Author's response to reviews

Title: The increase of vasomotor tone avoids the ability of the dynamic preload indicators to estimate fluid responsiveness.

Authors:

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Author's response to reviews: see over
**Reviewer's report**

**Title:** The increase of vasomotor tone avoids the ability of the dynamic preload indicators to estimate fluid responsiveness.

**Reviewer:** Jochen Renner

**Reviewer's report:**

Comments to the Author

Dynamic variables of fluid responsiveness have been extensively investigated in the past years, and indications and limitations are definitely better known today. One main issue is of course the question whether vasoactive agents affect the ability of these variables to accurately discriminate between responder and non-responder due to volume load. In this regard the study from Bouchacourt et al. is of some interest. Especially, since the available literature is not consistent. However, there are a few aspects that need to be addressed and need to be clarified by the authors.

First of all, in general, the manuscript is well written. However, the main problem with this manuscript is the divergence of the hypothesis (estimation of fluid responsiveness) and the setting of the study protocol (Baseline – Baseline + PHE – Hemorrhage – Hemorrhage + PHE), which is not designed to estimate fluid responsiveness, but to assess the influence of different loading conditions plus/minus PHE on dynamic variables. Whether these variables were able to accurately predict fluid responsiveness under these conditions, i.e. discriminate with acceptable sensitivity and specificity between responder and non-responder has not been shown in this manuscript.

As the reviewer correctly suggests, we modify the hypothesis and the aims of the paper: "We hypothesized that the use of a vasoconstrictor drug may hide the increase of dynamic indexes (SVV, PPV, SPV, PPV\_apnea) during hypovolemia. The first aim of this study was to investigate the effects of an increase of vascular tone on preload dynamic variables of fluid responsiveness in a rabbit model of hemorrhage. The second aim was to examine the ability of the arterial pressure surrogates dynamic indexes to track SVV changes during hypovolemia under increased vasomotor tone."

Nevertheless, this study is of some interest, especially since the influence of PHE on vasomotor tone and consequently on pulse pressure has been well shown. Consequently, the focus of this manuscript must be the influence of hemorrhage and PHE on the different variables assessed and the potential consequences of their ability to estimate fluid responsiveness have to be discussed (but are not justified by the presented data). The authors interpret the influence of PHE on dynamic variables as a pseudo normalisation, however, the very important point is whether they still have predictive power or not, since in daily clinical routine continuous administration of norepinephrine intraoperatively during major surgery is a common thing.

As the reviewer suggests we modified the first two paragraphs on the discussion section.

We also focused on the influence of the vasomotor tone on the dynamic indexes and the ability of predicting FR.

We removed the term “pseudo normalisation” and re-write this paragraph.

Another point regarding the decision to perform Bland Altman Analysis: Comparing stroke volume variation, pulse pressure variation and systolic pressure variation are in general variables yielding the same information, but in part with totally different threshold values. I
have never heard of any Bland Altman plots comparing CVP and PAOP to prove interchangeability. So what to?

We removed the Bland Altman Analysis and as suggested by reviewer 2 we used 4 quadrant plot and polar plot to assess the ability of the arterial pressure surrogates dynamic indexes to track SVV changes during hypovolemia under increased vasomotor tone. We choose SVV as the gold standard dynamic parameter to monitor volume responsiveness since it is the magnitude of respiratory changes in the LV SV, the primary indicator of preload reserve. Besides, the use of an ultrasonic flowprobe (precision 1%) to estimate SV allow us to estimate SV and SVV with a high certainty.

Please focus more on the assumed effect of PHE on dynamic variables; more pronounced during haemorrhage compared to euvolaemia? Potential effects on the accuracy to predict FR.

Any influence for our daily clinical routine? Another confounder/limitation?

To me it makes no sense to compare SVV / PPV / SPV using Bland Altman.

As we write above, we removed B-A analysis.

We demonstrate that the ability of the dynamic indexes to predict fluid responsiveness during hemorrhage under an isobaric increase of vasomotor tone (TPR and Ea dyn increase and C decrease) induced by phenylephrine administration (a pure α1-agonist) would not be acceptable: "Consequently, in clinical routine practice, we should be aware that vasopressors can substantially reduce the ability of the dynamic indicators to predict fluid responsiveness, masking the effective intravascular volume deficit".

Please discuss the findings of Monnet et al. Br J Anaesth. 2013 Feb;110(2):207-13. SVV, PPV and PVI under NE, influence of the Perfusion index!

We add the paper in Reference section (#33), and we add in the discussion section: "Regarding the pleth variability index (PVI), a non-invasive alternative to PPV and SVV, Monnet et al reported that the prediction of fluid responsiveness by PVI is less reliable than invasive indexes in patients with acute circulatory failure receiving norepinephrine (33)."
Reviewer's report

Title: The increase of vasomotor tone avoids the ability of the dynamic preload indicators to estimate fluid responsiveness.

Reviewer: Koichi Suehiro

Reviewer's report:

For the Authors:
General Comments:
The authors studied about the dynamic preload indicators in animal models, and concluded that all dynamic preload indicators (SVV, SPV, PPV and PPVapnea) were significantly reduced by phenylephrine administration during hemorrhage, masking the true fluid loss possibly by increasing the vasomotor tone. And they also indicated that arterial pressure surrogates are not interchangeable with SVV. This article is well written and it is easy to understand their results. However, the impact of the results seems to be few.

Suggestions for Revision:
1. Why did you choose SVV as a reference method in Bland-Altman analysis? In the present study, the bias in the Bland-Altman analysis was not acceptable. Many previous reports have shown the reliability of SVV, SPV, and SPV to predict fluid responsiveness in mechanically ventilated patients.

We choose SVV as the gold standard dynamic parameter to monitor volume responsiveness since it is the magnitude of respiratory changes in the LV SV, the primary indicator of preload reserve. Besides, the use of an ultrasonic flowprobe (precision 1%) to estimate SV allow us to estimate SV and SVV with a high certainty.

2. Please describe the reason why the bias in the Bland-Altman analysis became high (over 30%). You indicated that PPV, SPV and PPVapnea could not be interchangeable with SVV. However, all dynamic preload indicators (SVV, SPV, PPV and PPVapnea) have already been proved to be useful in many clinical settings. You think that these parameters except SVV should not be used as a predictor of fluid responsiveness?

As the reviewer suggests in 3., we performed the four-quadrant plot and polar plot analysis showing that in NORMAL VASOMOTOR TONE, there is an acceptable concordance rate and mean angular bias with radial limits of agreement between SVV and arterial pressure surrogate indexes. We think that, "in clinical practice, we should be aware that vasopressors can substantially REDUCE the ability of the dynamic indicators to predict fluid responsiveness, masking the effective intravascular volume deficit".

3. You should use 4 quadrant plot and polar plot to assess the tracking ability of all dynamic preload indicators after phenylephrine administration and hemorrhage. Four quadrant plot [1], and polar plot analysis [2] give an assessment whether the changes of the new method is acceptable compared with the reference method.

[2] Critchley LA, Yang XX, LeeA. Assessment of trending ability of cardiac output
We thanks a lot this suggestion and we think that greatly improved the paper. In accordance with the suggestion we have modified the following sections: Statistical analysis, results and conclusions.

We added both papers in reference section (#23, #24).

We substituted Fig 3 for a new version that includes the 4-quadrant plots and polar plots. We also added a Table 3 that summarized both new analysis.

4. As described in this paper, Cannesson, et al. has shown that the impact of phenylephrine administration on cardiac output is related to the position of the heart of Flank-Starling relationship. Similarly, the impact of PHE boluses on the dynamic preload indices is affected by systemic vascular resistance state?

We discussed the findings of Cannesson et al in page 10. In contrast to their findings, we showed that PHE infusion induced a further decrease in aortic flow with a significant SV decrease after blood withdrawal compared with normovolemia, secondary to a significant increase of vasomotor tone (increased total systemic peripheral vascular resistance).