Author's response to reviews

Title: Pulmonary vascular permeability index and global end-diastolic volume: are the data consistent in patients with femoral venous access for transpulmonary thermodilution: a prospective observational study

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Version: 3
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Author's response to reviews: see over
Dear Editors,

Thank you for giving us the opportunity to revise our manuscript now entitled "Pulmonary vascular permeability index and global end-diastolic volume: are the data consistent in patients with femoral venous access for transpulmonary thermodilution: a prospective observational study." (MS: 2001266861126786).

We are grateful for the questions, suggestions and comments of the Reviewers.

Attached please find our point-by-point response.

You will find a clean revised manuscript and a marked-up copy of the changes made.

We feel that our manuscript could be further improved, and we hope that our revised manuscript is worth to be published in BMC Anesthesiology.

Yours sincerely,

Wolfgang Huber, MD
Reviewer 1:
Reviewer's report
Title:
Pulmonary vascular permeability index in patients with femoral venous access for transpulmonary thermodilution: a prospective observational study
Version: 2
Date: 13 May 2014
Reviewer: Zsolt Molnar
Reviewer's report:
In this prospective study the authors evaluated how in their view pulmonary vascular permeability index (PVPI) should be calculated to provide consistent information when a femoral venous access is used. The major finding was, that applying a “correction approach” they published earlier regarding the global enddiastolic volume (GEDV), both bias and percentage error could be reduced, the latter from 22% to 4%.

Major comments
Understanding and interpreting data given by any monitor is of utmost importance, as without it spending money, time and effort on monitoring would be a waste of time. Therefore, the efforts of the team lead by Dr Huber, which produced several papers in this regard over the last years has to be congratulated. These are my comments:

1. I found the description of the method on p6 lines 6-17 a bit difficult to understand and also confusing in general.
This is a valuable comment. Indeed the manuscript contains numerous calculations and formulas. To clarify these parts we used several approaches in the revised manuscript:
1.) We omitted information not related to the endpoints of this study (e.g. CO and CI; see page 5, line 9).
2.) We added a Table (see Table 1 of the revised manuscript) to clarify the subscripts “displayed”, “calculated” and “corrected”.

a.) Values with the subscript “displayed” are the raw data as provided by the PiCCO-device and shown in the display.
b.) Some of the displayed PiCCO-parameters are products (e.g. Cardiac Power Index CPI, which is a product of MAP, Cardiac Index and a constant) or ratios such as the PVPI which is derived from a simple formula by dividing EVLW by 25% of GEDV (PVPI = EVLW*GEDV^{1+0.25^{-1}}).

Based on the studies by Schmidt et al. (REF. 15 of the manuscript) and our group (REF. 16) the manufacturer requires information about the CVC site (“jugular/subclavian” or “femoral”), and correction for femoral TPTD injection can be assumed.

The main purpose of the study was to investigate the consistency of displayed values by comparing displayed data (e.g. GEDV_{displayed}, PVPI_{displayed}) to the corresponding

<table>
<thead>
<tr>
<th>Subscript</th>
<th>Meaning</th>
<th>Parameters analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>“displayed”</td>
<td>Values as displayed by the PiCCO monitor</td>
<td>GEDV_{displayed} GEDV_{displayed} EVLW_{displayed} PVPI_{displayed}</td>
</tr>
<tr>
<td>“calculated”</td>
<td>Parameters calculated based on parameters displayed on the monitor. These parameters should be consistent with corresponding displayed values.</td>
<td>GEDV_{calculated} PVPI_{calculated}</td>
</tr>
<tr>
<td>“corrected”</td>
<td>Parameters derived from correction of the displayed values. Corrected parameters were used for comparison to calculated values (only used in case of inconsistency between displayed and calculated values).</td>
<td>PVPI_{corrected} GEDV_{uncorrected}</td>
</tr>
</tbody>
</table>
values derived from calculation specified with the subscript “calculated” (GEDV_{calculated}, PVPI_{calculated}).

The 1\textsuperscript{st} step was to analyze the consistency of GEDV_{displayed} and GEDV_{displayed}. This could be easily done by comparing GEDV_{displayed} to GEDV_{calculated} which was derived by multiplying GEDV_{displayed} by BSA_{predicted}. This step demonstrated nearly identical values for GEDV_{calculated} and GEDV_{displayed} (1459±365 mL vs. 1459±366mL) which strongly suggests consistent correction of femoral TPTD derived GEDV_{displayed} and GEDV_{displayed}.

In a 2\textsuperscript{nd} step we analyzed consistency of PVPI_{displayed} and PVPI_{calculated}. PVPI_{calculated} was derived from EVLW_{displayed} and GEDV_{displayed}. To our surprise, there was a marked difference between PVPI_{displayed} and PVPI_{calculated} (1.64±0.57 vs. 2.27±0.72; p<0.001) which could be explained by using an uncorrected GEDV instead of GEDV_{displayed} for calculating PVPI_{displayed}.

c.) If displayed and calculated values were inconsistent, we investigated whether the inconsistency could be explained by (non-) application of our correction formula for the displayed values parameters. In this case “ex post” correction by our formula should result in a consistency of the “corrected” values (with the subscript “corrected”) and the calculated values. A marginal difference between PVPI_{corrected} and PVPI_{calculated} strongly supports that PVPI_{displayed} is based on an uncorrected GEDV instead of GEDV_{displayed}.

3.) To facilitate the understanding of multiple calculations we tried to avoid misleading language such as “calculated corrected values”. E.g. line 3, page 9 was changed to “determined PVPI_{corrected}”.
2. Especially the sentence in line 9: ‘Parameters calculated from these displayed values were subscripted with “calculated”.’ What does calculation mean? I couldn’t find it.

Please see above.

3. The same applies for that sentence from line 13-17. I think it needs more clarification as an average reader may get lost and also lose interest at this point. BSA-predicted is not what the equipment uses? In my understanding, GEDV-displayed is what we measure during thermodilution, and then the monitor divides it with the BSA, which in the case of PiCCO 2 should be the predicted. Or I am wrong? If yes, then please explain.

In general we agree that by definition GEDVI should result from the thermodilution-derived “raw” value GEDV by dividing GEDV by predicted BSA. However, the correction formula suggested by our group only pertains to GEDVI, but not to GEDV (see REF. 16). To the best our knowledge it is unknown, if GEDV ist corrected to the same extent as GEDVI. Therefore, we investigated consistency of GEDV\(_{\text{displayed}}\) and GEDV\(_{\text{calculated}}\).

As shown in summary Figure 6, based on the data shown in this manuscript it can be assumed that GEDV (as determined by TPTD) was corrected for GEDV\(_{\text{displayed}}\). However, instead of using GEDV\(_{\text{displayed}}\) probably “GEDV as measured by thermodilution” (GEDV\(_{\text{uncorrected}}\)) was used for calculation of PVPI\(_{\text{displayed}}\). Obviously, this resulted in an inconsistency between PVPI\(_{\text{displayed}}\) and PVPI\(_{\text{calculated}}\). We now clarified the calculation of GEDV\(_{\text{calculated}}\) (page 6, line 6) and PVPI\(_{\text{calculated}}\) (Discussion).

4. Finally, I totally agree with the authors, mentioned in limitations, that these findings could be supported by parallel thermodilution measurements using a CVC in the superior vena cava and a femoral CVC line. I would go even a bit further: In my opinion, the only way to confirm their observation is, to do a comparison of the two simultaneous measurements. Of course it is not easy as it can only be done in patients who have both catheters for treatment purposes (on hemofiltration for example), as from the ethical point of view it would not work in any other way.
We totally agree that our findings should be confirmed by a study design as suggested by the Reviewer.

Nevertheless, parts of the findings are apparent:

1.) Among our three main findings, the consistency of $\text{GEDV}_{\text{displayed}}$ and $\text{GEDV}_{\text{calculated}}$ strongly suggests that the same principle of correction for femoral TPTD pertains to both GEDV and GEDVI.

2.) Furthermore, the inconsistency between $\text{PVPI}_{\text{displayed}}$ and $\text{PVPI}_{\text{calculated}}$ is obvious with a high statistical significance.

3.) However, we clearly have to admit that our explanations for this inconsistency cannot be proven definitely by our approach: Although correction of $\text{PVPI}_{\text{displayed}}$ by our formula results in $\text{PVPI}_{\text{corrected}}$ close to $\text{PVPI}_{\text{displayed}}$ (as mentioned by the Reviewer: “both bias and percentage error could be reduced, the latter from 22% to 4%”) the hypothesis of a “neglect” of correction of PBV has to be proven by a confirmatory study.

These considerations are now reported in the “limitations of the study” paragraph.

**Level of interest:**

**An article of importance in its field**
Reviewer 2

Reviewer's report

Title: Pulmonary vascular permeability index in patients with femoral venous access for transpulmonary thermodilution: a prospective observational study

Version: 2

Date: 17 May 2014

Reviewer: Matthew Sigakis

Reviewer's report:

Discretionary revisions:

1. The authors should consider revising the title to better reflect the study goals and outcome. For example, the authors might consider something like, “Accuracy of Pulmonary Vascular Permeability Index When Femoral Venous Access is Used in Less-Invasive Monitoring Devices.” The title should emphasize that the PVPI displayed in less-invasive monitors may not be accurate when a femoral CVC is used, as this was the outcome of your study. This is a valuable comment. As mentioned above we interpret the findings of our study as a “neglect” of correction of PBV and PVPI for femoral CVC used for TPTD. This could be very easily changed by the manufacturer, at least for the PiCCO device. Therefore, we hope to initiate improved calculation of PVPI by the manufacturer in a future PiCCO algorithm for the sake of improved care. In this case a title suggesting permanent miscalculation of PVPI could be misleading for future readers. Therefore, we changed the title to

Pulmonary vascular permeability index and global end-diastolic volume: are the data consistent in patients with femoral venous access for transpulmonary thermodilution: a prospective observational study.

2. It would be helpful to learn the authors’ perspective on other less-invasive monitors besides the PiCCO device. Do the authors suspect that other less-invasive monitors also underestimate PVPI? Is this finding unique to the PiCCO device?

This is a very important question. To the best of our knowledge, there is only one other device providing PVPI which is the Edwards EV 1000 VoluView. Despite some minor modifications this device is very similar to the PiCCO. There are two major differences:
1.) The EV-1000 requires information, if the patient has undergone lung resection which suggests that the device is able to correct for this potential confounder.
2.) The EV-1000 does not require information about the CVC site which suggests that the device is not able to correct for this marked confounder of GEDV(I) measurement.
This is now mentioned in the Discussion section (see limitations of the study).

We recently submitted a case report on a patient with both jugular and femoral CVC. Simultaneous measurements suggest a similar overestimation of GEDVI as shown for the PiCCO (without correction). The manuscript is now in the “revision required” state. Therefore, we would not like to allude to these unpublished data in the PVPI-manuscript.
However, we are grateful for your suggestion and we will also analyze PVPI for the revision of the EV-1000 case report. If it is of interest, we will provide this manuscript for personal information.

Minor revisions:
- Page 4, line 12: PVPI needs parentheses, this is the first time the abbreviation PVPI is used in the main body of the manuscript.
Parentheses have been introduced in the revised manuscript
- Page 6, line 24 and Page 7, line 9: Units are needed in the formula for predicted and ideal body weights.
The unit “kg” is given in brackets on page 6 (line 24) and page 7 (line 9).
- Page 9, line 4: Subscript for PVPI reads “displayed.d” and
The subscripts have been changed in the revised manuscript
Level of interest:
An article of importance in its field
Quality of written English:
Acceptable
Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
Declaration of competing interests: I declare that I have no competing interests.