Peer Review File

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Point-by-point reply

Reviewer(s)' Comments to Author:

Reviewer #1:

Point 1

I find it very surprising that the authors found no difference in MCFP between hypovolemia and normovolemia, despite the correlation between MCFP and MSFP and the fact that, as expected, MSFP was lowered during hypovolemia. If sample size does not explain this surprising finding, can the authors speculate as to what does?

Authors' response

We like to thank the reviewer for pointing this out and apologize for the omission. The absence of a significant different between hypo- and euvolemia with regards to the MCFP value may very well be explained by the small sample size. Like the reviewer rightly shows, the influence of the volumetric state on the MCFP was tested using an unpaired student's t-test. With that; increased intrasubject variability compared to the test for the MSFP and thus is theoretically less powerful. In addition, the MSFP values were obtained 3 times in each piglet, whereas the MCSP (for officious reasons) could only be obtained once. In our defense, the experiment was powered for the comparison of the MSFP values. Fact remains that the limitation section needs some nuance regarding the effect sizes.

Authors' actions

- Discussion, we rephrased the second sentence of the limitations section from 'That being said, the effect sizes of all findings supporting the presented conclusions were sufficiently powered' to 'That being said, the effect sizes support the presented conclusions - regarding the reconstructed VR curve - were sufficiently powered.'

Point 2

Pg 5 line 4: Please write in full before abbreviating, i.e. “Electrocardiogram (EKG)”

Authors’ actions

- Material and methods, we added ‘Electrocardiogram’ to the first line of section 2.4.

Point 3

Pg 6 line 14: “restore euvolemia”?

Authors’ response

We like to thank to reviewer for pointing out this inconsistency. We removed that part of the sentence for clarification.

Authors’ actions

- Results, we removed ‘, in order to restore hypovolemia’ in de second line of section 3.2

Reviewer #2:

Point 1

We have taken the liberty to summarized the point of reviewer 2: “Referring only to the criticisms of the concept as "controversial" is not strong enough”

Authors’ response

We couldn’t agree more with the reviewer. The characteristics of the VR curve are (falsely) formulated in a strictly causal fashion. As we indicated, the effects of an IHM is not limited to reducing cardiac output by increasing the backpressure to VR [1]. Not just because the effect of ventilatory pressure tends to spread out over the whole circulation, but also because of strong control systems. This makes using causal reasoning to understand and explain venous return challenging, and complicates its use for predicting clinical interventions.

The question should therefore is not per se; can we construct the VR curve using IHMs, but rather; does applying perturbations using IHMs provide information about

the hemodynamic state of the patient. Here we demonstrated that within a piglet the MSFP_IH was linked to the volumetric state, but the absolute value was unsuitable for guiding clinical therapy. Nevertheless, applying perturbations to a closed-loop physiological system for system identification does seem elegant. This system identification approach allows one to not pick sides in the conceptual issue whether RA pressure acts as back pressure to VR or whether it responds only passively to volume shifts when flow changes, as proposed by Levy [2] and Brengelmann [3]. Therefore, we agree with the reviewer and others that the validity of the concept whereat MSFP_IH is used as the upstream pressure, and CVP/RAP as the downstream pressure of VR in the beating-heart situation in its current form is controversial (reads useless) [4] and we feel that more studies in order to determine normative MSFP values are not useful [5].
We have tried to emphasize this in our discussion, by adding an additional phrase and reference from Brengelmann's latest article [6].

Authors' actions

- Discussion, we added 'Guyton's formulation of the VR curve was never about MSFP driving venous return [6], he' to section 4.4.

Bibliography

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2. Levy MN. The cardiac and vascular factors that determine systemic blood flow. *Circulation research* 1979; **44**: 739–47.
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Reviewer #3:

Point 1

According to the theory of venous return, the VR is associated with the gradient of Pmsf and CVP. The authors reported that a strong linear correlation between VR and CVP (R2 of 0.92). Very high correlation! Authors should comment this finding.

Authors' response

As stated in the manuscript: the presented linear relationship between cardiac output and CVP is in line with Guyton's theory on VR [1] and is also observed by multiple studies in both animal models [2,3] and humans [4], while in the past they left room for discussion on the linearity when flow approached zero.

Our results indeed show – to our surprise – a very strong linear relationship between CVP and VR even when VR approached zero. It was crucial here was that when induced an inspiratory hold that we took the CVP and VR when in steady state. This steady state was not achieved within – like others have done – the first 10 seconds. Showing that a healthy cardiac function in steady state is an elegant interplay between filling and output. Note, CVP is clearly not a substitute for VR/cardiac output in patients.

Authors' actions

- Discussion, we added 'strong' to the third sentence of section 4.3.

Point 2

MSFP is known to be associated with volume status. This concept is now novel.

Authors' response

MSFP is indeed known to be associated with volume status, just like we showed in our study. Normative values are however not available and will probably never will be. We do therefore not claim MSFP to be a novel concept, but rather show that in

our experimental setting with highly invasive cardiac output measurements and ‘extreme’ differences in intravascular volume this concept could not clearly discriminate between hypo- and euvolemia and with that not being of clinical value.

Point 3

As the authors states, the clinical value of MSFP monitoring remains unclear.

Authors’ response

We fully agree with the reviewer, see also our response to point 2. In additional, we feel that more studies in order to determine normative MSFP values are not useful.

Bibliography

1. Guyton AC. The relationship of cardiac output and arterial pressure control. *Circulation* 1981; **64**: 1079–88.
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