

Correspondence

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Anaesthesia and orphan disease: sugammadex in a patient with Huntington's disease undergoing thyroid lobectomy

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Editor,

Huntington's disease is an autosomal dominant disorder that affects the basal ganglia with a prevalence of four to 10 per 100 000 people.¹ Onset is typically between 30 and 50 years of age. There is also a juvenile onset of the disease wherein the symptoms begin before aged 20; this occurs in 10% of affected persons.² This latter group is more prone to seizures, has impaired glucose metabolism and often inherits the disease in a sex-linked manner from the father. Genetic tests can confirm the diagnosis, even prenatally. Symptoms include choreic movements, personality disorders and impairment of swallowing and gag reflexes. The anaesthetic management of a patient with Huntington's disease provides particular challenges due to the risk of pulmonary aspiration³ and altered responses to anaesthetic drugs.¹ Prolonged apnoea of between 1 and 2 h has been reported after the use of thiopentone and suxamethonium, and there is an increased sensitivity to anticholinergics.¹ Whether these patients have low levels of atypical pseudocholinesterases remains unanswered. We know of no previous reports of the use of sugammadex in the anaesthetic management of patients with Huntington's disease. We have obtained the patient's written consent for publication of this case report.

A 60-year-old woman, weighing 61 kg, diagnosed with Huntington's chorea 6 years previously was admitted for a thyroid lobectomy. On preoperative assessment it was found that she suffered abnormal choreiform movements, acid reflux and snoring but with no signs or symptoms suggestive of obstructive sleep apnoea. She had an

uneventful general anaesthetic 18 years previously for minor surgery. She was a nonsmoker and occasionally consumed alcohol. Full blood count, urea and electrolytes, liver function tests, thyroid function tests, chest radiograph and electrocardiogram performed preoperatively were all within normal limits. She had adequate mouth opening with a thyromental distance greater than 6.5 cm. There was no limitation of neck movement and the Mallampati Score was 2. Her regular medication included oxybutynin 20 mg and fexofenadine 100 mg for an unstable bladder and allergic rhinitis, respectively.

On arrival in the operating theatre, her blood pressure was 148/102 mmHg measured noninvasively, heart rate was 114 beats min⁻¹ and oxygen saturation was 99% on air. A 20 and a 16 G peripheral intravenous cannula were placed, one to be used only for infusions of propofol and remifentanyl. Bispectral index (BIS) monitor (Aspect Medical System, Inc., Norwood, MA, USA) and a Train of Four (TOF)-Watch (Organon Ltd., Durham, NC, USA) were also applied. The ulnar nerve was stimulated to observe the adductor pollicis response.

Due to the increased potential for oesophageal reflux, we planned a modified rapid sequence induction. She was preoxygenated and target controlled infusions (TCI) of propofol and remifentanyl were set up. For induction of anaesthesia, TCI was commenced at 6 µg ml⁻¹ for propofol and at 3 ng ml⁻¹ for remifentanyl. Once the patient started losing consciousness and the BIS value started to fall, cricoid pressure was applied and rocuronium 1 mg kg⁻¹ was given. The lungs were gently ventilated and the trachea was intubated when there was no TOF count detectable. A 6.0 mm internal diameter cuffed Nerve Integrity Monitor Electromyography tracheal tube (Medtronic Inc., Minneapolis, MN, USA) was used for monitoring of the recurrent laryngeal nerve, intraoperatively. There was a grade 1 laryngoscopic view. Intubation was followed by a unilateral superficial cervical plexus nerve block with 10 ml of 0.25% levobupivacaine.

The patient was artificially ventilated with a 50:50 mixture of O₂ and air. TCI plasma concentrations of propofol 3 to 5 µg ml⁻¹ and remifentanyl 1–3 ng ml⁻¹ were maintained to provide a deep plane of anaesthesia (BIS ranged between 30 and 42) in order to facilitate surgery and to avoid the use of repeated doses of muscle relaxant, so that the recurrent laryngeal nerve could be monitored throughout the duration of surgery.⁴ Fluid warming and a Bair Hugger were used to maintain normothermia, perioperatively. Intraoperatively, she remained haemodynamically stable and received 1 g of paracetamol, intravenously.

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A cumulative dose of propofol 1.2 g and remifentanyl 1.07 mg was used and the total anaesthetic time was 130 min. Intraoperatively, we did not administer any further doses of muscle relaxant, and all four twitches of the TOF were present on the completion of surgery. Neuromuscular blockade was reversed with sugammadex 100 mg at this point to prevent residual curarisation.⁵ With the return of her airway reflexes, she was extubated uneventfully.

The patient was alert, orientated and pain free before she left the operating room. She had two further doses of paracetamol at 6 h intervals on the ward and made an unremarkable recovery. She was ready for discharge the same day but remained in hospital overnight as she had a surgical drain *in situ* as a precautionary measure. She had no complaints of postoperative nausea and vomiting and was comfortable throughout her overnight stay in the ward.

This case presents, to our knowledge, the first known use of sugammadex for reversal of neuromuscular blockade in a patient with Huntington's disease. A low dose of sugammadex was used as all four twitches of the TOF response were detectable.

Sugammadex (Org 25969), a modified γ -cyclodextrin, in appropriate doses allows rapid and complete reversal from any depth of rocuronium induced block.⁶ It also provides effective and rapid reversal of profound neuromuscular block induced by vecuronium.⁷ It encapsulates and inactivates rocuronium and selectively binds to free rocuronium molecules with an affinity in a molar ratio of 1:1. The resulting inactive complex is eliminated from the body in the urine with an elimination half-life of 1.8 h. It appears to have an acceptable safety profile. Although various nondepolarising muscle relaxants have been used successfully in patients with Huntington's chorea,³ we chose to use rocuronium not only to avoid the adverse effects of suxamethonium but also because it could be reversed rapidly with sugammadex.⁶

We avoided the neostigmine to prevent exacerbation of choreiform movements which may occur with the use of anticholinergics in combination with neostigmine.² Moreover, sugammadex appears to reverse neuromuscular blockade more rapidly than neostigmine.⁸ After 100 mg sugammadex (corresponding to about 1.6 mg kg^{-1} in this patient) there was complete return of the airway reflexes, a desired effect in this group.

A Nerve Integrity Monitor Electromyography endotracheal tube was used to monitor the function of the recurrent laryngeal nerve, thereby avoiding inadvertent surgical injury of the nerve supply to the vocal cords, intraoperatively.⁹ We maintained an adequate depth of anaesthesia using TCI propofol and remifentanyl with a BIS of 30 to 42, which allowed the presence of three to four twitches on the TOF count and successful

intraoperative monitoring of the recurrent laryngeal nerve.⁴ The recommended dose for reversal of moderate block with sugammadex is 2 mg kg^{-1} .⁸

TCI allow precise titration of anaesthesia, ease of induction, and a rapid, controlled recovery that has previously been successful in patients with Huntington's chorea.¹⁰ TCI avoid the theoretical risk of generalised muscle spasm and prolonged shivering associated with inhalational agents,¹⁰ which may trigger life-threatening tonic spasms. There are conflicting reports on the incidence of postoperative shivering with high doses of remifentanyl which our patient did not experience.¹⁰ The superficial cervical plexus block decreased the need for analgesics, postoperatively.¹¹

We recommend the use of rocuronium as the ideal neuromuscular blocking agent in rapid sequence induction procedures in these groups of patients as sugammadex can be used for rapid reversal of neuromuscular blockade if necessary. We also recommend neuromuscular monitoring in Huntington's patients. The anaesthetic technique used in our patient appeared to be effective and well tolerated providing good analgesia and a rapid recovery. A thorough knowledge of the disease process and anaesthetic implications is essential for the successful anaesthetic management of a patient with Huntington's disease.

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Anaesthesia and orphan disease: anaesthetic management of a child with Pena-Shokeir syndrome

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Editor,

Pena-Shokeir syndrome is a rare, autosomal recessive disorder first identified by Pena and Shokeir¹ in 1974. It is characterised by foetal akinesia/hypokinesia, intrauterine growth restriction, arthrogryposis (contractures of the joints), various cranio-facial anomalies (micrognathia, microphthalmia, cataracts or microcephaly), camptodactyly and pulmonary hypoplasia. These manifestations vary in severity, but are usually severe and death generally occurs during the neonatal period or soon thereafter as a result of respiratory or neurological complications. Some of these patients require anaesthesia for tracheotomy and for the corrections of the deformities if they are able to survive. We describe the anaesthetic and airway management of a child with Pena-Shokeir syndrome after we obtained consent from the patient's parents to publish this report.

A 23-month-old girl, 10 kg in weight was scheduled for the correction of cleft palate deformity. She was born by caesarean section at term (39 weeks, 2600 g). She had respiratory insufficiency and difficulty in feeding and was treated in a neonatal ICU for 9 days (without ventilatory support). She was diagnosed as Pena-Shokeir syndrome with an atypical facial appearance: small eyes, a depressed nasal bridge, small mouth and retrognathia (Fig. 1); also, she had cleft palate deformity, arthrogryposis and pes equinovarus.

On preoperative examination she had respiratory crackles on auscultation of the lungs, but her

respiratory condition was determined by the paediatricians to be optimal. Her intelligence was not impaired and laboratory examinations were normal. In addition to the cranio-facial anomalies, she also had a short and rigid neck. She had two general anaesthesia attempts terminated because of failure of tracheal intubation in two different institutes when she was 9 and 17 months old.

After premedication with oral midazolam 5 mg, she was taken to the operating theatre and standard monitors were placed. The smallest tracheal tube that can be loaded onto the flexible fiberoptic bronchoscope available in our clinic has a 5.5 mm internal diameter that may have been traumatic to the child. So, as the first option, fiberoptic-assisted laryngoscopy was planned.

Anaesthesia was induced by facemask with sevoflurane and oxygen and there was no difficulty with mask ventilation. After insertion of an intravenous catheter, fentanyl 20 µg was administered and sevoflurane discontinued. Propofol infusion 10 mg kg⁻¹ h⁻¹ was started and the infusion rate was adjusted according to respiratory rate. While maintaining spontaneous ventilation, an anaesthetist performed laryngoscopy, and another performed endoscopy via the oral route using the fiberoptic endoscope. After the endoscopist identified the oesophagus and trachea, the patient was intubated with a 4 mm (internal diameter) armoured tracheal tube with cuff. Laryngoscopy was graded as Cormack & Lehane grade III.

After intubation, anaesthesia was maintained with propofol 6–10 mg kg⁻¹ h⁻¹ and remifentanyl 0.15–0.3 µg kg⁻¹ min⁻¹. Rocuronium 4 mg was administered prior to insertion of a mouth gag and no further neuromuscular blocking agent was used after this. The duration of surgery was 150 min. After cessation of remifentanyl, intravenous fentanyl 20 µg and rectal paracetamol 240 mg

Fig. 1



Twenty-three-month-old girl with Pena-Shokeir syndrome.

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were administered for postoperative analgesia. The patient also received intravenous methylprednisolone 20 mg. The anaesthesia and recovery were uneventful.

This child was a rare presentation of this syndrome, as her intelligence was not impaired and respiratory condition was relatively good. Although there are limited anaesthetic reports, difficult tracheal intubation, reactive airway and perioperative respiratory complications related to hypoplasia of the lungs must be considered during anaesthesia management of Pena-Shokeir syndrome.^{2,3} In one case report, two episodes of malignant hyperthermia were mentioned in the medical history of a patient with Pena-Shokeir syndrome, but the condition was not well documented.³ The risk for malignant hyperthermia in patients with arthrogryposis is controversial. In such patients, a malignant hyperthermia-like condition with increase in body temperature was commented as a hypermetabolic response to anaesthesia and surgery.^{4,5} In a review of 32 years' experience, no malignant hyperthermia was reported in 67 patients with arthrogryposis who underwent nearly 400 anaesthesia episodes with triggering agents.⁶ Our patient had two brief anaesthesia exposures with sevoflurane in her medical history without any sign of malignant hyperthermia. However, the triggering of malignant hyperthermia by drugs was suggested as a dose-dependent phenomenon.⁷ We did not persist with inhalation anaesthesia after we had ensured mask ventilation and had intravenous access. Total intravenous anaesthesia with propofol and remifentanyl and low-dose rocuronium was successfully used without incident for cleft palate repair.

Although, there is no strong evidence, we think that the possibility of malignant hyperthermia should be considered in Pena-Shokeir syndrome as in any child with musculoskeletal abnormality. Succinylcholine should be avoided due to the risk of hyperkalemia, as well as inhalational agents. Furthermore, difficult airway management should be anticipated in Pena-Shokeir syndrome.

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Anaesthesia and orphan disease: management of cardiac and perioperative risks in a patient with Emery–Dreifuss muscular dystrophy

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Editor,

Emery–Dreifuss muscular dystrophy (EDMD) is a heterogeneous genetic disorder characterised by early contractures, progressive muscle weakness and cardiomyopathy. Inheritance may be X-linked (EDMD1) or autosomal (EDMD2), both dominant and rarely recessive. Expressivity varies with the underlying gene mutation and delivers a range of clinical presentations and severity. The most common disease pattern begins with contractures of the Achilles tendons, elbows and postcervical muscles. This is followed by humeroperoneal muscle weakness which later involves the proximal limb girdles. Finally, in their second or third decade, patients usually develop cardiac conduction defects: PR interval prolongation and heart block. Occasionally, cardiac abnormalities arise in the absence of other characteristics and are thought to account for some cases of sudden cardiac death.^{1–3}

Anaesthetic considerations include difficult neuraxial and endotracheal access due to contractures. Respiratory muscle weakness, ventricular myopathy and arrhythmias may all exist to varying degrees. Previous case reports have made reference to perceived risks shared with commoner muscular dystrophies (prolonged neuromuscular blockade, delayed gastric emptying and anaesthesia-induced rhabdomyolysis),^{2,4} although evidence to support these links in EDMD is lacking.^{5,6} A full range of anaesthetic techniques have reportedly been used safely in this rare patient cohort.⁴

We would like to share our management of a 28-year-old female with a sporadic lamin A/C gene mutation. The patient has provided written consent to publication of the details. This fit mother of two had met all of her developmental milestones, but had, at the age of 7 years, developed lower limb weakness and Achilles tendon contractures. Initial investigation was hampered by lack

of consent for tissue biopsy and a presumed diagnosis of Charcot–Marie–Tooth disease was made. During her late teens and first pregnancy, she experienced palpitations and, at the age of 23 years, development of elbow contractures prompted further investigation and diagnosis of EDMD. At this time, an implantable cardioverter-defibrillator (ICD) was suggested but cardiac risks were not quantifiable; her young age guaranteed multiple ICD box changes and with her slight stature and breast hypoplasia, she had concerns about the box's cosmetic appearance. Having completed her family and with progression of her ECG abnormalities, she opted to combine ICD insertion with bilateral breast augmentation to hide the ICD unit and address her perceived masculine figure.

On examination, this 50-kg lady had obvious wasting of her upper arms and thighs, walked with a waddling gait and had a 30° extension deficit at both elbows. She had virtually no flexion in her cervical spine from neutral, rotation was limited to 40° both left and right, but extension was unaffected. Her airway assessment was unremarkable (Mallampati grade 1). Cardiac investigation revealed first degree atrioventricular block, with inferolateral T wave flattening and inversion; echocardiography was essentially normal. Her history was otherwise unremarkable apart from demonstrating her physiological reserve by having had two children by spontaneous vaginal delivery and having uneventfully undergone two previous, volatile-based general anaesthetics (enflurane) for Achilles tendon transfer procedures.

For this dual procedure, she received a standard anaesthetic induction with fentanyl 75 µg, propofol 180 mg and rocuronium 30 mg. Tracheal intubation was straightforward (grade 1 view using direct laryngoscopy). Anaesthesia was maintained with sevoflurane in oxygen and air. In addition to standard monitoring, we carefully monitored neuromuscular response with a simple nerve stimulator, nasopharyngeal temperature, invasive arterial pressure and depth of anaesthesia with Entropy (Datex-Ohmeda, GE Healthcare, Waukesha, Wisconsin, USA). External defibrillator pads were placed on the posterior aspect of her right shoulder and left axilla prior to commencing surgery. In the operating theatre, a single ICD wire was inserted through the left subclavian vein; its position was confirmed by radiographic screening and impedance check. A subpectoral pocket was then created for left breast augmentation, and the ICD wire was tunnelled to the superior aspect of this pocket and connected to the ICD unit. At this stage, the ICD was tested (two successful terminations of induced ventricular fibrillation) and deactivated until diathermy was complete. The ICD unit was then secured slightly above the breast implant and the breast augmentation process replicated on the right. The electrophysiology team remained on standby throughout, in case rapid ICD reactivation was

necessary. Observations were stable throughout the 3-h operation. A spontaneous return of four responses to 'train-of-four' stimulation was observed before waking and residual paralysis was reversed with neostigmine 1.25 mg to ensure optimum postoperative respiratory function. Recovery was quick and uneventful and the patient was discharged home on the first postoperative day. Figure 1 shows her postoperative chest radiograph.

This patient displayed EDMD2 due to a *de novo* mutation in the lamin A/C gene, the prevalence of which is unknown. This gene codes for the alternatively spliced lamin A and C proteins which make up a matrix that provides stability and strength to the nuclear envelope. Lamin A/C gene mutations may also result in the phenotypically similar limb-girdle muscular dystrophy type 1B (LGMD1B) and autosomal-dominant dilated cardiomyopathy with conduction defects (CMD1A). These three are all classified as laminopathies, can suffer the same cardiac abnormalities and may each manifest as the result of one identical inherited mutation.⁷

Individuals with EDMD who display a cardiac phenotype are at risk of both impaired ventricular function and conduction abnormalities. Normal myocardium is slowly replaced by fibro-adipose tissue, resulting in dilated cardiomyopathy and disruption of cardiac pacemaker cells. Clinically, this results in variable sino-atrial and atrio-ventricular conduction: low amplitude P waves, first degree heart block and eventually a junctional escape rhythm or complete heart block. Atrial standstill is pathognomonic of EDMD.^{2,8} The risk of sudden cardiac death in these individuals is difficult to quantify because the condition is so rare. A meta-analysis of 299 patients with lamin A/C mutations showed that 92% of those over

Fig. 1



Postoperative chest radiograph showing overlap of implantable cardioverter-defibrillator unit and breast implant.

Table 1 Perioperative management of Emery–Dreifuss muscular dystrophy patients.^{1,2,4–6,10–12}

Preoperative	Intraoperative	Postoperative
Careful airway assessment and preparation for a difficult intubation	Use external pacing pads or consider temporary pacing wires	Cautious use of opioids to prevent hypoventilation
Strict preoperative fast and consider prokinetics	Avoidance of hypothermia	Consider high-dependency care
Care with positioning contractures	Avoid succinylcholine and consider total intravenous anaesthesia or regional anaesthesia	
Cardiac assessment: ECG, echocardiography and 24-h telemetry may all be indicated	Titrate neuromuscular blockade to effect (duration may be prolonged up to three-fold)	
Consider definitive management of the arrhythmia risk with ICD (disable antitachyarrhythmia functions if using diathermy)	Low threshold for invasive arterial pressure monitoring and careful monitoring of electrolytes	
Possible increase in bleeding risk; consider antifibrinolytics		

ICD, implantable cardioverter-defibrillator.

30 years of age had dysrhythmias. Mean life expectancy was 46 years, with 12% of deaths attributed to heart failure and 46% of patients suffering sudden cardiac death.⁹ Unfortunately, quantifying this risk as a cumulative or annual risk which is meaningful to those affected remains difficult.⁷

Perioperative management of patients with EDMD requires careful preoperative evaluation, with a cardiac focus and cautious anaesthesia tailored to the scenario and guided by level 4 evidence (Table 1).^{1,2,4–6,10–12} We chose to use a volatile anaesthetic with muscle relaxant based on our patient's age and previous uneventful exposure. Theoretically, these patients may share the risk of rhabdomyolysis and arrhythmogenic electrolyte disturbance associated with the use of volatile agents and succinylcholine in Becker's and Duchenne's muscular dystrophy, and this should be considered particularly in the first decade of life.^{6,10}

This case illustrates that implantation of an ICD as part of a dual procedure is a safe and simple way of facilitating elective surgery which would otherwise carry a significant risk of perioperative arrhythmias. It also provides definitive management of EDMD sufferers' life-long risk of sudden death in line with emerging evidence.^{3,7}

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Anaesthesia and orphan disease: the child with 3M syndrome

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Editor,

3M syndrome is a recessive autosomal genetic growth disorder, characterised by significant prenatal and post-natal growth retardation.¹ 3M syndrome is listed as a rare or an 'orphan' disease having a prevalence in Europe of less than one person per 2000 in the general population or affecting less than 200 000 people in the US population.^{2,3} The name of the disease originates from the initials of the

three authors, Miller, McKusick and Malvaux, who first reported the syndrome in the literature.⁴ There is a lack of information about anaesthesia in children with 3M syndrome. Having obtained parental consent, we report this case in an attempt to contribute to knowledge about anaesthesia in children with rare diseases.^{5,6}

A 6-year-old boy, who was admitted to the hospital to undergo inguinal hernia repair, was referred for anaesthetic review. He was a short boy, weighing 11.5 kg, with facial dysmorphism, namely a triangular face, broad head and pointed chin. According to the history, he and his twin brother, who had the same facial characteristics and dwarfism, were born in the 32nd week of pregnancy by caesarean section. At that time, our patient weighed 746 g and was admitted for 10 days to the neonatal intensive care unit for mild respiratory insufficiency. No other data about the immediate postnatal period were available, because the child was not born in our country. His mother was a short lady with a height of 143 cm, who claimed to have been investigated as a child for dwarfism.

When our patient was 2 years of age, he was admitted to the Paediatric Department for investigation of growth retardation. At that time, he was below the 3rd percentile for weight and height. Thyroid function and the rest of the endocrine evaluation were normal. Genetic consultation diagnosed 3M syndrome. A hypercaloric diet was recommended.

In addition, he had a solitary kidney and normal cystography. Evaluation of kidney function with 99-Techetium dimercaptosuccinic acid revealed a normally functioning right kidney and a small, dysmorphic left kidney without functional involvement (0.1%). He was routinely re-evaluated by a nephrologist for this dysfunction.

During the preanaesthetic assessment, a review of his past records was undertaken. As the syndrome belongs to the rare diseases, we asked for a cardiologist's consultation, although the syndrome is not characterised by cardiac dysfunction. Cardiac auscultation revealed a systolic (1/6), innocent murmur. Echo and ECG showed no cardiac abnormalities. Biochemistry was completely normal despite kidney dysfunction, and blood pressure (BP) monitoring did not show any abnormalities. He had no history of chronic respiratory problems or recent respiratory infection. He appeared to have speech retardation and his movements were slow, but his intelligence was normal. He had a Mallampati class 1 airway, normal mouth opening and sufficient neck movement, while the thyromental distance was 6 cm.

On the day of surgery, he was premedicated with midazolam 0.3 mg kg^{-1} p.o. Monitoring consisted of ECG, non-invasive BP, pulse oximetry and capnography.

During induction of anaesthesia, propofol 3 mg kg^{-1} , fentanyl $2 \mu\text{g kg}^{-1}$ and rocuronium 1 mg kg^{-1} were administered. At laryngoscopy, a Cormack and Lehane grade 1 view was obtained and intubation was easily performed with a 5.5 mm endotracheal tube. Maintenance of anaesthesia was achieved with sevoflurane in oxygen and air, and a continuous infusion of remifentanyl. The rate of infusion was determined by heart rate and BP. Ondasetron 0.1 mg kg^{-1} and dexamethasone 0.2 mg kg^{-1} were the antiemetic agents given, and paracetamol 15 mg kg^{-1} intravenously in addition to local infiltration of the wound with ropivacaine was administered for postoperative analgesia. Haemodynamic and respiratory parameters remained within normal limits. At the end of surgery, neuromuscular blockade was reversed with neostigmine and atropine and the patient was extubated. Post-anaesthesia care was uneventful and the patient left the hospital later the same day.

3M syndrome is a rare disease with fewer than 100 patients having been reported in the medical literature since 1975.⁷ It belongs to the proportionate type of dwarfism, characterised by proportional but severely delayed growth, a process that begins in the uterus. It is a primordial growth disorder resulting in an adult height of 115 to 150 cm.⁸

Prenatal and postnatal retardation is accompanied by specific facial and skeletal features and normal intelligence.¹ Analytically, facial characteristics such as a triangular face, full eyebrows, hypoplastic midface, fleshy nose tip, upturned nares, long philtrum, prominent mouth and lips and pointed chin, are present. Head circumference often remains within the normal range, and in association with the prominent forehead, the impression of a disproportionately large head in comparison to body size is given.⁹ Skeletal anomalies consist of prominent trapezii, short broad neck, deformed sternum, short thorax, square shoulders, winged scapulae, short 5th fingers, prominent heels, hyperlordosis and loose joints (dislocated hips).¹⁰ Radiographic evidence of the disease includes slender long bones with diaphyseal constriction and flared metaphyses, tall vertebral bodies with reduced anterior-posterior and transverse diameter, anterior wedging of thoracic vertebral bodies, broad thorax with slender and horizontal ribs, thoracic kyphoscoliosis, small iliac wings and spina bifida occulta. These findings are prominent after the second year of life.^{7,10} Hypergonadotropic hypogonadism has been reported in boys with 3M syndrome. Testicles are small for pubertal size and oligo-azoospermia exists. A few boys have hypospadias, although the rest of the endocrine function is normal.¹⁰ Females usually have normal gonadal function, although both sexes are equally affected by the syndrome.¹¹ The usual indication for surgery is bone lengthening.⁷ Medical treatment with growth hormone, though usually administered, does not seem to be efficient.^{1,7}

The disease is caused by mutations in Cullin 7 (CUL7) gene on chromosome 6p21.1, accounting for 70% of cases, or in the Obscurin-like 1 (OBSL1) gene on chromosome 2q35–36.1 encoding a cytoskeletal adaptor protein.^{8,12} Absence of these mutations in 6% of the families tested may suggest the involvement of a third gene.¹

Regarding anaesthesia in adult patients with 3M syndrome, there is only one case of a lady undergoing emergency caesarean section reported.¹³ She had undergone several orthopaedic operations at a young age with no anaesthetic complications. When she underwent caesarean section at age 33, she had a Cormack and Lehane grade 3 view laryngoscopy and the trachea was intubated with a 6 mm endotracheal tube using a bougie. A conclusion cannot be made as to whether the intubation difficulty relates to the progression of the syndrome, to the pregnancy or to the combination of both.¹³

The experience from our patient makes us believe that anaesthesia in children with 3M syndrome is safe and is not connected to specific complications. The disease does not affect the respiratory, cardiac, endocrine or neuromuscular systems. Furthermore, the origin of the disorder precludes an effect on the metabolism of anaesthetic drugs, a fact that could lead to the preference of any specific anaesthetic technique, namely inhalational, total intravenous or regional.

However, it seems that intubation difficulties may arise at a later age, probably because of the progression of skeletal and facial abnormalities. The short neck, short vertebral column, kyphoscoliosis, midface and maxillary hypoplasia, prominent mouth, etc. are features that may accentuate difficulty in laryngoscopy and intubation during general anaesthesia or performance of regional techniques during regional anaesthesia in adulthood. Although the review of the literature supports the lack of specific anaesthetic implications of 3M syndrome, we believe that the preanaesthetic review should be thorough and should investigate the possible presence of other co-existing problems. In our case, kidney function was evaluated, due to the additional nephrological abnormality. The report of a sufficient (for an orphan disease) number of cases could lead to permanent conclusions about anaesthesia and children with 3M syndrome.

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Guidelines on doping

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Editor,

The guidelines for preoperative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery were produced jointly by the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA) and have been seen as an important step in the harmonisation of perioperative management in Europe.^{1–3} Shocking news came on 17 November 2011 that the chairperson of the guidelines taskforce, Professor Don Poldermans, was dismissed from his university position on the basis of scientific misconduct.^{4,5} An internal committee from the Erasmus institution had made inquiries about his clinical studies. Due to their time limitations, they recommended a more thorough investigation into some publications. However, their conclusion was that 'he be relieved of any further responsibility for scientific research'.⁵

Don Poldermans was highly respected and his research group produced apparently well designed prospective randomised studies and made extensive use of their clinical database.^{6,7} They had provided a substantial

contribution to the perioperative literature, especially on the use of perioperative medication. The guidelines were not produced by a single centre but by a large group of clinicians with academic backgrounds, which can be seen from the list of authors.^{1,2} The evidence base for the guidelines was, however, undermined by this event. Evidence is not abundant in the perioperative field due to a great number of confounding factors. The individual skills of the attending physician may be of decisive importance. Some factors, however, can be controlled and Poldermans *et al.*^{6,7} had focused on such variables. The relevance and quality of 'evidence' is dependent on study question, methods, statistics, selection of patients and finally whether the study results can be generalised into clinical management, that is the applicability of a study. Despite their many shortcomings, published studies are the best we have for recommendations. The dismissal of the Chair of the task force committee was not only an aesthetic problem. When an internationally renowned academic is dismissed, it indicates a serious crime despite the fact that the full extent of the scientific misconduct is not known.

The most recent extensive and serious single event of fraudulent publication in perioperative medicine resulted in the retraction of more than 80 papers authored by Dr Boldt in Germany.^{8,9} At present, we do not know the full extent of what has happened in Rotterdam, but there are no indications that the situation is of the same scale and gravity. However, the on-going Decrease VI study was stopped due to the 'lack of participant patients' written informed consent, which is in breach both of the legislations and regulations, and of the protocol approved by the METC; the method of data collection, the fabrication of data, and the method of reporting through the submitting of untrustworthy abstracts, all of which the Committee qualifies as academic misconduct'.⁵

The local committee found shortcomings in other studies and they recommended continued inquiries.⁵ Concerning the Decrease II study, there were flaws in informed consent procedures; in two studies, there were serious breaches of protocol and inconsistency of data collection. Despite the statement that no deliberate steering of research results was found, and that no patient seems to have been subjected to unwarranted treatment or examinations, inevitably, all studies of Poldermans *et al.* have now come under suspicion. As only one man was incriminated, it might be unwarranted and seems to be unfair. Until we know more, this must be the case.

Are the ESC/ESA guidelines still valid? Six days after the affair became known, the ESC issued a statement saying that there were no reasons for retracting the guidelines.¹⁰ The past-president of the ESA, Professor Paolo Pelosi, however, stated in the ESA newsletter¹¹

that the ESA was committed to contributing to: the revision of the guidelines; supplying the best possible guidance to practitioners in Anaesthesiology and Intensive Care Medicine to improve medical practice and ensure patients to receive the best treatment; and informing ESA members on ongoing developments. Meanwhile, the ESA recommends, for the time being, that the guidelines should be followed.

The ESC initiated the guidelines, provided most of the manpower and carried the major financial burden. Anaesthesiology has a joint responsibility through the ESA-appointed members of the taskforce (Drs De Hert, Pelosi and Sellevold). They aimed to carefully evaluate all the available evidence and assessment of level of evidence and grade of recommendation were made by consensus. A Chairperson can have a decisive influence on the end-product. In this case, the Chairman's primary focus was on core issues of the guidelines, among others, the use of perioperative medication such as β -blockers, statins, methods of preoperative evaluation and coronary revascularisation.^{1,6,7}

Trust is at stake. The clinical and scientific medical community has everything to lose from scientific misconduct and, therefore, damage control is vital. Guidelines are not like a single paper that can pass into oblivion. They should be used and cited. If one paper in a long reference list was found to be fraudulent, it would probably not only affect the end-product but when the Chair of the Guidelines committee is under suspicion, the whole product will also fall into the same category.

There are options. The guidelines can be claimed to valid, as the ESC has done.¹⁰ However, the Erasmus University has left no-one in doubt about its attitude to scientific misconduct by dismissing the professor. There are few arguments in favour of the medical community leaving a different message. We are now approaching 1 year since the news broke. The Guidelines were first published in 2009¹ and an update is legitimate in any case. Scientific fraud undermines the foundations of evidence. Doping in sports can only be stopped by a clear message from the authorities that there is no tolerance and that results are nullified. The medical community must signal the same attitude towards fraud. The best way is to abandon the guidelines – or at least nullify the old by substituting them with new ones – as soon as possible. Sometimes drastic measures are needed to restore and maintain confidence, despite the costs.

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Recurrent false alarm of extracorporeal membrane oxygenation at high noon

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Editor,

Extracorporeal membrane oxygenation (ECMO) is an established treatment for patients with severe pulmonary and/or cardiac failure unresponsive to conventional treatment. Its goal is to provide time for treatment and recovery from the underlying disease process, as a bridge to decision-making¹ or to transplantation.² ECMO is complex both medically and technically, requires a specialised team and equipment and its complications

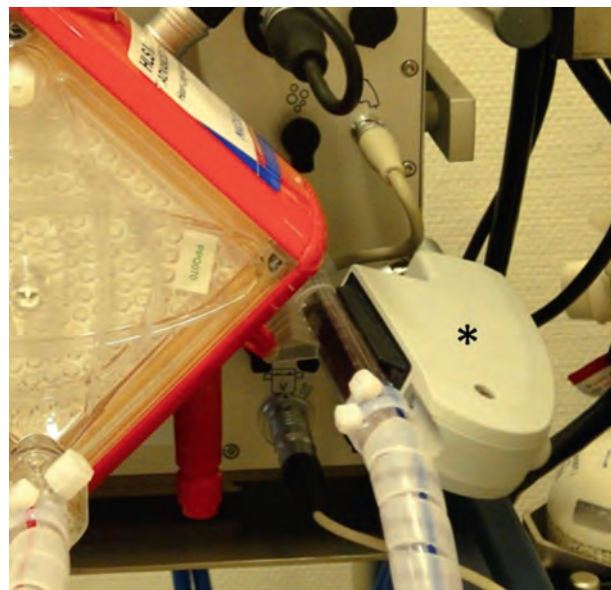
can be devastating. Accordingly, extensive monitoring of patients undergoing ECMO is essential.

We report the simultaneous and recurring malfunction of two new miniaturised ECMO devices due to environmental influences.

During the 2010/2011 influenza A (H1N1) pandemic, 14 patients suffering from adult respiratory distress syndrome (ARDS) due to community-acquired H1N1 infection were treated in our ICU using ECMO. In February 2011, we introduced into clinical practice a new ECMO device (Cardiohelp; Maquet Cardiopulmonary AG, Hirrlingen, Germany). This device is exceptionally small (315 × 255 × 427 mm), lightweight (<10 kg) and can be carried by a single person. Its cube-shaped disposable contains a centrifugal pump, a gas-exchanger/oxygenator and also provides several integrated pressure sensors and a blood temperature probe. Furthermore, an ultrasound flow sensor, which also serves as a sensitive bubble detector, and a sensor for continuous photometric measurement of haemoglobin concentration, haematocrit and venous oxygen saturation can be attached to the venous drainage line (Fig. 1).

In March 2011, three patients in our ICU simultaneously underwent ECMO for H1N1-associated ARDS. On one day at about 12.00 h, we encountered simultaneous alarms of two of the three machines that were located in adjacent rooms. Both devices failed to measure haemoglobin concentration, haematocrit and venous oxygen saturation and no numbers were given for the respective measurements. One of the nurses in charge complained

Fig. 1



The extracorporeal membrane oxygenation's photometric detector (*) attached to the venous drainage tubing of the device.

that both ECMO devices had given alarms for the same type of malfunction for a few days exactly 1 h before her shift changeover. The third ECMO device was in operation in a patient's room on the other side of the ICU and did not malfunction. We unsuccessfully attempted to alleviate the problem by recalibration of the probes according to the manufacturer's instructions. However, despite recalibration, the same malfunction occurred repeatedly around noon each day. Curiously, when a colleague by chance shaded the sensor of one device for a few seconds while trying to silence the alarm, this alone silenced the alarm and re-enabled measurements.

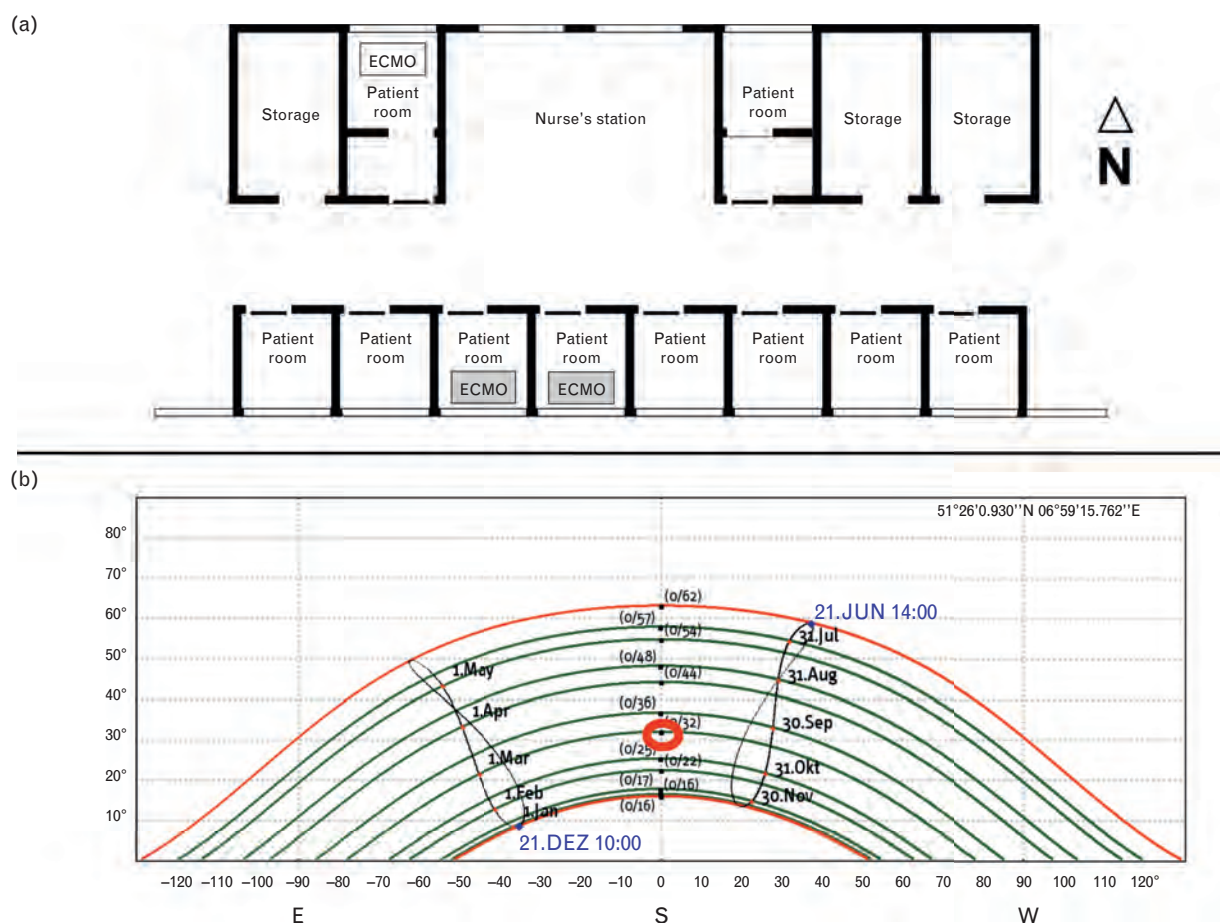
The same malfunction was encountered a few weeks later during transfer of a patient with severe ARDS on ECMO from a referring hospital. When sunlight fell on the probe through the back window of the ambulance,

alarms went off and measurements were disturbed. The problem was resolved by covering the window.

The observed malfunction of the ECMO device's photometric sensors occurred repeatedly around noon and was alleviated by shading the sensor. Our ICU is located on the ground floor of the medical centre and most of the windows face south (Fig. 2a). Although the windows are slightly opaque in their lower part to prevent pedestrians from looking into the ICU rooms, bright sunlight shines into the rooms around noon. This is true particularly during winter months when the sun is low above the horizon (Fig. 2b). It became apparent that, when the sun shone on the sensor, malfunction ensued.

Our report on sunlight-associated ECMO malfunction demonstrates that the spectrophotometric measurement probe of the Maquet Cardio Help ECMO can easily be

Fig. 2



(a) Diagram of our ICU with most of the patient rooms directed to the south. The extracorporeal membrane oxygenation (ECMO) devices with recurring malfunction at high noon are marked as shaded boxes. The ECMO device in the room orientated to the north (white box) did not experience the problem. (b) Sun path diagram for Essen, Germany, indicating the low position of the sun above the horizon in the month of March (red circle). This explains why the malfunction of the ECMO devices occurred for only a relatively short period around noon with the sun shining through the windows at a low angle.

disturbed by direct sunlight. This probe has three light-emitting diodes (LEDs) that produce light at three different wavelengths in the visible and infrared spectra. We were unable to reproduce the sunlight effect by attempting to produce malfunction with an LED flashlight (InGaN blue LED with Ce^{3+} :YAG coating) shining directly at the sensor; malfunction may be due to light of a specific wavelength. Several ambient light sources can generate the wavelengths sensed by pulse oximeter probes. However, it has been shown that different ambient lights (incandescent, quartz-halogen, infrared, fluorescent and bilirubin light) do not significantly affect pulse oximeter measurements.³ The spectrum of quartz-halogen and incandescent light ranges from 650 to 1000 nm, the spectrum of infrared lamps begins at 700 nm, bilirubin light peaks around 200 to 400 nm and fluorescent light at 405 to 579 nm.³ In contrast to ambient light, sunlight is composed of ultraviolet, visible and infrared light, with specific wavelengths of about 100 to 400 nm, 380 to 780 nm and more than 700 nm, respectively. Furthermore, the specific situation of the probe included in the ECMO circuit has to be considered. Whereas pulse oximeters measure ambient light during both static and pulsatile phases and use these measurements to null the incident energy from an ambient energy source,⁴ ECMO commonly uses continuous flow, making this method useless in abolishing errors caused by ambient light.

A representative of the company that manufactures the device was contacted and details of the phenomenon, as well as the possibility of solving the problem by covering the sensor, were described. The phenomenon had not been observed previously according to Maquet.

Although other possibilities to measure haemoglobin concentration, haematocrit and oxygen saturation exist

in an ICU setting, no fallback methods are available during interhospital transfer. To solve this issue, the manufacturer should provide a modification of the probe. In other devices, similar phenomena could be obviated by mounting the sensor on top of the tubing, a measure impossible with the fixed sensor position on this particular device. However, covering the sensor might help to re-enable the sensor with this device. Although measurements were made completely inoperable by sunlight in our cases, one might speculate whether different light conditions might affect measured variables and lead to erroneous values displayed by the photometric sensors of this or other devices. Accordingly, intensivists should be aware of sun-evoked erroneous alarms, particularly at high noon.

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