yielded conflicting results. Heier *et al.* concluded that skin temperature measurements do not reliably predict the temperature of the

adductor pollicis, based on measurements of skin temperature using a 1-cm diameter self-sticking probe.²⁴ Muravchick *et al.* found very close agreement between thumb or forearm muscle temperature and thenar skin temperature using a thermistor needle and flat thermistor probe, respectively.²⁵ Eriksson *et al.* found a close agreement between skin and muscle temperatures in anaesthetized humans in a skin temperature range of 32–27°C.¹⁴ Smith also found agreement between subcutaneous and intramuscular temperature measurement.²⁶ We used shielded thermistor probes for measurement of skin temperature like those used by Muravchick.²⁵ Perhaps the discrepancy in the findings of these investigators results from different techniques for temperature measurement.

Measurements of IEMG have been demonstrated to correlate with mechanical measurements of nondepolarizing blockade during normothermia.²⁷ However, mechanical measurements may lag behind IEMG during recovery.²⁸ Mechanical recovery of neuromuscular blockade may be prolonged by hypothermia while electrical recovery is not, thus neuromuscular transmission *per se* would not be affected.⁶ We have demonstrated that assessment of neuromuscular transmission as measured by IEMG is affected in extremities with temperatures <31°C.

Our goal was to duplicate conditions found in the clinical environment with cool operating rooms, exposed extremities and air currents. Placement of a small fan directing air flow over the arm effectively lowered its temperature. Active or passive cooling has been demonstrated to produce comparable decreases in twitch tension.²⁴

The mechanical response of the adductor pollicis muscle to ulnar nerve stimulation has been shown to be unaffected by temperature when the adductor pollicis temperature is maintained greater than 35.2°C in unparalyzed patients.²⁴ However, maintenance of body temperature at this level may be difficult at times and undesirable in those instances where mild hypothermia may be preferable.^{29,30}

In summary, this study demonstrates that localized hypothermia in the monitored extremity can influence the assessment of recovery from vecuronium-induced neuromuscular blockade. This has important clinical implications, insofar as the patient's level of neuromuscular blockade is usually monitored in an exposed, accessible arm which may be significantly colder than the rest of the body. Specifically, if administration or reversal of nondepolarizing relaxants is based on monitoring in a cold extremity, (1) an inadequate degree of neuromuscular blockade may exist, and (2) patients may be presumed (incorrectly) not to be "ready" for reversal of neuromuscular blockade. Monitoring of neuromuscular blockade

in an arm <25°C may result in the inability to obtain any evoked response.

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