Peer Review File

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Reviewer Comments: This study is well conducted and it seems analyzed appropriately as well. The author also take consideration of some details that most investigators might ignore such as the least significant change of the hedmoynamic parameter. However, I have several concerns below.

Major comments

Comment 1: This study suffers from the lacks in novelty as well as rationale of the hypothesis. The major novelty behind this study is to validate Flotrac/Vigileo derived SVV for intraoperative pediatric fluid responsiveness. However, the Flotrac/Vigileo derived stroke volume is unreliable in pediatric population (Intensive Care Med. 2011 Aug;37(8):1297-301.; Br J Anaesth . 2014 Apr;112(4):626-37.). Therefore, we consider that there is no solid evidence to support the primary interest of this study. The authors need to provide sufficient rationale to support the interest for investigation of the Flotrac/Vigileo derived SVV in children.

Reply 1: We deeply appreciate you for taking time to review our manuscript. We agree with you that the topic is not new. However, we think this is an important and unsolved topic worthy of staying focused. Currently, there are no consistently validated hemodynamic variables that predict fluid responsiveness in children, except for respiratory variation in aortic blood flow peak velocity (ΔVpeak). However, the lack of continuity and physicians with experience in performing echocardiographic exams decreases its utility in routine clinical practice. An accurate and handy predictive variable for fluid responsiveness in children is still urgently needed.

Works on plethysmographic variability index (PVI)'s role in pediatric patients have been increasing recently. High preoperative PVI was independently associated with propofol-induced hypotension in children (1). The PVI is effective in predicting fluid responsiveness in pediatric patients with lung-protective ventilation regardless of a lung recruitment manoeuvre (2). Previous works demonstrated conflicting results with respect to the predictive value of PVI in pediatric neurosurgical patients. Those studies included pediatric patients with great heterogeneity by enrolling 0-14-year-old patients. There are great differences among different ages of pediatric patients given the rapid growing cardiovascular and thoracopulmonary systems. Therefore, we included the pediatric neurosurgical patients aged 4-9 years. We consider that the results of the predictive values of PVI, PPV and SVV in the specific age group with similar physiology would be more convinced. The results from our manuscript would be more helpful for practitioners to apply PVI in >3-year-old children otherwise healthy. A study of PVI, PPV, and SVV's predictive values for fluid responsiveness in ≤3-year-old pediatric patients is currently undergoing in our hospital.

References:

1. Choi S, Ji S, Jang Y, Kim E, Lee J, Kim J, et al. Predicting hypotension during anesthesia: Variation in pulse oximetry plethysmography predicts propofol-induced hypotension in children. Paediatric anaesthesia (2021) 31(8):894-901. doi: 10.1111/pan.14223. PubMed PMID: 34018647.

2. Kim E, Lee J, Jang Y, Ji S, Kim H, Cho S, et al. Prediction of fluid responsiveness using lung recruitment manoeuvre in paediatric patients receiving lung-protective ventilation: A prospective observational study. European journal of anaesthesiology (2021) 38(5):452-8. doi: 10.1097/eja.0000000000001387. PubMed PMID: 33186310.

We totally agree with you that the FloTrac/Vigileo cardiac output monitoring system is not validated for cardiac index monitoring in the pediatric setting. However, SVV obtained from FloTrac/Vigileo is not subject to algorithm errors. As we described in the "Materials and Method" section, FloTrac/Vigileo analyzes the arterial pressure waveform and calculates stroke volume and SVV. The SV is based on the contribution of pulse pressure relative to stroke volume, which is proportional to the standard deviation of arterial pulse pressure (PP_{SD}). Therefore, $SV = PP_{SD} \times K$,

where K is an autocalibration factor that incorporates the quantification of arterial compliance and vascular resistance based on waveform contour analysis and patient characteristics derived from a multivariate regression model. K is recalculated every minute to adapt to changing vascular tone.

SVV was calculated simultaneously as the variation of SV from the mean value obtained from the previous 20 s. It was calculated as follows:

$SVV\ (\%) = 100 \times (SVmax - SVmin) / [(SVmax + SVmin) / 2]$

where SVmin and SVmax were the minimum and maximum stroke volumes over a time frame of 20 s.

That means,

$SVV\ (\%) = 100 \times (PP_{SD}max \times K - PP_{SD}min \times K) / [(PP_{SD}max \times K + PP_{SD}min \times K) / 2]$

K is a constant during SVV calculation within one minute. Therefore,

$SVV\ (\%) = 100 \times (PP_{SD}max - PP_{SD}min) / [(PP_{SD}max + PP_{SD}min) / 2]$

SVV calculated using FloTrac/Vigileo reflects PP_{SD}'s variation within 20 s. Although K is not validated in pediatric patients, leading to great errors in SV measurements using FloTrac/Vigileo, SVV is dependent on PP_{SD} max and PP_{SD} min within 20 s, which is not affected by inaccurate K. Therefore, SVV values in pediatric patients are as accurate as those in adult patients. The aim to validate Flotrac/Vigileo-derived SVV for intraoperative pediatric fluid responsiveness can be accurately achieved by our study. We detailed the calculation of FloTrac/Vigileo-derived SVV in the manuscript for further clarification. Please see "Methods" section: Page 8, line 163-178 in yellow color.

Changes in the text: We detailed the calculation of FloTrac/Vigileo-derived SVV in the manuscript in yellow color. Please see "Methods" section: Page 8, line 163-178 in yellow color.

Comment 2. The adequate intraoperative MAP is crucial for modern anesthetic care (Br J Anaesth. 2019 May;122(5):563-574.). The authors may consider to conduct the analysis of the abilities of dynamic elastance (PPV/SVV) and PI to predict the arterial pressure fluid responsiveness in this study. This additional analysis may augment the novelty of the present study because the dynamic elastance is less explored in pediatric population.

Reply 2: Your suggestion is well appreciated. We have added the analysis of the

abilities of dynamic elastance (PPV/SVV) and PI to predict the arterial pressure fluid responsiveness in re-submitted manuscript as advised.

Changes in the text: The analysis of the abilities of dynamic elastance (PPV/SVV) and PI to predict the arterial pressure fluid responsiveness has been added to the re-submitted manuscript. Please see "Methods" section: Page 9, line 197-199;
"Results" section: Page 13, line 30-304;
"Discussion" section: Page 17-18, line 397-406;
And "Conclusion" section: Page 19, line 441-443 in yellow color.

Comment 3. A more thorough discussion between the present study and the conflicting results among literatures is warranted. For instance, The authors should discuss the different findings between the present study and one previous meta-analysis of SVV application in children (Yi et al. PLoS One. 2017 May 12;12(5):e0177590.). In fact, the majority of literatures of SVV in pediatric population are based on transpulmonary thermodilution (eg. PiCCO) because this type of monitor is more reliable than uncalibrated sytem (Flotrac/Vigileo or ProAQT) for children. This is also the abovementioned concern.

Reply 3: We really appreciate your kind suggestion. We have added the relevant discussion as advised. Please see "Discussion" section: Page 16-17, line 358-380 in yellow color.

Changes in the text: We have added the relevant discussion as advised. Please see "Discussion" section: Page 16-17, line 353-375 in yellow color.

Comment 4. The change of PPV provide no predictive value to fluid responsiveness because the fluid challenge is already performed and thus this does not prevent excessive fluid. Therefore, the AUROC of changes in PPV provides only limited diagnostic value for intraoperative fluid therapy.

Reply 4: We totally agree with your comment about the change of PPV's role in predicting fluid responsiveness intraoperatively. We modified the description about the change of PPV's role in predicting fluid responsiveness as you advised.

The mini-fluid challenge is a clinical concept of predicting fluid responsiveness by rapidly infusing a small amount of intravenous fluids, and systematically assessing its hemodynamic effect. This method is meant to predict if a patient will respond to a subsequent, larger fluid challenge, with a significant increase in stroke volume (3,4). We consider, whether a mini-fluid challenge test (3 ml/kg, compared with a standard volume of 10 ml/kg) determining the change in PPV from baseline would be helpful, in discriminating fluid responsiveness in children with a PVI value in gray zone and guiding optimal perioperative fluid management in children. The above significance of the PPV change following fluid loading is described in the "Discussion" section. Please see Page 17, line 377-386 in yellow color.

References:

3. Zorio V, Lebreton T, Desgranges F, Bochaton T, Desebbe O, Chassard D, et al. Does a two-minute mini-fluid challenge predict fluid responsiveness in pediatric patients under general anesthesia? Paediatric anaesthesia (2020) 30:161-7. doi: 10.1111/pan.13793

4. Messina A, Lionetti G, Foti L, Bellotti E, Marcomini N, Cammarota G, et al. Mini fluid chAllenge aNd End-expiratory occlusion test to assess flUid responsiVEness in the opeRating room (MANEUVER study): A multicentre cohort study. European journal of anaesthesiology (2021) 38:422-31. doi: 10.1097/eja.0000000000001406

Changes in the text: We modified the description about the change of PPV's role in predicting fluid responsiveness. Please see "Discussion" section: Page 17, line 377-386 and "Conclusion" section: Page 19, line 439-443 in yellow color.

Minor comment

Comment 5: The title is unprecise because spot values of PVI, PPV and SVV instead of continuous values were analyzed in this study.

Reply 5: Your comment is well appreciated. We modified the title by deleting "continuous" as advised.

Changes in the text: Please see "Title".

Comment 6: Does the Fig 2 indicated a significant more changes in PPV after fluid loading among nonresponders than those among the responsders? The group legends of the "R" and the "NR" seems wrong.

Reply 6: We are really sorry about the wrong labeling of "R" and "NR". We corrected the labeling of Fig. 2 as advised.

Changes in the text: Please see Fig. 2.

Comment 7: The authors claimed the integrated the baseline value of PVI and change in PPV to predict fluid responsiveness for children in the conclusion. However, I did not found associated analysis in the present study. The statement is biased in my opinion because the baseline PVI and the change in PPV may be highly correlated with each other. Therefore, the integration of these two values may provide little additional predictive value than that of the individual parameter unless the author perform the analysis properly.

Reply 7: Your comment about this point is reasonable. The concept of integrating the two variables is totally speculative. We deleted this speculation as you advised.

Changes in the text: We deleted this speculation.