ESC HEART FAILURE
ESC Heart Failure 2022; **9**: 2762–2763
Published online 13 May 2022 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.13950

REPLY

Response to Letter to the editor regarding 'Discordance between estimated and measured changes in plasma volume among patients with acute heart failure'

Jutta S. Swolinsky[1], Bruce A. Molitoris[2] and Kai M. Schmidt-Ott[1,3]*

[1]*Department of Nephrology and Medical Intensive Care, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Hindenburgdamm 30, Berlin, 12203, Germany;* [2]*Department of Medicine, Indiana University, Indianapolis, IN, USA; and* [3]*Max Delbrück Center for Molecular Medicine in the Helmholtz Association, Berlin, Germany*

Received: 28 February 2022; Accepted: 4 April 2022
**Correspondence to: Kai M. Schmidt-Ott, Department of Nephrology and Medical Intensive Care, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Hindenburgdamm 30, 12203 Berlin, Germany. Tel: +49 30 450 414 671; Fax: +49 30 450 514 971. Email: kai.schmidt-ott@charite.de*

We thank Begos *et al*.[1] for their interest in our work[2] and would like to respond to their comments and questions regarding our study. The study considered 36 patients with acute heart failure and assessed the relationships of changes in measured plasma volume (mPV), using the FAST Biomedical Technology technique, and changes in estimates of plasma volume (ePV), using haemoglobin and haematocrit-based Strauss and Kaplan–Hakim equations during 48 h of decongestive therapy. The key finding of our study was an absence of a significant correlation between changes of mPV and changes of ePV over this period. This finding questions the validity of ePV equations in acute heart failure patients.

Begos *et al*. state in the first paragraph of their letter that 'changes in measured plasma volume correlated moderately well with the Kaplan–Hakim formula (r = 0.75), and also with the Strauss formula in a subgroup of 19 patients with a stable measured red cell volume (mRCV) (r = 0.78)'. We would like to note that this sentence does not adequately summarize our findings. The correlation coefficient r of changes in PV estimated by Kaplan–Hakim formula and actual changes of mPV was 0.23 and non-significant, indicating no value of Kaplan–Hakim formula in assessing changes of PV in acute heart failure patients. A similarly poor correlation was found for the Strauss formula (r = 0.24, non-significant) when considering the entire population.

Begos *et al*. suggested comparing patients with stable RCV against those with unstable RCV, because Strauss formula appeared to be more adequate in identifying true changes of PV in patients with a stable RCV. However, we did not find statistically meaningful clinical differences between stable and unstable RCV groups regarding baseline characteristics (including age, sex, weight, height, body mass index, blood pressure, heart rate, left ventricular ejection fraction, chronic kidney disease stage, N-terminal pro-brain natriuretic peptide levels, and comorbidities). Thus, it appears difficult to predict a priori, which patients would exhibit a stable RCV.

Begos *et al*. also pointed out the exclusion criterion of internal bleeding and asked why the four patients with clinical evidence of bleeding, or need for blood transfusions, were not excluded. The reason is that none of these patients had signs or symptoms of active bleeding at the time of study inclusion. Hence, these patients were enrolled as per study protocol, and the blood losses or requirement for blood transfusions developed later during the course of the study. However, even after exclusion of these four patients, the correlations of ePV changes and mPV changes remained poor (Kaplan–Hakim, r = 0.33; Strauss, r = 0.33; both non-significant).

Begos *et al*. point out that Kaplan–Hakim formula includes 'dry weight' and draw attention to the difficulties in defining 'dry weight' in heart failure patients. We agree that this is an additional limitation of Kaplan–Hakim formula. We did test different definitions of dry weight, but correlations of changes of mPV and changes of ePV (Kaplan–Hakim) remained weak and non-significant.

Begos *et al*. further questioned the accuracy of PV measurements during our study because of the duration of the sample acquisition and the potential lack of steady state conditions in heart failure patients. As pointed out in the Methods section, we obtained blood samples during a relatively short period of 1 h to determine the concentrations of the fluorescent PV tracer FD003. We also have reported in our original publication of the study that the concentration of FD003 remained stable throughout the sampling period

without evidence of changing PV over time.[3] Hence, PV assessments in our study population are accurate.

Begos *et al*. cite a number of studies that report the association of ePV with clinical outcomes suggesting ePV might be useful for clinical decision-making. We would like to emphasize that we are less enthusiastic about the clinical utility of ePV equations because PV-independent factors also drive the association of these estimates with outcomes. For instance, low or declining haemoglobin concentrations and haematocrit values will result in high or increasing PV estimates when applying ePV formulas. Nevertheless, low or declining haemoglobin or haematocrit may simply signify bleeding or worsening anaemia, known adverse prognostic factors. Hence, the association of 'rising ePV' with poor outcomes may simply be driven by the anticipated inverse association of falling haemoglobin or haematocrit with poor outcomes.

In sum, our study highlights the limitations of PV estimating formulas in patients with acute heart failure and emphasizes the potential need for direct PV measurements to overcome these limitations. We concur with Begos *et al*. in their call for a large prospective study to compare various methods of PV determination and correlation of such measures with clinical outcomes.

References

1. Begos D, Milojkovic B. Letter to the editor regarding 'Discordance between estimated and measured changes in plasma volume among patients with acute heart failure'. *ESC Heart Failure*. 2022. https://doi.org/10.1002/ehf2.13874
2. Swolinsky JS, Tuvshinbat E, Leistner DM, Edelmann F, Knebel F, Nerger NP, Lemke C, Roehle R, Haase M, Costanzo MR, Rauch G, Mitrovic V, Gasanin E, Meier D, McCullough PA, Eckardt K-U, Molitoris BA, Schmidt-Ott KM. Discordance between estimated and measured changes in plasma volume among patients with acute heart failure. *ESC Heart Failure*. 2022; **9**: 66–76.
3. Swolinsky JS, Nerger NP, Leistner DM, Edelmann F, Knebel F, Tuvshinbat E, Lemke C, Roehle R, Haase M, Costanzo MR, Rauch G, Mitrovic V, Gasanin E, Meier D, McCullough PA, Eckardt K-U, Molitoris BA, Schmidt-Ott KM. Serum creatinine and cystatin C-based estimates of glomerular filtration rate are misleading in acute heart failure. *ESC Heart Failure*. 2021; **8**: 3070–3081.