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Hypothermic Cardiopulmonary Bypass and Neuromuscular Blockade by Pancuronium and Vecuronium

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In patients undergoing coronary artery bypass grafting, vecuronium has fewer cardiovascular effects than pancuronium.[1] Yet, the impact of hypothermic cardiopulmonary bypass on the neuromuscular blocking effect of vecuronium has not been investigated. We therefore compared the response of pancuronium- and vecuronium-induced neuromuscular blockades during hypothermic cardiopulmonary bypass.

MATERIALS AND METHODS

Twenty patients, ASA classes III and IV, undergoing open heart surgery under nitrous oxide–narcotic anesthesia gave informed consent to participate in this study. They were assigned randomly to receive either pancuronium or vecuronium. Patients with evidence of neuromuscular, kidney, or liver disease or under medication known to affect neuromuscular transmission were excluded from the study. All patients received triflupromazine 0.15 $mg \cdot kg^{-1}$, meperidine 0.7 $mg \cdot kg^{-1}$, and atropine 0.007 $mg \cdot kg^{-1}$ im 45 min before induction of anesthesia, which was with triflunitrazepam 1–2 mg and fentanyl 0.5–1.0 mg iv. After topical application of local anesthesia, the trachea was intubated without the aid of a muscle relaxant. Anesthesia was maintained with 50% nitrous oxide in oxygen, fentanyl 0.01–0.02 $mg \cdot kg^{-1} \cdot h^{-1}$ and controlled ventilation. Monitoring included continuous intraarterial and central venous blood pressure, arterial blood gas analysis every 15 min, and serum electrolytes before induction of anesthesia, after cessation of bypass, and at the end of surgery. Temperature was monitored by a nasopharyngeal, rectal, and skin probe at the right thenar. The pump was primed with lactated Ringer's solution 500 ml, oxypolygelatin 500 ml, and heparinized blood 500 ml. The pump rate was 55 $ml \cdot kg^{-1} \cdot h^{-1}$ (table 1). Neuromuscular transmission was monitored with the evoked compound electromyogram (EMG) of the right thenar in response to supramaximal trains of four stimuli every 15 s (pulse width 0.1 ms) delivered to the ulnar nerve at the wrist. The EMG action potentials were measured from peak to peak, and their changes were related to nasopharyngeal temperature. The electromyograph used in this study was a modification of a device described by Lee *et al.*[2]

After obtaining a stable baseline and after at least 30 min following induction of anesthesia, Group 1 received 0.075 $mg \cdot kg^{-1}$ of pancuronium and Group 2 received the same dose of vecuronium. Maintenance doses of 0.015 $mg \cdot kg^{-1}$ of either drug were injected into an internal jugular catheter, whenever the size of the EMG action potentials had recovered 25% of control. No antagonists to neuromuscular blockade were administered. The time from end of injection of the loading and the maintenance doses to recovery of 25% of control neuromuscular transmission are referred to as DUR_L25 and DUR_M25, respectively. All numbers are expressed as means and standard deviations. Student's t test was used to assess statistical significance.

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TABLE 1. Cardiopulmonary Bypass (CPB) Data ($\bar{X} \pm SD$)

	Group 1 Pancuronium (n = 10)	Group 2 Vecuronium (n = 10)
Injection of loading dose of muscle relaxant to start CPB (min)	87 ±30	71 ±27
Start CPB to minimum temperature (min)	18 ± 5	18 ± 6
Minimum temperature (°C)	26.4 ± 1	26.1 ± 1
Duration of hypothermic CPB < 34° C (min)	72 ±18	62 ±16
Duration of normothermic CPB > 34° C (min)	32 ±14	26 ±10
Total duration of CPB (min)	107 ±24	93 ±25
End CPB to end surgery (min)	91 ±27	86 ±23
Rewarming period to 34° C (min)	20 ± 7	15 ± 8

RESULTS

Both groups of patients were comparable with respect to age, body weight, and surgical procedures (Group 1: 53 ± 9 years, 82 ± 12 kg, eight coronary bypass graftings, one aortic valve replacement, one aortic and mitral valve replacement; Group 2: 52 ± 12 years, 63 ± 22 kg, six coronary bypass graftings, four aortic valve replacements). After injection of the loading doses of pancuronium and vecuronium, the amplitudes of the EMG action potentials decreased to 13 ± 6% and 10 ± 6% of control, respectively. The corresponding figures related to the maintenance doses were 11 ± 4% and 12 ± 6% of control. Both differences were not significant. The data of cardiopulmonary bypass are listed in table 1. Before the institution of cardiopulmonary bypass, the loading and maintenance doses of pancuronium acted 1.8 and 2.5 times longer, respectively, than those of vecuronium (DUR_L25 and DUR_M25; table 2, figs. 1 and 2). During hypothermic bypass, the DUR_M25 of pancuroniun and vecuronium increased 1.8- and 5-fold, respectively. Thus, during hypothermic bypass, there was do difference between the duration of action of pancuronium and vecuronium. If, after the administration of the last prebypass maintenance dose, cooling was initiated before recovery of 25% of control neuromuscular transmission, the DUR_M25 was prolonged up to 50 min with pancuronium (n = 3) and up to 25 min with vecuronium (n = 3) as compared with an average of 26 and 12 min, respectively, in the absence of cardiopulmonary bypass. In all patients the prolonged duration of neuromuscular blockade was attenuated by rewarming, and recovery of neuromuscular transmission was accelerated as soon as nasopharyngeal temperature exceeded 30° C. Rectal and thenar skin temperature were still decreasing at this stage of the procedure and, as opposed to nasopharyngeal temperature, did not show any parallelism to the modifications of neuromuscular transmission. During normothermic perfusion the average duration of action of pancuronium was still 1.5 times longer than before bypass, and no further change occurred after the cessation of bypass. However, due to the small number of observations, these figures could not be evaluated statistically. During normothermic perfusion, the mean DUR_M25 of vecuronium was more than 50% shorter than during hypothermia but still 1.7 times longer than before bypass (table 2, fig. 2). At the end of surgery, eight patients of the pancuronium group and five patients of the vecuronium group failed to recover at least 75% of control neuromuscular transmission. In the remaining patients the average recovery time from pancuronium and vecuronium was 1.9 and 3.6 times as long, respectively, as before bypass.

DISCUSSION

Earlier studies performed both in animals and humans during surface-induced hypothermia with *d*-tubocurarine[3-5] and recently *in vitro* with *d*-tubocurarine, metocurine, gallamine, and pancuronium[6] indicated that hypothermia attenuates a nondepolarizing neuromuscular blockade except the one from pancuronium. Studies with cardiopulmonary bypass–induced hypothermia[7-9] yielded essentially the same results, although, besides hypothermia, cardiopulmonary bypass is associated with other factors that are likely to alter neuromuscular

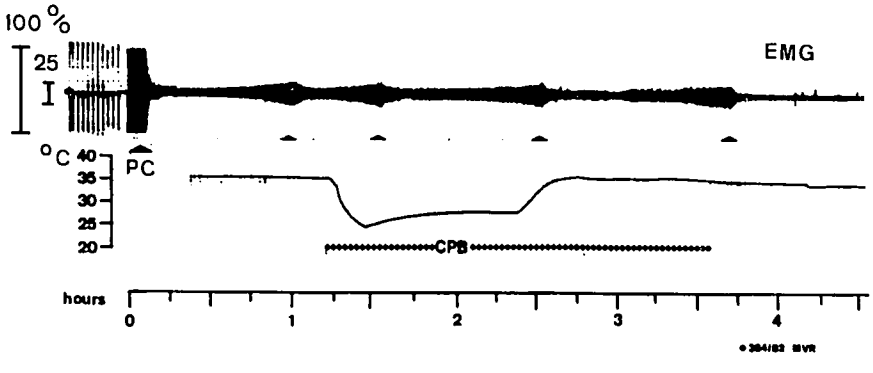

FIG. 1. The impact of hypothermic cardiopulmonary bypass on the duration of pancuronium (PC) neuromuscular blockade. Upper trace: evoked compound EMG of the right thenar. Lower trace: nasopharyngeal temperature. Diamond line (CPB): duration of cardiopulmonary bypass. Large arrow (PC): iv injection of 0.075 $mg \cdot kg^{-1}$ pancuronium. Small arrows: iv injection of 0.015 $mg \cdot kg^{-1}$ pancuronium when EMG amplitudes had recovered to 25% of control.

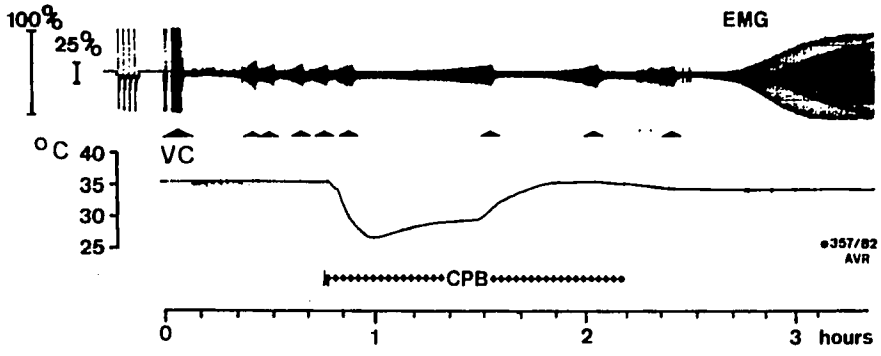

FIG. 2. The impact of hypothermic cardiopulmonary bypass on the duration of vecuronium (VC) neuromuscular blockade. Upper trace: evoked compound EMG of the right thenar. Lower trace: nasopharyngeal temperature. Diamond line (CPB): duration of cardiopulmonary bypass. Large arrow (VC): iv injection of 0.075 mg·kg^{-1} pancuronium. Small arrows: iv injection of 0.015 mg·kg^{-1} vecuronium when EMG amplitudes had recovered 25% of control.

blockade such as hemodilution and electrolyte imbalance. Conversely, Park and MacNamara[10] reported that the blockade of *d*-tubocurarine and pancuronium were attenuated only transiently by hypothermic cardiopulmonary bypass but ultimately augmented by continued hypothermia.

We also found that hypothermic cardiopulmonary bypass prolonged the duration of neuromuscular blockade from equipotent doses of both pancuronium and vecuronium. This effect was reversed partially by rewarming, and no significant change ensued during normothermic perfusion or after cessation of bypass. The prolongation of pancuronium and vecuronium neuromuscular blockade has thus to be attributed to hypothermia rather than to other factors of cardiopulmonary bypass. In addition, in the present study, the large proportion of patients having failed to recover 75% of control neuromuscular transmission at the end of surgery and the extraordinarily long recovery time in the remaining patients reflect a major impairment of neuromuscular transmission outlasting the duration of cardiopulmonary bypass for a considerable length of time.

The mechanism increasing the duration of neuromuscular blockade during hypothermia is still subject to debate. Flynn *et al.*[11] reported that 43% less atracurium had to be infused during, than before, hypothermic cardiopulmonary bypass to maintain a 90 to 95% depression of twitch tension. They explained the increased potency of atracurium during hypothermia by a reduced rate of Hofmann elimination, which is believed to control the duration of action of this muscle relaxant.[12] Yet, neither has the importance of Hofmann elimination been documented in humans, nor do pancuronium and vecuronium undergo metabolic degradation in a clinically significant extent.[13–15] Compromised plasma clearance during hypothermic bypass as a source of increased neuromuscular blocking potency of pancuronium was excluded by d'Hollander *et al.*[16] Using a demand infusion during cardiopulmonary bypass, these authors found that the pancuronium requirement for stable 90% depression of twitch tension decreased during hypothermia, although the mean plasma concentration was only 73% of the prebypass level. We therefore conclude that hypothermia increases the effect of muscle relaxants at the level of the neuromuscular junction rather than at the level of drug disposition or degradation. This view is supported by the above mentioned *in vitro* experiments[6] and by the findings of Miller *et al.*,[17] who found an increased sensitivity of the neuromuscular junction to pancuronium in cats secondary to surface cooling. Also, in these animals, the duration of pancuronium's blockade was 2.5 to 3 times longer at 29° C than under normothermic conditions. Further information on the impact of hypothermia on neuromuscular blockade might be expected from correlating the duration of neuromuscular blockade (DUR_M25) with body temperature. However, this procedure could not be performed with the data of the present study, because, relative to the DUR_M25 values, cooling and rewarming of the patients occurred

TABLE 2. Time Variables ($\bar{X}$ ± SD in Minutes) of Neuromuscular Blockade Before, During, and after Cardiopulmonary Bypass (CPB)

	Group 1 Pancuronium (10 patients)	Group 2 Vecuronium (10 patients)
DUR_I25	42 ± 19 (n = 10)*	23 ± 7 (n = 10)
DUR_M25 before CPB	26 ± 9 (n = 17)*	12 ± 4 (n = 35)
DUR_M25 during hypothermic CPB (<34° C)	* 51 ± 22 (n = 11)	* 47 ± 20 (n = 10)
DUR_M25 normothermic CPB (>35° C)	39 ± 23 (n = 3)	* 20 ± 8 (n = 10)
DUR_M25 after CPB	42 (n = 2)	29 ± 10 (n = 15)
Recovery time (25–75%)	50 (n = 2)	43 ± 53 (n = 5)

Time of onset = time from end of injection to maximum block; DUR_I25 and DUR_M25 = duration of action of loading and maintenance doses, respectively, from end of injection to recovery of 25% of control neuromuscular transmission (overall values); recovery time (25–75%) = time from recovery of 25–75% of control size of evoked EMG action potential. n = number of doses.

* $P < 0.0005$.

too fast and because the range of minimum temperature was too narrow.

For the use of pancuronium and vecuronium in open heart surgery we conclude that hypothermic cardiopulmonary bypass augments the duration of action of both muscle relaxants. During hypothermic bypass, vecuronium is no longer a shorter-acting agent than pancuronium. The effect of hypothermia is reversed partially by rewarming. With both muscle relaxants, compromised recovery of neuromuscular transmission may even outlast the duration of cardiopulmonary bypass, resulting in significantly prolonged muscle weakness. By the end of surgery, total recovery is more likely to occur from vecuronium than from pancuronium neuromuscular blockade. However, since prophylactic controlled ventilation is part of the routine management in most cardiac surgery centers, this difference is not a major clinical importance.

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