PEER REVIEW HISTORY

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ARTICLE DETAILS

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<th>TITLE (PROVISIONAL)</th>
<th>The impact of upright positioning in bed after acute stroke</th>
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<tr>
<td>AUTHORS</td>
<td>Aries, Marcel; Elling, Jan Willem; Stewart, Roy; De Keyser, Jacques; Kremer, Hubertus; Vroomen, Patrick</td>
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VERSION 1 - REVIEW

<table>
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<th>REVIEWER</th>
<th>Reinhard, Matthias</th>
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<td></td>
<td>University of Freiburg, Department of Neurology</td>
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<td>REVIEW RETURNED</td>
<td>19-Apr-2013</td>
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GENERAL COMMENTS

This is a very well-designed and important study on the interplay between posture and cerebral hemodynamics in acute ischemic stroke.

A. Major:
1. Regarding the concept of the penumbra, it seems of importance whether mobilization happens during the occlusion or the reperfusion period. Could the authors provide data on that topic in their patients?

2. Conclusions regarding flow augmentation or reduction in the Penumbra based on the present results (e.g. p. 11 first two lines) should be made with caution, since this study does not provide details on regional CBF and includes a typical but also heterogenous patient population (different types of stroke, etiologies, mostly mild to moderate severity).

3. Although rather a case series, for their discussion the authors might consider the SPECT study of Jack et al. Age Ageing. 2001 Sep;30(5):428. The importance of posture in the early stages of stroke: its influence on cerebral perfusion.

4. The authors considered stroke subtype as a confounder. Given the results of Immink et al. Stroke 2005 with lacunar stroke, it could be of interest to also consider stroke etiology. For stroke subtype it could also be of interest to consider size of affected MCA territory instead of only PACI/TACI (optional comment).

B. Minor:
1. The mode of orthostatic correction of MAP might be explained in more detail.
2. Table 3 / p.10, para 2, 3rd sentence: MAPmca... : sentence is a bit difficult to understand at first sight, normalized MAP of 1.05: normalized to what period/value, please clarify, e.g. in Table legend.
3. Inclusion 6- to 16 hrs after onset (p. 6) or within 24 hrs (p. 8) ? Please clarify.
4. First author name of Ref. 9 should be corrected.
**THE STUDY**

I don't think this study is designed to suggest that any change in position subacutely after stroke will alter the NIHSS.

The patients described are a very select proportion of stroke patients that perhaps changes in positioning may not adversely effect cerebral dynamics. What clinicians are unclear about is how to position patients with moderate to severe stroke and including these patients perhaps would have been more relevant.

Table 2 clearly shows that there are significant changes in a number of physiological parameters with differences in positioning (ie with affected hemisphere and healthy controls), but then the key message from the paper is that there are no significant changes. Perhaps the authors need to really spell out the changes as this was difficult to read from the text and the supplementary tables.

There are few typos noted.

Hargroves et al (NIRS, Age and Ageing, 2008) was omitted from referencing detailing a smaller study.

**RESULTS & CONCLUSIONS**

The study has answered that there are changes in a number of brain physiological variables but it does not tell us whether these changes are clinically safe and what affect they have on outcome. The study is too small in size to answer this question. There are a number of articles in the literature that have described these findings.

I think there is too much data presented in the tables which makes it rather difficult to read. Perhaps using more graphics would have spelled out the key messages better. In view of this, the messages are not clear.

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**VERSION 1 – AUTHOR RESPONSE**

Reviewer: Matthias Reinhard, University of Freiburg, Department of Neurology

This is a very well-designed and important study on the interplay between posture and cerebral hemodynamics in acute ischemic stroke.

A. Major comments:

1. Regarding the concept of the penumbra, it seems of importance whether mobilization happens during the occlusion or the reperfusion period. Could the authors provide data on that topic in their patients?

Reply of the authors:

First, patients with MCA (M1) occlusion were excluded from the study. This information is already in the manuscript (Methods, procedure section, page 7, line 15-16) but not bundled with the other exclusion criteria. The first part of the Methods section was changed accordingly.

It now reads: ‘Patients had to be conscious, cooperative, hemodynamically stable without fever and display flow in both M1 segments of the MCA’. (Methods, page 7, line 15-16)
Second, we agree with the reviewer that accurate data on vessel patency, recanalisation (proximal and distal) or flow patterns would be of interest but unfortunately these data (for example with CT/MRI angiography or CT/MRI perfusion) are not available in our stroke population. Including these data (close to the actual measurement) would have extended the measurement protocol much (in time and complexity). Besides, various authors have reported cerebral recanalization or perfusion scores after stroke, but without fully describing the features of each grade and ignoring the issues of original or primary recanalization versus distal perfusion.

We agree with the reviewer that at the moment only theoretical thoughts regarding ‘critical hypofusion’ or ‘penumbra at risk’ during mobilisation in the acute stroke phase can be made.

In order to improve the understanding of the readers, we changed three sentences in the Introduction and Discussion of the revised manuscript:

a. ‘Any activity that alters CBF during the acute phase of ischemic stroke may directly contribute to extension of penumbra to ischemic core and compromise clinical outcome’ was changed into ‘Any activity that alters CBF during the acute phase of ischemic stroke may – at least theoretically - directly contribute to extension of penumbra to ischemic core and compromise clinical outcome. (Introduction, page 5, line 4-6)

b. ‘The potential of the Trendelenburg position to augment flow and recovery of penumbra seems to be limited and may not outweigh concurrent cardiopulmonary complications.’ was changed into ‘The potential of the Trendelenburg position to augment CBF seems to be limited and may not outweigh concurrent cardiopulmonary complications.’ (Discussion, page 12-13, line 23/1-2).

c. We added ‘recanalisation information’ to the ‘future research’ paragraph in the Discussion and referring to the comment paper of Tomsick in 2007 (on recanalization scores).1 It now reads: ‘Further research should also include more detailed (follow-up) information from extra- and intracranial vessels pathology (using validated radiological or ultrasound criteria), recanalisation (proximal and distal), penumbra configuration and/or the presence of collaterals. (Discussion, page 15-16, line 22-24/1)

2. Conclusions regarding flow augmentation or reduction in the Penumbra based on the present results (e.g. p. 11 first two lines) should be made with caution, since this study does not provide details on regional CBF and includes a typical but also heterogeneous patient population (different types of stroke, etiologies, mostly mild to moderate severity).

Reply of the authors:
We agree with the reviewer and the appropriate sentence was changed. (Discussion, page 12-13, line 23/1-2). Please see ‘Major comment 1’ of reviewer 2 (Dr. M. Reinhard).

3. Although rather a case series, for their discussion the authors might consider the SPECT study of Jack et al. Age Ageing. 2001 Sep;30(5):428. The importance of posture in the early stages of stroke: its influence on cerebral perfusion.

Reply of the authors:
We included the suggested SPECT study of Jack et al. (2001) concerning subacute stroke patients.2 Unfortunately, no clear explanations for the improved local perfusion in the more upright position were given by the authors. Also respiratory changes (EtCO2 data) and demographics were lacking. It now reads in the revised manuscript: ‘Different results were obtained in a single-photon-emission
computer tomography (SPECT) stroke study. Seven out of eight (sub) acute stroke patients had a clear visual improvement in single-photon-emission computer tomography (SPECT) perfusion to either affected frontal, temporal or parietal lobes in the semi-recumbent (30-45°) compared to supine position. No differences in BP were found. Unfortunately, no demographics, any clinical effect or respiratory changes of the more upright position were reported'. (Discussion, page 14, line 9-15)

4. The authors considered stroke subtype as a confounder. Given the results of Immink et al. Stroke 2005 with lacunar stroke, it could be of interest to also consider stroke etiology. For stroke subtype it could also be of interest to consider size of affected MCA territory instead of only PACI/TACI (optional comment).

Reply of the authors:
First, we also included ‘stroke etiology’ (using the TOAST criteria) in the multi-level analysis as a confounder (with no significant effects on the results) but because of the correlation between ‘stroke subtype’ and ‘stroke etiology’ and ‘stroke etiology’ and ‘significant carotid stenosis’ (statistical problem of multicollinearity) we decided to leave ‘stroke etiology’ from the final model.

To make the readers more aware we changed a sentence in the Methodology section. It now reads: ‘Significant carotid stenosis, stroke subtype (or stroke etiology (TOAST criteria), NIHSS, age and sex were used as potential confounding covariates in stroke group comparisons.’ (Methodology, page 9, line 14-16)

We also added the reference of Immink et al.(2005) to the revised manuscript.3 (Methodology, page 9, line 16)

Second, we don’t have data about the size of affected MCA territory. In our stroke (monitoring) protocol a follow-up CT scan is only made on indication. However, the infarct size is to certain extent represented by the neurological examination (NIH stroke scale) but we agree that the correlation with diagnostic imaging might not be perfect.4

B. Minor comments

5. The mode of orthostatic correction of MAP might be explained in more detail.

Reply of the authors:
The sentence ‘Mean arterial pressure (MAP) at the MCA level (MAPmca, mmHg) was automatically calculated from the MAP measured at heart level and the vertical finger-to-TCD probe distance’ was changed into: ‘Mean arterial pressure (MAP) at the MCA level (MAPmca, mmHg) was automatically calculated from the MAP measured at heart level and the vertical finger-to-TCD probe distance. In the upright and Trendelenburg positions great care was taken to secure the hand with Finapres cuff at heart level (approaching right atrium level).’ (Methods, page 8, line 6-10)

6. Table 3 / p.10, paragraph 2, 3rd sentence: MAPmca... : sentence is a bit difficult to understand at first sight, normalized MAP of 1.05: normalized to what period/value, please clarify, e.g. in Table legend.

Reply of the authors:
As stated in the Methods section all physiological data (bilateral TCD/BP/bilateral NIRS/EtCO2) were
first normalized to the baseline supine values. All was done to be able to compare physiological responses between patients, healthy controls and hemispheres where absolute values might differ from baseline.

To make the readers more aware the following changes were made in the revised manuscript:

a. ‘To compare responses in each position, percentage changes in the variables (MCA CBFVmean, rSO2, MAPmca, HR, EtCO2) were calculated as the differences between the positions after normalization to the mean baseline supine value’ was changed into ‘To compare responses in each position, percentage changes in the variables (MCA CBFVmean, rSO2, MAPmca, HR, EtCO2) were calculated as the differences between the positions after normalization to the mean baseline (e.g. first) supine value. Normalization was done to be able to compare physiological responses between patients, healthy controls and hemispheres, where absolute individual values might differ from baseline.’ (Methods, page 9, line 4-6)

b. As suggested by reviewer 3 the table 2 and 3 were removed from the revised manuscript. Please see reply to comments of reviewers 3 below (this document).

c. The following sentence was added to table e1: ‘CBFVmean and rSO2 values were first normalized to the mean baseline (e.g. first) supine values. \( \Delta \) represents the averaged difference between the normalized values of two positions in stroke patients.’ (Table e1, supplementary material, page1, line 3-5)

d. The following sentence was added to table e2: ‘CBFVmean and rSO2 values were first normalized to the mean baseline (e.g. first) supine values. \( \Delta \) represents the averaged difference between the normalized values of patients and healthy controls in different positions.’ (Table e2, supplementary material, page 2, line 3-6)

e. The following sentence was added to table e3: ‘CBFVmean and rSO2 values were first normalized to the mean baseline (e.g. first) supine values. The difference between the affected and unaffected hemisphere normalized values for CBFVmean was calculated for every heart beat and averaged for each position to obtain a new variable ‘CBFVmean difference’. \( \Delta \) represents the averaged difference of the new variable between two positions in stroke patients. The same was done for the variable rSO2.’ (Table e3, supplementary material, page 3, line 5-9)

7. Inclusion 6- to 16 hrs after onset (p. 6) or within 24 hrs (p. 8) ? Please clarify.

Reply of the authors:
We agree that this might be confusing. The ‘inclusion 6-16 hrs after stroke symptom onset’ statement had to do with the fact that we wanted to limit the time path of inclusion of patients after stroke onset to make timing of early mobilisation comparable between patients. So we tried to measure patients arriving during the late evening or night at least within 16 hrs after symptom onset. Patients arriving during the day would be measured around 6 hrs after stroke onset and installation on the stroke unit.

To make the readers more aware of our choices two sentences were changed in the revised manuscript:
1. ‘Our protocol dedicated that the measurements had to be completed between 6 to 16 hrs after stroke symptom onset, mimicking the period of early in bed mobilisation initiation during daytime’. (Methods, page 6, line 7-9)

2. The sentence ‘The measurement was performed within 24 h after symptom onset’ was removed. (Methods, page 8, line 20-21)

8. First author name of Ref. 9 should be corrected

Reply of the authors:
The reviewer is presumably correct but in PUBMED the article is cited as: ‘Wojner-Alexander’ (Neurology 2005).

Reviewer: Ajay Bhalla, consultant stroke physician, st Thomas' hospital, London. UK

1. I don't think this study is designed to suggest that any change in position sub-acutely after stroke will alter the NIHSS.

Reply of the authors:
We agree with the reviewer that our aim was to investigate the postural physiological responses (using surrogates for cerebral blood flow and oxygenation) in acute stroke patients. During these positional changes we recorded the motor NIHSS to look for apparent changes and - if present- for any correlation with (probably large) changes in the two physiological (postural) parameters. The reviewer is correct that neurological status was not the main objective of this study as might be suggested by the title of our manuscript. Please see also the comment of reviewer 1 (managing editor).

Several changes were made in the revised manuscript to make the readers more aware:

a. The title was changed into ‘Cerebral blood flow velocity during upright positioning in bed after acute stroke: an observational study’. (Title, page 1)

b. In the Abstract, the Conclusion paragraph were changed into: ‘Conclusions No indications were found that upright positioning in bed of mildly to moderately affected stroke patients compromises flow and oxygenation significantly during the subacute phase of stroke. Supine or Trendelenburg positioning does not seem to augment real time flow variables.’ (Abstract, page 3, line 7-10)

c. In the Results section the order of presenting the results is changed. The focus is more on the cerebral hemodynamic results. (Results, page 9-12)

d. In the Discussion the sentence: ‘However, our results indicate that sitting is well tolerated in mildly to moderately affected stroke patients.’ was changed into ‘ However, our physiological results indicate that sitting is probably well tolerated in mildly to moderately affected stroke patients. In 2008 the ‘A Very Early Rehabilitation Trail’ showed that very early out of bed mobilisation was safe and feasible in stroke patients. (AVERT) (Discussion, page 15, line 11-14)

e. In the Discussion the sentence ‘This study found no indications that upright positioning compromises flow or neurological function in the affected MCA territory in mild to moderately affected
acute stroke patients’ was changed into ‘This study found no indications that upright positioning compromises flow or (frontal) oxygenation significantly in the affected MCA territory in mild to moderately affected acute stroke patients. (Discussion, page 12, line 17-20)

f. The Conclusion section of the manuscript was rewritten. It now reads: 'In conclusion, upright positioning in the stroke unit of mildly to moderately affected stroke patients does not give significant reduction of CBF and (frontal) oxygenation surrogates during the subacute phase on the stroke unit. Supine or Trendelenburg positioning seems not to augment MCA CBFV. (Conclusion, page 16, line 11-15)

2. The patients described are a very select proportion of stroke patients that perhaps changes in positioning may not adversely affect cerebral dynamics. What clinicians are unclear about is how to position patients with moderate to severe stroke and including these patients perhaps would have been more relevant.

Reply of the authors:
A couple of studies have investigated professional opinion about early mobilization after stroke.5-8 The spread in opinion reflects the absence of clear guidelines and knowledge in this area of stroke recovery and rehabilitation, which suggests further research is required. Interestingly, the papers focus on ‘when’ mobilization should be started and ‘what’ the definition of early mobilisation should be. But no clear opinion of ‘what kind of stroke patients’ should be mobilized and to ‘what extent’ (in bed or out of bed mobilisation). Also in the ‘A Very Early Rehabilitation Trail for Stroke (AVERT)’ no assumptions were made concerning early mobilisation and stroke severity (not a formal exclusion criteria). The NIHSS score at entry was 10 ± 7, with 76% of the patients representing as mild (NIHSS 1-7) to moderate (NIHSS 8-16) strokes.9 Moreover, so far postural cerebral dynamic studies included patients with severe strokes (NIHSS>16), not being representative of a general stroke unit population.10;11 Therefore in our study, we decided not to limit inclusion to only moderate to severe strokes.

The reviewer is correct that also our study is underpowered to perform reliable subgroup analysis (like according to stroke severity). Because > 75% of the study population consisted of mild to moderate strokes, we limited our conclusions to mild to moderate stroke patients. (Discussion, page 12, line 20-22) (Conclusion, page 16, line 11-14)

To make the readers more aware of this limitation the following sentence was changed in the revised manuscript: ‘Replication of this study should be considered studying the (hyper) acute phase, longer sitting periods and using more sophisticated and direct methods that measure CBF regionally and estimate cerebral oxygen metabolism. Inclusion of more severely disabled patients (NHISS around10) would be preferable to be able to compare upright cerebral hemodynamics with the results from the ongoing ‘early mobilisation’ trails.9’ (Discussion, page 15, line 19-22)

3. Table 2 clearly shows that there are significant changes in a number of physiological parameters with differences in positioning (i.e. with affected hemisphere and healthy controls), but then the key message from the paper is that there are no significant changes. Perhaps the authors need to really spell out the changes as this was difficult to read from the text and the supplementary tables.

Reply of the authors:
In Table 2 changes of CBFVmean and rSO2 are shown in stroke patients and healthy controls going from the supine to the upright (70⁰) position. In stroke patients values for both hemispheres (affected
and unaffected) were calculated. The reviewer is correct that for both stroke patients and healthy controls statistically significant changes were obtained with changing position. But are these changes clinically significant and do they represent or indicate impaired cerebral hemodynamics? Or just represent (normal) physiological changes (for example due to EtCO2 changes) with upright positioning. The found changes were smaller than expected (15-20%) from the scarce stroke studies with even less upright positioning.10-12 The results were smaller than studies in healthy (elderly) controls with the same measurement setup (TCD/NIRS) but with some moving to the standing position.13-15 For example, CBFVmean changed around 15% in healthy volunteers with standing, but this maneuver was also accompanied with EtCO2 changes around 12%.15

To be more sure, we included a ‘control’ group and tested in our model whether found changes were really different (clinically significant) between patients and healthy controls. Finally, we concluded that the postural cerebral hemodynamic responses were not (statistically and clinically) different between healthy controls and acute stroke patient (representing the key message).

We made a couple of changes in the revised manuscript to guide the readers more clearly through the data (results) and used more graphics (as suggested by reviewer 3):

a. The beginning of the results section was changed with the introduction of the two figures (1 and 2 (new!)) and referring to an overview of the complete dataset in the supplemental (online) tables e1-3. It now reads: ‘We compared the cerebral hemodynamic postural (MCA CBFVmean and rSO2) changes between different positions, stroke patients and healthy controls and between affected and unaffected hemispheres. A complete overview of the comparisons is presented in the supplemental tables e1-3 (http://bmjopen.bmj.com). Figure 1 shows that cerebral hemodynamic changes were most pronounced when moving from the supine to the sitting position (70°) for both patients (affected hemisphere) and controls (figure 1). The results presented below therefore focus on changes from the supine to the sitting position. The accompanying systemic hemodynamic (MAPmca and HR) and respiratory responses (EtCO2) are shown in figure 2. (Results, page 10, line 1-11)

b. Table 2 (‘Changes of MCA CBFVmean and rSO2 in supine and going to sitting position (normalized values) in acute strokes and healthy controls’) is removed from the revised manuscript because these data are already present in figure 1 and the supplemental tables (e1 and e2). Besides, the results are clearly written down in the results section after proper introduction.

c. A new figure (figure 2) was composed instead of table 3 (‘Changes of MAPmca, HR and EtCO2 in supine (0°) and going to sitting (70°) position (normalized values)’). (Figure 2, page 21)

d. Referral to the new figure was added. Referrals to table 2 and 3 were removed.

There are few typos noted.

4. Hargroves et al (NIRS, Age and Ageing, 2008) was omitted from referencing detailing a smaller study.

Reply of the authors:
We added the study of Hargroves (2008) to the Discussion of the manuscript. It now reads: ‘In the study of Hargroves et al. cerebral oxygenation as measured by NIRS in the first 7
days after stroke was lowest in the upright position and highest in the supine position (difference estimated around 2-6%). These changes were also present in the unaffected hemisphere, although on visual inspection less marked.’ (Discussion, page 14-15, line 22-24/1)

5. The study has answered that there are changes in a number of brain physiological variables but it does not tell us whether this changes are clinically safe and what affect they have on outcome. The study is too small in size to answer this question. There are a number of articles in the literature that have described these findings.

Reply of the authors:
First, the reviewer is correct that with our data no firm or definite conclusions on safety of upright mobilisation and a relationship with stroke outcome can be drawn. We agree that we should focus more on the physiological variables that were studied after changing position. To make this more clear, several changes were made in the revised manuscript. These changes were discussed in our answer to a. comment 1 of reviewer 3 (dr. Bhalla) and b. the comment of reviewer 1 (managing editor).

Second, the reviewer probably refers to the AVERT study (and sub analyses) that investigated the safety of early (out of bed) mobilisation after acute stroke. The results of the phase II (safety and feasibility) study in 71 patients were published from 2008.16;17 We added the results of the AVERT study to the Discussion of the manuscript.
It now reads: ‘However, our physiological results indicate that sitting is probably well tolerated in mildly to moderately affected stroke patients. In 2008 the ‘A Very Early Rehabilitation trail showed that very early out of bed mobilisation was safe and feasible in stroke patients. (AVERT) (Discussion, page 15, line 11-14)

6. I think there is too much data presented in the tables which makes it rather difficult to read. Perhaps using more graphics would have spelt out the key messages better. In view of this, the messages are not clear.

Reply of the authors:
We would like to refer to our answer 3 to reviewer 3 (please see above). The results section was changed with removing two tables (2 and 3) and adding one new figure (figure 2, replacing table 3). Furthermore the results are more introduced in the new results section which bundles more the (key) messages for the readers.