

To Mr Fang-Fang Ji,
Science Editor, Editorial Office
Baishideng Publishing Group Inc
E-mail: f.f.ji@wjgnet.com,

Antwerp, 2016-09-15

RE: Manuscript revision for World Journal of Critical Care Medicine

ESPS manuscript NO : 28314

Dear Sir,

Thank you for the suggested changes and providing us with the opportunity to revise our manuscript "*Exertional rhabdomyolysis and/or heat stroke : beware of volatile anesthetic sedation*" that we hereby submit for revision.

Changes requested by the reviewers have been addressed in the new manuscript file (additions are underlined, omissions are crossed out), and listed below.

We are looking forward to your further evaluation.

Sincerely yours,

Karel Heytens

Answers to Reviewer 00502903

My main comment would be to expand on the abbreviations for MHS and MHN on page 6 and GCS on page 7

- abbreviations replaced by plain text

Answers to Reviewer 00742429

- abstract reduced by +/- 50 words
- Paragraph 6, line 5 : pathological cut-off
- Paragraph 7 now reads: With adequate treatment, complications still occur in 20% of patients. The most common complication is renal dysfunction and acute renal failure.
- Paragraph 8 : last line Chromosome 1
- Many of the assertions in the Introduction lack references : references have been added to the introduction
- Discussion: Paragraph 2, line 2 : Technical advances, however,...
- Line 10 breath-by-breath replaced by breath by breath
- Paragraph 8 : rephrased "In this paper we want to warn for the use of volatile anesthetic sedation in a second subset of ICU-patients, in particular those with...
- Paragraph 11: ,however,
- References with more than 6 authors? In the *Guidelines for Manuscript Preparation and Submission: Minireviews* Last updated June 29, 2015 is stated : (5) *Format for references: Examples Print journals English language journal article (list all authors and include the PMID and DOI, where applicable)*

Answers to Reviewer 00506276

However, the Abstract should be improved to become more informative. In the current form it is not entirely clear what is the specific aim of this paper.

Abstract : rephrased, please see revised text

In addition, some figure(s) presenting the role of RYR1 in muscle (patho)physiology related to diseases addressed in this paper would be suitable.

Illustration (figure 1) added to revised manuscript

Answers to Reviewer 00037018

The aim of this review and case reports should be explicitly mentioned in the abstract and text of the manuscript.

Aim of review has been more clearly phrased in the abstract : to warn against the use of volatile anesthetic sedation in patients with exertional rhabdomyolysis and heatstroke, and on the basis of a literature review other diseases (malignant hyperthermia susceptibility, congenital myopathies, Duchenne muscular dystrophy and intracranial hypertension)

More details should be also provided on the molecular mechanism by which volatile anesthetic damage the muscular tissue particularly in patients with exertional rhabdomyolysis.

As illustrated in figure 1, muscle from patients harboring RYR1 and/or DHPR mutations upon exposure to volatile anesthetics has been shown to exhibit an increased calcium-conductivity and massive calcium release from the SR, in turn resulting in sustained muscle contraction, a catabolic state and hyperacute muscle breakdown^[3].

Minor points :

Minor points Title: please revise "and/or" choose one of the two logical options... Abstract: please revise "semi-marathon". Perhaps change "insight" with "insights"? Last sentence is unclear. Main text: please define the acronyms: "ETCO2" and "OR". Please find and revise "can to be repeated", "has been shown to demonstrate". Why 20% of the COOH terminal? Please add a figure summarizing the features of the RYR1 gene and gene product. Please revise "chrom" with "chromosome"

Title changed to "Exertional rhabdomyolysis and heat stroke : beware of volatile anesthetic sedation"

(Semi)marathon replaced by (half)marathon

Insight omitted

Last sentence of abstract changed in more decisive one

Main text : ETCO2 replaced by end tidal CO2 OR replaced by operating room

Can to be repeated replaced by can be repeated

It has been shown to demonstrate both chromosomal and allelic heterogeneity replaced by 'Both chromosomal and allelic heterogeneity have been demonstrated'.

Why 20% of the COOH terminal : no particular reason for the '20%'. This part of the gene codes for the transmembrane channel domains.

Figure added to text explaining the effect of volatile anesthetics on mutated RYR1 channels

Chrom replaced by Chromosome