Response to reviewers

We are grateful for the reviewers, editors, and staff involved in the analysis and critique of our manuscript. We enjoyed writing this paper titled, "One Approach to Circulation and Blood Flow in the Critical Care Unit" and we hope it has proved a concise but interesting scientific review.

Reviewer #1 (02480177)

The manuscript is well written.

- We very much appreciate your time and feedback

Reviewer #2 (00502932)

Excellent concise review of a complex subject. In the interest of brevity, I think Table 6 could be deleted.

- We agree with the reviewer suggestion of shaping this document into an important educational tool. In order to improve, we have removed Table 6 and added examples of the commonly used vasopressors to the section of "vasopressors and corticosteroids". Thank you for the careful evaluation of our manuscript.

Reviewer #3 (03555433)

In this review, the authors create a minimalistic guide to the clinical information relevant when assessing critically ill patients with failing circulation. In addition, the authors present clinical advice for patient care and medical training. There are several comments for this review. 1. The subtitle of "organ blood flow" may need revision. It focus more on the relationships among MAP, cardiac output, and SVR for whole body. The readers may look forward to learning more information of measurement, pathophysiology, and heterogeneity of blood flow in specific organs. 2. The authors may consider use the correct subscript of all the abbreviations. 3. A major concern is raised about the following information. "However, what if the patient is not

mechanically ventilated, is spontaneously breathing, does not have a regular heart rate or on adequate tidal volume – can PPV and SPV still be used? The answer is yes, they can. The requirement for specific ventilatory parameters has been challenged, and both PPV and SPV tests work well in patients breathing spontaneously, with an AUC (area under the curve) of more than 0.8 for both.39,40" The authors may need to clarify that the requirement of a specific breathing pattern is mandatory and the cut-off value might be different in different conditions. In an untrained spontaneously breathing patients in ICU, the use of PPC and SPV should be very careful.

- We thank the reviewer for the thorough evaluation and critical review.
- 1. The subtitle "organ blood flow" may misrepresent our description of the regulation of blood flow with changes in hemodynamic parameter and with failing circulation. In order to improve, we have changed the subtitle to "Regulation of Blood Flow". Although fascinating from the physiology stand point, we will not be adding any further description specific to a certain organ blood flow at this time as it would change the main focus of our review.
- 2. We agree, and it has been corrected.
- 3. Thank you for this important comment. We have modified our document in order to emphasize caution when using PPV/SPV with spontaneously breathing patients due to the varying reliability and results with changes in breathing patterns (***Zöllei E**, Bertalan V, Németh A, et al. Non-invasive detection of hypovolemia or fluid responsiveness in spontaneously breathing subjects. BMC Anesthesiol 2013;13:40)(**Hong DM**, Lee JM, Seo JH, Min JJ, Jeon Y, Bahk JH. Pulse pressure variation to predict fluid responsiveness in spontaneously breathing patients: tidal vs. forced inspiratory breathing. Anaesthesia 2014;69:717-22).*

Comments:

- *"Some of the figures are adapted from other articles. Please check and confirm the permissions are granted from the copyright holders. If the permissions have been granted, please provide the permission email records or permission documents. Please login the system, and download the edited manuscript document."*

Response to comments:

Dear Dr. Jin-Lei Wang,

I am sincerely sorry for this problem. I was occupied with the literature review and draft revisions and overlooked the need for copyrights. This has been corrected:

- As requested for figures 1, 2, 4, 5, 6, 7 the respective permission records have been obtained and uploaded. Since there was not a specific section to upload the copyright permissions at the F6Publishing system a Microsoft Word document was created and uploaded as "supplementary material" with the printable licenses copied and pasted on it; including the email records for Figure 2. In addition an email was sent to j.l.wang@wjgnet.com with the original copyright files.
- The reference #61 used for figure 1 has been updated to reflect for: ***Mattson DL,*** *Lu S, Roman RJ, Cowley AW. Relationship between renal perfusion pressure and blood flow in different regions of the kidney. Am J Physiol 1993;* ***264****(3 Pt 2): R578-583 [PMID: 8457011 DOI: 10.1152/ajpregu.1993.264.3.R578*, as it reflects the original paper where the figure was adapted, and the copyrights were obtained from.
- Figure 2 was reproduced with permission of the Society of Photo Optical Instrumentation Engineers (SPIE)

- On page number 8 and around the second paragraph of the topic "***Circulating volume/volume status*",** I noted the word filling had been spelled with one "L" and thus it was corrected and highlighted.

Once again, writing this review has been our pleasure. I hope all the high standards for publication are met and please let me know if there is anything else needed.

Best Regards,

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