Use of the caffeine-halothane contracture test for the diagnosis of malignant hyperthermia in Brazil

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Abstract

Malignant hyperthermia (MH) is a pharmacogenetic disease triggered by volatile anesthetics and succinylcholine. Deaths due to MH have been reported in Brazil. The first Malignant Hyperthermia Diagnostic and Research Center in Latin America was inaugurated in 1993 at the Federal University of Rio de Janeiro, Brazil. The center followed the diagnostic protocols of the North American MH Group, in which the contractures of biopsies from the vastus lateralis muscle are analyzed after exposure to caffeine and halothane (CHCT). CHCT was performed in individuals who survived, their relatives and those with signs/symptoms somewhat related to MH susceptibility (MHS). Here, we report data from 194 patients collected over 16 years. The Southeast (N = 110) and South (N = 71) represented the majority of patients. Median age was 25 (4-70) years, with similar numbers of males (104) and females (90). MHS was found in 90 patients and 104 patients were normal. Abnormal responses to both caffeine and halothane were observed in 59 patients and to caffeine or halothane in 20 and 11 patients, respectively. The contracture of biopsies from MHS exposed to caffeine and halothane was 1.027 ± 0.075 g (N = 285) and 4.021 ± 0.255 g (N = 226), respectively. MHS was found in patients with either low or high blood creatine kinase and also with a low score on the clinical grading scale. Thus, these parameters cannot be used with certainty to predict MHS. We conclude that the CHCT protocol described by the North American MH Group contributed to identification of MHS in suspected individuals at an MH center in Brazil with 100% sensitivity and 65.7% specificity.

Key words: Malignant hyperthermia; Diagnosis; Skeletal muscle; Anesthesia

Introduction

Malignant hyperthermia (MH) is an autosomal dominant pharmacogenetic disease, with crises triggered in susceptible individuals (MHS) by exposure to halogenated general anesthetics and/or succinylcholine, a depolarizing muscle relaxant (1). Hypermetabolic signs such as increased oxygen consumption and carbon dioxide production and tachycardia may be observed a few minutes after contact of MHS patient with these compounds, followed by severe muscle rigidity and rapid body temperature elevation, which can reach more than 44°C, rhabdomyolysis, bleeding, acute renal failure, and cardiac arrhythmias (1). Death occurs in approximately 75% of untreated patients (2).

The MH crisis enhances Ca^{2+} release from the sarcoplasmic reticulum (3) through the type 1 ryanodine receptor (RyR1). Mutations in the RyR1 gene are associated with 50-70% of the families affected by MH (4). RyR1 is one of the largest proteins in the body, is coded by a complex gene of 158 kb and 106 exons (5) and more than 100 different mutations associated with MH have been described (6). Mutations in sodium channels (7) and the alpha subunit of the dihydropyridine receptor (8,9) are associated with MH, but are very rare. Different mutations can produce different MH phenotypes. Recently, new mutations have been suggested to be associated with MH such as carnitine palmitoyltransferase II (CPT II) deficiency with heterozygous R506C mutation (10) and mutation in the calsequestrin 1...
MH has a low incidence but a high mortality rate. The incidence of MH is 1:15,000 and 1:50,000-100,000 in children and adults receiving anesthetics, respectively (12). After the clinical introduction of dantrolene sodium to treat MH, mortality decreased from 75% to less than 5% (12). However, the mortality of MH is increasing in the United States (11.7%) (13), Japan (15%) (14) and Taiwan (28.7%) (15). No data regarding MH incidence or death have been reported in Brazil.

Early detection of susceptibility is valuable in preventing MH mortality. The gold standard method to diagnose MH susceptibility is based on measuring the intensity of muscle biopsy contracture in response to caffeine and halothane (caffeine and halothane contracture test, CHCT), compounds that activate Ca\(^{2+}\) release from the sarcoplasmic reticulum through RyR1 (16,17). There are two diagnostic protocols for MH from the North American MH Group (17) and the European MH Group (18). The North American protocol consists of exposing the muscle biopsy to incremental concentrations of caffeine (0.5-32 mM) and a single concentration of halothane (3%). The European protocol uses the same dose-response curve for caffeine, but increases halothane concentrations (0.5-3%). The North American protocol of CHCT has 97% sensitivity and 78% specificity (19).

Global MH centers can use genetic diagnostic methods for MH, which are less invasive for the patient than the CHCT. Once a causative mutation has been detected in the proband or index patient, it can be used to test relatives who have not yet been tested by CHCT. Mutation carriers should consequently be regarded as susceptible to MH. However, only 30 mutations have been shown to cause MH directly, with an increase of Ca\(^{2+}\) efflux through RyR1 observed in \textit{in vitro} studies. Family members who do not carry the mutation observed in the pedigree should still undergo CHCT investigation (20).

MH can also be predicted after the development of a hypermetabolic crisis during general anesthesia. Larach et al. (21) described a clinical grading scale based on clinical signs and symptoms associated with MH. This scale ranks the qualitative likelihood that an adverse anesthetic event indicates MH. Factors like MH family history and signs of MH crisis during anesthesia such as muscular rigidity, muscle breakdown, respiratory acidosis, increased temperature, and cardiac arrhythmias are used as indicators to diagnose MH. However, currently this scale cannot be used to determine the diagnosis or treatment during an MH-like episode because clinical symptoms of an MH crisis are nonspecific, and the diagnosis can be difficult to establish only with clinical signs (20). The final diagnosis is only confirmed by the CHCT.

Many case reports at the Brazilian National Society of Anesthesiologists meetings have reported lethal MH episodes. In 1993, the first Malignant Hyperthermia Diagnostic and Research Center in Latin America was created in Rio de Janeiro, Brazil. This MH Center has brought significant benefit to the families and anesthesiologists involved with patients who present unexplainable complications during general anesthesia. The purpose of this article is to present data from the Center for the past 16 years and compare them to international data.

Subjects and Methods

Subjects

The Institutional Ethics Committee of the Federal University of Rio de Janeiro, Brazil, approved the study.

Control CHCT was performed in 32 volunteers, and Drs. Thomas Nelson and Henry Rosenberg, members of the North American MH Group, evaluated and approved the viability of the Center in 1992. Since then, the Brazilian MH Center in Rio de Janeiro has performed 194 biopsies with an average of 11.6 biopsies per year.

The patient selection protocol for CHCT was based on that described by the Malignant Hyperthermia Association of the United States (MHAUS); people who survived an MH crisis or presented an incomplete MH episode during general anesthesia (i.e., muscular rigidity without hyperthermia), relatives of MHS individuals, including relatives who suffered unexplainable death during general anesthesia, and patients who had never undergone general anesthesia, but had signs/symptoms or laboratory exams indicative of MH (i.e., frequent cramps, congenital anomalies, or increased creatine kinase (CK) levels). Most of the patients were referred to the MH Brazilian Center by their doctors due to a suspected clinical episode of MH. Other patients were recommended by relatives when MH susceptibility was suspected due to family deaths, survival or susceptibility confirmed by the North American protocol of CHCT. Patients with muscle atrophy, weighing less than 20 kg, or less than 4 years old were excluded from the exam.

A written informed consent form to participate in the study was signed by all subjects in accordance with the North American protocol of CHCT. Patients submitted to the CHCT were admitted to the hospital one day before the biopsy was taken and their general health was evaluated during the pre-anesthesia visit. A blood sample for CK measurement was collected in the operating room before performing the biopsy.

Caffeine-halothane contracture test

A biopsy of the vastus lateralis muscle approximately 3.5 cm long, 2.0 cm wide and 1.5 cm deep was performed under local anesthesia of the femoral and femoral-cutaneous nerves with a mixture of lidocaine (1.5%) and epinephrine (1:200,000) in adults, and under general anesthesia with a combination of propofol (1.5 mg·kg\(^{-1}\)·min\(^{-1}\) iv bolus followed by infusion of 100 µg·kg\(^{-1}\)·min\(^{-1}\)) and remifentanil (2 µg/kg iv bolus) in children less than 14 years old. The muscle...
was immediately immersed in a temperature-controlled flask filled with Ringer-Krebs solution (118.1 mM NaCl, 3.4 mM KCl, 0.8 mM MgSO$_4$·7H$_2$O, 1.2 mM KH$_2$PO$_4$, 25 mM NaHCO$_3$, 2.5 mM CaCl$_2$·2H$_2$O, 11.1 mM glucose), pH 7.4, oxygenated with a carbogen mixture (95% O$_2$ plus 5% CO$_2$). In the laboratory, 3-4 smaller fragments 1.5-2.0 cm long and 2.5-3.0 mm wide were dissected and positioned in vertical chambers (50 mL) in which one end of each muscle was attached to a fixed clamp and the other to an FT-03 force transducer (AstroMed Grass Instruments, USA) for isometric tension recording. The chambers were filled with oxygenated Ringer-Krebs solution maintained at 37 ± 0.1°C, pH 7.4 ± 0.02. Muscle twitches were elicited by electric field stimulation (50 V, 2-ms duration, 0.2 Hz). A Cyberamp (Axon Instruments, Inc., USA) conditioned the signals generated by the force transducer. These signals were digitalized (Digidata 1322, Axon Instruments, Inc., USA), displayed, and stored on a computer for further analysis using the Axoscope software (Axon Instruments, Inc., USA). The length-tension curve was constructed for each muscle fragment to obtain the maximal twitch response. After 30 min of adaptation, caffeine (Sigma-Aldrich, USA) was added to the solution in incremental concentrations (0.5, 1, 2, 4, 8, and 32 mM) at intervals of 4 min or after plateau contractions were reached. The stock solution of caffeine was freshly prepared in Ringer-Krebs solution. After the end of the caffeine contracture test, the chambers were carefully washed to eliminate contamination with caffeine and, using the same procedure, 3-4 additional muscle fragments were prepared for isometric tension recording. After a period of adaptation, a gas mixture containing 3% halothane (Cristália, Brazil) and carbogen was bubbled into the Ringer-Krebs solution for 10 min. A calibrated vaporizer (Fluovapor 1220, K. Takaoka, Brazil) was used to measure halothane concentration.

Muscle twitches (Pt; mean ± SEM = 2.928 ± 0.072 g, N = 1428) were used as a parameter of muscle viability but not for diagnostic purposes. Fragments with no twitches were discarded. The baseline tension for a diagnosis of MH was 0.2 and 0.7 g in response to caffeine (2 mM) and halothane (3%), respectively, measured in any muscle fragment independently of the type of protocol.

Clinical grading of patients

Patient information collected before biopsy included muscle rigidity, abnormal increase of CK, rhabdomyolysis-like signs, increased oxygen consumption and production of carbon dioxide by muscle metabolism, high temperature, tachycardia, arrhythmias, acidosis, response to dantrolene, and family history and was used to rank patients on a clinical scale to predict MH (21): 1 (almost never), 2 (unlikely), 3 (somewhat unlikely), 4 (somewhat likely), 5 (very likely), and 6 (almost certain). The MH susceptibility obtained from the North American protocol of CHCT was compared to that predicted by clinical grading.

Statistical analysis

Data are reported as means ± SEM. The average between two groups was compared by the Student t-test. Statistical significance was defined as P < 0.05. The GraphPad Prism version 4 software was used for statistical analysis.

Results

Demographic data

From February 1993 to October 2009, 194 patients were eligible for diagnosis by CHCT. Table 1 shows that 110 patients came from the Southeast region of Brazil, 71 from the South, 8 from the Central West, and 3 from the Northeast. Rio de Janeiro (30.4%), Santa Catarina (28.9%), and São Paulo (11.3%) were the Brazilian states that more contributed to the total number of patients submitted to the CHCT. No patient came from the North region. CHCT was also performed in 1 patient from Argentina and 1 from Portugal.

Similar numbers of males (104) and females (90) were submitted to the test. Patients were predominantly young, with 55.7% of them being less than 29 years old (Table 2). The youngest patient was 4, the oldest 70, and the median age was 25 years.

Caffeine-halothane contracture test

A typical recording of a CHCT is shown in Figure 1. The tension response of the muscle was dependent on Table 1. Distribution of 192 Brazilian patients submitted to the North American caffeine halothane contracture test (CHCT) for the diagnosis of malignant hyperthermia from 1993 to 2009.

<table>
<thead>
<tr>
<th>Region/State</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>North</td>
<td>0</td>
</tr>
<tr>
<td>Northeast</td>
<td>3</td>
</tr>
<tr>
<td>Pernambuco</td>
<td>2</td>
</tr>
<tr>
<td>Sergipe</td>
<td>1</td>
</tr>
<tr>
<td>Central West</td>
<td>8</td>
</tr>
<tr>
<td>Mato Grosso</td>
<td>1</td>
</tr>
<tr>
<td>Mato Grosso do Sul</td>
<td>2</td>
</tr>
<tr>
<td>Goiás</td>
<td>3</td>
</tr>
<tr>
<td>Distrito Federal</td>
<td>2</td>
</tr>
<tr>
<td>Southeast</td>
<td>110</td>
</tr>
<tr>
<td>Minas Gerais</td>
<td>14</td>
</tr>
<tr>
<td>Espírito Santo</td>
<td>15</td>
</tr>
<tr>
<td>São Paulo</td>
<td>22</td>
</tr>
<tr>
<td>Rio de Janeiro</td>
<td>59</td>
</tr>
<tr>
<td>South</td>
<td>71</td>
</tr>
<tr>
<td>Paraná</td>
<td>6</td>
</tr>
<tr>
<td>Rio Grande do Sul</td>
<td>9</td>
</tr>
<tr>
<td>Santa Catarina</td>
<td>56</td>
</tr>
</tbody>
</table>
caffeine concentration and MH susceptibility. While twitches were increased at concentrations lower than 4 mM, no increases of baseline (contracture) was noted when non-MHS (MHN) muscle was exposed to caffeine (Figure 1A). The intensity of muscle contracture increased in a dose-dependent manner at concentrations above the threshold. MHS muscle showed baseline contraction of more than 0.2 g after 2 mM caffeine (Figure 1B). MHN muscle was also less sensitive to halothane (3%), with increased muscle twitches but no increase in baseline tension (Figure 1C). In contrast, halothane increased MHS muscle tension above 0.7 g (Figure 1D).

MHS was detected in 90 of 194 patients (46.4%) and not detected in 104 patients (53.6%) (Figure 2). Biopsies from 59 of 90 patients (65.6%) responded positively to caffeine and halothane, 20 only to caffeine, and 11 only to halothane. MHS patients were split between females (36) and males (54). The average baseline tension (contracture) of MHN muscle after 2 mM caffeine or 3% halothane was 0.007 ± 0.001 g (N = 432) and 0.050 ± 0.011 g (N = 485), respectively. The number of muscle specimens was higher than the number of patients because 3-4 specimens for each patient were used for the caffeine or halothane test. The average tension from MHS fragments was 1.027 ± 0.075 g (N = 285) and 4.021 ± 0.255 g (N = 226), respectively (P

Table 2. Age distribution of 194 patients submitted to the North American caffeine halothane contracture test (CHCT) for the diagnosis of malignant hyperthermia.

<table>
<thead>
<tr>
<th>Age range (years)</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-9</td>
<td>43</td>
</tr>
<tr>
<td>10-19</td>
<td>37</td>
</tr>
<tr>
<td>20-29</td>
<td>28</td>
</tr>
<tr>
<td>30-39</td>
<td>38</td>
</tr>
<tr>
<td>40-49</td>
<td>29</td>
</tr>
<tr>
<td>50-59</td>
<td>13</td>
</tr>
<tr>
<td>60-69</td>
<td>5</td>
</tr>
<tr>
<td>70-79</td>
<td>1</td>
</tr>
</tbody>
</table>

Figure 1. Typical isometric tension recording of the vastus lateralis muscle of MHN (A and C) and MHS (B and D) patients in the presence of caffeine (0.5, 1, 2, 4, 8, and 32 mM) and halothane (3%). Note that after adding caffeine to the solution (arrows) the height of twitches increased in a dose-dependent manner. The threshold to increase baseline tension (contracture) was lower for MHS (B) than for MHN muscle fragments (A). Halothane was bubbled into the solution for 10 min. The threshold of MHS muscle response (D) to halothane was lower than that of MHN muscle (C). MHN = malignant hyperthermia non-susceptible patient; MHS = malignant hyperthermia susceptible patient.

Figure 2. Malignant hyperthermia susceptibility of patients submitted to the caffeine (Caff) and halothane (Hal) contracture test. The patients were divided into malignant hyperthermia non-susceptible (MHN) and malignant hyperthermia susceptible (MHS) subjects. The MHS group of patients was divided into 3 subgroups representing those who responded positively to both caffeine and halothane, to caffeine only and to halothane only. Patient distribution according to MH susceptibility is shown in parentheses.
The CK levels measured in MHN (192.8 ± 65.3 U/L, N = 104) and MHS patients (216.3 ± 53.4 U/L, N = 90) were similar. Most MHN patients (91) had CK levels within the normal range (Figure 3). Surprisingly, 65 MHS patients (72.2%) showed normal CK levels (Figure 3), with only 25 patients (27.7%) showing above normal levels. Most MHS patients (67.8%) that positively responded to both caffeine and halothane had normal CK levels, with 19 patients (32.2%) showing above normal levels. Most MHS patients that responded to caffeine or halothane had normal CK levels (Figure 3).

**Correlation between CHCT and clinical grading**

We next correlated CHCT and the MH rank described by Larach et al. (21) (Table 4). Of 59 patients at low risk to develop MH (ranks 1 and 2), 40 (67.8%) were diagnosed as MHN and 19 (32.2%) as MHS. One hundred and twenty-five patients were distributed in the median rank (ranks 3 and 4), with a mix of MHN (N = 62, 49.6%) and MHS (N = 63; 50.4%). Twenty of 90 MHS patients (22.2%) and 41 of 104 MHN patients (39.4%) suffered a suspected MH crisis during general anesthesia. All grade 6 patients (N = 4) who survived a completely clinically detected MH crisis presented a positive response to CHCT. Eighty percent of grade 5 and 6 patients presented a positive response.

The sensitivity and specificity obtained from CHCT was calculated based on subjects ranked 6 from the scale (“almost certain” to be MHS), and from subjects ranked 1 (unlikely to be MHS). The calculated specificity and sensitivity from this center were 100% and 65.7%, respectively.

<table>
<thead>
<tr>
<th>MH rank</th>
<th>Description of likelihood</th>
<th>MHN</th>
<th>MHS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Almost never</td>
<td>23/35</td>
<td>12/35</td>
</tr>
<tr>
<td>2</td>
<td>Unlikely</td>
<td>17/24</td>
<td>7/24</td>
</tr>
<tr>
<td>3</td>
<td>Somewhat less than likely</td>
<td>57/98</td>
<td>41/98</td>
</tr>
<tr>
<td>4</td>
<td>Somewhat greater than likely</td>
<td>5/27</td>
<td>22/27</td>
</tr>
<tr>
<td>5</td>
<td>Very likely</td>
<td>2/6</td>
<td>4/6</td>
</tr>
<tr>
<td>6</td>
<td>Almost certain</td>
<td>0/4</td>
<td>4/4</td>
</tr>
</tbody>
</table>

MHN = malignant hyperthermia non-susceptible patient; MHS = malignant hyperthermia susceptible patient.

**Table 3.** Vastus lateralis muscle contracture in response to exposure to 2 mM caffeine and 3% halothane (CHCT).

<table>
<thead>
<tr>
<th>Contracture of muscle fragments (g)</th>
<th>MHN</th>
<th>MHS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caffeine</td>
<td>0.007 ± 0.001 (N = 432)</td>
<td>1.027 ± 0.075* (N = 285)</td>
</tr>
<tr>
<td>Halothane</td>
<td>0.050 ± 0.011 (N = 485)</td>
<td>4.021 ± 0.255* (N = 226)</td>
</tr>
</tbody>
</table>

Data are reported as means ± SEM. MHN = malignant hyperthermia non-susceptible patient; MHS = malignant hyperthermia susceptible patient. *P < 0.05 compared to MHN (Student t-test).
Discussion

Malignant hyperthermia is a potentially lethal pharmacogenetic disorder of skeletal muscle induced by exposure to the inhalation of general anesthetics and/or succinylcholine (1). The high mortality of MH (ca. 75%) has been reduced by research on the disease, development of diagnostic protocols, and specific drug treatments for acute MH symptoms. The CHCT is still a reliable and highly sensitive test for detecting MH susceptibility. We present here data obtained for 16 years using the CHCT protocol approved by the North American MH Group at the MH Diagnostic Center of the Federal University of Rio de Janeiro.

The distribution of 194 patients submitted to the CHCT was not homogeneous from the 11 Brazilian states, probably because of the center’s location. Most patients (N = 110, 56.7%) came from the Southeast, including the State of Rio de Janeiro, where the diagnostic center is located. However, 71 patients (36.6%) were from the South, which is located farther than the Southeast. Santa Catarina, with 56 patients, is more than twice as far as São Paulo from the diagnostic center, and São Paulo State is approximately 6.9 times larger than Santa Catarina. Thus, geographic localization is not the only factor that explains the high MH density. In fact, patients from Santa Catarina are related to three families of German origin, and the mutation could have resulted from European ancestors. This is in agreement with another large family of Italian heritage from São Paulo showing a severe MH crisis with death during general anesthesia. Additionally, an important explanation for the reduced number of patients from São Paulo in comparison to Santa Catarina is related to the development of an MH Diagnostic Center in that state at the Federal University of São Paulo (UNIFESP). Families from the Northeast, where colonization was from Holland, can show MH crises as well.

No native Brazilian Indians received the test. Absence of an MH Diagnostic Center in Argentina brought one patient with family episodes of MH from that country, and relatives living in Brazil recommended another patient, also with a family history of MH, from Portugal. MH susceptibility was confirmed only in the Argentinian patient.

Most (75.3%) patients were less than 40 years old, with a median age of 25 years, indicating that MH is more prevalent in young individuals.

MH susceptibility was found in 46.4% of the patients (90/194), in agreement with rates from laboratories from Denmark and Toronto, 51.8 and 31.8% (22), respectively, where 1082/2214 patients were found to be susceptible to MH (48.9%) (23). MH susceptibility was lower (21.1%) in 10 laboratories from the North American MH Association (19). We detected muscle contracture to both caffeine and halothane in 59 of 90 MHS patients, and a selective response to caffeine or halothane in 20 and 11 patients, respectively. This apparent discrepancy in the reaction of the muscle to caffeine or halothane may occur because of the diversity of RyR1 mutations (24). According to the North American MH group (17), patients with abnormal reactions to caffeine or halothane are considered to be MHS. According to the European MH group (18), which has some differences in the protocol, one positive test means the individual is considered to be MH equivocal (MHE). Thus, 34.4% of the Brazilian MHS patients could be classified as MHE, similar to two Danish laboratories, with 34.8 and 34.5% (25) and to 22 centers of the European MH group, with 33.5% (26).

The hypermetabolism and breakdown of muscle membranes induced by increased Ca\(^{2+}\) concentration during an MH crisis may cause hyperkalemia, hyperphosphatemia, hypocalcemia, and increased serum levels of CK. Increased CK levels correlate with MHS incidence but are not sufficient as a screening test (27). Weglinski et al. (28) reported that 49% of 49 patients with high CK levels had a positive CHCT. However, Malandrini et al. (29) described only one MHS and one MHE patient of 37 with idiopathic hyperkalemia, or elevated serum CK levels without weaknesses or other neuromuscular symptoms. CK levels above normal (25-170 U/L) were observed in 13/104 (12.5%) and 25/90 (27.8%) of MHN and MHS patients, respectively, indicating a lack of correlation of CK levels with MH susceptibility.

We correlated the clinical signs and symptoms suggested by the North American MH Registry (21) to our in vitro test. A high correlation (>80%) was found in high-risk patients (rank 4-6), but a CHCT above the normal level was observed in 32.2% of rank 1-2 patients (low risk). We concluded that the clinically based score cannot predict that patients in the low probability rank are not susceptible to MH crises. MH clinical grading may therefore underestimate the likelihood of an MH event if an anesthetic was aborted early in the course of a reaction or in the absence of complete monitoring with capnography and arterial blood gas analysis (30). Recently, at the 3rd International Symposium on MH, Larach et al. (31) showed a similar lack of correlation between clinical grading and CHCT in North American patients. The clinical presentation of MH is highly variable and clinical data were frequently incomplete, making the MH risk difficult to measure using a clinical scale (32).

Genetic testing for detecting MH susceptibility (20) requires the consideration of mutations specific to a population, such as North America (33). However, not all mutations show a similar prevalence, and most of them are found in a single family. Our MH Center has already described a specific mutation in two Brazilian families (34).

In summary, the recommended CHCT described by the North American Malignant Hyperthermia Group was successfully applied at the Brazilian MH Center in Rio de Janeiro for the identification of MH susceptibility in 194 patients recommended for the test over 16 years of existence of the center.
Acknowledgments

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References


