

## How rational is muscle relaxation during cardiac surgery ?

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**Abstract :** The incidence of postoperative residual curarisation after a neuromuscular blocking drug infusion is important. The greater risk for postoperative residual curarisation than with a single bolus can only be tackled by neuromuscular transmission monitoring, and selectively antagonising the block. Such monitoring is seldom used in cardiac surgery. If the neuromuscular block is not monitored intraoperatively in patients who receive a continuous infusion of a neuromuscular blocking drug, adequate sedation should be provided until proper recovery of neuromuscular function, which can take multiple hours. Therefore, we should avoid administering large doses of neuromuscular blocking drugs, even in the context of planned postoperative ventilation. One single bolus of neuromuscular blocking drug, given at induction to facilitate intubation, should provide, first of all, a rapid free airway, which is often compromised after opioid induction in cardiac surgery. For these purposes, rocuronium is particularly indicated. Moreover, by only administering a single neuromuscular blocking drug bolus at induction, postoperative residual curarisation can be avoided, becoming more and more important in fast tracking. Finally, in patients undergoing cardiac surgery, cost-effective combinations of drugs and techniques need to be used that provide adequate anaesthesia and analgesia, as well as appropriate muscle relaxation, while offering ideal operative conditions with minimal risk of myocardial ischaemia and residual curarisation. Therefore the continuous administration of neuromuscular blocking drugs, during cardiac surgery, seems unnecessary.

**Key words :** Anaesthesia, general ; thoracic surgery ; neuromuscular blocking agents, competitive.

### WHY DO WE USE NEUROMUSCULAR BLOCKING DRUGS IN CARDIAC SURGERY ?

Without any doubt *facilitation of intubation* by means of neuromuscular blocking drugs (NMBDs) attributes to a smooth induction of anaesthesia which is of utmost importance in cardiac anaesthesia. Moreover, NMBDs are the sole drugs which can adequately *counter opioid-induced rigidity*, an issue often encountered during opioid induction in cardiac anaesthesia. Opioid-induced rigidity often makes bag-mask ventilation difficult or impossible

during induction of anaesthesia. Difficult ventilation may result from chest wall rigidity, upper airway closure, or both. In a study from Bennett in 1997, 30 patients, undergoing elective cardiac surgery, received anaesthesia induction with 3 µg/kg sufentanil administered during a period of 2 min. Pancuronium (0.1 mg/kg) provided muscle relaxation. Twenty-eight of 30 patients exhibited decreased pulmonary compliance and closed vocal cords after opioid induction. Both subjective and objective compliances increased from severely compromised values after narcotic-induced anaesthesia to normal values after patients received the NMBD. Photo scores documented open cords before induction, progressing to closed cords after the opioid, and opening again after a NMBD was administered. Closure of vocal cords seemed the major cause of difficult ventilation after opioid-induced anaesthesia (3). Bypassing these structures with an endotracheal tube overcomes the usual decreased ventilatory compliance. Particularly in the condition of opioid-induced rigidity, rapid airway control is mandatory ; therefore, rocuronium – with its fast onset – is particularly indicated.

NMBDs can probably *aid mechanical ventilation, as well as avoid patient movement*. This, however, means that the anaesthetic (hypnotic) regimen is insufficient for preventing spontaneous breathing or patient movement.

Finally, some reports document that NMBDs should *decrease oxygen consumption* during cardiac surgery and more especially during cardiopulmonary bypass (CPB) (26). Another, somewhat comparable, condition for which NMBDs tended to be used in cardiac surgery is the treatment of *shivering*. Shivering after cardiac surgery can produce adverse haemodynamic and metabolic sequelae. In a study from Cruise and colleagues, the metabolic

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effects of shivering and the efficacy of treatment with meperidine or pancuronium were studied in patients who had undergone cardiac surgery. About half of the patients shivered and mean  $\text{VO}_2$  and  $\text{VCO}_2$  values were greater in the shivering group than in the nonshivering patients. It was concluded that drug treatment with meperidine was not as effective as pancuronium in alleviating the metabolic effects of shivering in these patients (17).

WHAT ARE THE MAIN PROBLEMS WITH NMBDs, PARTICULARLY IN CARDIAC SURGERY ?

### *Tachycardia*

Potent opioids, alone or in combination with various intravenous sedative-hypnotics, are widely used for induction of anaesthesia in adults undergoing cardiac surgery. The ongoing interest in the haemodynamic effects of different relaxants is caused, in part, by the lack of substantial differences in the haemodynamic effects of fentanyl and sufentanil (55). Early investigations compared pancuronium, which has sympathomimetic/antimuscarinic effects (1, 51), with "cleaner" NMBDs that have little or no sympathomimetic effects (41, 57). More recent studies have compared newer NMBDs such as rocuronium with older drugs like vecuronium or pancuronium (31, 40). Moreover, it was shown that during sufentanil anaesthesia, the haemodynamic effects of NMBDs depend on the premedication used (56). Investigators suggest that the sympatholytic effects of benzodiazepines are also evident after oral premedication (54, 56). Deliberately slowing heart rate is a cornerstone of anti-anginal therapy and is presumably beneficial for patients with ischaemic heart disease undergoing cardiac or noncardiac surgery. In patients premedicated with morphine-scopolamine, using pancuronium is accompanied by a greater incidence of myocardial ischaemia compared with NMBDs with less sympathomimetic activity (46, 57). Moreover, case reports indicate that the profoundly sympatholytic effects of a sedative-hypnotic plus opioid induction will occasionally cause severe bradyarrhythmias if a 'clean' non-depolarizing NMBD, or even succinylcholine, is used. Although the choice of NMBDs for cardiac patients is important, none of the currently available drugs is intrinsically considered as the best option in all clinical scenarios. Assessment of "outcome" has received much attention in the anaesthesia literature: there are admittedly no data that support the conclusion that

the choice of NMBDs influences outcome in cardiac surgical patients (25). Concerning NMBD-induced cardiovascular effects, apart from tachycardia, it is known that succinylcholine-induced bradycardia and cardiac arrest have a relatively high incidence in high-risk patients such as children, patients with spinal cord and other neuromuscular disorders (43).

### *Postoperative residual curarisation*

Available data suggest that the choice of NMBDs can influence early clinical recovery of the fast-track cardiac surgical patient. A postal survey of cardiac anaesthesiologists by Murphy and co-workers demonstrated that long-acting NMBDs are often administered to fast-track cardiac patients in the United States. Peripheral nerve stimulator monitoring is rarely used in the operating room or intensive care unit (ICU), and reversal drugs (anticholinesterases) are infrequently administered in the postoperative period (38). Residual neuromuscular block [train-of-four (TOF) ratio < 0.7] is common after cardiac surgery but the incidence is less when pancuronium is replaced by rocuronium (32). Also Van Oldenbeek and co-workers found that if pancuronium was used during cardiac surgery, a significant proportion of patients remained partially paralysed when they would normally be allowed to emerge from anaesthesia in the ICU (59). Thomas and colleagues found that in adult patients scheduled for elective 'fast-track' cardiac surgery, median times for the TOF ratio to recover to 0.9, were 3 h 38 min for rocuronium and 7 h 52 min for pancuronium. None of the patients in the rocuronium group and seven of 10 patients in the pancuronium group had their extubations delayed because of residual neuromuscular blockade. These authors stated that, unless fast-track patients have neuromuscular function assessed before extubation, pancuronium should *not* be used for the purpose of fast-track (53). In another study by MURPHY *et al.*, the duration of weaning of ventilatory support significantly increased with patients who received pancuronium (median, 180 min; range, 50-780 min) compared with a rocuronium group (median, 110 min; range, 45-250 min). Tracheal extubation was significantly delayed in the pancuronium group (median, 500 min; range, 240-1,305 min) compared with the rocuronium group (median, 350 min; range, 210-1,140 min). Subjects in the pancuronium group experienced more mild to severe weakness in the ICU. However, the choice of muscle relaxant did not influence ICU length of stay (36). Finally, the

same group of authors evaluated in another study the incidence and severity of residual neuromuscular blockade after cardiac surgery in patients randomized to receive either pancuronium (0.08-0.1 mg/kg) or rocuronium (0.6-0.8 mg/kg). NMBD maintenance dosing was standardised. When weaning of ventilatory support was initiated, significant neuromuscular blockade was present in the pancuronium subjects (TOF ratio : median, 0.14 ; range, 0.00-1.11) compared with the rocuronium subjects (TOF ratio : median, 0.99 ; range, 0.87-1.21). Patients in the rocuronium group were more likely to be free of signs and symptoms of residual paresis than patients in the pancuronium group. Their findings suggested that the use of longer-acting muscle relaxants in cardiac surgical patients is associated not only with impaired neuromuscular recovery, but also with signs and symptoms of residual muscle weakness in the early postoperative period (37).

Continuous infusions are still associated with (important) postoperative residual curarisation (PORC), even with the newer NMBDs. Although Ouattara and colleagues suggest that their results support the use of cisatracurium as a suitable NMBD for fast-track cardiac surgery, all their patients had residual paralysis on arrival in ICU. Neuromuscular block had been maintained by a continuous infusion of cisatracurium until sternal closure. The mean time to reaching a TOF ratio of at least 0.9 was 102 min (range 74-144 min) after discontinuation of the cisatracurium infusion. Eighty three % of their patients were successfully extubated during the *first 8 h* after stopping the cisatracurium infusion. One patient showed residual paralysis when sedation was discontinued (44). The same conclusion of PORC after intraoperative infusions was drawn in a recent study where it took  $56 \pm 41$  min for cardiac surgical patients to recover from a continuous cisatracurium block (13).

Finally, the performance of a computer-controlled infusion of atracurium and vecuronium was investigated during cardiac surgery requiring hypothermic CPB. Except during hypothermic CPB, the controller kept the neuromuscular blockade near the set point (EMG T1 = 10%) in both groups. When CPB was initiated, the mean rates of infusion of the muscle relaxants increased from the pre-CPB values. During the remainder of CPB, the infusion requirements of both muscle relaxants were greatly reduced, but rewarming essentially returned the infusion requirements to pre-CPB values. The authors concluded that the computer-controlled infusion can be used for the administra-

tion of atracurium and vecuronium during CPB (28). However, whether this tool is able to prevent PORC caused by the continuous infusion of NMBDs, has not been studied and is far from being expected.

#### *Interaction of NMBDs*

**Magnesium** potentiates the effect of non-depolarizing NMBDs. It is used in cardiac anaesthesia to prevent hypertension and arrhythmias. In patients undergoing cardiac surgery, administration of magnesium sulfate, resulting in ionized levels of 1.3 mmol/L, results in a 30-35 min prolongation of the neuromuscular blockade induced with intubating and maintenance doses of cisatracurium but does not alter haemodynamic stability (47).

**Inhalational agents** potentiate NMBDs (4, 15, 29, 49). In general, volatile anaesthetics potentiate drug-induced neuromuscular blocks in a dose-related fashion, but the results of the Suzuki trial indicate that the duration of sevoflurane anaesthesia also influences the dose-response of vecuronium (52). Moreover, neostigmine was found to reverse a vecuronium-induced but not a sevoflurane-induced neuromuscular block (34). In children receiving a continuous infusion of atracurium, BRANDON *et al.* found a 30% decrease in dose requirement when halothane or isoflurane was used (6). Also, the newer NMBDs, cisatracurium and rocuronium, are potentiated by inhalational anaesthetics (35) ; in a study by BOCK *et al.* there was a statistically significant reduction in the ED<sub>90</sub> of rocuronium by desflurane, sevoflurane and isoflurane compared with propofol, but no significant differences between the three inhalational anaesthetics in relation to the potency, infusion requirements or recovery characteristics of rocuronium (5). NAKATA *et al.* compared vecuronium-induced neuromuscular blockade during xenon or sevoflurane anaesthesia in humans and found that the mean time from the administration of vecuronium to 25% recovery of the first twitch of the TOF response was significantly shorter in the xenon than the sevoflurane group (39).

**Antibiotic interactions** between  $\beta$ -lactams, particularly acylaminopenicillins, and vecuronium lead to prolonged neuromuscular blockade (58). However, CONDON *et al.* showed that cefoxitin and piperacillin, administered pre- or intraoperatively, are not associated with a clinically important prolongation of neuromuscular block induced by vecuronium (16). Aminoglycosides, especially

neomycin and streptomycin, potentiate a depolarizing as well as a non-depolarizing block (2); moreover, this block is enhanced by magnesium. The blockade can be antagonized by calcium and by anticholinesterases. A clinical report from 1996 describes the failure of rocuronium reversal in a patient who had received neomycin (23). Polymyxins have a postjunctional effect that is difficult to reverse. Lincosamines, clindamycin and lincomycin, have pre- and postjunctional effects; no reversal is possible with calcium or anticholinesterases. The management of this kind of block is thus difficult (7).

#### *Allergic reactions*

NMBDs induce more histamine release than other drugs used in anaesthesia. The overall incidence of anaphylaxis is, however, low (30). For sure, succinylcholine produces the highest incidence of serious immunological histamine release. Moreover, the 'temporary' crisis around rocuronium and its possible propensities to allergic reactions, initially published by Laxenaire, were based on debatable perceptions (21, 33, 48).

Of the anaphylactic and anaphylactoid reactions during cardiac surgery in the Ford study, 60% occurred before CPB, and these were caused by antibiotics and gelatin solution: cephalosporin antibiotics (30%) and gelatin solutions (Hemacel) (26%). The results from this limited database showed that cardiac surgery proceeded without complications after cardiovascular collapse caused by anaphylactic or anaphylactoid reactions. Rapid institution of CPB may be life-saving and should be immediately considered (20).

ARE ALL THE ARGUMENTS IN FAVOUR OF A CONTINUED NEUROMUSCULAR BLOCK DURING CARDIAC SURGERY CORRECT ?

#### *Prevention of movements*

Moving or spontaneous breathing is actually impossible to occur, provided there is sufficient depth of anaesthesia / analgesia.

#### *Decreased oxygen consumption*

Palmisano found that, if repeated or regular movement is not present before paralysis, paralysis does not decrease  $VO_2$ . These data suggest that in normoxic patients, muscle paralysis does not signif-

icantly alter  $VO_2$  and therefore should not be used *for this purpose* (45). Moreover, in a study of the effect of neuromuscular blockade on oxygen supply, oxygen consumption and total chest compliance in patients with high oxygen requirements undergoing mechanical ventilation in the ICU, it was found that neuromuscular blockade could not be assumed to reduce the oxygen requirements or improve total lung compliance (50).

In 1991, however, Irish and colleagues (26) demonstrated that in the unconscious and unmoving patient during hypothermic CPB, administration of muscle relaxant to achieve complete neuromuscular blockade, could reduce systemic oxygen consumption with up to 30%. However, in an actual study, we compared two groups of patients planned for a cardiosurgical procedure with hypothermic CPB: a first group received a  $3 \times ED_{95}$  bolus dose of cisatracurium at induction and thereafter no more NMBD; a second group received a continuous infusion of cisatracurium during the entire procedure. Both groups received a standardized anaesthetic with BIS-guided propofol TCI and a remifentanyl infusion steered by haemodynamic changes. Venous oxygen saturation was continuously determined during CPB. Propofol consumption was  $5.4 \pm 1.7$  and  $4.4 \pm 1.0$  mg/kg/h in groups 1 and 2, respectively ( $P = 0.07$ ). Remifentanyl consumption was  $0.15 \pm 0.05$  and  $0.17 \pm 0.05$   $\mu$ g/kg/min in groups 1 and 2, respectively ( $P = 0.19$ ). In groups 1 and 2, no patient recalled any intraoperative phenomena; none moved or had diaphragmatic contractions. During CPB, venous oxygen saturation was  $81.3 \pm 3.2\%$  [76-85%] in group 1 and  $80.6 \pm 3.1\%$  [73-85%] in group 2 ( $P = 0.53$ ). Our study thus suggests that it was the continuous maintenance of depth of anaesthesia and analgesia with propofol-remifentanyl that prevented muscular activity and a decrease of venous oxygen saturation. In the actual study, omitting the continuous administration of NMBDs during CPB did not increase the anaesthetic requirements. No intraoperative movements occurred, nor was there decreased venous oxygen saturation during CPB. With propofol-remifentanyl one can reduce the consumption of NMBDs considerably without significant effects on venous oxygen saturation during extracorporeal circulation (13).

There are some methodological differences between the Irish report and the study we performed (13, 26). First, we did not measure oxygen consumption, but rather venous oxygen saturation. Although this may partly explain the different findings in the Irish study, we want to stress that

venous oxygen saturation is the only parameter used in this context in clinical practice. Second, the performance characteristics of membrane oxygenators have changed from a maximal oxygen transfer rate of 55 ml/min/l in Irish's study (Bentley BCM 7 oxygenator; Bentley Laboratories, Irvine, CA, USA) to 65 ml/min/l in our investigation (Trillium Affinity NT Oxygenator; Medtronic Inc, Minneapolis, MN, USA). Third, the patients in the Irish study had a slightly larger BSA and thus may have been more at risk for incurring an oxygen debt during CPB. Fourth, there was an important difference in the choice of anaesthetic drugs between both studies. In the Irish manuscript, the patients were anaesthetized with sufentanil, 15 µg/kg, and, thereafter, anaesthesia was maintained with incremental doses of sufentanil as needed for haemodynamic stability, without administration of inhalational agents. Increased muscle tone is a common side-effect of high-dose narcotics. Muscle rigidity is a well-known side-effect of remifentanil (27) too, but we used fairly low doses (an average of 0.16 µg/kg/min). In contrast to our investigation, no hypnotic drug was given in the Irish study. Finally, the concept of 'unmoving patients' used by Irish and co-authors, is not well defined.

SHOULD WE CHANGE MUSCLE RELAXATION PRACTICE, IN PARTICULAR IN CARDIAC SURGERY... ?

When continuous infusions of NMBDs are administered during lengthy interventions and whether or not routine monitoring of their effects is applied, there is a dramatic incidence of residual curarisation. Even routine pharmacological antagonism does not preclude TOF values < 90% (11, 12).

Some suggestions can be made to try to reduce PORC in the setting of continuous infusions. First, one should optimise the NMBD infusion dose requirements over time, as a fixed dose regimen implies a high PORC rate (9, 12). There are the dose adaptations due to reduced Hofmann elimination (hypothermia) or reduced hepatic metabolic function. The atracurium rate of infusion during hypothermia was significantly slower than that during normothermia. Thus, the temperature-dependent inactivation of atracurium was used to advantage because less drug was required during induced hypothermia (19). We investigated the influence of mild hypothermic CPB on the dose requirements of cisatracurium or rocuronium used as a continuous infusion. Cisatracurium infusion rates could be halved during CPB. Even after CPB, requirements

were reduced. The same tendency occurred with rocuronium, but the changes in infusion rate were not statistically significant (10).

Second, we investigated whether a high bolus dose of cisatracurium ( $8 \times ED_{95}$ ) given at induction could provide muscle relaxation for the major part of a cardiac procedure with hypothermic CPB, avoid important postoperative residual curarisation and cause no waste of product. Patients in Group 1 were given cisatracurium in a high bolus dose (0.4 mg/kg). Those in Group 2 received cisatracurium 0.1 mg/kg at induction followed after 30 min by a continuous infusion of cisatracurium. In Group 1 (large cisatracurium bolus dose), the clinical duration of effect (until T1/T0 = 25%) was 110 min. The total amount of cisatracurium used in the bolus and infusion groups was  $34.5 \pm 7.8$  and  $21.3 \pm 5.7$  mg, respectively ( $P = 0.0004$ ). For continued neuromuscular block during hypothermic cardiac surgery, a high bolus dose of cisatracurium appeared to be safe, although it was not an alternative to a continuous infusion, as its neuromuscular blockade did not cover the intraoperative period. The consumption of cisatracurium by high bolus was significantly greater than with a continuous infusion (9).

Whatever measurements taken, residual paralysis after cardiac surgery is the result of continuous perioperative neuromuscular blockade (32, 36, 37, 44, 53, 59). The incidence of residual postoperative paralysis is still significant with repetitive or continuous perioperative muscle relaxation, despite the use of intermediate-acting NMBDs (32, 36, 37, 59). The administration in a single dose to facilitate endotracheal intubation does not result in residual postoperative paralysis (13). The progressive decay of paralysis does not have any negative impact on surgical conditions (13) and allows early tracheal extubation. Therefore, in fast-track cardiac surgery, it seems unnecessary to maintain paralysis by repetitive bolus injection or continuous infusion of NMBD which in turn will only delay extubation in patients fulfilling all other extubation criteria (32, 36, 37, 59). It may even result in tracheally extubated patients still under the effect of residual paralysis (22).

## CONCLUSION

The incidence of PORC after a NMBD infusion is important. With continuous infusions of NMBDs, the greater risk for PORC than with a single bolus can only be tackled by measuring the effect by neuromuscular transmission monitoring

(and selectively antagonising the block) (8-12, 14). Neuromuscular transmission monitoring is seldom used in cardiac surgery. If the neuromuscular block is not monitored intraoperatively in patients who receive a continuous infusion of NMBD, adequate sedation should be provided until proper recovery of neuromuscular function, which can take over ten hours (42). Therefore, we should avoid administering large doses of NMBDs, even in the context of planned postoperative ventilation. One single bolus of NMBD, given at induction to facilitate intubation, should provide, first of all, a rapid free airway, which is often compromised after opioid induction in cardiac surgery. For these purposes, rocuronium is particularly indicated. Moreover, the haemodynamic profile of a 0.6 mg/kg bolus of rocuronium is acceptable for patients with cardiovascular disease (24). In our practice, we even routinely administer 0.9 mg/kg for induction of cardiac surgical cases.

Secondly, by only administering a single NMBD bolus at induction, PORC can be avoided, a phenomenon becoming more and more important in fast tracking. Finally, drugs should be safe and efficacious but also cost-effective; the need for a continued neuromuscular block during cardiac surgery needs to be proven by clinical data, not merely extrapolated from theoretical considerations. Moreover, it is clear that the clinician's vision needs to extend beyond the intraoperative period to include pre- and postoperative events as well (18), such as is the case for PORC after a continuous NMBD infusion.

Just as anaesthesiologists will continue to use pulse oximetry in patients undergoing cardiac surgery, they will continue to choose combinations of drugs and techniques that provide adequate anaesthesia and analgesia, as well as appropriate muscle relaxation, while providing ideal operative conditions with minimal risk of myocardial ischaemia and residual curarisation. Therefore the continuous administration of NMBDs, to maintain paralysis during cardiac surgery, seems unnecessary.

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