

# Population Volume Kinetics in Volunteers: Comment

## Competing Interests

The author declares no competing interests.

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To the Editor:

I have read the article by Nyberg *et al.*<sup>1</sup> with interest, and would like to comment on their approach to model fluid volume kinetics.

The two-volume model they used is well known to become unstable if the plasma dilution time curve has a flat appearance postinfusion.<sup>2</sup> To prevent this problem, the customary procedure is to equalize the elimination to the urinary excretion. The authors quantified the excreted urine by weighing but did not use this information. Their choice resulted in an unstable model, which is evidenced by a coefficient of variation as large as 123% for the elimination rate constant ( $k_e$ ). Recent articles using the same population kinetic model report a coefficient of variation for  $k_e$  of only 5% to 15%.<sup>3-5</sup>

The key result requires clarification. The study compared the plasma dilution in bled volunteers who did and did not receive isoflurane anesthesia. The Abstract says that the maximum plasma dilution was 35% higher, and that the area under the curve for the plasma dilution was 99% larger, in the group that received isoflurane anesthesia. However, the observed data plotted in figs. 6 and 7, as well as my own simulation based on table 1, show that the plasma dilution was similar between both groups and was even slightly lower among those who received isoflurane.

I still assume that the Abstract is correct because previous studies show that induction of epidural, spinal, or general anesthesia increase the plasma dilution resulting from infused crystalloid fluid. The magnitude of this dilution depends directly on the decrease in arterial pressure.<sup>6-8</sup> The reason is retarded distribution.<sup>8</sup> No excessive dilution occurs if the pressure is unchanged.<sup>6,9</sup> Nyberg *et al.* established arterial access and measured the pressure, but they did not consider the anesthesia-induced hypotension in their model.

Finally, the mean arterial pressure was the strongest predictor of  $k_e$  in a population volume kinetic analysis of 78 conscious and anesthetized humans receiving crystalloid fluid,<sup>4</sup> as well as in another cohort of anesthetized patients.<sup>10</sup> This potential covariate does not seem to have been considered either.

## References

1. Nyberg J, Li H, Wessmark P, Winther V, Prough DS, Kinsky MP, Svensén CH: Population kinetics of 0.9% saline distribution in hemorrhaged awake and isoflurane-anesthetized volunteers. *ANESTHESIOLOGY* 2019; 131:501-11
2. Hahn RG, Drobin D: Urinary excretion as an input variable in volume kinetic analysis of Ringer's solution. *Br J Anaesth* 1998; 80:183-8
3. Hahn RG: The elimination half-life of crystalloid fluid is shorter in female than in male volunteers: A retrospective population kinetic analysis. *Biol Sex Diff* 2016; 7: 54
4. Hahn RG: Arterial pressure and the elimination of crystalloid fluid: A population-based study. *Anesth Analg* 2017; 124:1824-33
5. Hahn RG: Influences of the red blood cell count on the distribution and elimination of crystalloid fluid. *Medicina* 2017; 53:233-41
6. Hahn RG: Haemoglobin dilution from epidural-induced hypotension with and without fluid loading. *Acta Anaesthesiol Scand* 1992; 36:241-4
7. Drobin D, Hahn RG: Time course of increased haemodilution in hypotension induced by extradural anaesthesia. *Br J Anaesth* 1996; 77:223-6
8. Li Y, Zhu S, Hahn RG: The kinetics of Ringer's solution in young and elderly patients during induction of general and epidural anesthesia. *Acta Anaesth Scand* 2007; 51:880-7
9. Hahn RG, Lindahl CC, Drobin D: Volume kinetics of acetated Ringer's solution during experimental spinal anaesthesia. *Acta Anaesthesiol Scand* 2011; 55:987-94
10. Lee JH, Choo YJ, Lee YH, Rhim JH, Lee SH, Choi BM, Oh ST, Choi KT, Noh GJ: Population-based volume kinetics of Ringer's lactate solution in patients undergoing open gastrectomy. *Acta Pharmacol Sin* 2019; 40:710-6

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# Population Volume Kinetics in Volunteers: Reply

## In Reply:

We thank Dr. Hahn for his excellent comments<sup>1</sup> and thorough interest in our study.<sup>2</sup> In this study, we tried to identify important covariates that could be used for designing future volume kinetic studies.

We acknowledge our study limitations. Namely, in the present study, imprecise urine data were obtained *via* bladder ultrasound resulting in an uncertainty in urinary output with regard to timing and volume. Thus, to not introduce bias, urine measurements were not incorporated in the modeling. We appreciate that this drawback potentially resulted in a less stable model with higher interindividual variability. In addition, the design of the study, the study population, and the low number of subjects<sup>3</sup> and observations could also result in higher estimated interindividual variability of the elimination rate constant ( $k_e$ ) compared with previous studies.

In our study, mean arterial pressure was strongly associated with the subject's state (*e.g.*, being either anesthetized or awake). Including highly associated covariates in a stepwise covariate model building procedure will result in high imprecision and instability in the covariate analysis.<sup>4,5</sup> Therefore, we chose to only include the subject's state as covariate. Additionally, because the subject's state would likely be known before any intervention, this covariate could be easier to apply when designing future studies. Consequently, because the correlation between mean arterial pressure and the subject's state is high, we do not believe that including anesthetized-induced hypotension would improve the model fit but instead would likely dilute the impact of the subject's state covariate.

We have thoroughly reexamined table 1 in the original manuscript<sup>2</sup> and confirm that the estimates from the model building are correct. Thus, the model (represented by table 1)<sup>2</sup> could be used for extrapolation and design of future studies. There is, however, a typographical error in the simulations, switching the central-to-peripheral transfer rate constant to the peripheral-to-central transfer rate constant when simulating the subject's state effect. This error would impact the simulations for the subject's state (anesthetized

or awake) in the opposite direction (*i.e.*, resulting in a slightly lower area under the curve and maximum plasma dilution with anesthetized subjects compared with awake subjects). We thank Dr. Hahn for detecting this error.

## Competing Interests

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## References

1. Hahn RG: Population volume kinetics in volunteers: Comment. *ANESTHESIOLOGY* 2020; 132:•••••
2. Nyberg J, Li H, Wessmark P, Winther V, Prough DS, Kinsky MP, Svensén CH: Population kinetics of 0.9% saline distribution in hemorrhaged awake and isoflurane-anesthetized volunteers. *ANESTHESIOLOGY* 2019; 131:501–11
3. Pradhan S, Song B, Lee J, Chae JW, Kim KI, Back HM, Han N, Kwon KI, Yun HY: Performance comparison of first-order conditional estimation with interaction and Bayesian estimation methods for estimating the population parameters and its distribution from data sets with a low number of subjects. *BMC Med Res Methodol* 2017; 17:154
4. Ahamadi M, Largajolli A, Diderichsen PM, de Greef R, Kerbusch T, Witjes H, Chawla A, Davis CB, Gheyas F: Operating characteristics of stepwise covariate selection in pharmacometric modeling. *J Pharmacokinet Pharmacodyn* 2019; 46:273–85
5. Ribbing J, Jonsson EN: Power, selection bias and predictive performance of the population pharmacokinetic covariate model. *J Pharmacokinet Pharmacodyn* 2004; 31:109–34

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