Author's response to reviews

Title: Dynamic preload indicators decrease when the abdomen is opened

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Version: 3
Date: 5 September 2014

Author's response to reviews: see over
Response to reviewers

Dear Professor Rowles,

Thank you very much for the evaluation of our manuscript. Below, we have provided a point-to-point response to the reviewer’s issues. We have also included detailed description of all changes compared to the previous version of the manuscript.

Reviewer #1
Comments of the reviewer:
Their question, does SVV and PPV change in concert with altered compliance as the abdomen is opened is clear. Whether or not this is a relevant question is another matter. The authors present findings suggesting PPV and SVV are reduced as the abdomen is opened, and posit that threshold levels of variation expected to predict fluid responsiveness be changed. If opening the abdomen lowers estimates of variation, patients should be less likely to be predicted to be fluid responsive. The authors, however, don’t test this hypothesis (and probably couldn’t with such a small sample size). Moreover, while they cite a small number of studies to support the supposition that goal-directed fluid therapy is helpful in operative patients, in general, a large number, perhaps the majority, of studies of fluid-responsiveness/goal-directed fluid therapy in the operative arena were done with patients having open abdominal surgeries, and these studies generally have a result favoring the PPV, SPV, SVV arm. That is, whether or not the PPV or SPV changes with an open abdomen, and despite the authors calls for different thresholds, a large body of work supports the practice of measuring SPV or PPV in open abdomen cases with existing standards and thresholds.

Author’s response: The reviewer correctly states that there is literature supporting the practice of measuring SPV or PPV in open abdominal cases, even with the commonly used thresholds. It is not the intention of the authors to claim otherwise. However, our results clearly show that opening the abdomen does influence the value of the dynamic indices. Whether or not the opening of the abdomen also influences fluid responsiveness has yet to be determined. Our results only suggest that using the thresholds determined in studies with closed abdomen might not be optimal for the use in patients with open abdomen. Adaptation of this threshold might therefore improve the predictive value of dynamic indices in these situations. Future work to the sensitivity and specificity of several thresholds at open and closed abdomen might answer this question (this study was not designed for this).

Author’s action: In the discussion we included more explicitly that our goal was not to claim that the currently used thresholds are not applicable in open abdomen cases but only to show the influence of opening the abdomen on the value of the dynamic indices:

“While several studies have suggested that dynamic preload indicators are still able to predict fluid responsiveness during abdominal surgery to a certain extent, our findings are concordant with the results of other studies that their predictive value regarding fluid responsiveness might be reduced compared to values obtained on the ICU.”

“Finally, the aim of this observational study was to show the influence of opening the abdomen on the value of the dynamic indices. The study was not designed to quantify the impact on the predictive value neither to propose new thresholds because we did not
measure the actual fluid responsiveness of our patients. Because of the major impact of opening the abdomen on the value of the dynamic indices, further research is needed in order to quantify and validate thresholds that are corrected for the abdominal condition of the patient.”

Comments of reviewer:
They posit that the lowering of the variability estimate means the traditional thresholds wouldn’t apply, or would be too high to be useful, but they don’t really prove that. They seem to be presuming that the lowering of the estimate means some number of patients who don’t reach the traditional threshold would still be volume responsive, but they don’t demonstrate this, reducing their assertion to speculation.

Author’s response: The reviewer is correct that we do not prove that threshold corrected for an open abdomen show better results with respect to sensitivity and specificity. This observational study, in which we did not measure fluid responsiveness, was designed to show the physiological influence of opening the abdomen. From the results, showing a strong significant change in the dynamic indices when opening the abdomen in only a relatively small number of patients, we reason that the abdominal condition (open or not) should definitely be taken into account when the commonly used thresholds are applied. These results also imply that more research is needed in order to quantify and validate thresholds that are corrected for the abdominal condition of the patient.

Author’s action: We agree with the reviewer that this could be mentioned more explicitly to the reader and added the following paragraph to the discussion (limitations) (in accordance to our action on the first comment of the reviewer):

“Finally, the aim of this observational study was to show the influence of opening the abdomen on the value of the dynamic indices. The study was not designed to quantify the impact on the predictive value neither to propose new thresholds because we did not measure the actual fluid responsiveness of our patients. Because of the major impact of opening the abdomen on the value of the dynamic indices, further research is needed in order to quantify and validate thresholds that are corrected for the abdominal condition of the patient.”

Comments of reviewer:
I assume by “opening the abdomen,” they refer to the opening of the fascia, rather than the skin, but I would make this explicit.

Author’s response: “opening of the abdomen” indeed refers to the opening of the fascia.
Author’s action: We have made this explicit in the manuscript (in the methods section).

Comments of reviewer:
Their sample size is quite small and the authors do not describe how they arrived at this number. Did they do a power analysis and arrive at 13? Did they get to 13 and fall tired of recruiting? Or did they analyze the data in real-time and stop when they got to the result they expected?

Author’s response: The design of this observational study was exploratory and hypothesis generating in nature, therefore it was hard to perform a formal power analysis. We based
our preliminary sample size calculation on a mean initial PPV of 12% (μ(0)), a standard deviation of 2.5% (based on our previous research), a μ(1) of 10% (educated guess) and power and alpha of .80 and .05, respectively (one-sided test). Based on these numbers, our minimal sample size was 10, and because of the uncertainty, we had chosen to include some extra patients.

**Author's action:** Because our sample size calculation of our observational study includes some uncertainties and we had chosen to include some extra patients, we suggest not to include the sample size calculation in the manuscript.

**Comments of reviewer:**
They use a non-traditional blood pressure source for the calculation of CI and SVI. While this might be a validated device, its novelty does introduce uncertainty for the reader.

**Author’s response:** It is correct that we use a non-traditional blood pressure source for the calculation of CI and SVI. This is also why we describe this issue in our discussion (limitations section) and cited some articles that show that this non-invasive technique is well capable of measuring the blood pressure. However, the reviewer is right that this not implicate the correct calculation of CI and SVI. Therefore, we added a reference to a review study showing that also the calculation of CI and SVI from this signal is accurate (Truijen, 2012 J Clin Monit Comput). Furthermore, for our results and conclusions, the change in CI and SVI was actually more important, and the non-invasive technique is even better in tracking changes in CI/SVI (same reference). Therefore, we don’t think this has influenced our results.

**Author’s action:** In the discussion we mention as a first limitation of our study that we measured the arterial pressure with the non-invasive method (using a finger cuff). In order to remove potential uncertainty for the reader, we refer to a research study and a literature review that show that the non-invasive measurement of the blood pressure as well as the calculation of the dynamic indices and the tracking of the changes in CI and SVI can be done accurately with the used technique (Lansdorp, 2011, BJA and Truijen, 2012, J Clin Monit Comput).

**Comments of reviewer:**
The mean Vt achieved in these patients (7.3 and 7.6 mL/kg) is below the Vt commonly accepted to create enough intrathoracic pressure to reveal respiratory variability (8 mL/kg). This is a small difference, but it does deviate from accepted norms.

**Author’s response:** The reviewer is correct that the used tidal volumes are below the TV used in several benchmark studies defining the commonly used thresholds. The reason for this is that in our institute, lower values of TV are preferred for critically ill patients because of the risk of ALI and ARDS (in line with literature from Girard, Chest 2007; Eichacker, AJRCCM 2002 and Schultz, Anesthesiology 2007). However, as the reviewer is also mentioning, the average tidal volume does not differ very much commonly accepted TV (8.0 versus 7.6/7.3), and based on the results of our recent publication in CCM (Lansdorp, 2014), this would probably only influence the PPV with 8%. This influence of the low tidal volume is relatively low compared to the influence of the opening of the abdomen. This is therefore not likely to influence our results and conclusions.

Furthermore, our study is not designed to validate or redefine the commonly used thresholds, so the absolute value of the PPV (influenced by the amount of TV) is not
influencing our conclusion.

Author’s action: We agree with the reviewer that it is good to make the reader aware of this deviation and incorporated this, together with our thoughts on why this does not influence our results, in the discussion:

“... the mean tidal volume that was used to ventilate the patients was somewhat less than the tidal volume used in most studies about the predictive value of dynamic indices (8ml/kg vs. 7.6 and 7.3ml/kg). This is because nowadays, lower values of tidal volume are preferred (Girard, Chest 2007; Eichacker, AJRCCM 2002). However, based on a recent publication (Lansdorp, CCM 2014) and the fact that this difference was rather small (0.4 and 0.7 ml/kg) the influence of the reduced tidal volume is suggested to be relatively low compared to the influence of the opening of the abdomen. Also, our study is not designed or used to validate or redefine the commonly used thresholds, so the potentially lowered absolute value of the PPV (influenced by the amount of TV) is not likely to influencing our results or conclusions.”

Comments of reviewer:
In line 173, they state that their results confirm other studies which suggest variability estimates are better predictors in ICU patients compared to OR patients. Their study did not compare OR to ICU, nor did the studies they cited to make this point. In fact, they missed the opportunity to cite a number of studies in OR, open abdomen patients that did show a benefit to using variability estimates to guide fluid therapy.

Author’s response: We thank the reviewer for his thoughtful remark on the additional references on this subject and incorporated them in the manuscript. Dynamic indices are indeed able to predict hypovolemia in the OR, however, due to decreased cardiopulmonary interactions variations become less pronounced in the presence of an open abdominal compartment. Hence, a more severe degree of hypovolemia is precluded to induce the same respiratory induced arterial variations during open abdominal surgery as compared to a situation where the abdominal wall integrity is not compromised.

Author’s action:
(line 187 old) While several studies have suggested that dynamic preload indicators are still able to predict fluid responsiveness during abdominal surgery to a certain extent1–2, our findings confirms the results of other studies that their predictive value regarding fluid responsiveness is reduced compared to values obtained on the ICU. 3–5

(line 187 new) While several studies have suggested that dynamic preload indicators are still able to predict fluid responsiveness during abdominal surgery to a certain extent1–2 [Benes, et al., Critical Care, 2010, Forget, et al, A/A, 2010 are included as references], our findings are concordant with the results of other studies that their predictive value regarding fluid responsiveness might be reduced compared to values obtained on the ICU. 3–5
Reviewer #2

Comments for the Author:
“This reviewer thinks that the question that the authors posed was well written and worth addressing. Because a relationship can exist between abdominal pressure and cardiac filling indices, this is a question worth addressing. To be able to address this question non-invasively will be of interest.”

Comments of reviewer:
The authors do not address, and this reviewer considers it to be unexpected that PPV and SVV should be present in subjects who are demonstrating a CI of 3 (Figure 1.) In euvelemic patients with volume limited ventilation the measured PPV and SVV averages border on hypovolemia. This reviewer then wonders about additional details of the anesthetic management. Did the epidural test dose contribute here?

Author’s response: We do agree with the reviewer that the average CI mentioned in Figure 1 is reasonably high. However, we know from literature that the absolute value of CI does not implicate fluid responsiveness. Additionally, we don’t claim in our manuscript that our patients are fluid responders or not (we have not tested this). However, we can assume, since at baseline the value of PPV is below the commonly used threshold, that most of the patients are non-responders, which is in line with the measured CI. Furthermore, because dynamic parameters are continuous, even in non-responders PPV and SVV will be present, and the influence of opening the abdomen can also be tested in these patients. Furthermore, it is not likely that the epidural test dose influenced our results because of the low dose (which will only block a few segments) and the time interval until the measurement (at least 25 minutes).

Author's action: In the discussion, we included the arguments that the test dose will only block a few segments and that with the time interval of 25 minutes it is not likely that the test dose influenced our measurement.

Comments of reviewer:
The abdominal pressure changes with laparotomy, however other changes can occur with surgical incision as well. This reviewer wondered if the primary change that was measured relates most directly to sympathetic reflexes triggered by surgical incision. Given the reported anesthetic levels, it would be expected that some patients would mount sympathetic responses.

Author’s response:
We agree with the reviewer. A surgical stimulus could indeed induce sympathetic reflexes. However in that case one would expect changes in heart rate and blood pressure. Since these did not occur we consider influence of the sympathetic reflexes to be of lesser importance.

Author’s action:
The following sentence was added to the discussion section of the manuscript: “Sympathetic reflexes triggered by surgical incision could have attributed to our findings, however since no changes in heart rate and blood pressure occurred we considered its effect to be of lesser importance.”
**Comments of reviewer:**
Was there a standard laparotomy used? Were retractors placed? How big were these incisions? In line 184 and following, the authors propose a physiologic explanation for the lack of change in the bladder pressure. If no retractors were placed, why wouldn’t the same gravitational effect that produces no change in the bladder pressure cause the abdominal contents to exert a similar effect on the diaphragm?

**Author’s response:** Operating procedures were performed according to standard clinical practice regarding laparotomy. After the abdominal compartment was opened, no retractors were placed during the measurement to avoid strain on the compartment induced by the retractors on the abdominal tissue. It could well be that the same gravitational effect that produces no change in the bladder pressure cause the abdominal contents to exert a similar effect on the diaphragm. However, in addition to these gravitational forces abdominal pressure can rise during inspiration induced compression of the abdominal compartment. The design of the experiment aimed to assess the effects of the absence of rise in abdominal pressure and its subsequent effect on dynamic indices.

**Author’s action:** We added the following sentences to the method section. “Operating procedures were performed according to standard clinical practice. After opening the abdominal compartment, no retractors were placed during the measurement to avoid strain induced by the retractors on the abdominal tissue.”

**Comments of reviewer:**
Given the small trial, having 3 patients drop out for technical issues is a problem. Are we to understand that more than 20 percent of the data couldn’t be analyzed? Still, the subjects appear in table 1?

**Author’s response:** For unknown reasons, Stroke Volume Variation could not be determined due to difficulties using the online pulse contour method incorporated in the Nexfin Monitor to derive beat to beat stroke volume. However, pulse pressure variation and systolic pressure variation could still be calculated in these patients, since these parameters were calculated offline and using Matlab.

**Author’s action:**
(line 138 old) In three patients SVV could not be determined due to technical difficulties.

(line 138 new) In three patients SVV could not be determined due to difficulties with the algorithm that derives beat to beat stroke volume from the arterial blood pressure signal.

**Comments of reviewer:**
Why did the authors choose a Tidal Volume less than 8ml/kg predicted body weight? (the reviewer is assuming that the ml / kg-1 is in predicted body weight?)

**Author’s response:** First of all, the reviewer is correct when assuming the tidal volume was based on predicted body weight. Furthermore, we did not choose the tidal volume with which the patients were ventilated; this was part of the standard care (the study had an observational character). Because nowadays, in our institute, lower values of TV are preferred for critically ill patients because of the risk of ALI and ARDS, the average TV was
below 8ml/kg. This use of low tidal volume is based on evidence from literature showing the negative effects of high tidal volume (see Girard, Chest 2007; Eichacker, AJRCCM 2002 and Schultz, Anesthesiology 2007).

Additionally, the average tidal volume does not differ very much from the mentioned 8ml/kg (being 7.6), so based on the results of our recent publication in CCM (Lansdorp, 2014), this would probably only influence the PPV with 8%, and this is relatively low compared to the influence of the opening of the abdomen. This is therefore not likely to influence our results and conclusions.

Furthermore, our study is not designed to validate or redefine the commonly used thresholds, so the absolute value of the PPV (influenced by the amount of TV) is not influencing our conclusion.

Author’s action: We agree with the reviewer that it is good to make the reader aware of this deviation in used tidal volume (compared to the tidal volume used in several benchmark studies defining the commonly used thresholds) and incorporated this, together with our thoughts on why this does not influence our results, in the discussion:

“... the mean tidal volume that was used to ventilate the patients was somewhat less than the tidal volume used in most studies about the predictive value of dynamic indices (8ml/kg vs. 7.6 and 7.3ml/kg). This is because nowadays, lower values of tidal volume are preferred (Girard, Chest 2007; Eichacker, AJRCCM 2002). However, based on a recent publication (Lansdorp, CCM 2014) and the fact that this difference was rather small (0.4 and 0.7 ml/kg) the influence of the reduced tidal volume is suggested to be relatively low compared to the influence of the opening of the abdomen. Also, our study is not designed or used to validate or redefine the commonly used thresholds, so the potentially lowered absolute value of the PPV (influenced by the amount of TV) is not likely to influencing our results or conclusions.”

Comments of reviewer:
Line 179 – the authors discuss “decreased pleural pressures.” Where is the evidence for this? If the airway pressures did not change, and the tidal volumes remain the same, I don’t see evidence of a compliance change. If compliance calculations were done, please provide those data.

Author’s response: Unfortunately no compliance calculations are available for evaluation of the decrease in pleural pressure due to alterations in abdominal compartment integrity. Attributing the change in dynamic indicators after opening the abdominal compartment is hypothetical and based on previous observations of the influence of thoracic compliance by our group. (Lansdorp et al, CCM, 2014). It revealed that cardiopulmonary interactions that dictate the magnitude of dynamic indicators were altered when thoracic compliance was decreased, resulting in increased pleural pressure swings and a concomitant increase in dynamic indicators.

Author’s action:
(line 178 old) Since the tidal volume, the main determinant for the change in intrathoracic pressure,8 did not change, the observed decrease of the dynamic preload indicators must be
a result of the decreased swings in pleural pressure due to the increase in thoracic compliance (or more specific, the increased compliance of the diaphragm as a result of the increased abdominal compliance).

(line 178 new) Since the tidal volume, the main determinant for the change in intrathoracic pressure, did not change, the observed decrease of the dynamic preload indicators could well be attributed to a decrease in pleural pressure amplitude due to the increase in thoracic compliance (e.g. the diaphragm experiences less resistance from the abdominal compartment during inspiration).

Comments of reviewer:
The opening sentence in the abstract and background (Lines 27 and 52) is likely to engender debate. The authors might consider a softer statement like “optimizing stroke volume is of interest to many…”

Author’s response: We agree with the reviewer and modified the manuscript according to his suggestion

Author’s action:
(line 27 old) Optimizing cardiac stroke volume during major surgery decreases the incidence of postoperative complications.
(line 27 new) Optimizing cardiac stroke volume during major surgery is of interest to many as a therapeutic target to decrease the incidence of postoperative complications.
(line 52 old) Optimizing cardiac stroke volume during major surgery decreases the incidence of postoperative complications and the length of stay in the ICU.
(line 52 new) Optimizing cardiac stroke volume during major surgery is of interest to many as a therapeutic target to decrease postoperative complications and the length of stay in the ICU.

Comments of reviewer:
Line 61 – some physiologists describe the “compliance of the respiratory system” to include lungs, chest and abdomen. The authors might consider whether a more inclusive description of respiratory compliance would be useful in their discussion.

Author’s response: We agree that compliance of the respiratory system indeed depends on the compliance of the lungs and thoracic compartment, in which the latter constitutes of chest wall compliance and diaphragmatic compliance dictated by abdominal pressure. The extent to which the intrathoracic pressure increases depends, in case of volume controlled positive pressure ventilation, upon the space occupied by the inflated lungs within the thoracic compartment, hence tidal volume, and the compliance of the thoracic compartment itself.

Author’s action: We have rewritten this sentence of the introduction.

(line 62 old) The extent to which positive pressure ventilation increases intrathoracic pressure and interacts with the intrathoracic circulation depends on the tidal volume and
the compliance of the chest wall.

(line 62 new) New The amplitude of the intrathoracic pressure depends, in case of positive pressure ventilation, upon the space occupied by the inflated lungs within the thoracic compartment, hence tidal volume, and the compliance of the thoracic cavity.

Comments of reviewer:
Line 139 – additional commentary would be helpful – hard drive malfunction is different than probe slipped off the finger.

Author’s response: Stroke Volume Variation could not be determined due to difficulties during offline data analysis using dedicated software provided by the manufacturer, BeatScope. During this analysis the algorithm that derives the stroke volume upon the waveform of the arterial blood pressure signal was unable to calculate a beat to beat stroke volume, unfortunately for unknown reasons.

Author’s action:
(line 138 old) In three patients SVV could not be determined due to technical difficulties.

(line 138 new) In three patients SVV could not be determined due to difficulties with the algorithm that derives beat to beat stroke volume from the arterial blood pressure signal.

Comments of reviewer:
I would appreciate seeing a suggestion for what follow-on trial might be appropriate.

Author’s response:
Although our results suggest that using the thresholds determined in studies with closed abdomen might not be optimal for the use in patients with open abdomen and adaptation of this threshold might therefore improve the predictive value of dynamic indices in these situations, we don’t test fluid responsiveness ourselves and therefore we can’t test the predictive value of any adapted thresholds. Future work to the sensitivity and specificity of several thresholds at open and closed abdomen might answer this question. This is why we think additional research is needed in order to quantify and validate thresholds that are corrected for the abdominal condition of the patient.

Author’s action: We added the following sentence to the discussion section of the manuscript.

“Because of the major impact of opening the abdomen on the value of the dynamic indices, further research is needed in order to quantify and validate thresholds that are corrected for the abdominal condition of the patient.”

We thank the reviewers for their constructive comments. We believe the quality of our manuscript has increased thanks to the review process and we hope that the revised manuscript is acceptable for publication.