Anaesthetic management of labour and delivery in the parturient with mitochondrial myopathy

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Purpose: We describe the anaesthetic management for Caesarean section in a parturient with a defect in complex III of the respiratory chain who had increased lactate concentrations at rest and with exercise.

Clinical features: We administered effective epidural anaesthesia with lidocaine for Caesarean delivery. The serum lactate concentration was less than the preoperative value both during and after surgery. Shivering during the perioperative period was avoided by administering warm iv fluids, warm local anaesthetic solution and epidural meperidine. Pain relief after surgery was provided with iv PCA morphine augmented by local infiltration with bupivacaine to fascia and skin edges and epidural injection with meperidine.

Conclusion: Mitochondrial myopathies are an uncommon group of disorders in which mitochondrial dysfunction leads to clinical disease of muscle and sometimes of other organs with high energy requirements. The management of labour and delivery in women with mitochondrial myopathies should be individualized according to severity of disease and formulated by consultation between attending physicians and the anaesthetist. Epidural analgesia reduces stress and work associated with labour and reduces oxygen demand during labour. However, parturients with defects of the respiratory chain with documented increased lactate concentrations at rest and with exercise are best managed with elective Caesarean deliv-

ery with regional anaesthesia to prevent life-threatening lactic acidosis during labour. The association between malignant hyperthermia and these disorders has not been proved, but it appears prudent to consider these women as MH susceptible until definitive data regarding this possible relationship are available.

Objectif: Présenter la gestion anesthésique d'un césarienne réalisée chez une parturiente porteuse d'une anomalie du complexe III de la chaîne respiratoire avec des concentrations de lactate élevées tant au repos qu'à l'exercice.

Caractéristiques cliniques: Les auteurs ont réalisé avec succès une épidurale à la lidocaïne pour la césarienne. La concentration de lactate a été moins élevée pendant et après la chirurgie qu'à la période préopératoire. Le frisson a été prévenu par l'administration de liquides et d'une solution anesthésique et de mepéridine réchauffées. Après la chirurgie, la douleur a été traitée avec de la morphine i.v. auto-administrée après une infiltration de bupivacaine dans les fascia et les lèvres de la plaie et l'administration de mepéridine épidurale.

Conclusion: Les myopathies mitochondriales constituent un groupe rare d'affections caractérisées par le dysfonctionnement des mitochondries qui atteint les muscles et quelquefois d'autres organes dont les besoins énergétiques sont élevés. La gestion du travail et de l'accouchement des porteuses de myopathies mitochondriales doivent tenir compte de la gravité de la maladie et amener les médecins traitants et l'anesthésiste à se consulter. L'analgésie épidurale diminue le stress et l'effort qui accompagnent le travail et réduit la consommation en oxygène. Cependant, la prise en charge des parturientes dont la chaîne respiratoire est déficiente et qui présentent une augmentation documentée de la lactasémie au repos et à l'exercice nécessite l'exécution d'une césarienne en chirurgie programmée et réglée sous anesthésie régionale dans le but de prévenir une acidose lactique potentiellement fatale pendant le travail. L'association entre l'hyperthermie maligne et ces affections n'a pas été prouvée mais il est sage de considérer ces patientes comme susceptibles jusqu'à ce que des données définitives concernant cette relation soient disponibles.

Key words

ANAESTHESIA: obstetrical;
ANAESTHETIC TECHNIQUES: epidural;
MITOCHONDRIA: muscle;
MITOCHONDRIAL MYOPATHIES;
SURGERY: Caesarean section.

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Mitochondrial myopathies are a heterogeneous group of disorders of muscle energy metabolism. The mitochondria produce the energy requirements of muscle cells through the redox reactions of the electron transfer chain and oxidative phosphorylation, thereby producing ATP.¹ There are reports of pregnancy and uneventful vaginal delivery in a woman with metabolic myopathy and pre-eclampsia,² and of Caesarean delivery in a woman with carnitine palmitoyl transferase (CPT) deficiency.³ However, there is no report of pregnancy in a woman with mitochondrial myopathy due to a defect of the respiratory chain and elevated serum lactate concentrations at rest and with exercise. We describe the results of exercise testing in this patient and our experience of the anaesthetic management for Caesarean section.

Case report

The patient developed initial muscle cramps and exercise intolerance at 12 yr of age. Ten years later she was referred to a respirologist because of increasing shortness of breath and leg cramps on walking more than two flights of stairs. More strenuous exercise caused palpitations, nausea and vomiting. After 15–20 min rest the symptoms would abate. She has 10 siblings who are all well, and there is no family history of a similar condition. Initial investigations at 22 yr revealed BP 110/70 mmHg with heart rate of $80 \cdot \text{min}^{-1}$ and respiratory rate of $18 \cdot \text{min}^{-1}$ at rest. Musculo-skeletal and neurological examinations were normal. The ECG showed Wolf-Parkinson-White (WPW) syndrome, but echocardiography confirmed normal ventricular size and function without valvular abnormalities. Her spirometry was normal with a vital capacity of 3 L (86% of predicted). Arterial blood gas analysis at rest was also normal. Maximum inspiratory pressure was $-25 \text{ cm H}_2\text{O}$. (normal -50 to $-100 \text{ cm H}_2\text{O}$). An exercise test was performed at light workloads with and without an indwelling pulmonary artery catheter for five minutes with 20 min rest between measurements (Table I). This test showed low oxygen consumption with greater CO_2 production than predicted, indicating impaired oxygen utilization by exercising muscles. Cardiac output increased appropriately indicating a normal cardiac response to exercise. Profound metabolic acidosis developed during exercise as a result of lactate accumulation. Microscopic examination of muscle fibres from the quadriceps revealed frequent "red-ragged fibres" with subsarcolemmal accumulation of red material in Gomori stain, a frequent finding in patients with mitochondrial myopathy. Biochemical examination indicated a defect in complex III of the electron transport chain. She was

TABLE I Exercise testing

	Units	Rest	Workload		
			100 kpm	150 kpm	200 kpm*
Heart rate	min^{-1}	80	165	185	180
Respiratory rate	min^{-1}	22	24	56	60
Minute ventilation	$\text{L} \cdot \text{min}^{-1}$	7.9	33	49	66
VO_2	$\text{ml} \cdot \text{min}^{-1}$	203	362	571	349
VCO_2	$\text{ml} \cdot \text{min}^{-1}$	241	749	758	903
Respiratory quotient		1.19	2.1	1.3	2.6
pH		7.35	7.29	7.21	7.07
PaO_2	mmHg	100	132	134	270†
PaCO_2	mmHg	33	30	24	25
HCO_3^-	$\text{mM} \cdot \text{L}^{-1}$	21	14	9	7
Lactate	$\text{mM} \cdot \text{L}^{-1}$	3.8	12.7	17.4	—
Cardiac output	$\text{L} \cdot \text{min}^{-1}$	3.3	7.7	8.2	—

*Exercise testing at 200 kpm was performed without a pulmonary artery catheter at 22 yr, four months before exercise testing at 100 kpm and 150 kpm with an *in situ* balloon tipped pulmonary artery catheter.

†Measurement error.

therefore prescribed ascorbic acid 1G q.i.d. and Vitamin K 10 mg o.d. and discharged home.

In 1987, at 26 yr, she delivered a live female infant at 25 wk gestation. This infant died of respiratory complications due to prematurity. The following year she was admitted at 26 wk gestation with spontaneous uterine contractions which abated following *iv* fluid bolus and bedrest. Before admission she had experienced increasing dyspnea with minor exertion and intermittent palpitations. Her ECG showed a PR interval of 0.10 sec with delta waves consistent with WPW syndrome. A cardiac Doppler study was normal. She was scheduled for elective Caesarean delivery at 38 wk gestation, but at 36 wk gestation she developed regular, painful contractions. Arterial blood gas analysis two hours after the onset of labour, when she became increasingly distressed, revealed a compensated metabolic acidosis (Table II). There were also intermittent late fetal heart rate decelerations at this time. It was decided to proceed to Caesarean section. Epidural anaesthesia was induced with incremental injections of carbonated lidocaine with 1: 200 000 epinephrine to achieve a T_6 sensory block. Arterial and central venous catheters were inserted for monitoring. Sodium bicarbonate, 25 mEq *iv*, was given and arterial blood gas analysis was repeated at delivery (Table II). Fentanyl, 50 μg , was administered via the epidural catheter after delivery of the infant. The weight of the newborn was 2.39 kg and Apgar scores were 4 and 9 at one and five minutes after delivery. The neonate was easily resuscitated with a brief period of positive pressure ventilation with 100% oxygen via face

TABLE II Arterial blood gas and lactate analysis

Time	pH	PO ₂ (mmHg)	PCO ₂ (mmHg)	HCO ₃ (mM·L ⁻¹)	Lactate (mM·L ⁻¹)
<i>1988</i>					
2 hr after onset of pre-term labour	7.42	162	23	15	
3 hr after onset of preterm labour, @ CS (after 25 mEq NaHCO ₃ iv)	7.47	159	24	17	
<i>1994</i>					
Day before elective CS	—	—	—	—	7.12
Skin incision @ CS	7.44	112	31	21	4.29
At delivery	7.46	116	28	20	4.51
Arrival in recovery room	7.40	83	37	23	3.17
4th post-partum day	—	—	—	—	2.81

CS = Caesarean section.

mask. Both newborn and mother did well after delivery and were discharged home on the eighth postoperative day.

At 33 yr of age she was admitted again to the prenatal ward at 26 wk gestation with irregular uterine contractions. Although the contractions stopped she remained in hospital for monitoring of her condition and for intermittent assessment of fetal growth. Arterial blood gas analysis was performed regularly to detect the development of lactic acidosis. At 34 wk gestation parenteral corticosteroids were administered to the mother to promote fetal lung maturity. Subsequent amniocentesis revealed a favourable L/S ratio. Caesarean section was planned for the following day to avoid the risks of metabolic acidosis and respiratory distress which had occurred during her last labour in 1988. Serum lactate concentration was 7.12 mM·L⁻¹ the day before surgery (Table II). Total CPK was 305 U·L⁻¹ (normal 20–60 U·L⁻¹). One litre of warm saline *iv* was administered before epidural injections with lidocaine. Epidural anaesthesia was induced with increments of warm carbonated lidocaine with 1:200 000 epinephrine. A total dose of 340 mg of lidocaine was administered to achieve a T₄ sensory block. A #20 gauge cannula was inserted into the radial artery. Surgery was uneventful and a vigorous 2.6 kg infant was delivered with Apgar scores of 8 and 9 at one and five minutes after delivery. Arterial blood gas analysis was performed at the times of skin incision, delivery and arrival in recovery room (Table II). The arterial blood gas values were normal at these times except for the lactate concentrations which were lower than before surgery. After delivery, 50 mg meperidine (10 mg·ml⁻¹) were administered via the

epidural catheter to provide postoperative pain relief and to decrease the risk of shivering. A total of 40 ml plain bupivacaine 0.25% was injected into the fascia and skin edges of the Pfannenstiel incision to augment pain relief in the early postoperative period. Intravenous patient-controlled analgesia (PCA) with morphine provided good analgesia during the first two days after delivery. The mother's serum lactate concentrations decreased further after delivery (Table II), and mother and baby were discharged home in good condition on the sixth post-partum day.

Discussion

The respiratory chain consists of four multi-enzyme complexes located on the inner mitochondrial membrane. Enzyme defects in the mitochondrial respiratory chain result in exercise intolerance, fatigue, muscle pain and progressive weakness.⁴ The morphological hallmark is large subsarcolemmal accumulation of abnormal mitochondria which appear as red-staining granules with the Gomori stain ("red-ragged fibres").⁵ Disorders of mitochondrial metabolism may also involve other organ systems with high demand for energy (brain, liver, kidney, heart),⁶ although this was not the case in this patient. Medical treatment with Vitamin K and ascorbic acid has been shown to lead to biochemical improvement (i.e., increased ATP production) as well as increased functional ability in a study of a patient with a deficiency in cytochrome b containing complex III of the electron transport chain.⁷

Oxygen consumption is increased by approximately 20% during pregnancy compared with non-pregnant women.⁸ Painful uterine contractions result in a further 63% increase in oxygen consumption. Epidural labour analgesia prevents this increase in oxygen consumption.⁹ The administration of epidural analgesia is, therefore, of particular benefit to a patient with a defect of muscle energy metabolism with documented low oxygen uptake during exercise testing. Lactic acidosis is a frequent feature of disorders of electron transport, but not so in mitochondrial myopathies resulting from impaired transmembrane lipid transport (e.g., CPT deficiency). The development of metabolic acidosis early during the first stage of labour in our patient's second pregnancy in 1988 indicates that elective Caesarean delivery is the preferred method of delivery as soon as fetal lung maturity has been confirmed. Although epidural analgesia decreases the stress of labour as evidenced by a decrease in oxygen consumption it is likely that lactic acidosis will develop in parturients with a respiratory chain defect, possibly augmented by lactate production from contracting uterine smooth muscle.

Fatigue and exhaustion during labour can be predicted from observations during previous exercise testing. In a woman with CPT deficiency who underwent uneventful Caesarean section due to failure to progress during first stage of labour biopsies of uterine and skeletal muscle were both deficient in CPT,³ indicating that smooth muscle may also be affected in some disorders of mitochondrial metabolism. Rapid progression of muscle weakness was also noted after pregnancy in a woman with carnitine deficiency which led to cardio-respiratory failure and death.¹⁰

Anaesthetic management of the parturient with mitochondrial myopathy presenting for Caesarean section should begin with a thorough review of the patient's history, physical examination and previous investigations, preferably in consultation with the attending internist. The preoperative assessment will thus give a clear indication of vital organ function and reserve. We elected to proceed with epidural anaesthesia for several reasons. Firstly, incremental doses of local anaesthetic via the epidural catheter permit a gradual, controlled cephalad progression of the block thus avoiding respiratory compromise. Secondly, it allows administration of epidural opioids to provide postoperative pain relief. Thirdly, it avoids administration of general anaesthesia and muscle relaxants which may cause postoperative residual muscle blockade in a person with demonstrated muscle weakness and decreased maximum inspiratory pressure. Although central core disease is the only neuromuscular disease shown to be genetically linked to malignant hyperthermia (MH),¹¹ there is one report of a patient with CPT having an abnormal response to contracture testing with halothane 3%.¹² Thus, it appears prudent to consider patients with mitochondrial myopathies to be MH susceptible and therefore avoid administration of drugs known to trigger MH. Spinal anaesthesia would have been an acceptable alternative to epidural anaesthesia for Caesarean delivery in this parturient. It is important to maintain body temperature during the perioperative period and to prevent shivering. Intravenous fluids and epidural local anaesthetic solutions should be warmed to body temperature. Epidural and *iv* administration of opioids decrease the incidence and severity of shivering during Caesarean section.^{13,14} Effective postoperative analgesia is important to provide comfort and promote early ambulation. We chose a multi-modal approach to postoperative pain management by administering epidural meperidine and infiltration of bupivacaine to fascia and skin edges, in addition to *iv* PCA morphine. Epidural meperidine provides three to five hours of analgesia,¹⁵ whereas local infiltration with bupivacaine at Caesarean delivery may provide up to 12 hr of pain relief.¹⁶

The management of this patient was determined after consultations among perinatologist, neonatologist, internist and obstetric anaesthetist. We believe that parturients with mitochondrial myopathies should be treated on an individual basis, but that women with deficiencies of the electron transport chain with elevated lactate concentrations at rest and exercise are best managed with elective Caesarean delivery using regional anaesthesia. We recommend that known MH triggering agents not be administered to patients with mitochondrial myopathy until more is known about the possible association between these disorders. It is also important to avoid shivering during the perioperative period and to administer effective pain relief and ensure early mobilization after surgery.

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