Response to comments

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Response to comments

We appreciate the interest in our randomized controlled trial evaluating the effect of using peri-operative goal-directed therapy in high-risk abdominal surgery and the opportunity to respond to the letters to the editor from Hasanin et al. and Luo [1–3].

Dr. Hasanin and colleagues raised questions about methodology and specific treatments in both the Perioperative Goal-Directed Therapy group and the control group. Regarding their first question, we would have agreed with the statement of Hasanin et al. on adjustment for confounding variables in case our study had been an observational comparison between perioperative goal-directed fluid therapy and a control group. However, treatment allocation was randomized and hence, confounding has been accounted for by design. This holds both for potential confounders that have been measured in our study, and unknown or otherwise unmeasured confounders. This is one of the key points of the randomized design [4]. Any differences between groups that occur after randomization, such as those that may have occurred during surgery, may not have been independent of treatment allocation. In that case, surgical characteristics that differ between groups are not confounding variables, but mediators. In no case should a mediating variable be adjusted for in the analysis, as this would cause biased estimates of between-group differences [5]. We are confident that characteristics during surgery that differed to any clinically meaningful extent were not due to chance events, as our randomization procedure was stratified, not only for center, but also for type of surgery. With blocks of sizes 2 and 4, chance-differences between groups are very unlikely to occur. For that reason, we only judged clinical meaningful differences between groups at baseline (i.e., before treatment starts) to inform whether multivariable adjustment would be warranted, not those occurring later during the study.

A higher incidence of pulmonary oedema in the control group is somewhat surprising indeed, as lower volumes of infused fluids and blood products were administered intraoperatively in this group. However, there were no significant differences in other patient outcomes between both groups, such as PACU/ICU and hospital length of stay, and 30 days mortality.

We did not perform repeated measures analyses on creatinine data, or any other outcome for that matter. In our pre-specified statistical analysis plan, we chose to include only cross-sectional comparisons of between-group differences. Although longitudinal analyses would involve many more observations because each participant contributes more than one value and hence, statistical power could increase, the strong expected correlation between repeated measures of the same quantity within patients diminishes that potential benefit. No analysis with increased statistical power would have any effect on the interpretation of the clinical meaningfulness of the differences that we have observed.

Regarding their fourth question, we did not define background infusions in both groups. This was free at the discretion of the attending anesthesiologist.

Another question raised by Hasanin was the eventual initiation of an intervention if the mean arterial pressure decreased. We agree that maintenance of mean arterial pressures >60–65 mmHg is essential in patients. Mean arterial pressures were not significant between groups ($p = 0.49$) (Fig. 1). Moreover, average mean arterial pressures were above 70 mmHg, with lower levels (average - standard deviation) most often above 65 mmHg, with, as published previously, low Odds ratios for adverse outcomes [6]. In addition, we reported in the manuscript that a total of 939 interventions based on the protocol in the PGDT group were analyzed. Besides these per protocol interventions, other interventions were possible at the discretion of the attending anesthesiologist when blood pressures were lower, or urine production was lower with adequate cardiac index above the threshold cardiac index. These non-algorithm-based interventions were not recorded in the case record form and therefore not evaluated.

Hemodynamic management in the control group was at the discretion of the attending anesthesiologists as the control group should represent every day's practice instead of another obliged type of hemodynamic management. As mentioned in the manuscript, dobutamine was more often used intraoperatively and postoperatively in the PGDT group, whereas phenylephrine was more often used in the control group during the operation. A possible explanation for this finding might be the awareness of lower cardiac output with adequate filling necessitating inotropes to improve cardiac output in the PGDT group. On the contrary, not measuring cardiac output with lower blood pressure may trigger anesthesiologists to use phenylephrine to counteract anesthetics induced vasodilation to obtain adequate blood pressures (neglecting flow). Moreover, phenylephrine was intraoperatively used in 102 patients and postoperatively in 6 patients in the control group. The suggestion by Hasanin that this study appeared to be a comparison between a vasopressor – versus inotropic guided approach is not supported as such.

Finally, a probable superiority of fluid management in the control group compared to the PGDT group as suggested by Hasanin et al., cannot be explained from the obtained 30 days outcomes.

Dr. Luo has concerns about the statistical analysis used. We used the intention-to-treat principle for the analyses of our RCT on perioperative goal-directed fluid therapy exemplified in our manuscript. We recognize some ambiguity in our manuscript text ("*In the intention to-treat-analysis, excluding those patients who did not receive allocated treatment…*"), but as the *n* for those analyses suggests, we did not exclude participants just because they did not receive the intended treatment protocol. Some patients were not included in the analysis, as can be seen from the CONSORT flow diagram. Only those who had been lost to follow-up have been excluded, as no outcome data of these patients were

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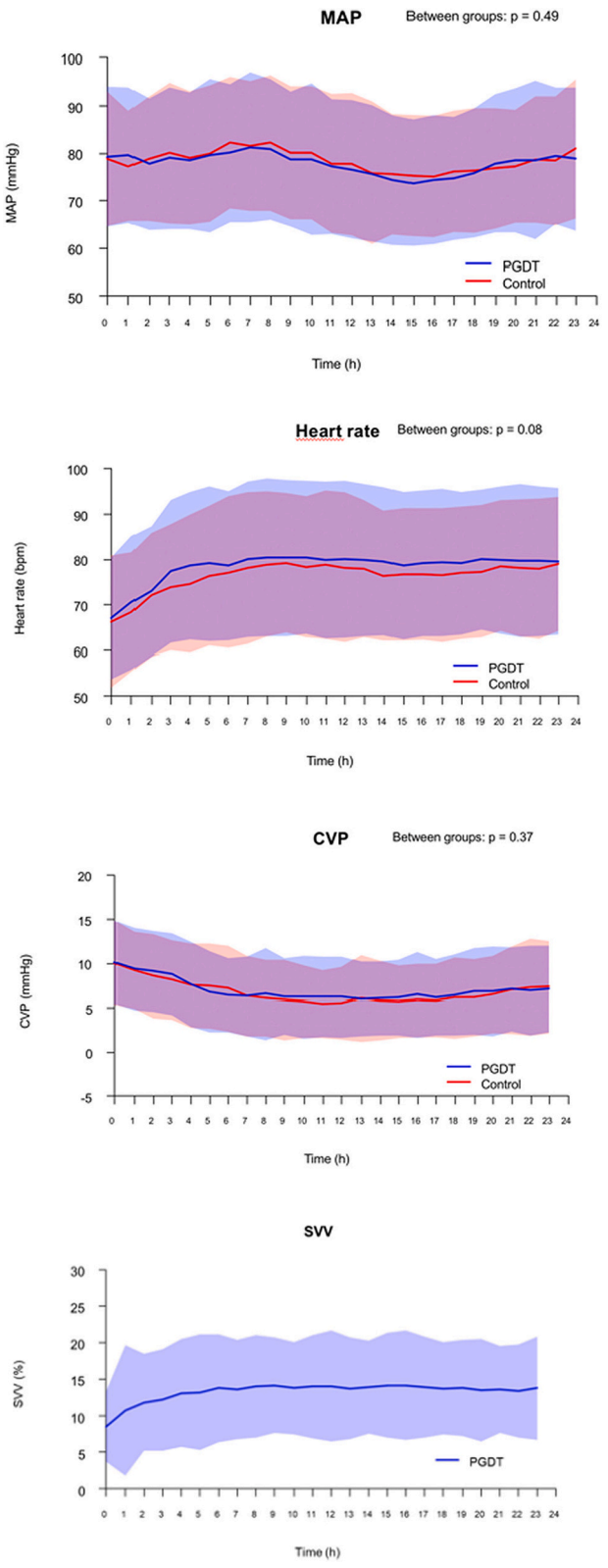

Fig. 1. Mean arterial pressure (MAP), Heart rate and Central Venous Pressure for both groups (control versus PGDT) as well as stroke volume variation (SVV) from PGDT group over a 24-h monitoring period starting after induction of anesthesia. Data are mean ± SD. (Blue line and background: PGDT; red line and background Controls; purple background overlap of both backgrounds). PGDT = perioperative goal-directed therapy. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

available for further analyses. Therefore, we did not produce a synthetic part of the data using data-imputation methods, to allow inclusion of those lost to follow-up in the analysis.

It is highly unlikely that between-group differences at baseline were due to the small proportion of patients that were lost to follow-up, as the reasons for that were unrelated to treatment allocation. Therefore, both groups should still be comparable at baseline due to random allocation of treatments. We observed some small differences in baseline descriptive statistics between groups, but not to a clinically meaningful extent. We would like to kindly point out that assessing 'significance' of baseline differences would be meaningless, as all differences between groups at baseline would by definition be due to chance alone, and therefore by type-I errors, as the intervention has not been performed yet [7]. For that reason, we did not test for between-group differences at baseline.

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Declaration of Competing Interest

WB has received honoraria for lectures and was consultant for both Pulsion Medical Systems/Maquet and Edwards Lifesciences. TS received research grants and honoraria from Edwards Lifesciences and Masimo Inc. for consulting and lecturing, and from Pulsion Medical Systems/Maquet for lecturing (all payments made to institution). The other authors declare that they don't have competing financial interests nor personal relationships that could have appeared to influence the work reported in this manuscript.

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