Rev Bras Anestesiol. 2019;69(4):335–341

REVISTA
BRASILEIRA DE
ANESTESIOLOGIA

Publicação Oficial da Sociedade Brasileira de Anestesiologia
www.sba.com.br

SCIENTIFIC ARTICLE

Anesthesia for muscle biopsy to test susceptibility to malignant hyperthermia

Helga Cristina Almeida da Silva *, Elton Shinji Onari, Isac de Castro, Marcelo Vaz Perez, Alexandre Hortensi, José Luiz Gomes do Amaral

Universidade Federal de São Paulo (Unifesp), Escola Paulista de Medicina (EPM), Disciplina Anestesiologia, Dor e Terapia Intensiva Centro de Estudo, Diagnóstico e Investigação de Hipertermia Maligna (Cedhima), São Paulo, SP, Brazil

Received 25 September 2018; accepted 6 February 2019
Available online 31 July 2019

KEYWORDS
Malignant hyperthermia;
Anesthesia;
Nerve block

Abstract
Introduction: Malignant hyperthermia is an autosomal dominant pharmacogenetic disorder, characterized by hypermetabolic crisis triggered by halogenated anesthetics and/or succinylcholine. The standard method for diagnosing malignant hyperthermia susceptibility is the in vitro muscle contracture test in response to halothane-caffeine, which requires muscle biopsy under anesthesia. We describe a series of anesthetic procedures without triggering agents in malignant hyperthermia, comparing peripheral nerve block and subarachnoid anesthesia.
Method: We assessed the anesthetic record charts of 69 patients suspected of malignant hyperthermia susceptibility who underwent muscle biopsy for in vitro muscle contracture in the period of 7 years. Demographic data, indication for malignant hyperthermia investigation, in vitro muscle contracture test results, and surgery/anesthesia/recovery data were analyzed.
Results: Sample with 34 ± 13.7 years, 60.9% women, 65.2% of in vitro muscle contracture test positive. Techniques used: peripheral nerve blocks — lateral femoral and femoral cutaneous, latency 65 ± 41 min — (47.8%); subarachnoid anesthesia (49.3%), and total venous anesthesia (1.4%). There was 39.4% failure of peripheral nerve block and 11.8% of subarachnoid anesthesia. Adverse events (8.7%) occurred only with subarachnoid blockade (bradycardia, nausea, and transient neurological syndrome). All patients remained in the post-anesthesia care unit until discharge. Age and weight were significantly higher in patients with blockade failure (ROC cut-off point of 23.5 years and 59.5 kg) and blockade failure was more frequent in the presence of increased idiopathic creatine kinase.
Conclusion: Anesthesia with non-triggering agents has been shown to be safe in patients with malignant hyperthermia susceptibility. Variables such as age, weight, and history of increased idiopathic creatine kinase may be useful in selecting the anesthetic technique for this group of patients.

* Corresponding author.
E-mail: halsilva@uol.com.br (H.C.A. Silva).

https://doi.org/10.1016/j.bjane.2019.02.003

PALAVRAS-CHAVE
Hipertermia maligna;
Anestesia;
Bloqueio nervoso

Anestesia durante biópsia muscular para teste de suscetibilidade à hipertermia maligna

Resumo
Introdução: Hipertermia maligna é uma doença farmacogenética autossômica dominante, caracterizada por crise hipermetabólica desencadeada por anestésicos halogenados e/ou succinilcolina. O padrão para diagnóstico da suscetibilidade à hipertermia maligna é o teste de contratura muscular *in vitro* em resposta ao halotano-cafeína, para o qual é necessária biopsia muscular sob anestesia. Descrevemos uma série de anestesias sem agentes desencadeantes na hipertermia maligna e comparamos bloqueios de nervo periférico e anestesias subaracnóideas.
Método: Foram analisados os prontuários/fichas anestésicas de 69 pacientes suspeitos de susceptibilidade à hipertermia maligna, submetidos à biópsia muscular para teste de contratura muscular *in vitro* durante sete anos. Analisamos dados demográficos, indicação para investigação de hipertermia maligna, resultado do teste de contratura muscular *in vitro* e dados da cirurgia/anestesia/recuperação.
Resultados: Amostra com 34 ± 13,7 anos, 60,9% mulheres, 65,2% de teste de contratura muscular *in vitro* positivos. Técnicas empregadas: 47,8% bloqueios de nervo periférico (femoral e cutâneo femoral lateral, latência 65 ± 41 minutos), 49,3% anestesias subaracnóideas e 1,4% anestesia venosa total. Falha em 39,4% dos bloqueios de nervo periférico e 11,8% das anestesias subaracnóideas. Eventos adversos (8,7%) como bradicardia, náuseas e síndrome neurológica transitória só ocorreram com bloqueio subaracnóideo. Todos os pacientes permaneceram na sala de recuperação pós-anestésica até liberação. Idade e peso foram significativamente maiores nos pacientes com falha no bloqueio (ponto de corte da curva ROC de 23,5 anos e 59,5 Kg) e esta foi mais frequente na presença de aumento idiopático de creatinoquinase.
Conclusão: Anestesia com agentes não desencadeantes mostrou-se segura em pacientes suscetíveis à hipertermia maligna. Variáveis como idade, peso e antecedente de aumento idiopático de creatinoquinase podem ser úteis para selecionar a técnica anestésica nesse grupo.

Introduction

Malignant hyperthermia (MH), first described by Denborough and Lovell in 1960, is a hypermetabolic syndrome characterized by tachycardia, tachypnea, hypercarbia, hyperthermia, muscle rigidity, rhabdomyolysis, and acidosis. It is triggered by halogenated anesthetics (isoflurane, sevoflurane, desflurane, enflurane and halothane) and/or depolarizing muscle relaxant (succinylcholine) in genetically susceptible patients (50–70% have a mutation in the ryanodine receptor type 1 gene).[1,2]

The estimated incidence of anesthesia-related MH is 1:10,000 in children and 1:50,000 in adults, which may affect individuals from all ethnic groups.[3] In 1970, MH mortality was over 80% and currently decreased to less than 10% due to the widespread use of dantrolene (the only specific drug for MH management) and increased knowledge of physicians regarding early diagnosis and treatment.[4,5]

The in vitro muscle contracture test (IVCT) in response to halothane-caffeine is the international gold standard for diagnosing MH-susceptibility. There are two protocols for the susceptibility test, from the European Malignant Hyperthermia Group (EMHG) and the North American Malignant Hyperthermia Group (NAMHG).[6–8] In order to undergo skeletal muscle biopsy for the test, general anesthesia, subarachnoid anesthesia or peripheral nerve block (femoral nerve and lateral femoral cutaneous nerve) is performed.[2]

It is considered safe to use non-triggering anesthetic drugs in MH-susceptible patients.[9,10] Barbiturates, benzodiazepines, etomidate, propofol, ketamine, opioids, nitrous oxide, and non-depolarizing muscle relaxants are among the non-triggering anesthetic drugs that may be used for anesthetic induction.[9] However, even in the absence of triggering anesthetic drugs, 0.46% of MH-susceptible patients could theoretically present with some clinical signs suggestive of MH; therefore, even in the absence of triggering agents, the anesthesiologist must have adequate means for diagnosis and treatment.[4,11]

Background and objectives

The aim of this study was to investigate the characteristics and safety of anesthesia with non-triggering agents in muscle biopsy for IVCT in a sample of patients suspected of MH-susceptibility and compare peripheral nerve block and subarachnoid anesthesia.

Method

This was a longitudinal and uncontrolled, documentary and retrospective, historical and observational study approved by the institutional Research Ethics Committee (No. 0970/08). Anesthetic records of MH-suspected patients undergoing muscle biopsy for IVCT from 2004 to 2010 were analyzed. This period was chosen because it allows the comparison of two phases in which subarachnoid anesthesia (spinal anesthesia) and peripheral nerve block were preferentially used. Of the 69 records, 68 had sufficient data for analysis.

The study center provides the outpatient care of MH-suspected patients and MH investigation through IVCT, according to the European protocol.[6] The assessment begins with a medical history, with emphasis on the MH crisis description and obtaining a report from the original service. The following physical/neurological examination is performed and laboratory tests (blood count, blood glucose, renal function, electrolytes, creatine kinase, blood clotting, chest X-ray, ECG) are ordered. When IVCT is indicated, the patient is initially referred to a preanesthetic evaluation. Special care is taken to temporarily change or suspend, when possible, the medications that may theoretically interfere with the test result, such as calcium channel blockers,[12] beta blockers,[13] serotonin reuptake inhibitors,[14] phosphodiesterase III inhibitors (anrinone/enoximone).[15] IVCT is performed in patients above 20 kg and at least 3 months after the HM crisis, after obtaining written informed consent.[2] For IVCT, it is recommended that the time between collecting the material (muscle biopsy) and the end of the test does not exceed 5 h. Therefore, the patient should be in the investigation center.

The room and anesthesia machine are prepared in advance. Anesthesia is scheduled for the first hour of the morning, and the room is not used for previous halogenated procedures. Preparation of the anesthesia machine was performed previously for all procedures consisting of:

- Removal of all halogenated vaporizers;
- Replacement of soda lime canister, corrugated tubes, and reservoir balloon;
- Continuous cleaning of the anesthesia machine with a high flow of 100% oxygen (10 L.min^{-1}), during time dependent on the anesthesia machine (usually 2 h). While older machines required at least 10 min, the new ones may require up to 120 min.[16,17]

Central and peripheral catheterization equipment, nasogastric and vesical probes, soda lime, blood sample tubes, syringes and needles of different sizes, ice, and thermal blanket were available. All medications required for any eventuality (arrhythmias, acidosis, and cardiopulmonary resuscitation), such as dantrolene, antiarrhythmic drugs (procainamide, amiodarone, lidocaine, beta blockers), sodium bicarbonate, furosemide, mannitol, and insulin were also available. Prophylaxis with dantrolene was not used in susceptible patients.[9]

All patients were fasted before the procedure; patients with an additional history of rhabdomyolysis associated with fasting or physical exertion received intravenous glucose. Midazolam (0.15 mg.kg^{-1}) was given as preanesthetic medication. Monitoring consisted of cardioscopy, oximetry, noninvasive blood pressure, tympanic thermometer; if general anesthesia was performed, the end-expired fraction of CO_2 was measured by capnography.[2]

The choice of the anesthetic technique used had two phases, that is, until 2007, all patients underwent spinal anesthesia, and from 2008 the first choice technique was the peripheral nerve block (femoral nerve and lateral femoral cutaneous branch). In femoral nerve block guided by Doppler ultrasound and/or peripheral nerve stimulator, the nerve was identified and 15 mL of 1.5% lidocaine with 1:200,000 adrenaline were injected around the nerve. For the lateral femoral cutaneous nerve, as it was purely sensitive, landmarks and Doppler ultrasound were used, with an injection of 20 mL of 1.5% lidocaine with 1:200,000 adrenaline. Block success was tested with cotton soaked in alcohol (thermal sensation) and painful sensation. If, after 30 min, there was no adequate blockage, that is failure, the spinal anesthesia or total venous anesthesia was the last choice.

The material was collected by quadriceps muscle biopsy (portion of the vastus lateralis) to remove four fragments of 2×0.5 cm. In order to avoid interference with the results the use of local anesthetics should be avoided at the muscle biopsy site.[6] Patients were monitored for at least 6 h in the post-anesthesia care unit (PACU), with pulse oximetry, temperature, heart rate, respiratory rate, blood pressure, and pain monitoring. Subsequently, they were discharged with guidance to seek out the emergency room and call if there was any intercurrence. Sutures were removed at the health service near the patient's home after 7 days. After 30 days, the patient returned to the outpatient clinic to get the results, the surgical wound healing was assessed.

In this review, data from the records/anesthetic charts were collected according to a standardized form, including demographic data, indication for MH investigation and IVCT result, data from surgery, anesthesia and recovery. The collected data were entered in a spreadsheet and presented as measures of central tendency and dispersion or percentages. Variables were tested for normality (K-S distance). Subsequently, comparisons were made between groups for continuous variables (unpaired *t*-test) and categorical (chi-square test), with cut-off point calculation for the ROC curve. To obtain a sample size that allowed the analysis of the variables possibly associated with block failure, we grouped the patients according to the regional anesthesia used (spinal or peripheral block) in order to have one group without block failure and another group with block failure.

Results

In the studied period, 69 patients underwent muscle biopsy for IVCT, 60.9% were female, with a mean age of 34 ± 13.7 years. The mean weight (available in 46 patients) was 71.19 ± 21.7 kg; the mean height (available in 41 patients) was 163 ± 9.9 cm, with BMI (available in 41 patients) of 25.9 ± 5.9 kg.m^{-2}.

The indication for IVCT was based on the presence of one of the following factors:

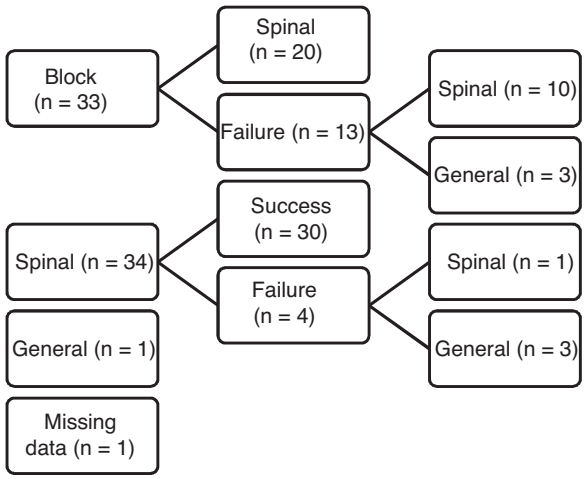

Figure 1 Sample distribution according to the type of anesthetic technique performed (block: peripheral nerve block; spinal: spinal anesthesia; *n*: number).

- Personal or family history of malignant hyperthermia, masseter trismus or rhabdomyolysis (55 patients);
- Idiopathic increase of creatine kinase (5 patients);
- Central core disease (CCD)—a pathogenic mutation not yet identified (9 patients).

There was a previous complaint of muscle weakness or myalgia in 17 patients and CK was increased in 17. IVCT was positive in 65.2% of patients, indicating susceptibility to MH, with 74% of men and 59.5% of women susceptible.

The anesthesia mean time was 95 ± 29 min, while the duration of surgery was 49 ± 15 min. Sedation was used in 54 patients, with midazolam in 53 (isolated in 34, associated with propofol in two, and associated with fentanyl in 17) and diazepam in one patient. The analgesic medication prescribed for postoperative pain was intravenous dipyrone (2 g), which was used in 12 patients.

Thirty-four (49.3%) patients initially underwent spinal anesthesia, with block failure in four (11.8%), of which three underwent general anesthesia and one spinal anesthesia again. One patient (1.4%) underwent general anesthesia, and, in one patient (1.4%) data regarding the anesthetic technique used was missing. The remaining 33 patients (47.8%) initially underwent femoral and lateral femoral cutaneous nerve block, with block failure in 13 (39.4%); 10 patients underwent spinal anesthesia and three patients underwent general anesthesia (Fig. 1). There were significantly more failures in nerve block than in spinal anesthesia ($p < 0.01$, chi-square test).

Spinal anesthesia was given by median approach in all cases. The peripheral nerve identification method was reported in 24 of 33 patients undergoing peripheral nerve block: isolated peripheral nerve stimulator was used in nine cases, isolated Doppler ultrasound was used in four cases, and peripheral nerve stimulator and Doppler ultrasound was used in 11 cases.

All patients remained in the PACU for at least 6 h postoperatively, none of which required ICU admission. None of the patients in the present study had symptoms or signs suggestive of malignant hyperthermia during or after anesthesia for muscle biopsy. However, six patients (8.7%) had other anesthesia-related adverse effects for muscle biopsy, such as nausea ($n = 4$; 5.8%), transient neurologic syndrome ($n = 1$; 1.4%), and bradycardia ($n = 1$; 1.4%), all of which occurred in patients undergoing spinal anesthesia. One patient who presented with nausea and those who presented with transient neurological syndrome (equine tail syndrome) and bradycardia initially underwent peripheral nerve block and, due to block failure, they underwent spinal anesthesia. These six patients were referred for MH investigation due to personal or family history of malignant hyperthermia (4), idiopathic increase of creatinine kinase (1), and myopathy (1). There were significantly more adverse effects after spinal anesthesia than after peripheral nerve block alone ($p < 0.05$; chi-square test). Note that three patients who received spinal anesthesia had unsuccessfully received peripheral nerve block.

Blockade latency time was 65 ± 41 min for all anesthetic techniques. If we considered the effective block in the first attempt, it was 45 min for general anesthesia ($n = 1$ patient), 25 ± 13 min for spinal anesthesia ($n = 30$ patients), and 36 ± 20 min for peripheral nerve block ($n = 20$ patients). Blockade duration was significantly lower in the group undergoing spinal anesthesia ($p < 0.05$, unpaired *t*-test).

Medications used for the three anesthesia techniques

In peripheral nerve block, 1.5% lidocaine associated with 1:200,000 adrenaline ($n = 6$) patients) and 0.375% bupivacaine associated with 1:200,000 adrenaline ($n = 27$) were used. In spinal anesthesia, 0.5% hyperbaric bupivacaine was used ($n = 44$). In general anesthesia, propofol and fentanyl ($n = 4$) or etomidate and fentanyl ($n = 3$) were used.

Subgroup analysis of subjects without vs. with block failure (spinal or peripheral block)

Age was significantly higher in patients with block failure (Table 1). In addition, weight was significantly greater in patients with block failure (83.91 ± 7.58 kg in 11 patients with block failure vs. 66.82 ± 3.33 kg in 34 patients with block success) ($p < 0.05$, unpaired *t*-test). There was no difference in height between 40 patients with and without block failure (165.2 ± 2.98 cm vs. 162.6 ± 1.91 cm) (p = ns, unpaired *t*-test).

Moreover, there was an association between block failure and the reason indicated for MH-susceptibility investigation; thus, block failure was significantly more frequent in patients with idiopathic creatine kinase increase (failure in 3 of 5 [60%] patients) than in patients with a family history of malignant hyperthermia (failure in 10 of 53 [19%] patients); there was no difference regarding central core myopathy (failure in 4 of 9 [44%] patients) (Table 1).

In the 53 patients with a personal or family history of malignant hyperthermia, there was failure in seven (13%) patients undergoing peripheral nerve block and in three (5.6%) undergoing spinal anesthesia. In the nine patients with myopathy, there was failure in three (33%) patients undergoing femoral block and in one (11%) undergoing spinal anesthesia. In the five patients with idiopathic creatine

Table 1 Comparison of block failure/success between groups.

Variable	Failure ($n = 17$)	Success ($n = 50$)	p
Age (years)	39.53 ± 12.89	31.68 ± 13.45	$p < 0.05$[a]
Up to 23.5	1 (1 PNB)	15	
>23.5	16 (12 PNB)	35	
Female	8 (47%)	33 (65%)	ns[b]
Weakness or myalgia	6 (35%)	11 (22%)	ns[b]
Indication for IVCT			$p < 0.05$[b,c]
Malignant hyperthermia	10 (59%)	43 (86%)	
Increased idiopathic CK	3 (18%)	2 (4%)	
Myopathy	4 (23%)	5 (10%)	
Increased CK	4 (23%)	12 (24%)	ns[b]
Positive IVCT	12 (71%)	32 (64%)	ns[b]
Preanesthetic midazolam	12 (71%)	39 (78%)	ns[b]

PNB, peripheral nerve block; CK, creatinine kinase; *n*, number; ns, not significant; IVCT, in vitro contracture test.
[a] Unpaired *t*-test.
[b] Chi-square test.
[c] Significantly more block failure in increased idiopathic CK than in malignant hyperthermia.

kinase increase, there was failed in three (60%) patients undergoing femoral block.

There was no association between block failure and the following variables: gender, previous complaint of weakness or myalgia, increased CK, positive result for IVCT or use of midazolam as preanesthetic medication (Table 1).

The cut-off point for age and weight regarding block failure was established by the ROC curve for sensitivity values $\geq$90%, 23.5 years and 59.5 kg, respectively (Table 1). In patients weighing more than 59.5 kg ($n = 30$), there was failure of femoral block in 7 of 14 (50%) patients and failure of spinal anesthesia in 3 of 16 (18.7%); in patients weighing up to 59.5 kg, there was failure of femoral block in 1 of 7 (14%); none of the 8 patients showed spinal block failure.

Over the 24 months (from April 2008 to March 2010) in which the 33 peripheral blocks were analyzed, the percentage of block failure was 28.5% (6 failures in 21 blocks) in the first 12 months and 58.3% (7 failures in 12 blocks) in the last 12 months.

Discussion

In this study, the anesthesia using non-triggering agents, specifically benzodiazepines, opioids, propofol, etomidate, and local anesthetics with vasoconstrictor (in spinal anesthesia and peripheral nerve block), showed to be safe in MH-susceptible patients in the appropriate monitoring scenario and previous setting of the anesthesia room/machine for MH. Despite the higher number of women in the present sample, this study shows a higher incidence of MH-susceptibility in men by the positive IVCT results, similar to that found in the international literature.[2] Children were not included in this study due to the minimum age limit (10 years) for IVCT in our protocol; however, another group has already demonstrated that regional block is safe in children with suspected MH.[18]

While spinal anesthesia had a lower failure rate and shorter latency time compared to peripheral nerve block, it also had more complications. The adverse events found in this study are in agreement with the previously mentioned: Scala et al.[10] reported 8% of nausea and vomiting in patients tested for MH susceptibility, while in this study 5.8% presented such complaints. Some of the patients undergoing IVCT in the present study had CCD myopathy as a test indication. There are controversies regarding the safety of regional anesthesia in patients with neuromuscular diseases; the following precautions in regional anesthesia are suggested for these patients: avoid the paraesthesia technique, use less potent local anesthetics with lower doses and concentrations, and avoid the use of vasoconstrictors.[19,20]

The patients remained in the post-anesthesia care unit for 6 h under continuous monitoring and were discharge from hospital on the same day. Studies suggest that ambulatory anesthesia is safe for MH-susceptible patients; the recommended time required for monitoring serious adverse events has declined over the years, from four to up to 1 h, depending on the procedure and monitoring site.[9,21–23]

To our knowledge, the lower frequency of block failure in patients with a family history of malignant hyperthermia, compared to those with increased idiopathic creatine kinase, has not been previously described. As it has been reported that patients with a family history of malignant hyperthermia may have muscular hypertrophy, it would be possible that in these patients the procedure would be easier due to the better definition of the landmarks. This hypothesis is in agreement with the association, in the present study, between block failure and presence of increased idiopathic creatine kinase, probably due to changes in the muscle structures of these patients, which would hinder both femoral and spinal blockades. In lumbar puncture, the association between block failure and older age and/or higher body weight should probably be due to spinal abnormalities, such as kyphosis, scoliosis, ligament calcification,

and consequences of osteoporosis; while in peripheral nerve block, it would be due to obesity.[24]

Currently, with the required care mentioned in this article, the anesthesia with non-triggering agents is safe in MH-risk patients.[25,26] Recently, activated charcoal filters have started to be used as an option to rapidly clean the anesthesia machine from halogenated waste. However, this resource is not yet available in Brazil.[27] In future anesthesia procedures these MH-susceptible patients (with positive IVCT) should be anesthetized without triggering agents, with adequate monitoring and previous setting of the anesthesia room/machine. On the other hand, patients without MH susceptibility (with negative IVCT) may be safely exposed to triggering agents.[28] However, it is imperative to bear in mind that the isolated genetic test does not rule out the diagnosis of MH susceptibility due to the genetic heterogeneity of this syndrome and the presence of more than one mutation in some families.[2,8]

Conclusion

Anesthesia with non-triggering agents has shown to be safe in MH-susceptible patients. There was a higher frequency of failure in femoral nerve block than in spinal block, although there were complications only in spinal block, with the exception that three patients undergoing spinal anesthesia had unsuccessfully received peripheral nerve block.

Block failure was correlated with older patients, with higher body weight and presence of increased idiopathic creatine kinase. These variables may be useful in selecting the anesthetic technique for this sample.

Funding

This work was carried out with support from the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPQ), Coordenação de Aperfeiçoamento de Pessoal de Nivel Superior-Brasil (CAPES) – Funding Code 001, and Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) – 1996/2222-3 and 1996/08743-5.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Denborough MA, Forster JF, Lovell RR, et al. Anaesthetic deaths in a family. Br J Anaesth. 1962;34:395–6.
2. Rosenberg H, Sambuughin N, Riazi S, et al. Malignant hyperthermia susceptibility. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2015, 1993-2015. 12.19.2003 [accessed 01.31.2013]. [Online]. Available: http://www.ncbi.nlm.nih.gov/books/NBK1146/
3. da Silva HC, Almeida CS, Brandao JC, et al. Malignant hyperthermia in Brazil: analysis of hotline activity in 2009. Braz J Anesthesiol. 2013;63:13–9.
4. Carr AS, Lerman J, Cunliffe M, et al. Incidence of malignant hyperthermia reactions in 2,214 patients undergoing muscle biopsy. Can J Anaesth. 1995;42:281–6.
5. Rosero EB, Adesanya AO, Timaran CH, et al. Trends and outcomes of malignant hyperthermia in the United States, 2000 to 2005. Anesthesiology. 2009;110:89–94.
6. Ellis FR, Halsall PJ, Ording H, et al. A protocol for the investigation of malignant hyperpyrexia (MH) susceptibility. Br J Anaesth. 1984;56:1267–9.
7. Larach MG, for the North American Malignant Hyperthermia Group. Standardization of the caffeine halothane muscle contracture test. Anesth Analg. 1989;69:511–5.
8. Hopkins PM, Rüffert H, Snoeck MM, et al. European Malignant Hyperthermia Group guidelines for investigation of malignant hyperthermia susceptibility. Br J Anaesth. 2015;115:531–9.
9. Wappler F. Anesthesia for patients with a history of malignant hyperthermia. Curr Opin Anaesthesiol. 2010;23:417–22.
10. Scala D, Di Martino A, Cozzolino S, et al. Follow-up of patients tested for malignant hyperthermia susceptibility. Eur J Anaesthesiol. 2006;23:801–5.
11. Grinberg R, Edelist G, Gordon A. Postoperative malignant hyperthermia episodes in patients who received ''safe'' anaesthetics. Can Anaesth Soc J. 1983;30:273–6.
12. Adnet PJ, Krivosic-Horber RM, Haudecoeur G, et al. Diltiazem and nifedipine reduce the in vitro contracture response to halothane in malignant hyperthermia-susceptible muscle. Can J Anaesth. 1990;37:556–9.
13. Ording H. Influence of propranolol on the in vitro response to caffeine and halothane in malignant hyperthermia-susceptible muscle. Acta Anaesthesiol Scand. 1989;33:405–8.
14. Wappler F, Fiege M, Schulte am Esch J. Pathophysiological role of the serotonin system in malignant hyperthermia. Br J Anaest. 2001;87:794–8.
15. Fiege M, Wappler F, Scholz J, et al. Effects of the phosphodiesterase-III inhibitor enoximone on skeletal muscle specimens from malignant hyperthermia susceptible patients. J Clin Anesth. 2000;12:123–8.
16. Gunter JB, Ball J, Than-Win S. Preparation of the Drager Fabius anesthesia machine for the malignant-hyperthermia susceptible patient. Anesth Analg. 2008;107:1936–45.
17. Kim TW, Nemergut ME. Preparation of modern anesthesia workstations for malignant hyperthermia-susceptible patients: a review of past and present practice. Anesthesiology. 2011;114:205–12.
18. Maccani RM, Wedel DJ, Melton A, et al. Femoral and lateral femoral cutaneous nerve block for muscle biopsies in children. Paediatr Anaesth. 1995;5:223–7.
19. Veering BT. Regional anesthesia and the patient with preexisting neurological disease. Curr Opin Anaesthesiol. 2009;22:634–6.
20. Vercauteren M, Heytens L. Anaesthetic considerations for patients with a pre-existing neurological deficit: are neuraxial techniques safe? Acta Anaesthesiol Scand. 2007;51:831–8.
21. Brandom BW. Ambulatory surgery and malignant hyperthermia. Curr Opin Anaesthesiol. 2009;22:744–7.
22. Pollock N, Langton E, McDonnell N, et al. Malignant hyperthermia and day stay surgery. Anaesth Intensive Care. 2006;34:40–5.
23. Barnes C, Stowell KM, Bulger T, et al. Safe duration of postoperative monitoring for malignant hyperthermia patients administered non-triggering anaesthesia: an update. Anaesth Intensive Care. 2015;43:98–104.
24. Fettes PD, Jansson JR, Wildsmith JA. Failed spinal anaesthesia: mechanisms, management, and prevention. Br J Anaesth. 2009;102:739–48.

25. Glahn KP, Ellis FR, Halsall PJ, et al. Recognizing and managing a malignant hyperthermia crisis: guidelines from the European Malignant Hyperthermia Group. Br J Anaesth. 2010; 105:417–20.
26. Riazi S, Kraeva N, Hopkins PM. Updated guide for the management of malignant hyperthermia. Can J Anaesth. 2018;65:709–21.
27. Bilmen JG, Hopkins PM. The use of charcoal filters in malignant hyperthermia: have they found their place? Anaesthesia. 2019;74:13–6.
28. Frei D, Stowell KM, Langton EE, et al. Administration of anaesthetic triggering agents to patients tested malignant hyperthermia normal and their relatives in New Zealand: an update. Anaesth Intensive Care. 2017;45:611–8.