Author's response to reviews

Title: Acute posthypoxic myoclonus after cardiopulmonary resuscitation

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

Please find enclosed our revised manuscript entitled “Acute posthypoxic myoclonus after cardiopulmonary resuscitation” (7871761196666064). We would like to thank you for the opportunity to resubmit our manuscript.

Furthermore, we would like to thank all reviewers for reading and providing important and valuable comments. We have considered all comments and changes have been made to the manuscript accordingly. All changes in the manuscript have been highlighted.

In the remainder of this letter we provide our responses to the reviewer's comments. Please let me know if you require any additional information. On behalf of my co-authors I would like to thank you in advance and look forward to your editorial decision.

Reviewer: Jeanne Teitelbaum

This is an interesting article where the authors look at the origin of post-arrest myoclonus in patients undergoing moderate hypothermia after resuscitation from cardiac arrest. They postulate that recognizing the origin of such myoclonus might guide therapy and perhaps inform prognosis.

Response to Reviewer #1
Thank you very much for reading our manuscript and your valuable comments.

1) The question is an interesting one. The study, however, is retrospective and not all patients were investigated thoroughly. There is a lack of description of the myoclonus, there is incomplete electrophysiological evaluation, and those who
are tested are at the discretion of the treating physician, which can introduce bias. If at all possible, it would be important to separate the primarily hypoxic arrests (hypoxia with secondary bradycardia the asystole and arrest) from the primarily cardiac arrest as the prognosis in general and the type of myoclonus are different.

We agree that primary hypoxia as cause of CPR differs from primary cardiac cause of CPR.

We have added to the Lance-Adams part in the introduction that this syndrome is often caused by a primarily hypoxic arrest. We have added in Table 1 the number of patients with a primary cardiac arrest and the number of patients with a primary hypoxic arrest. We have added to the Results section that the patients with a good outcome and a known primary cause of CPR were patients with a primary cardiac arrest.

2) The results reported are confusing, and this part should be redone to more clearly inform us on exactly how many patients had which type of myoclonus and when after injury. When referring to acute PMH, we are talking about all patients with myoclonus as stated in the abstract. This should be redefined clearly in the methods or in the results. Is all generalized myoclonus considered status? Is multifocal myoclonus automatically generalized or status? This needs to be better defined.

Thank you for this comment. We have rewritten the Results section in order to clarify how many patients had which type of myoclonus at what moment after admission. In the Methods section and in the Results section we have stated that the diagnosis acute posthypoxic myoclonus refers to patients with focal myoclonus or status myoclonus. We have stated in the Methods section that myoclonus was scored on the case record form with no further differentiation of the severity and clinical characteristics.

3) When stating that 12% of patients with acute myoclonus had a good outcome, it should be mentioned in the text that most of the patients without good outcome are dead, not just shown in the board. And is there a difference between focal and status?
Thank you for this comment. We have modified the Results section to emphasize that all but one patient with a poor outcome died. This patient was severely disabled after 6 months. In the majority of the patients, acute PHM was reported as focal myoclonus (47/79 patients (59%)), of whom 8 patients (17%) had a good outcome. Status myoclonus was reported in 32/79 patients (41%), 1 patient survived and made a good recovery. As previously mentioned, we have rewritten this part of the Results section.

4) Conclusions regarding persistent myoclonus are unreliable because of the small sample and loss to follow-up.

We agree that conclusions regarding persistent myoclonus are unreliable because of the small sample and loss to follow-up. Therefore, we have decided to leave this out of the Discussion section. However, we do believe that information of the follow-up in these patients is scarce and therefore useful to mention in the Results section.

5) In the discussion, the word infaust is used. I do not know what this means. Also, the sentence: A giant SEP potential is compatible with hyperexcitability of the sensorimotor cortex and proofs the cortical origin of myoclonus in nonresuscitated patients. What is a nonresuscitated patient, a normal patient? A patient who arrested but was not resuscitated? (unlikely I suppose). This should be re-written more clearly.

Thank you for notifying. We apologize for the use of the word “infaust”, as this is incorrect English. We have changed this sentence into: “Our data also suggest that the outcome in patients with myoclonus after CPR, irrespective of their origin, is not invariably correlated with poor outcome as previously described in literature.” Furthermore, we agree that “nonresuscitated patient” was used improperly and changed this into “A giant SEP potential is compatible with hyperexcitability of the sensorimotor cortex and proves the cortical origin of myoclonus in patients. These giant SEPs are especially found in patients with progressive myoclonic epilepsy.”.

6) In the discussion on why there could be a cortical origin without giant SEP, there needs to be alternate explanation, since drugs were present in cases with giant SEP and this is not a valid explanation. The rest of the discussion is acceptable.
Thank you for raising this valuable comment. We agree that this is an important, but also complex subject, especially in these patients with severe brain damage. Actually, we have no really valid explanation for our findings in these two patients. Therefore, we have adjusted the paragraph in the Discussion section with making our findings less prominent.

7) *In the conclusion, I think it is too much of a stretch to say that outcome was better without again mentioning the study’s limitations.*

We agree and have changed the Conclusion section accordingly: “Despite the limitations mentioned above, we think that acute PHM originates from subcortical, as well as cortical structures and that the outcome of patients admitted after CPR who develop acute PHM might be better than previously reported. The broad variety of drugs used for treatment shows the existing uncertainty about optimal treatment.”

**Reviewer: Peter Kaplan**

**Response to Reviewer #2**
Thank you very much for reading our manuscript and your valuable comments.

**Minor Essential Revisions:**
1) Abstract/methods: "...cohort study including patients treated with hypothermia". *Were all patients treated with hypothermia. If so state this.*

Thank you for this comment. Indeed, all patients were treated with hypothermia after cardiopulmonary resuscitation. We have modified this in the Abstract and Methods sections.

2) "*Criteria for cortical origin ...was epileptic activity*" (but there is the caveat that backaveraging was not used - see also comment in authors’ Introduction, line 23).

We agree that back-averaging is preferred to evaluate the cortical origin of the myoclonus. Aside the comment in the Introduction section and as one of the limitations in the Discussion section, we have added this to the Methods part of the Abstract, in order to clarify that this technique was not used in our study.
3) In Conclusions of the abstract where the authors note that the outcome was better than previously reported, was this comparing post hypothermia studies to pre-hypothermia studies (as they note on line 10-11 of the introduction)?

Thank you for this comment. We have rewritten this paragraph of the Discussion section and especially added more references concerning the patients treated with hypothermia after CPR.

4) On page 7, results, the authors note that 3 patients made a good recovery but had no reactivity on EEG. This should be commented on in the discussion as it is at variance with the results of Rossetti et al.

Thank you very much for attributing this comment. We agree that the Discussion section should contain a paragraph of our findings of the reactivity on the EEG compared with those of Rossetti et al. and have added this paragraph accordingly.

5) Page 7, last line, what does "infaust" mean?

We apologize for the use of the word “infaust”, as this is incorrect English. We have changed this sentence into: “Our data also suggest that the outcome in patients with myoclonus after CPR, irrespective of their origin, is not invariably correlated with poor outcome as previously described in literature.”

6) Page 8, line 3, use "proves" instead of "proofs".

Thank you very much. We have changed “proofs” into “proves”.

7) "performed at." rather than "performed on." Page 8, line 19.

We have changed “performed on” into “performed at”.

8) Did patients with stimulus induced periodic discharges have a different outcome?

Thank you for this question, this interesting phenomenon was not investigated in these patients’ EEGs.
9) Page 9, line 14 "benzodiazepines is" rather than "are", as it relates to "treatments...or".

Thank you, we have changed “are” into “is”.

Yours sincerely,

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