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Post-Operative Residual Curarization (PORC): A Big Issue for Patients' Safety

A. Castagnoli, M. Adversi, G. Innocenti, G.F. Di Nino and R.M. Melotti
*Anesthesiology and Intensive Care, S. Orsola-Malpighi Hospital, University of Bologna,
Italy*

1. Introduction

The post-operative residual curarization (PORC) indicates incomplete recovery of muscle function following the administration of neuromuscular blocking agents. The phenomenon of residual curarization actually exists and has a significant impact which is often underestimated. The complications that can result are severe, in terms of patient's outcomes, costs and legal issues. The neuromuscular blocking agents may give as main side effects hypersensitivity reactions or residual curarization.

Recent surveys have estimated the real impact of PORC to be between 4 and 50%. The absence of residual paralysis can be defined as the patient's ability to breathe and cough normally, and the presence of airway reflexes in order to prevent the inhalation of gastric material. On the other hand, a residual paralysis is associated with hypoxia, weakness leading to respiratory failure and increased perioperative morbidity. It is not uncommon for these features to be more or less obvious in the postoperative period, but symptoms are generally not attributed to residual curarization.

The PORC increases the risk of complications, especially if the patient is suffering from respiratory comorbidity and if after the intervention he's transferred directly to the ward (rather than in a protected environment like a recovery room or ICU) lacking adequate monitoring and oxygen supply.

Subjects such as "postoperative residual curarization" and "inadequate intraoperative curarization" are frequently met by disinterest in anesthesiologists, since they are problems that are widely underestimated and poorly understood, in our experience. The monitoring of neuromuscular functions is not mandatory in the operating room, and several investigations (Di Marco et al. , 2010; Naguib et al. , 2010) have shown that the equipment necessary to do so is not sufficiently available in the vast majority of hospitals.

However, the Ministry of Health in Italy in 2009 issued a handbook on safety in the operating room with specific objectives, which included preventing damage from anesthesia and guaranteeing vital functions. Among the requirements: "devices to monitor neuromuscular transmission must always be available."

Currently, there is a gap in terms of guidelines and recommendations of scientific societies on this issue, and in daily practice this coincides with a variety of management strategies for

neuromuscular blockade. It is hoped that in the near future, guidelines and recommendations will be made in order to enable specific strategies to standardize the management of neuromuscular blocking agents.

The objective of this work is therefore to update the state of the art on PORC and risk management of patients with persistent neuromuscular blockade. We integrate our expertise with significant publications on the subject. We carry out a careful review of the literature using electronic databases, analysing original papers, systematic reviews and guidelines.

We aim to provide evidences, in terms of problem definition and epidemiology, on appropriate neuromuscular monitoring, and pharmacokinetics and dynamics of the most commonly used drugs for neuromuscular blocking and reversal. We also provide a brief description of the "Incident Reporting" system, a useful tool to monitor errors and near misses. We also suggest possible ways to correctly prevent or manage PORC, in order to optimize the use of available resources.

The outline of the following chapter reflects this order: starting from the evidences we found in literature about PORC, first we define the phenomenon and its epidemiology, then we describe pharmacological features of NMBAs, ways of neuromuscular monitoring, and NMBAs reversal drugs. Finally, we propose risk management tools, as the "incident reporting" system, together with a specific algorithm.

2. Literature review

A proper analysis of the problem is essential for the in-hospital management of the patient, as a guarantee of his safety and of the anesthesia best practice. We analyse in detail the incidence of the problem and the perception of those directly involved.

In order to update knowledge of the phenomenon of non-monitored curarization and related adverse events, we performed a literature search aimed at identifying the most relevant and recent evidence. The databases and research strategy are:

- Primary studies and case reports: Medline and Cinhal.
- Systematic reviews: Cochrane Library.
- Best Practice Guidelines: National Guidelines Plan (PNLG): <http://www.snlg-iss.it/>; Agency for Healthcare Research and Quality (AHRQ): <http://www.ahrq.gov>; National Guideline Clearinghouse: <http://www.guideline.gov>; Haute Autorité de Sante: <http://www.has-sante.fr>; Expert Consensus Guidelines (EKS): <http://www.psychguides.com>, American Psychiatric Association, <http://www.psych.org>, American Academy of Neurology: <http://www.aan.com>, National Institute for Health and Clinical Excellence <http://www.nice.org.uk>; Scottish Intercollegiate Guidelines Network: <http://www.sign.ac.uk>; Canadian Medical Association: <http://www.cma.ca>; Canadian Task Force on Preventive Health Care: <http://www.ctfphc.org>; New Zealand Guidelines Group: <http://www.nzgg.org.nz>;
- Search strategy used: "Neuromuscular Blockade" [MeSH] OR "Neuromuscular Blocking Agents" [MeSH] OR "Anesthesia Recovery Period" [MeSH] OR "Neuromuscular Blockade" [TIAB] OR "Neuromuscular Blocking Agents" [TIAB] OR "Residual curarization" [TIAB] OR "PORC" [TIAB]. The selected studies are listed in the bibliography.

We selected the studies basing on the value of the discussed topics and on the structural coherence of the articles. We found a poor perception of the problem but also some potential strategies for the prevention and proper management of PORC: different ways of neuromuscular monitoring, correct knowledge of the pharmacology of different NMBAs and reversals, available systems of incident reporting and appropriate hospital wards where to manage patients.

In this paper we want to integrate the strategies we found in literature in a coherent and concrete path of "Risk Management".

3. Post-operative residual curarization (PORC)

We start out our discussion of PORC by properly defining the term (3.a); afterwards, we go through its epidemiology and related guidelines and legal issues.(3.b and c); then, we end this section describing the pharmacological key features of neuromuscular blocking agents. (3.d).

3.1 PORC: Post-operative residual curarization – Definition

PORC is an abbreviation for postoperative residual curarization, identified by instrumental signs (TOFRatio <0.9 -1.0) and clinical signs such as:

- evident muscle fatigue or 'fade' due to continuing occupation of presynaptic receptors by molecules of curare
- attenuation of the hypoxic reflex due to the inhibition of functional nicotinic cholinergic receptors of the carotid glomus
- pharyngolaryngeal dysfunction with loss of airway patency and the risk of "aspiration". The muscles involved in swallowing, such as those of the tongue or pharynx, decurarizate with more difficulty and are therefore implicated in the PORC phenomena
- Reduction of the cough reflex, and reduced expansion of the rib cage, with superficial ventilation and often inadequate and decreased clearance of tracheobronchial secretions

Pulmonary postoperative complications (POPC) include acute respiratory failure and aspiration pneumonia. The possibility of an acute respiratory failure, due to the collapse of the hypopharynx and the tongue base, to a deficiency of the diaphragm and intercostal muscle pump and to a compromised hypoxic reflex, suggests to hold the patient in a "recovery room" after the operation, for the purpose of monitoring and prompt treatment. This occurrence, if not readily diagnosed and treated by experienced staff, establishes a condition of severe hypoxia with psychomotor agitation that can result in severe multiple anoxic organ damage and psychiatric post-traumatic syndromes, which are debilitating and difficult to manage.

Pneumonia caused by "aspiration" secondary to inhalation after extubation, due to lack of pharyngolaryngeal muscle function or secondary to repeated microinhalations in the early hours of admission to the ward (due to persistence of partial neuromuscular block) is not clinically detectable in patients not monitored with TOF, while it increases the morbidity and mortality of the patient, frequently requiring prolonged antibiotic therapy and ventilatory support in an intensive environment.

Volatile and intravenous anaesthetics and analgesics effects that persist after surgery (also those used for pain control) contribute to POPC. These drugs help to maintain a modest level of hypnosis with partial abolition of airway protective reflexes. (Fagerlund MJ et al., 2010; Murphy GS et al., 2010; Papazian L et al., 2010)

3.2 Epidemiology and perception of the problem

Several studies (Butterly A. et al. , 2010; Plaud, B et al. , 2010) have documented that neuromuscular block often persists in the post-anaesthetic care unit (PACU), even with the administration of acetylcholinesterase inhibitors. The frequency of this phenomenon, which has been called "residual curarization," "residual neuromuscular block," "postoperative residual curarization," or "residual paralysis," ranges between 4 and 50% depending on the diagnostic criteria, the type of nondepolarizing neuromuscular blocking drug (NMBD) used, the administration of a reversal agent and, to a lesser extent, the use of neuromuscular monitoring.

Murphy and Brull in a 2010 article, report similarly a wide variability of incidence of residual neuromuscular block in literature, with reported frequencies ranging from 2% to 64%. The problem is obviously clinically relevant, because residual paralysis after emergence from anaesthesia is associated with muscle weakness, oxygen desaturation, pulmonary collapse, and acute respiratory failure that could lead to severe permanent brain damage or death.

A recent survey (Naguib et al. 2007) conducted in Europe and the United States shows a general lack of knowledge and consideration of the PORC phenomenon and monitoring of neuromuscular function: the majority of respondents considered the residual curarization to have an incidence lower than 1%; in Europe only one third of the sample, and 10% in the United States, considered it necessary to monitor the neuromuscular block with the train of four (TOF). The decurarization was always completed by only 18% of the sample in Europe and 34% in the United States.

The criteria by which it is more often decided not to decurarize are the time elapsed between the last dose of neuromuscular blocking and awakening, the total dose administered and subjective clinical parameters indicative of residual weakness. Only 45% of anaesthetists in Europe and 12% in the United States base their decision on the TOF.

Even a recent survey conducted in Italy (Di Marco et al. 2010) shows little understanding of the PORC phenomenon; most anaesthesiologists use clinical trials with subjective interpretation to assess the degree of residual curarization: head raising, protruding of the tongue, hand shaking, opening of the eyes; these are actually examinations which are not very sensitive and specific. When asked about TOF monitoring, only 24% of respondents know that it's necessary to reach a TOF ratio of at least 0.9 to consider the curarization of a patient to be adequately resolved.

Today, it is necessary to ensure an adequate level of quality and safety in anaesthesia, using objective monitoring of the level of curarization. Among the devices on the market, the TOF ensures maximum reliability, specificity and sensitivity.

Despite extensive documentation of such residual paralysis in the literature, the awareness of its clinical consequences remains surprisingly limited, and the use of NMBDs, neuromuscular monitoring, and reversal agents are dictated more by tradition and local practices than by evidence-based medicine.

In an internet-based survey conducted among European and US anaesthetists, a high percentage of respondents had never observed patients in the postanesthesia care unit with residual neuromuscular weakness after intraoperative administration of a muscle relaxant. Respondents from the US were more likely than their European counterparts to estimate that the incidence of clinically significant postoperative residual neuromuscular weakness was $< 1\%$.

In the light of evidence reported (A.F. Kopman, 2007) it is reasonable to conclude that "few clinicians perceive residual block as an important safety issue", both for the relatively low incidence of this phenomenon in some postsurgical settings, and for the lack of clinical recognition of the phenomenon by the anaesthetist.

Inadequate management of curarization in terms of non TOF monitored onset and offset of curare, is associated as previously mentioned with another typically intraoperative event: inadequate intraoperative neuromuscular blockade, an essential aspect to ensure the success of the surgery involving the curarization of the patient.

Inadequate curarization can result in unexpected and sudden movements of the patient with the risk of laceration of internal organs by the surgeon who's operating, distortion of the limbs which had been fixed, or accidental removal of tools placed by the anaesthesiologist. (Baillard C et al., 2005; Di Marco P et al., 2010; Naguib M et al., 2010; Naguib M et al., 2007)

3.3 Guidelines on PORC and legal issues: State of the art

The issues concerning patient safety are real and pressing. Medicine today faces a growing demand for efficiency, safety and quality.

The increasingly wide circulation of knowledge in the field of health goes hand in hand with an increase in disputes over medical-legal issues. Right or wrong, the media disseminate news about real or presumed cases of medical malpractice almost daily.

Premiums on professional insurance policies are constantly increasing and a few companies have even refused to grant coverage. As complaints and lawsuits continue to pile up, the doctor is no longer seen as the sole undisputed custodian of medical knowledge and place of refuge in case of sickness.

Errors in medicine are possible, but we must try to avoid them. Medical science is not infallible and diseases do not follow mathematical laws, but are subject to the variables in the individual. This line of reasoning, if generally accepted in theory, is easily forgotten when coping with an adverse event that is actually happening, while the search for a guilty party and the quest for indemnity get immediately under way.

Confronted with this situation, in no way can doctors today do without the equipment and procedures necessary to ensure the minimization of risks for the patient.

The need to ensure adequate standards of quality and reproducibility in one's activity has led to a routine use of guidelines, evidence and protocols, which now form the basis of common practice and are the indispensable tools of legal defence against allegations of malpractice.

At the same time there is a growing awareness of the importance of risk management and the need to build default shared paths to prevent and manage the risks arising from medical practice.

In this context, so-called defensive medicine takes hold: in a recent survey conducted by the Order of the Italian Doctors in Rome (2008), more than 80% of doctors considered it a realistic risk to receive a complaint from their patients, whereas only 7% excluded this possibility; 99% of surgeons and 97% of anaesthetists felt intimidated.

The fear of retaliation leads to increased costs due to prescription of drugs, diagnostic tests and specialist advice, in excess of actual needs. Even in the operating room safety is a very significant issue.

In 2008, the Italian Ministry of Labour, Health and Social Policies issued specific recommendations and safety standards, ranging from the correct positioning of the patient, airways management, medication, anaesthesia wake up and documentation.

The anaesthetist is among those who take the greatest risks. The anaesthetist can make mistakes like everybody else, but the consequences can be more serious and expensive.

The most complete data on anaesthesia claims are to be found in the American Society of Anaesthesiologists Closed Claims Project (ASACCP), which has been running effectively for more than 20 years. More recently, Japanese and Danish authors have reported on the scope and costs of anaesthesia-related complications and their medical-legal claims.

In the UK, the National Health Service Litigation Authority (NHSLA) Manages legal claims (both clinical and non-clinical) made against the NHS: a survey done in England on medical-legal disputes recorded from 1995 to 2007 (Cook TM et al. 2009) demonstrates that the majority are related to obstetrics and gynaecology or surgery problems, and 2.5% of the cases is related to anaesthesia. Among these, 11% can be attributed to problems related to drug delivery: needle exchange, incorrect dosage, allergic reactions, adverse events, neuromuscular blockers.

3.4 Neuromuscular blocking agents, key features

3.4.1 Pharmacodynamics and pharmacokinetics

The neuromuscular blocking agents used in anesthesia are also known as muscle relaxants. Through the specific and reversible blockade of the neuromuscular junction they allow to obtain an adequate skeletal muscle relaxation.

The molecules now commercially available belong to two classes according to the mechanism of action: depolarizing agents, among which the only one still sold is succinylcholine and nondepolarizing agent, which include benzyliisoquinolinium molecules and steroidal compounds.

3.4.2 Depolarizing muscle relaxants

The depolarizing muscle relaxants (succinylcholine) bind to pre/post synaptic and extra-junctional acetylcholine receptors acting like it, thus depolarizing the terminal plate. Unlike acetylcholine, however, which is metabolized in less than 1 msec, succinylcholine remains bound for a time sufficient to cause desensitization of the receptor and therefore neuromuscular blockade.

The rapid metabolism is by plasma cholinesterase, with a half-life of less than a minute.

The main side effects include bradycardia, anaphylaxis, muscle pain, increased intraocular pressure and intracranial hyperkalaemia.

3.4.3 Non depolarizing muscle relaxants

These competitively bind postsynaptic receptors as antagonists.

There are many molecules on the market, with different characteristics. (Table 1)

The features include the organ-independent elimination of derivatives benzyliisoquinolinium, the absence of vagolytic effects, a different release of histamine for different molecules and the substantial lack of accumulation. A distinctive feature of the molecules of this class is the enzymatic degradation that occurs in plasma, through the reaction of Hoffmann, influenced by pH and temperature.

Molecule	ED95 (mcg/kg)	Onset (min)	Time for the recovery of T1 (min)
Atracurium (B)	200	5-6	20-25
Cis-Atracurium (B)	50	5-6	20-25
Vecuronium(S)	80	5-6	20
Rocuronium (S)	300	2-3	20
Mivacurium (B)	80-150	2-3	20
Pancuronium (S)	60	4-5	60

Table 1. Main non depolarizing blocking agents - curares. ED95 = effective dose (ED) that will produce a specified response (neuromuscular block) in 95 percent of a population. S = aminosteroid; B = benzyliisoquinolinium

Atracurium, non-depolarizing benzyliisoquinolinium, is metabolized by two non-oxidative mechanisms: esterase hydrolysis (70%) and to a lesser extent by the Hoffmann reaction (30%).

The isomer cis-atracurium, characterized by a greater power of action and a slower onset, is mainly degraded (80%) by the reaction of Hoffmann and causes less histamine release.

The nondepolarizing molecules with aminosteroid structure, metabolized by the liver, include pancuronium, vecuronium and rocuronium. The molecules of this class do not release histamine, depend on liver and kidney for their metabolism and exert a variable degree, specific for each molecule, of muscarinic receptor stimulation.

The clinical profile of the molecules differs significantly in some respects: the vagolytic effects of pancuronium results in often evident hypertension and tachycardia; vecuronium

demonstrates an efficient hepatic metabolism, thus causing fewer problems of accumulation for repeated administration than the others; rocuronium, the newest addition to this family of drugs, is characterized by the lack of production of active metabolites during the metabolic cascade and by a quick onset, which at the dosage of 4ED95, can be compared to succinylcholine. (De Miranda LC et al., 2008)

3.4.4 Use in clinical practice

In choosing the most suitable anesthetic procedure, beyond the specific requirements related to the type of surgery, the characteristics of muscle relaxants anesthesiologists have always sought are the speed of action (onset) and the equally rapid resolution of neuromuscular block (offset).

The clinical use of muscle relaxants, however, is characterized by a considerable variability and a different intensity of response with the same amount of drug used in different patients, this having a multifactorial genesis: determining factors are individual characteristics such as age, race, cardiac output, enzymatic activity, sex, genetic polymorphism, environmental factors, as well as the type of surgery undergone by the patient, the combination of therapies that interfere with the function of the neuromuscular junction (antibiotics, drugs acting on central nervous system) and the pre-existing conditions (electrolyte alterations, obesity, neuromuscular diseases, sepsis). A special mention must be accorded to hypothermia, which alone is able to alter the kinetics, drug distribution and rate of liver degradation of all muscle relaxants.

With regard to obesity, some studies conducted using cis-atracurium and rocuronium have shown a significantly prolonged duration of action of both drugs in patients with severe obesity (BMI > 40) and dose calculated according to the actual body weight, than in obese people with doses calculated on ideal body weight, and in the control group.

Concomitant therapy may modify the action profile of the drug. For example antibiotics like neomycin and streptomycin, and anticonvulsant MAO inhibitors strengthen the action of neuromuscular blockers, while phenytoin and carbamazepine decrease it.

Sympathomimetics reduce the onset of muscle relaxants, but also the duration of action. Halogenated anesthetics enhance the block in proportion to the dose.

Particular attention should be paid to patients suffering from conditions such as multiple sclerosis, myasthenia gravis, Duchenne muscular dystrophy, myotonic dystrophy, spinal cord injury, septic conditions.

All neuromuscular disorders are more or less characterized by the presence of receptors with altered conformation and sensitivity towards neuromuscular blocking agents. When confronted by these anomalies, the anesthesiologist must be particularly careful in preoperative evaluation in order to make the proper choice of anesthetic technique and drugs to be used. A quantitative monitoring of neuromuscular blockade is also mandatory. (Meyhoff CS et al., 2009; Singh H et al., 2009)

4. Neuromuscular monitoring

During anesthesia we generally induce deep levels of paralysis to facilitate tracheal intubation and surgery.

At the end of surgery, before awakening and extubation, we must obtain a full recovery of neuromuscular and respiratory functions: respiratory depression from residual curarization is a significant cause of mortality and morbidity related to anesthesia.

Why monitor:

1. To improve a patient's safety
2. To analyse onset-time, clinics, duration, recovery index, total duration
3. To better manage medication and NMBAs antagonists
4. To establish the right time to use a reversal
5. To establish the right time to extubate
6. For the continuous infusion of neuromuscular agents, in order to avoid unwanted accumulation
7. To manage particular patients by increasing their safety (myasthenic, Lambert-Eaton syndrome, dystrophic, neuropathy, atypical cholinesterase, burns, etc..)
8. To reduce the incidence of PORC
9. To find the degree of neuromuscular block and thereby better manage the dosage of the antagonists
10. To collect uniform data on NMBAs and antagonists

(Kopman AF et al., 2010)

4.1 Stimulation modes

There are different ways to stimulate peripheral nerves and thereby muscles (Table 2)

Type	Frequency	Duration	Interval	Repetition	Application
Single twitch	0,1 Hz	0,2 msec	1-10 sec	10-1 sec	Anesthesia induction
Tetanus	50 Hz	5 sec		> 6 min	
TOF	2 Hz	2 sec	10 sec	10 sec	Induction, maintenance, Intubation, Awakening, ICU
PTC	50 Hz	2 sec		> 6 min	Deep block
DBS	50 Hz	40 msec	750 msec	> 6 min	Residual curarization

Table 2. Characteristics of neuromuscular stimuli

Single twitch: single supramaximal stimulus repeated with a frequency between 0.1 and 1 Hz. The intensity of the response is compared with a control obtained before the implementation of the block. It has poor clinical applications because it requires a control value as a starting point reference, before paralyzing the patient, against which to evaluate the muscle response.

Tetanus: Perhaps the most stressful method of stimulating the neuromuscular junction. It is very painful and therefore not suitable for unanaesthetised patients. It has very little place in daily clinical anaesthesia except in the context of post tetanic count. Optimal rate of tetanic stimulation: a frequency of 50Hz is similar to that generated during maximal voluntary effort. 100Hz or 200Hz may be more stressful and thus a more sensitive indicator of smaller degrees of neuromuscular blockade. High frequency stimulation (50Hz or more) results in sustained or tetanic contraction of the muscle during normal neuromuscular transmission, despite decrement in acetylcholine release. During tetanus, progressive depletion of acetylcholine output is balanced by increased synthesis and transfer of transmitter from its mobilization stores. The presence of nondepolarizing muscle relaxants reduces the number of free cholinergic receptors and impairs the mobilization of acetylcholine within the nerve terminal thereby contributing to the fade in the response to tetanic and TOF stimulation. Fade is first noted at 70% receptor occupancy. The tetanic fade ratio at the end of 1 second is comparable to that of T4/T1. It facilitates the neuromuscular response during and after its application, artificially shifting all subsequent neuromuscular events towards normality.

Train of Four: gold standard for the assessment of neuromuscular blockade. The technique records the response of a muscle to an electrical stimulus, quantifying in numerical terms the degree of muscle relaxation.

The transmission of an electrical stimulation through electrodes placed on the skin along the course of peripheral nerves evokes muscle response and acceleration, which can be measured.

The response to stimulation depends on the applied current, the duration, the position of the electrodes, the skin condition (dry/wet), the functionality of the stimulated muscles.

The recovery of neuromuscular function depends on the type of muscle relaxant used, on the duration of administration and on individual variability.

It is performed with the patient asleep because it's particularly painful.

There is a sequence of 4 stimuli at 2 Hz frequency, preceded by the search for a supramaximal stimulus. The 4 stimuli T1-T2-T3-T4 are repeated every 12-15 seconds and the response is measured by acceleromyography: 0 out of 4 responses indicates deep muscle relaxation; 1 out of 4 indicates that the patient is still paralyzed, 2 out of 4 indicate the need for administration of a new dose, 3 out of 4 indicates the possibility of administering the anticholinesterase; 4 out of 4 indicates that we are in an advanced stage of decurarization; then the TOF ratio appears (the percentage ratio between the height of the fourth and the first response) and it is proportional to the degree of recovery. Several studies have shown a good correlation between the TOF-ratio values and clinical signs of decurarization: with a TOF-R of 40% the patient is barely able to breathe, with 60% he's able to lift his head and protrude his tongue, with 75% he recovers a valid cough reflex, and only with 90% there is a complete recovery of lung function.

Post-tetanic count: it is used during the deep phase of the block, when there's no response to TOF, to evaluate the time needed before the return of an answer. It depends on the principle of post-tetanic facilitation: we apply a tetanus at 50 Hz for 5 seconds, followed by a pause of 3 seconds and then by 1 Hz stimulation. For each drug, the number of visible post-tetanic contractions is inversely proportional to the time required for the appearance of a response to the TOF.

Double burst stimulation: two short bursts of 50 Hz separated by 750 msec. This is mostly used in visual-tactile evaluations of neuromuscular blockade.

4.2 Recording modes

Visual and tactile evaluation (for surface muscles): Subjective method and therefore dependent on the individual assessment.

Among the various clinical criteria, there are some proved unreliable (tongue protrusion, eye opening, normal or near normal vital capacity, inspiratory pressure < -25 cm H2O, arm raised toward the opposite shoulder), others not very reliable (head lift test, holding hand for 5 seconds, lifting leg for 5 seconds, maximum inspiratory pressure > - 50 cmH2O), and finally the only one that seems pretty reliable, the tongue depressor test, which seems to correspond to a value of TOF> 0.8 -0.9. (Table 3)

Induction of muscle relaxation
Reduction or disappearance of the respiratory movements
Fasciculations (succinylcholine)
Easy extension of the head
Easy positive pressure mask ventilation
mouth opening
Easy tracheal intubation
Absence of cough during intubation
Maintenance of muscle relaxation
Relaxation of the abdominal muscles
If partial paralysis: maladaptation to mechanical ventilation, diaphragmatic movements, increased peripheral muscle tone, contraction of frontal muscles, eyelid reflex
Recovery of muscle relaxation: Testing of awakening
Ability to lift the eyelids
Ability to protrude the tongue
Ability to cough
Ability to shake hands
Ability to keep an arm raised
Ability to lift head
Vital capacity greater than 15 ml / kg
Inspiratory force of at least -25 cmH2O
Tongue-depressor test: ability to squeeze an object between the teeth, resisting the removal

Table 3. Clinical tests used to assess adequacy of reversal for neuromuscular blockade

Force measurement: a force transducer records the muscular responses to electrical impulses and sends them to a screen. Applicable only to the thumb adductor.

Electromyography: it records the electrical response in the muscle, through the use of properly positioned electrodes.

It can be used at the adductor of the thumb, hypothenar eminence and first dorsal interosseous, innervated by the ulnar nerve.

Accelerometry: it measures the acceleration. From the second law of Newton, we know that the acceleration (a) is proportional to force (F). Provided that the mass (m) remains constant, acceleration becomes a direct measurement of the force of contraction and can be used for the quantification of the neuromuscular block. An acceleration transducer is easily put in place but must move freely for reliable measurement.

Applicable to the adductor of the thumb.

4.3 Muscle choice

In principle, any superficially located peripheral motor nerve may be stimulated, but not all the skeletal muscles show the same sensitivity to neuromuscular blocking agents.

Sites of stimulation most frequently used: ulnar nerve, posterior tibial nerve, common peroneal nerve, facial nerve.

From a practical point of view, no difference in sensitivity exists between the arm (adductor pollicis muscle) and the leg (flexor hallucis brevis muscle).

In some surgical procedures, the patient is positioned in such a way that the arm is not available for monitoring neuromuscular relaxation. The leg is then a good alternative. Another alternative is the stimulation of the facial nerve. Monitoring of the orbicularis oculi muscle can provide also information about the degree of neuromuscular relaxation in those situation where both arm and leg are not available. Not all monitoring equipment is suitable for use with this location.

After the administration we may measure different times as onset, maximum block and recovery. We ideally should measure the function of clinically relevant muscles (abdominal, airways, breathing), but alternatively we can record the activity of muscles with a similar response: for example the eye orbicular is a good indicator of the conditions of intubation, while the thumb adductor is a good indicator of upper airway's muscles.

Adductor of the thumb: accessible during most surgical procedures, innervated by the ulnar nerve. At the induction it has a longer onset than central muscles and recovery is slower than the diaphragm, the rectus abdominis and the adductor of the larynx.

Periorbital muscles: the facial nerve is normally used when the ulnar nerve is not available.

It is located anterior to the ear, where the the electrodes must be put. The transducer must be applied to the orbicularis oculi.

This muscle's function shows a good correlation with the diaphragm. It may overestimate the decurarization, so it's better to perform a calibration to increase its sensitivity.

Muscles of the foot: the posterior tibial nerve can be stimulated behind the inner ankle bone and provokes the flexion of the big toe. The response is comparable to that of the adductor of the thumb.

Since when administering a neuromuscular blocking agent the patient is under general anesthesia, it's not possible to measure actions by asking him to perform volunteer movements. We must therefore stimulate a nerve somehow in order to evoke an automatic and unconscious response; then, in a visual and/or tactile way or, even better, instrumentally, we can detect and then evaluate muscle contractions. The ulnar nerve, whose stimulation causes contraction of the thumb adductor, or the posterior tibial nerve, whose stimulation causes contraction of the flexor allucis brevis, are normally used to monitor curarization and to provide profiles that can be seen to be very similar.

In clinical routine, the ulnar nerve is the most widely used, since it is easily accessible: it runs on the forearm, parallel to the ulnar artery: on stimulation of the ulnar nerve, the adductor muscle contracts. Electrodes are commonly applied to the wrist but alternative locations are possible. The use of a relatively sensitive muscle such as the adductor pollicis has the disadvantage that even after the total elimination of response to TOF or ST, the possibility of movement of the diaphragm, such as coughing or hiccuping, can not be ruled out. Equipment that offers the PTC simulation pattern can of course still monitor the degree of relaxation during intense block. On the positive side, the chance of overdosing the patients during surgery is smaller when the most sensitive muscle is used for monitoring. More important, during recovery, when the adductor pollicis has recovered sufficiently (TOF ratio > 70%), it can safely be assumed that no residual neuromuscular blockade exists in the diaphragm (which recovers faster than the adductor pollicis).

During induction of muscle paralysis, the single stimulus repeated every second (1Hz) is the easiest and most suitable way for observing the exact time of establishment of neuromuscular block, i.e. the onset time. During maintenance of the neuromuscular block it is more convenient to use the TOF, i.e. a train of 4 stimuli (Train of Four). The first one of the 4 stimuli (T1) is sent to the ulnar nerve 13 seconds after the previous 4th TOF stimulation. In addition, the TOF allows the evaluation of a particular phenomenon called "muscle fatigue" or "Fade": when acetylcholine is released in response to depolarization of the motor neuron, it acts on both postsynaptic nicotinic receptors (or post-junctional), and pre-synaptic nicotinic receptors (or pre-junctional). The agonist action of acetylcholine on presynaptic receptors results in a physiological recruitment of presynaptic vesicles such that they can more easily release additional acetylcholine (positive feed-back or presynaptic facilitation, which supports muscle contraction facilitating it). In contrast, in presence of a non-depolarizing curare, these receptors are inefficient to varying degrees: acetylcholine slows down its ready availability and the subsequent release, so that muscle contraction is weakened gradually, also because the muscle fiber is partially blocked by the presence of low or moderate concentrations of curare bound to postsynaptic receptors. The more a curare shows affinity for presynaptic receptors, the more intense the fade effect will be. However, an interval of 10 seconds between one TOF and the next is enough to recover the amount of acetylcholine necessary to produce a new T1, at least of the same height as the previous one. Here is the importance of the TOF, which not only

allows one to control the depth of the block (occupancy of postsynaptic receptors) through the first response (T1) but also allows the measurement of the degree of "fade" (occupancy of presynaptic receptors) by TOF ratio (TR), the ratio between the amplitude of the last of the four answers (T4) and the first one (T1). Only when the TR is ≥ 0.9 , the recovery from neuromuscular block is sufficient, and the patient can be considered self-sustaining in his respiratory autonomy, at least in muscle tone. Better yet, it's good to aim for full recovery (TR 1.0) before sending the patient to the ward. (Vincenti 2010)

In a 2005 study by Glenn et al. the authors assessed the incidence and severity of residual neuromuscular block at the time of tracheal extubation. Clinicians were instructed to reverse neuromuscular blockade only at a TOF count of 2-3 and to delay tracheal extubation if the TOF ratio was 0.6-0.7, regardless of the clinical evaluation of the patient. In fact, severe residual paresis (TOF 0.7) was noted in 70 Patients (58%) at the time the anesthesia care provider had estimated the block to have been recovered sufficiently enough to exclude residual paralysis. The inability of clinicians in this investigation to detect a residual block in the operating room is not unexpected. A 5-second head lift or hand grip (used by all clinicians in the study) can be maintained in some patients with postoperative TOF ratios as low as 0.25-0.4. In conclusion, the authors determined that significant residual paralysis was present in the majority of patients at the time of tracheal extubation. Despite directing the use of a strict monitoring protocol and reversal of an intermediate-acting muscle relaxant, and the performance of a careful clinical examination for signs of muscle weakness, clinicians were unable to achieve consistently acceptable levels of neuromuscular recovery in the OR. In order for anesthesiologists to be assured that neuromuscular recovery is complete and pharyngeal muscle and respiratory functions have returned to normal, the authors suggest that quantitative neuromuscular monitoring is required. (Murphy et al., 2005; Lee HJ et al., 2009)

5. Reversal of neuromuscular blockade

In order to pharmacologically antagonize the effect of NMBA, we can use specific drugs, which belong to two classes: anticholinesterases and sugammadex. They have completely different pharmacodynamics and pharmacokinetics.

5.1 Anticholinesterases

The usual practice of anesthesia, as indicated by numerous surveys, contemplates the use of anticholinesterases such as neostigmine, in order to antagonize neuromuscular block. This practice varies in frequency and indications depending on the setting considered, but in recent decades it has become the gold standard treatment for post-operative residual curarization (PORC). Although this practice is called pharmacological antagonism, the actual function of neostigmine is to increase levels of acetylcholine in the synapse with the aim of displacing curare molecules still there, thus depolarizing the neuromuscular junction. The destiny of curare molecules removed by the junction's receptors is not taken into account. However, in the presence of long-acting curare or of conditions that increase the half-life of administered curare, there is a risk that, once the action of acetylcholine comes to an end, the remnant molecules reoccupy the plaque, thus establishing a neuromuscular late block. In addition, the therapeutic dose of neostigmine is sometimes insufficient to determine an optimal recovery of a neuromuscular function, particularly in the presence of

abundant residual curare with a high affinity for pre- or post-synaptic receptors. This condition can lead, in case of awakening and tracheal extubation not monitored by TOF, to residual curarization and real risks of complications. Finally, severe bradycardia and parasympathomimetic effects related to the use of neostigmine may be responsible, if not treated promptly, for an increase in morbidity and mortality of the treated patient.

The recommended dosage to antagonize muscle relaxation due to the curare and curare-like molecules is about 0.5-2 mg, administered by slow intravenous bolus, combined with atropine in order to oppose the muscarinic effects. (Jonsson Fagerlund M et al., 2009)

5.2 Sugammadex

Sugammadex is a new molecule synthesized for the selective reversal of neuromuscular blockade induced by rocuronium or vecuronium, curares belonging to the family of aminosteroids. It is therefore a SBRA: Selective Relaxant Binding Agent.

Chemically it is a gamma-cyclodextrin (suitably modified to improve the encapsulation of aminosteroids) consisting of an inner portion interacting with the lipophilic steroidal structure of rocuronium or vecuronium, and a hydrophilic outer surface that completely dissolves in water. Unlike drugs currently used for the "reversal" of neuromuscular blockade (anticholinesterases such as neostigmine) Sugammadex can antagonize a deep neuromuscular blockade, if administered in appropriate dosage, without having to wait for a partial recovery of neuromuscular function. Sugammadex, which represents a new concept of antagonism, can be called an "injectable receptor." (Vincenti 2010).

Below we list the basic information concerning the recommended doses and safety features of the drug:

- 2 mg/kg in the presence of a spontaneous recovery with the reappearance of T2. To support the use of this dose, 9 dose-finding studies have been conducted: administering 2 mg/kg of sugammadex, the TOF-ratio reaches 0,9 within 2.8 minutes. Doubling the dose, within 2,6.
- 4 mg/kg if the recovery from block induced by rocuronium or vecuronium has reached a value of at least 1-2 as post-tetanic counts (PTC). In literature, the average time to restore a TOF-ratio of 0.9 was 3.2 minutes. Doubling the dose, there is a reduction of 1 minute.
- For immediate reversal of a rocuronium block the dosage is 16 mg/kg. No studies have been conducted with vecuronium.

Respiratory and anesthetic complications, such as the detection of residual blockade or re-emergence of the block, are more frequent with neostigmine, but we need to further confirm these observations. Studies have found hypersensitivity to Sugammadex and a significant prolongation of the QT interval, especially in case of concomitant use of sevoflurane, though without torsades de pointes. The administration must be modified in patients with renal diseases, adjusting the dosage to the actual renal function. The security in dialyzed patients is limited and the use is not recommended in severe renal failure (creatinine clearance < 30 ml/min) (Abrishami et al., 2010; Della Rocca G et al., 2009; Duvaldestin P et al., 2009; Khuenl-Brady KS et al., 2010; Lee C et al., 2009; McDonagh DL et al., 2011; Plaud B et al., 2009; Schaller SJ et al., 2010; Staals LM et al., 2010; White PF et al., 2009)

6. Incident reporting: Perceptions of the problem by operators and development of actions for improvement

The "Risk management in health facilities" program of the Regional Health Agency of Emilia Romagna, Italy, is committed to developing several tools to be used for the identification and analysis of risk in healthcare organizations. Among these, there is one that's particularly useful during risk identification and analysis: the incident reporting system.

The report, done firstly by operators, of significant events (accidents or near misses, which means events that could develop into accidents) is relevant and useful if it is made and inserted into a systematic approach, whose primary aim is to improve patients' and workers' safety in the healthcare facilities.

Incident reporting is the way of collecting reports of adverse events, near misses and accidents in a structured way. It provides a basis for the analysis and preparation of strategies for improvement, aiming to prevent such incidents from happening again in the future. This system, first introduced in the aircraft industry for the voluntary and confidential reporting of events by pilots and air traffic controllers, in order to improve aviation safety, has been imported for some years by the Anglo-Saxon health systems (Australia, Britain, United States) to fit the health organizations, with the aim of improving patients' safety.

The approach is based on the psycho-sociology of organizations and especially on model interpretation of adverse events (accidents with or without damage) or near-events introduced twenty years ago by James Reason and widespread in risk management of organizations that need to ensure high reliability (traffic, space, nuclear, offshore). Based on this approach, already widely known in healthcare organizations, improving the safety of the environment is possible if we admit the possibility that "something can go wrong" and if we use the information derived from the analysis of events to develop corrective actions or improvements.

To achieve this it is necessary, however, to guarantee a friendly and protective context, because what we want to achieve is the development of a widespread culture of risk, based on the voluntary membership of the operators.

The Italian program has been developed referring to foreign operational practices, that have been adapted to the local context. Among these, incident reporting is one of the available instruments, and it is particularly useful during the process of risk management, identification and analysis. It is not the only tool used, but international analyses show that it is particularly useful for long-term factors, to study rare events, or to identify the most frequent causes. Its utility is also supported by its low costs.

In general we can say that the establishment of reporting systems has two main functions:

1. They provide a measure of the reliability of organizations observed (external role)
2. They provide useful information to those who work for the improvement of the organization, particularly in security aspects (internal role)

When the main purpose is to provide reliability, these systems are mandatory by law or specific rules, with specific authorities appointed to investigate and evaluate cases and if required, to impose sanctions. The focus of these systems is on particularly relevant events, usually with serious results, up to death.

The achievable goals can be summarized as follows:

1. to provide users with a minimum level of protection, ensuring that the most serious cases are reported and investigated, and that follow-up actions are taken;
2. to provide healthcare organizations with incentives to improve patient safety, in order to avoid potential sanctions and bad name resulting from negative situations;
3. to enhance the awareness of health care organizations as to developing forms of activity in the field of security.

However, events that have serious consequences are only a small part of all events that occur daily, since errors and accidents are typically intercepted before they lead to consequences, or the consequences are not critical.

The reporting systems focused on risk management improvement are therefore directed to broaden the traditional field of observation, also considering the events that do not result in damages (near miss) or in minimal ones. The main purpose of such an approach is to better understand the organization, in particular to identify system defects that favor the occurrence of events before they do come about with potentially damaging consequences.

These reporting systems are typically voluntary, they manage confidential information and don't entail penalties and punishment. The characteristic strengths of this approach can be summarized as follows:

1. to enable the identification of types of events that occur infrequently and therefore can hardly be ascertained by a single structure;
2. to enable the correlation of events so as to identify issues that run throughout the organization;
3. to read a single event in a systemic manner, so that it is no longer perceived as random, but placed against large-scale trends which can be interpreted;
4. to identify unusual or emerging events, which are reported because they are perceived as unusual;
5. to be able to react quickly to situations, because the alert is normally simultaneous with the event.

Even in this case, the people in charge of collecting and analyzing reports may be internal, allowing only consideration about what is happening in a specific organization, or external to the health facilities, which affords a greater quantity of data that may allow one to take advantage of all the strengths of this type of system.

The salient features of an effective system of voluntary reporting are:

1. confidentiality and an absence of punitive behavior, to be pursued as follows:
 - creating parallel systems: responsibilities must relate to required systems, that co-exist with so-called "quality" systems, internal to companies, whose sole purpose is to create information aimed at improving the company's safety;
 - making the reported events anonymous, through the elimination of all elements of recognition. This process should be done during the analysis of events, since the possibility of reconstructing what happened is crucial for their understanding and for the analysis of related issues.
2. giving priority to reports about situations of near misses rather than those that caused damage;

3. to answer to the information received through the adoption of measures consistent with the findings from reports, letting people know that:
 - reports were received;
 - reports were elaborated;
 - reports were used to design interventions to solve problems that may arise

In summary, the higher values of an incident reporting system are:

- to provide an empirical basis of reference for the design and adoption of corrective actions / improvements;
- to create awareness among the operators on safety issues

The adoption of an incident reporting system provides the operators (those who report) the capability of recognizing the events that should be reported. A moment of initial training and retention of capacity (together with the "restitution of the information", as discussed above) are therefore necessary to create a first basis of attention to safety issues.

The commitment of the direction that establishes and maintains the incident reporting system, is a sign of importance given to the issue.

Finally, the reporting is done by the operator and it thus highlights both his responsibility of identifying events, and his attention to behaviors. It is clear, however, that:

- if the operators ask for activities and initiatives to increase competence and improve risk management skills (regardless of the initial condition), the incident reporting system can help through a work of knowledge, understanding and improvement of security;
- if the operators are not interested in learning more about topics like adverse events, risk, safety, the incident reporting is unable to provide satisfactory results, or - by itself - to create improvements.

Dealing with "negative" (potential or actual incidents) events, in fact, it is not stimulating in a context with lack of tranquillity and will to improve.

To date, the Emilia Romagna risk management system, hasn't recorded any incident reporting about PORC, this confirming the underestimation and lack of knowledge of the problem.

7. Closure and future work

Both the literature reviewed and our experience suggest the urgent need to formulate appropriate Guidelines and to prepare a Risk Management program for the patient undergoing curarization.

- The evidences discussed above suggest first of all to read up properly on pharmacokinetics and pharmacodynamics of curares that will be used, in order to optimize the dosage and timing of administration according to the patient and the surgical procedure that must be applied.
- It looks mandatory, basing on the evidences, to monitor neuromuscular function using the TOF in order to objectify and document the degree of muscle relaxation achieved (essential also for medico-legal disputes) and to maintain such monitoring up to extubation, in order to reduce the incidence of PORC.

At the end of the intervention it's prudent and advisable to obtain and evaluate both the TOF ratio (TR) and the T1 or single twitch.

- The TOF ratio is useful to assess the extent of the residual "fade", that is suggestive of pre-junctional receptor occupancy; the value of T1 or a "single twitch" should be compared to the baseline value obtained with the patient not yet paralyzed, in order to assess the depth of residual blockade, that is suggestive of the post-junctional receptor occupancy. The monitoring of T1 or the single twitch becomes particularly important in case of PORC due to accidental administration of succinylcholine in patients with plasma cholinesterase deficiency or suffering from Myasthenia Gravis, with unexpected prolongation of neuromuscular blockade. Succinylcholine doesn't provoke "fade", unlike non-depolarizing neuromuscular blocking molecules, and the T1/T4 ratio is therefore normal, while there's a uniform reduction in all twitch (T1: 50%, T2: 50%, T3: 50 %, T4: 50%) that can be detected by monitoring the T1 or a single twitch, that must be compared to the value recorded pre-curarization.
- The preventive use of neostigmine in all patients receiving neuromuscular blockade monitored with TOF does not appear reasonable in light of the possible side effects induced by the drug. It seems rather reasonable to antagonize neuromuscular persistent block (PORC) in a patient extubated with TR > 0.9-1.0. The pharmacological considerations set out above would favor the preferential use of sugammadex in the absence of severe impairment of renal function or pre-existing QT lengthening. However the high cost of supply of the drug make it unavailable in many settings with limited budgets. In the presence of PORC in patients with neuromuscular diseases, sepsis, hypothermia, or morbid obesity, unpredictable and predisposing conditions for a significant prolongation of neuromuscular blockade, it seems reasonable to make a reversal of the block in the first instance directly with Sugammadex, in order to achieve a real antagonism and to prevent the recurrence of a late block. In the absence of these comorbidities, in order to optimize the cost-effectiveness, it seems reasonable to use neostigmine and atropine in the first instance, in the presence of clinical and instrumental partial recovery from the block, and to restrict the use of sugammadex to PORC with a deep block, to blocks not regressed after Prostigmine at therapeutic doses or in patients with unexpected difficult intubation paralyzed with rocuronium or vecuronium.
- The "Incident Reporting" is an usual practice of a hospital that aims to record the operational incidents that occur within it, to analyze it carefully, and to bring back the annual incidence and trends over time discussing it within business meetings with the aim to formulate corrective actions and improvement. Such events would promote a greater awareness of the problem by the professionals involved and would objectify the real incidence of the problem in the structure in which they operate. We suggest to adopt this practice in any hospital setting and to integrate it within a path of "Risk Management" for the prevention of the PORC.
- In case of respiratory complications and/or heart disease attributable to rapidly regressed PORC, it seems reasonable to extend the observation of the patient in a "Recovery Room" or to consider a transfer to intensive environment, where his vital signs can be monitored and he can be assisted, with particular attention to neuromuscular function, which should be controlled by TOF until complete regression of neuromuscular blockade.

Schematic risk management algorithm:

1. Choose the most suitable curare in relation to the patient and the surgery
2. TOF monitoring? Always recommended!!
3. Intrastigmine or Sugammadex?
4. ICU or "Recovery Room" if PORC
5. Fill in the "Incident Reporting" Card in the event of PORC

Referring to the comments made in this chapter, we consider it essential to structure a proper management path for PORC and POPC. We hope that the awareness of the problem induced by this work and the "Risk Management" tools will help to reduce the epidemiology of PORC and POPC.

We recognize the limitations of our work, in terms of databases explored and search strategy used. We aim to expand in the future to other bibliographic databases and periodically update the location of "Risk Management" on the basis of present knowledge, to ensure the patient undergoing anesthesia and curarization with the most correct and updated medical management, and to allow the nurse's and physicians' team to reach high performance and safety levels. (Brull SJ, et al., 2010)

8. Acknowledgments

We thank the 'Regional Health Agency of Emilia Romagna ASR-RER) for sharing the material relating to Incident Reporting and for helping to implement this tool within the University Hospital S. Orsola-Malpighi, Bologna.

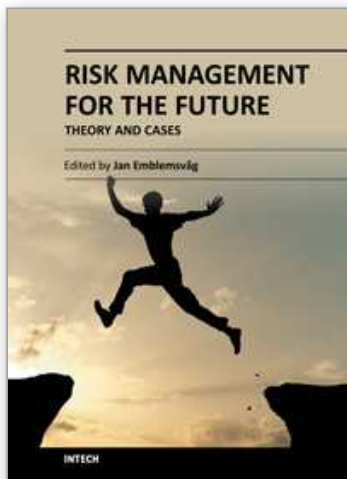
We thank the nursing and anesthesia team of the Prof. Di Nino Operating Room and the Polyvalent Intensive Care Unit of S.Orsola-Malpighi hospital for their interest in the topic and for the support they gave us in the realization of a model of "Risk Management" of the patient under neuromuscular blockade.

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Risk Management for the Future - Theory and Cases

Edited by Dr Jan Emblemsvåg

ISBN 978-953-51-0571-8

Hard cover, 496 pages

Publisher InTech

Published online 25, April, 2012

Published in print edition April, 2012

A large part of academic literature, business literature as well as practices in real life are resting on the assumption that uncertainty and risk does not exist. We all know that this is not true, yet, a whole variety of methods, tools and practices are not attuned to the fact that the future is uncertain and that risks are all around us. However, despite risk management entering the agenda some decades ago, it has introduced risks on its own as illustrated by the financial crisis. Here is a book that goes beyond risk management as it is today and tries to discuss what needs to be improved further. The book also offers some cases.

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A. Castagnoli, M. Adversi, G. Innocenti, G.F. Di Nino and R.M. Melotti (2012). Post-Operative Residual Curarization (PORC): A Big Issue for Patients' Safety, Risk Management for the Future - Theory and Cases, Dr Jan Emblemsvåg (Ed.), ISBN: 978-953-51-0571-8, InTech, Available from:
<http://www.intechopen.com/books/risk-management-for-the-future-theory-and-cases/post-operative-residual-curarization-porc-a-big-issue-for-patients-safety>

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Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
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Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
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Phone: +86-21-62489820
Fax: +86-21-62489821

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