Author's response to reviews

Title: Evaluation of suspected malignant hyperthermia events during anaesthesia

Authors:

Frank Schuster (schuster_f@klinik.uni-wuerzburg.de)
Stephan Johannsen (johannsen_s@klinik.uni-wuerzburg.de)
Daniel Schneiderbanger (schneiderb_d@klinik.uni-wuerzburg.de)
Norbert Roewer (Anaesthesie-Direktion@klinik.uni-wuerzburg.de)

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Author's response to reviews: see over
Dear Dr. Rowles,
Dear reviewers,

enclosed to the revised manuscript we would like to reply to the specific questions and comments of the reviews and outline the corrections and modifications of the manuscript.

Thank you and all the reviewers for your great effort to improve content and language of our manuscript. Your suggestions concerning better use of language have gratefully been accepted and integrated into the revised version without being mentioned again one by one in this letter. Furthermore, prior to revision the manuscript was proofread by an English teacher to improve linguistic quality. To keep this reply as short as possible we also refrained from citing each altered paragraph and kindly ask you to consider the highlighted modifications in the context of the entire manuscript, which we attached at the end of the cover letter.

Again we would like to thank you for your valuable comments and would be glad if the revised manuscript would meet with your approval.

Sincerely,

Frank Schuster

**Reviewer: Joseph R Tobin**

Reviewer's report:
The hypothesis that modern volatile anesthetics are less potent triggers is introduced in the background and referring to reference 5. This has been disputed by japanese investigators published in Anesthesia and Analgesia in 2012. MH is still relevant to anesthesiologists today. Genetic analysis reveals far more abnormalities than previously described. In this manuscript, 124 patients were referred to this one center (Univ of Wuerzburg) over five years. This probably underrepresents the actual number of patients who had clinical signs of MH but were never referred. Of the 124 patients, 21 were determined to be MH susceptible and 20 patients were classified as MH equivocal.
The authors cannot conclude whether more modern anesthetics are associated with less risk for an MH episode.

Indeed, as stated in the background section, the MH-trigger potency of newer volatile anesthetics is beyond doubt. In fact, the aim of the presented study was not to show that newer anesthetics have a lower risk to induce MH. The reason, why the authors decided to write this manuscript was to keep MH in the mind of anesthesiologist, since authors were irritated to be confronted on an infrequent but persistent basis of anesthesiologists who query the need to be concerned about MH, since halothane is not longer used in clinical routine. So we would like to bring MH back in the mind of these colleagues by demonstrating that even newer inhalation anesthetics induce MH.

Although the use of succinylcholine in the patients is reported, the actual exposure to which volatile anesthetic and the MAC dose used are not reported.

In the revised version of our manuscript we present the used volatile anesthetics in table 1. We totally agree with the reviewer, that the MAC values would be of interest. However, du to
the lack of information concerning the applied doses, we are not able to give MAC doses. In most of the cases we received information about the course of a suspected MH episode from letters of the responsible anesthesiologist. Here, only the applied drugs were mentioned, but unfortunately not the doses. We hope that presenting the applied MH-trigger agents would satisfy the reviewer.

Major Compulsory Revision:

The authors do not make clear what is new or novel in their manuscript. Although it reads well, as a reviewer I do not note anything that has not been previously reported. Following the Background statement regarding 'modern volatile anesthetics that pretend to be less potent', is not discussed later in the manuscript. The analysis of MHS/MHN and MHE patients referred does not confer any new information about prevalence, or specificity of clinical signs as to whether MH is still a relevant issue. It is a relevant issue by the referral of 100+ patients to one center in a short interval of 5 years.

We agree with the reviewer that it would be helpful to discuss the MH trigger potency of newer anesthetics, hence we included a new paragraph in the discussion section on this issue (page 8, paragraph 2).

Indeed, we were not able to offer new information concerning the prevalence of MH, which regional differs. However, we were able to present the distribution of clinical signs of MH in the presented patients.

Reviewer: Neil A Pollock

Reviewer's report:

major compulsory revisions.

1. The numbers of cases in the results section do not appear consistent e.g. 19 patients were referred because of a suspected MH event. The 3rd paragraph of the result indicates that succinylcholine was used in 11 MHS patients – which group did these 11 patients belong to. It would also be useful to indicate how many of the 19 patients had masseter spasm and were volatile agents continued in 13 of the suspected MH reactions. The numbers are not clear.

To clarify the analysed cases, the authors rewrote the result section. For instance, we divided the results now in: “diagnostic findings”, “clinical presentation and trigger application” as well as “blood gas analysis”. Furthermore, the results, presented in one table, are now displayed in three different tables for better and easier reproducing of the data by the reader. Especially, the applied trigger agents were clarified. For details, please see table 1-3 and page 5 and 6 of the revised manuscript.

2. The authors have mentioned cardiac arrhythmias but have not indicated the type of arrhythmia. It would be useful to detail these

According to available medical records, sinus tachycardia and tachyarrhythmia were documented, but further details were not given by the referring anesthesiologists. The reported cardiac alterations are known mentioned in the result section (page 6, paragraph 2), in table 2 and in the discussion section (page 8, last paragraph).
3. 3 MHS patients had a positive DNA test. (Table 1) it would be useful to detail the mutations identified in these patients and also to indicate if the mutations were causative.

All MHS patients that were included in our study had undergone genetic screening for RYR1 mutations. We did not include this data in the first version of the manuscript, because they were heterogenous within the MHS group: Only 3 MHS patients have RYR1 mutations. But we agree that genotype is an important information although the results of our study cannot be attributed to a certain genotype. Therefore the detected RYR1 mutations were now added to the results (Table 1, page 5, 2. paragraph) and addressed in the discussion (page 9, last paragraph).

4. What is a significant metabolic acidosis. The authors are referred to an article by Wappler Eur J Anaesth 2001; 18;632-652.

According to authors’ assumption a severe metabolic acidosis is defined, when the following changes in blood acid status are noticed: pH ≤ 7.2, base excess ≤ -5 mmol/l and PaCO₂ ≥ 50 mmHg. This definition is now mentioned in the method section (page 4) to clarify inclusion criteria. Furthermore, we addressed this relevant information in the result section (page 6, last paragraph) and discussed our findings concerning blood gas analysis on page 9, paragraph 2 of the discussion section.

5. on page 4 line 8, what intraoperative procedures were the authors referring to

This phrase was deleted in the revised manuscript. Instead, the inclusion criteria were more clarified (method section, page 4, paragraph 1)

6. page 7, paragraph 3. This whole paragraph is unclear. Needs to be rewritten . intraoperative courses of the general anaesthesia - what does that mean and the reference to ICU is not clear.

We apologize for this confusing statement. The authors rewrote the complete paragraph. Furthermore, to improve the quality of reading, the paragraph was moved to page 9.

7. paragraph 3 of the discussion, last 2 lines - what does this mean. 'the presented collective of patients'

The phrases should describe the patients that were analyzed in our investigation. Since this statement confuses the reader, the phrase was deleted and the authors rewrote this part of the discussion.

8. On page 7, 2nd page of the discussion - did the patients with a temperature increase only have MH confirmed by a positive muscle biopsy

Unfortunately, in only two patients a body temperature increase > 38.5°C was reported. After reevaluation of available data, no genetic variant was detected in these patients. Hence, the MH diagnosis was solely confirmed by IVCT. For further details, please see Table 2 and page 9, paragraph 3 of the discussion.
Minor essential revisions

there are many particularly relating to the quality of English.

To improve the quality of English, the manuscript was proofread and corrected by an English teacher.

Reviewer: Sheila Riazi

Reviewer's report:

Major Compulsory Revisions:

1- Authors mentioned evaluation of severity of the suspected MH episodes in the abstract. There is no result on severity. Did they mean severity according to the clinical grading scale, or complications? please clarify.

We agree with the reviewer, that this phrase confuses the reader. According to the hypothesis in the background section, we rewrote this part of the abstract to clarify the underlying hypothesis. For details, please see the rewritten part of the abstract (page 2, paragraph 1)

2- Retrospective studies are limited due to unavailability of the data. However it would be interesting to review the suspected reaction, not only with regards to signs, but also complications. Can authors tell us also about the occurrence of complications? This shows the severity of the episodes.

Several reports demonstrated severe complications after surviving an MH episode. The authors would like to thank the reviewer for her suggestion to include this information in the revised manuscript. We addressed this relevant information in the method (page 3, paragraph 1), result (page 6, paragraph 3) as well as in the discussion section (page 10, paragraph 10). Fortunately, in no patients any serious complication was seen after the suspected MH episode.

3- Method section: The authors should specifically mention what signs they reviewed in the charts, did they look at tachycardia as well (is this part of the cardiac arrhythmias they mentioned?), how about serum/urine myoglobin? They calculated CGS score at the end, but many variables they were looking at, may not have been available for each patient. In addition the definition of the signs should be clear in the methods. In the result, they mentioned increased ETCO2, or metabolic acidosis, what are the definition for these according to authors?

The suggestion to define the screened variables is now included in the method section (page 4, paragraph 1). Furthermore, cardiac sensations observed after MH trigger application were described as far as possible (table 2). Unfortunately, in only two patients myoglobin values were documented and hence, not given in the manuscript. The authors think, that this approach is acceptable, since conclusion concerning the muscle response in course of an MH episode would be sufficiently documented by CK levels.
The lack of available patients’ data is the main limiting fact in calculating the CGS. This fact is addressed in the discussion section (page 10, paragraph 4).

4- Results: Since the focus of the paper is on the probands with suspected reactions, I think the demographics (female, male) should be described only on the 19 patients.

We agree with the reviewer in this point, and described the demographic data of the 19 patients with a suspected MH episode (page 5, paragraph 2).

5- Three patients who had their reactions in 1990s were also recruited, as their IVCT was performed within the study period. However, specifically the patient who had the reaction in 1992, is over 20 years ago. This may contradict the objective of the study, unless the volatile used was sevo/des, is this the case?? If it is, it should be explained.

The triggering agent in these three patients was halothane + succinylcholine, enflurane + succinylcholine or isoflurane + succinylcholine (table 1 & 2). Even if two of the applied agents are not longer used in clinical routine, we would be grateful, if the reviewer would agree to keep these patients in this investigation, since muscle biopsy and IVCT was performed within the study period.

6- It is very informative to know the number of patients with each signs, however, it might be more useful if they also use percentages (as denominator may not be clear to reader all the time).

7- Discussion, end of the third paragraph, again the numbers for patients with MMR should be stated as percentages as well.

8- Discussion-fifth paragraph, please mention the percentage for occurrence of MMR in your group of patients.

9- Discussion-second page, third paragraph-mention the percentage of your patient who received dantrolene.

Ad 6-9: We agree with the reviewer, that presentation of percentage increases clarity of the presented data. Hence, in the revised manuscript data are presented as percentage in the method and in the discussion section.

10-Discussion - Can the authors explain why succinylcholine was used in elective surgeries, was that for possible difficult airway?

In table 1 the reason for surgery is given. In some cases the reason why succinylcholine was used in the patients was a high risk of aspiration due to trauma or abdominal surgery. We addressed this issue in the discussion section on page 8, paragraph 1.

11-Discussion: Third paragraph, the authors mention the patients who had a reaction solely with succinylcholine. There were 3 MHEh patients within this group, who should be mentioned here. As they are treated as MH clinically, and according to North American criteria they are labeled as MHS as well.
The paragraph describing the effect of succinylcholine in MH patients has been completely rewritten to clarify the impact of succinylcholine. In this case, we hope that the role of succinylcholine to induce MH is now discussed to reviewer’s satisfaction.

Minor Essential Revisions:

1- Background: MH is mostly “an: inherited... (delete “a” before mostly
2- Background: trigger potency of currently applied volatile anesthetics “seems” (delete “is”).

Ad 1&2: The linguistic suggestions are now included in the revised version of the manuscript.

3- Results: the first paragraph can be rewritten to clarify the recruitment, maybe a diagram can clarify it better.

   We agree that the first version of this paragraph was a little bit confusion, hence in the revised version the whole result section was rewritten and is now defied into three section according to the presented tables (diagnostic findings, trigger application and clinical symptoms, and finally, blood gas analysis).

4- The table can be reorganized into three columns, according to IVCT results, with rows containing the triggers, signs, etc. The present format of the table looks more like a raw data table, and difficult to draw up conclusion.

   According to the suggestion of the reviewer the table was revised. Furthermore, the data are now presented in three tables (table 1: diagnostic findings, table 2: clinical presentation and applied trigger, table 3: blood gas analysis). We hope that this procedure increases the clarity of the presented data.

Discretionary Revisions:

1- The full description of IVCT can be shortened, and a reference can be used instead.

   The paragraph has been shortened substantially, more detailed information about standards for IVCT are available from the references.
Evaluation of suspected malignant hyperthermia events during anesthesia

Frank Schuster, MD, MHBA* Consultant Anesthesiologist, University of Wuerzburg, Department of Anaesthesia and Critical Care Wuerzburg, Germany
Email: schuster_f@klinik.uni-wuerzburg.de

Stephan Johannsen, MD Resident, University of Wuerzburg, Department of Anaesthesia and Critical Care Wuerzburg, Germany
Email: johannsen_s@klinik.uni-wuerzburg.de

Daniel Schneiderbanger, MD Resident, University of Wuerzburg Department of Anaesthesia and Critical Care Wuerzburg, Germany
Email: schneiderb_d@klinik.uni-wuerzburg.de

Norbert Roewer, MD Professor and Chair, University of Wuerzburg Department of Anaesthesia and Critical Care Wuerzburg, Germany
Email: Anaesthesie-Direktion@klinik.uni-wuerzburg.de

Corresponding author:
Priv.-Doz. Dr. med. Frank Schuster, MHBA
University of Wuerzburg
Department of Anesthesia and Critical Care
Oberduerrbacher Str. 6, D-97080 Wuerzburg
โทร +49 – 931 -201 30038; Fax: +49 – 931 -201 30039
Email: Schuster_F@klinik.uni-wuerzburg.de

Conflict of interest: The authors declare that they have no competing interests
Abstract

Background:
Malignant hyperthermia (MH), a metabolic myopathy triggered by volatile anesthetics and depolarizing muscle relaxants, is a potentially lethal complication of general anesthesia in susceptible patients. The implementation of modern inhalation anesthetics that research indicates are less potent trigger substances and the recommended limitations of succinylcholine use, suggests there may be considerable decline of fulminant MH cases. In the presented study the authors analyzed suspected MH episodes during general anesthesia of patients that were referred to the Wuerzburg MH unit between 2007 and 2011, assuming that MH is still a relevant anesthetic problem in our days.

Methods:
With approval of the local ethics committee data of patients that underwent muscle biopsy and in vitro contracture test (IVCT) between 2007 and 2011 were analyzed. Only patients with a history of suspected MH crisis were included in the study. The incidents were evaluated retrospectively using anesthetic documentation and medical records.

Results:
Between 2007 and 2011 a total of 124 patients were tested. 19 of them were referred because of suspected MH events; 7 patients were diagnosed MH-susceptible, 4 MH-equivocal and 8 MH-non-susceptible by IVCT. In a majority of cases masseter spasm after succinylcholine had been the primary symptom. Cardiac arrhythmias and hypercapnia frequently occurred early in the course of events. Interestingly, dantrolene treatment was initiated in a few cases only.

Discussion:
MH is still an important anesthetic complication. Every anesthetist must be aware of this life-threatening syndrome at any time. The rapid onset of adequate therapy is crucial to avoid major harm and possibly lethal outcome. Dantrolene must be readily available wherever MH triggering agents are used for anesthesia.

Keywords: malignant hyperthermia, In vitro contracture test, succinylcholine, volatile anesthetics
Background

Malignant hyperthermia (MH) is mostly an inherited subclinical myopathy triggered by volatile anesthetics and depolarizing muscle relaxants in susceptible individuals, leading to a potentially lethal hypermetabolic reaction of skeletal muscle due to a disturbance of myoplasmic calcium homeostasis. Characteristic clinical signs of MH during a general anesthesia include hypoxemia, hypercapnia, tachycardia, muscular rigidity, acidosis, hyperkalemia and hyperthermia [1]. While expected genetic predisposition for MH is stated to be as frequent as 1:2.000, the prevalence of MH episodes varies regionally from 1:10.000 to 1:220.000 [2,3]. In contrast to fulminant MH episodes, abortive courses might occur more frequently, but are difficult to diagnose due to the alleviated symptoms.

Recent developments in anesthesiology apparently have lead to a decrease in severe MH crisis over the last years: Halothane, a potent MH triggering agent, is no longer used in clinical routine in western countries [4] and currently applied volatile anesthetics, e.g. isoflurane, sevoflurane or desflurane, in some cases significantly decelerate the onset of an MH reaction compared to halothane [5,6] and are more likely to lead to abortive MH with eased symptoms. Furthermore, the recommended indications for succinylcholine, another possible MH triggering agent, have been limited by international anesthesia societies [7].

Considering all these facts, the aim of the present study was to investigate, whether MH is still a relevant anesthetic problem in our days.
Materials and Methods
With approval of the local ethics committee (application number: 263/11, ethics committee of the University of Wuerzburg) data of the patients who where referred to the MH unit of the Department of Anesthesia and Critical Care of the University of Wuerzburg for diagnostic muscle biopsy and subsequent in vitro contracture testing (IVCT) between 2007 and 2011 were evaluated. Based on available patient documents and medical records the intraoperative events were examined. Besides the applied triggering agents, clinical symptoms e.g. cardiac arrhythmia, increase of end-tidal carbon dioxide ≥ 45 mmHg, rises of patients' body temperature ≥ 38.5°C and possible use of dantrolene, were analyzed to confirm the suspicion of an MH crisis. Besides that, the medical records were reviewed for severe postoperative complications, e.g. neurological deficits, disseminated intravascular coagulation (DIC), acute renal failure or signs of rhabdomyolysis according to maximum creatine kinase (CK) levels. If blood gas analysis were implemented, pH ≤ 7.2, base excess ≤ -5 mmol/l and PaCO₂ ≥ 50 mmHg defined a severe metabolic response. Only patients with a suspected MH episode during general anesthesia due to the estimation of the responsible anesthesiologist, completed IVCT and genetic analysis of the ryanodine receptor gene were included in the investigation.

In referred patients a diagnostic IVCT with increasing caffeine and halothane concentrations in separated tissue baths was performed according to the guidelines of the European MH Group [8]. A contracture ≥ 2 mN at caffeine 2 mM and halothane 0.44 mM lead to the diagnosis MH susceptible (MHS). If significant contractures occurred after one of the drugs only, patients were classified as MH equivocal (MHE, MHE for halothane (MHEh) or caffeine (MHEc). If no significant contracture was observed the patients were rated MH non-susceptible (MHN).

In addition, for each patient, the clinical grading scale (CGS) by Larach and colleagues, which includes metabolic and muscular parameters as well as changes in cardiac rhythm and body temperature, was applied retrospectively. According to the grading scale 3 to 15 points were calculated for each parameter and added to receive a score. This score allowed allocation to individual MH-ranks (0 = MH almost never, 3-9 = MH unlikely, 10-19 = MH somewhat less than likely, 20-34 = MH somewhat greater than likely, 35-49 =MH very likely, > 50 = MH almost certain) [9].
Results
Between 2007 and 2011 a total of 124 patients underwent a muscle biopsy followed by IVCT at the MH lab of the University of Wuerzburg. 19 of these patients had been referred to the MH unit because of a suspected MH event during general anesthesia on the basis of estimation of the attending anesthesiologists. In the remaining patients MH diagnostics were initiated due to MH susceptibility in the family history, an unexplained rhabdomyolysis or to exclude a myopathic disorder in association with persistently elevated CK levels.

Diagnostic findings
The applied CGS rated the probability of an MH crisis as “almost certain” (> 50 points) in 2 MHS patients and “very likely” (35 – 49 points) in 5 MHS and 1 MHEh patients, while in 3 MHEh patients the likelihood was classified as “less than likely” (10 - 19 points). In the MHN group, MH susceptibility was assumed by CGS “greater than likely” (20 – 34 points) in 6 patients and “less than likely” or “almost never” in 1 patient each. Subsequently, performed muscle biopsy and IVCT detected MH susceptibility in 7 (37 %; 7 male) of the 19 patients. In 8 patients (42 %; 3 male, 5 female) MH susceptibility could be excluded. Muscle bundles of 4 patients (21 %; 1 male, 3 female) developed a pathologic contracture only after exposure to halothane but not after caffeine (MHEh). Genetic screening detected mutations in the ryanodine receptor gene (Gly4037Alafs, Glu2174Ala, Val4234Leu) of 3 MHS patients. In 16 (84 %) patients the suspected MH event occurred between 2006 and 2010 (6 MHS, 3 MHEh, 7 MHN). The remaining 3 patients had been 10 years old or younger at the time of incident (1992, 1995, 1998) and therefore muscle biopsy in these patients was delayed until the age of 16 years according to our hospital standard operating procedures. Since the MH diagnostic was performed within the study period these 3 patients were include in the evaluation, even if the applied triggers were halothane or enflurane respectively. Interestingly, 2 MHS individuals with suspected MH in their history had undergone at least one uneventful general anesthesia in the past. The histopathological examinations revealed a myopathic tissue syndrome in combination with cell clumps indicating a possibly neurogenic component in 1 MHEh patient, who had received succinylcholine as sole trigger agent. In the other patients there was no evidence of a muscular pathology (table 1).

Trigger agents and clinical presentations
21% of the MH suspected patients only received an inhalation anesthetic (sevoflurane: 1 MHS; isoflurane: 1 MHN; desflurane: 2 MHN), while in 47% of the cases (6 MHS, 1 MHEh, 2 MHN) a combination of succinylcholine with a volatile anesthetic, e.g. halothane (1 MHEh), enflurane (1 MHN) isoflurane (3 MHS, 1 MHN), sevoflurane (2 MHS) or desflurane (1 MHS) was used. In 28% (3 MHEh, 3 MHN) succinylcholine was applied as solely MH trigger.
Masseter spasm was observed in 63% of the patients (2 MHS, 4 MHEh, 6 MHN), thereof in 28% of the cases (3 MHEh, 3 MHN) after succinylcholine administration. Based on the available patient records, application of volatile anesthetics or succinylcholine was stopped in all of the 19 patients and anesthesia was continued intravenously.

Cardiac arrhythmias were reported in 42% of the 19 cases. Hereof, an unexplained sinus tachycardia with heart rates between 90 to 135 per minutes were documented in 38% of the patients (3 MHS), while in 62% (2 MHS, 1 MHEh, 2 MHN) tachyarrhythmia were observed. In 11% of the patients, who received sevoflurane (1 MHS) or succinylcholine (1 MHEh) solely no arrhythmias were seen. In the remaining suspected cases the cardiac rhythm was not documented in patients’ medical records. An increase of end-tidal carbon dioxide > 45 mmHg during the course of anesthesia was noticed in 42% (5 MHS, 3 MHN). However, body temperature increases ≥ 38.5°C were only reported in 11% of the analyzed cases (1 MHS, 1 MHN). In 47% of the MH suspected cases (7 MHS, 1 MHEh, 1 MHN) an increase of CK levels > 10,000 U/L following MH trigger application was observed. Despite the suspected MH diagnosis, dantrolene was administered only in 37% (5 MHS, 1 MHEh, 1 MHN) for treatment of the observed symptoms (table 2).

According to the medical records of the referred patients, no persistent or temporary complications e.g. DIC, acute renal failure or neurological deficits were reported during recovery after the suspected MH episode.

**Blood gas analysis**
Interestingly, in only 37% of the patients with suspected MH event an arterial blood gas analysis was documented to verify the assumed MH diagnosis. However, a relevant metabolic acidosis with pH ≤ 7.2, base excess ≤ -5 mmol/l and PaCO₂ ≥ 50 mmHg was observed in 21% (3 MHS, 1 MHN). Besides that, serum potassium levels of 16% (2 MHS, 1 MHN) were remarkable elevated ≥ 5 mmol/l (table 3).
Discussion

Even though MH is a rare complication of general anesthesia, the presented cases clearly demonstrate that this life threatening muscular hypermetabolism is still a relevant risk requiring immediate and consequent treatment by the responsible anesthesiologist to avoid serious harm to the patient.

After the first description of MH by Denborough numerous cases of fulminant MH as well as in vitro investigations had been published in the following years, identifying halothane and succinylcholine as potential MH triggering agents [10]. While the metabolic deterioration in the course of an MH crisis induced by halothane seems to be a direct consequence of an interaction with the sarcoplasmic ryanodine receptor, the pathophysiological mode of action of succinylcholine has remained unknown. For instance, in vitro succinylcholine increased halothane-induced muscular contractions of MHS patients, but no contracture could be observed after exposition to succinylcholine alone [11]. Even systemic application of succinylcholine could not reproducibly elicit an MH episode in susceptible swine [12,13]. In humans, according to an evaluation of the North American MH Registry and a recently performed European multicentric study, succinylcholine triggered MH in absence of an inhalation anesthetic only in 0.7% or 1% respectively of the investigated cases [14,15]. Since the definitively underlying mode of action of succinylcholine to elicit MH remains unclear so far, the pharmacological characteristics of this agent may enable a possible explanation of it’s role to induce MH. Following intravenous application succinylcholine activates the nicotinergic acetylcholine receptor and provokes a local depolarization of the cell membrane. The transient depolarization of voltage-gated receptors in combination with an influx of extracellular calcium via acetylcholine receptors could lead to a significant increase of intracellular calcium concentrations and after exceeding a certain threshold MH may occurs in affected individuals. In this context, muscular fasciculation and rigidity caused by succinylcholine was considered to be causal for MH. Consequently, a masseter spasm following succinylcholine was postulated to be an early sign of an imminent MH episode. However, specificity of this clinical sign is limited due to the subjective appraisal and the fact, that jaw tightness is a common side effect of succinylcholine, but only in half of the patients associated with MH susceptibility [16]. Similar results were obtained in our investigation. MH susceptibility was confirmed in only 50% of the suspected MH cases, where a succinylcholine-induced masseter spasm was noticed. Interestingly, histological examination of 1 MHEh patient who solely received succinylcholine revealed suspected myopathological finding. Although, neuromuscular disorders are common in MHE patients [17], it remains unclear, if these muscular alterations were responsible for the increased sensitivity to succinylcholine in this patient.
Generally, the likelihood of succinylcholine-induced MH seems to be extremely low, however there is little doubt, that a combination with a volatile anesthetic potentiates the onset and the clinical symptoms of an MH event [18]. Remarkably, despite the possibly serious side-effects like MH, hyperkalemia and cardiac arrest, succinylcholine was actually applied to secure the airway in 79% of the referred patients. In part, this approach was reasonable due the higher risk of aspiration in case of trauma or abdominal surgery. However, according to published guidelines the use of the non-depolarising muscle relaxant rocuronium and if needed followed by application of sugammadex to reverse the neuromuscular blockade might be an adequate alternative to avoid succinylcholine associated adverse effects [7,19].

In contrast to succinylcholine, the impact of all inhalation anesthetics used in daily clinical routine in the development of an MH crisis is beyond dispute. However, dependent on the applied volatile anesthetic the time interval between induction of anesthesia and clinical symptoms of an MH episode seems to vary. For instance, Hopkins and colleagues reported, that in susceptible patients the onset of MH was statistically significant faster after halothane exposure compared to enflurane or sevoflurane [5]. Equally, fulminant MH episodes after isoflurane, sevoflurane or desflurane seem to occur with temporal delay [20,21], while halothane may induce MH within minutes [5]. In MHS animals, similar results were seen after intramuscular injection of halothane o sevoflurane. The induced local hypermetabolic responses measured by local muscular lactate and carbon dioxide pressure increase were more distinct after halothane than after sevoflurane application [22,23]. Furthermore, in vitro, the effect on muscular contractures of MHS muscle bundles varies between halothane and modern volatile anesthetics at equivalent concentrations [24]. These different clinical appearances of MH following volatile anesthetic application might be caused due to differences in the calcium releasing potency of these diverse agents. For example, sarcoplasmic calcium release at cellular level was significant smaller after sevoflurane or desflurane exposure compared to equimolar halothane concentrations [25,26]. In the analyzed anesthetic events of the present evaluation MH episodes were induced by established MH triggers like halothane and isoflurane as well as by modern volatile anesthetics, e.g. sevoflurane and desflurane. Although, in the majority of the cases inhalation anesthetics were combined with succinylcholine and only in one case sevoflurane was applied solely, our findings emphasized the MH trigger potency of newer volatile anesthetics.

Beside masseter spasm cardiac arrhythmias are further early symptoms of imminent MH. Equally to a retrospective analysis from the United States, where the incidence was estimated 40% [14], in the presented investigation the occurrence of unexplained cardiac
alterations was 42%. On closer examination the incidence of cardiac symptoms was even higher in the MHS group with either sinus tachycardia or tachyarrythmia as the leading signs.

The low incidence of testified metabolic acidosis might be attributed to the failure to obtain arterial blood gas analysis in the acute phase of the MH reaction or due to dantrolene pretreatment. For example, one patient’s blood gas analysis was performed not until the arrival on the intensive care unit and after treatment with dantrolene, showing an unremarkable blood acid status, while in contrast the intraoperative end-tidal carbon dioxide increased relevant to 56 mmHg in this patient. Overall, in only 37% of the MH suspected cases a blood gas analysis was conducted to verify the suspected diagnosis. This line of action is remarkable, since the present of an acidosis should give reason to consider MH as causal for observed alterations.

Hyperthermia is a dramatic but often late sign of MH, reflecting the proceeding metabolic breakdown in affected individuals. Hence, temperature monitoring during general anesthesia is recommended if MH triggers are used, since in a couple of cases hyperthermia was the only sign of MH [14]. Fulminant MH episodes may be marked by a rapid increase in body temperature at a rate of 1-2°C every five minutes [27]. Stunningly, only in 11% of the suspected MH cases (1 MHS and 1 MHN) a remarkable hyperthermia with an increase in core temperature \( \geq 38.5 \)°C was noticed. The overall low incidence of core temperature rises in the presented study might be attributable to the initiated dantrolene treatment or the possible absence of temperature monitoring.

The pathological changes during MH crisis are based on an uncontrolled increase of myoplasmic calcium, resulting in an ongoing skeletal muscular contracture and loss of cellular integrity leading to hyperkalemia and rhabdomyolysis [28]. Although the surgical trauma itself might cause a significant increase in CK levels, postoperative unexplained excessive hyperCKemia should lead to a diagnostic workup to exclude MH susceptibility as underlying pathology. The reason for the remarkable CK increase up to 24.732 U/L in one of the MHN patients following succinylcholine remains unclear. A not yet diagnosed myopathy could not definitely be excluded, but based on the advanced age of the patient and the inconspicuous histological findings it seems very unlikely.

In contrast to the estimation, that nearly 70% of MH families carry mutations in the ryanodine receptor gene [29], the genetic prevalence of 27% in the analyzed MHS cases was overall low. Noteworthy, even if the Val4234Leu variant of one MHS patient has recently been mentioned in context of a novel exome sequencing method for MH relevant mutations [30],
none of the detected genetic variants had been accepted as causative for MH according to the European MH Group database, which includes so far 31 approved mutations of the more than 200 identified ryanodine receptor gene variants [31]. However, it is important to mention, that absence of a causative mutation does not reliably exclude MH susceptibility. To confirm or exclude MH a muscle biopsy followed by an IVCT must be carried out in these patients [32].

After introduction of dantrolene in clinical use a causal treatment of MH is available since the late 1970’s. The mode of action of this drug is based on inhibition of the sarcoplasmic reticulum calcium release without increasing the reuptake of calcium ions into the sarcoplasmic reticulum [33]. According to current guidelines application of dantrolene is an essential part in the treatment of an MH crisis [34,35]. However, only 37% of the patients in the presented investigation received dantrolene for causal MH therapy. Nevertheless, the importance of consequent dantrolene treatment is absolutely clear [36], even if the hypermetabolic state in some of the presented cases was already terminated by discontinuation of MH trigger substances.

Once surviving fulminate MH episodes several reports documented severe complications, e.g. acute renal failure from rhabdomyolysis, DIC, congestive heart failure or intestinal ischemia due to the uncontrolled metabolic reaction and myocyte death [27]. Fortunately, the review of the medical records of the referred patients, did not detect any serious harms to the patients after an MH episodes, which importantly delayed recovery.

To draw conclusions about the likelihood of MH among the suspected incidents, the “Clinical Grading Scale” (CGS) established by Larach and colleagues assessed clinical and metabolic parameters, e.g. muscle rigidity, rhabdomyolysis, acidosis, increases in body temperature and cardiac arrhythmias [9]. The validity of the CGS may be reduced due to limited availability of complete data sets and hence, often does not satisfactorily correlate with the IVCT results [37]. The false negatives as well as the false positive diagnosis obtained by CGS calculation in our analysis are likely a result of the fragmentary available medical records. Thus, sole evaluation of the CGS seems not to be adequate to prove MH susceptibility.

Finally, anesthesiologists must be aware that uneventful previous general anesthesia does not exclude MH susceptibility [14]. For instance, two of the MHS patients reported a history of exposure anesthesia in the past. The reason why some patients develop MH after first exposition to MH triggering agents, while others do not, still remains unclear and might be
explained by an individual cellular compensation mechanism lowering myoplasmic calcium concentrations.
Conclusions
Analysis of the presented data might be limited by partly incomplete documentation as well as the individual interpretation. Nevertheless, in conclusion MH still is a relevant complication these days and every anesthesiologist must be prepared to recognize the symptoms of MH crisis and to start sufficient treatment. While fulminate courses of MH are easy to diagnose, abortive presentations with solitary or alleviated symptoms are more difficult to detect and pose an enormous challenge to the attending anesthesiologist. The initiation of an adequate and consequent treatment including the application of dantrolene and termination of MH trigger application is essential for patients’ prognosis and survival. Besides that, every patient after a suspected MH event the patient should be referred to a MH center for further counseling.
Abbreviations

CGS  clinical grading scale
CK   creatine kinase
IVCT in vitro contracture test
MH   malignant hyperthermia
MHEh malignant hyperthermia equivocal to halothane
MHN  malignant hyperthermia non-susceptible
MHS  malignant hyperthermia susceptible
**Authors' contributions**

FS conceived the study, accompanied the data acquisition, collected and analyzed the data and drafted the manuscript. SJ collected data and helped writing the manuscript. DS collected data. NR participated in the design of the study. All authors read and approved the final manuscript.
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