Author's response to reviews

Title: Maximum inspiratory pressure, a surrogate parameter for the assessment of critical illness polyneuromyopathy

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Author's response to reviews: see over
Reviewer's report
Title: Maximum inspiratory pressure, a surrogate parameter for the assessment of critical illness polyneuromyopathy
Version: 2
Reviewer number: 1
Referee's comments to the author(s)
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The authors correlate the findings of MIP testing in ventilated patients with MRC examination when awake, and relate both of these (the latter being well studied in the past) with weaning outcomes. The major strength of this study is the ability to predict weakness/respiratory involvement early, using a one-way valve that allows measurement of MIP in non-cooperative patients. This technique was feasible in a greater proportion of the cohort than MRC testing.
Major concerns include:
1. The diagnosis here is really "ICU-acquired weakness" (ICU-AW) and not truly CIPNM - although the former is itself a well-described surrogate for the latter. However, in this study the authors use yet another surrogate of (this time respiratory) weakness (MIP), to predict a surrogate (MRC grading), and do not provide any "confirmatory" (i.e. more diagnostic) testing such as EMG/NCS. While the use of MRC grading to diagnose ICU-AW is reasonable, and the explanation of ICU-AW as being based on CIPNM is also founded - it is more of a leap between MIP and CIPNM. i.e. There is no gold standard to really know if those with lower MIP have neuropathic or myopathic abnormalities. All we that say is they are weak. This might require the focus of the paper to be (slightly) shifted towards ICU-AW and less focus on "CIPNM" (a clinical/EMG diagnosis).
2. This is a relatively small study (74 patients) made even smaller by the fact that over HALF the patients could not have MRC and MIP testing done concurrently (i.e. no diagnosis of ICU-AW / CIPNM made in 50%+). This makes it hard to interpret the results of the study as it relates to the ICU-AW / CIPNM.
3. The relationship (as acknowledged by the authors) between abnormal respiratory parameters (e.g. MIP) and weakness/neuropathy has previously been reported (i.e. De Jonghe 2007, reference 17). While this is discussed in the submission, it still remains unclear how this paper differs and offers novel findings (apart from the use of a valve which allows MIP measurement at closer
to FRC). That study also found a relationship between abnormally low MIP and longer time to wean.

4. What is novel and most important about this study (independent of exact "diagnosis" and correlation between MRC and MIP, which seem less compelling) is the ability to test MIP in such patients and have it correlate well with weaning duration (and important clinical issue). Perhaps this can be stressed / focused on more, as the most solid aspect of this analysis.

5. Figure 1 is interesting as it seems to display two separate cohorts (affected vs. unaffected?) shown in two quadrants of the scatter plot. First those with low MIP cluster around MRC <= 48 while those with normal strength almost always have good MIP. This is a core point of the paper. While this seems to validate the similar course of peripheral and respiratory muscle weakness (almost as a present vs. absent phenomenon), could this also represent bias in mental status (those with worse encephalopathy also may have artifactually lower MIP and lower MRC due to lack of cooperation). By only testing MRC when patients can follow commands reduces this bias somewhat. Further exploration of these dichotomous populations may be warranted.

6. Those with lower MIP were clearly "sicker" with higher APACHE/SAPS. This would obviously necessitate longer ICU stays and longer weaning periods. Can the authors demonstrate that low MIP is an INDEPENDENT predictor of weakness/long weaning, even after controlling for the imbalance disease severities. I would focus on this aspect throughout the paper (if it turns out to be a useful test in the final analysis).

7. The relationship between ICU-AW (low MRC) and longer vent weans is not at all new (and not the objective of the study). It might keep the paper more focused (on MIP) if longer sections on how MRC predicts weaning, etc. were omitted (as repetitive, non-novel). This might include Figure 2. Similarly Tables 1 and 2 could be simplified (e.g. comorbidities do not ALL need to be listed) and perhaps even combined (with two columns for the two groups).

Minor issues:
1. What was the delay between MIP testing and mean first MRC testing? The authors state MRC testing was done within 48 hours if possible, but a significant
number could never have MRC done "safely". How often, in the remainder, was the MRC within 48 hours of the MIP?

**Reviewer's report**

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**Version:** 2

**Reviewer number:** 2

**Referee's comments to the author(s)**

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**General comments:**
The report is interesting and well written. However, I am troubled by some of the assumptions that the authors make in the experimental design.

1. The diagnosis of CIPNM is established clinically by strength testing, rather than electrophysiological means. How can we be sure that all the patients who were weak had CIPNM, not myopathy, myasthenia gravis, or muscle wasting due to hypermetabolism/starvation? The authors cite appropriate references to justify their approach to the diagnosis, but I remain concerned that some of the patients in the study group did not have CIPNM but another cause of muscle weakness.

2. It is not surprising to me that respiratory muscle weakness correlates well with peripheral muscle weakness. I am concerned that lack of peripheral muscle effort also correlates with lack of respiratory effort. The authors address my concerns about lack of maximum efforts, but I would have liked to see an actual measurement of maximum inspiratory effort as well as performance. This study is limited by the small sample size, lack of diagnostic certainty, and reliance on maximum voluntary patient effort.
We thank the reviewers for their insightful comments.

Answer to reviewer number 1

Major comments

1. Physical examination has been advocated as a primary determinant of critical illness polyneuromyopathy CIPNM. Clinical, electrophysiological and histological approaches have been used for the diagnosis. Clinical detection is based on the assessment of skeletal muscle weakness. A standardized and reliable method to evaluate limb muscle groups is the Medical Research Council (MRC) muscle strength score which has been used for the diagnosis of CIPNM. The term of CIPNM has been also used previously to describe the syndrome that is diagnosed with clinical examination by MRC muscle strength score (Nanas S et al. Acta Neurol Scand 2008-Reference 9, De Jonghe et al. Crit Care Med 2007-Reference 17).

2. A limitation of our study is the limited number of patients that eventually regained consciousness and were evaluated by both, the MRC scale and MIP. A reliable assessment of neuromuscular function (eg with MRC scale muscle strength score) cannot be performed in patients not fully awake or when cognitive function is not intact and this is a very frequent problem in intensive care units. However, the evaluation of muscle strength with the method of the unidirectional valve does not require the coordination of the patient and such a method to assess muscle strength in patients that are not able yet to cooperate after critical illness recovery has not been described so far.

3. The novel findings of this study are that the method we use to assess MIP, with the unidirectional valve, is different from others previously reported (i.e. De Jonghe 2007, reference 17) and permits MIP assessment at lung volumes progressively
closer to residual volume and closer to real MIP. Another point of our study is that MIP assessment can be conducted in patients that do not cooperate.

4. This aspect is mentioned in the discussion.

5. Some patients of our population have high MRC and lower MIP than expected from the above mentioned correlation. A limitation of our study is that we did not assess ventilatory drive before MIP assessment. We think that if ventilatory drive had been assessed and patients with depressed ventilatory drive had been excluded from the analysis that would have resulted in an even greater correlation.

6. Low MIP clearly predicts a longer weaning period and ICU-stay (De Jonghe et al. 2007). However, in the present study, as in all studies estimating MIP in the context of critical illness polyneuromyopathy (CIPNM), MIP cannot be seen independently from the generalized neuromuscular weakness, the development of which is associated with the severity of illness at the time of admission and other risk factors (administration of amynoglycoside antibiotics, high blood glucose levels), as has been already shown by other studies (Nanas et al. 2008). Therefore, MIP is similarly affected by all risk factors predisposing for CIPNM. In fact, the present study evaluates MIP as a surrogate parameter for the assessment of CIPNM; to produce reliable results, we did not include patients with pre-existing causes of respiratory muscle weakness (as the phrenic nerve damage after thoracotomy) which would increase weaning period and ICU-stay independently from other causes and not as far as CIPNM development is concerned.

7. Following the suggestions of the reviewers we combined the two tables in the Table 1.
Minor issue

1. 67% of the 33 patients evaluated for MIP and with MRC muscle strength scale, the MRC was within 48 hours of the MIP

Answer to reviewer number 2

1. The diagnosis of CIPNM in our study was clinical, by MRC muscle strength scale. Myasthenia Gravis and other known pre-existing causes of neuromuscular weakness where in the exclusion criteria of our study.

2. The MIP assessment with the unidirectional valve method does not require the cooperation of the patient and the voluntary maximal efforts.

A limitation of our study is the limited number of patients that eventually regained consciousness and were evaluated by both, the MRC scale and MIP. The diagnosis of CIPNM in our study is clinical with the MRC muscle strength scale, as it has been previously used in former studies (Nanas S et al. Acta Neurol Scand 2008- Reference 9, De Jonghe et al. Crit Care Med 2007- Reference 17).

This method does not require voluntary patient effort. It can be used also in patients that do not cooperate.