# Challenge of the Mini-fluid Challenge: Filling Twice without Creating a Self-fulfilling Prophecy Design

*To the Editor:*

We read with great interest Biais *et al.*'s study[1] investigating the mini-fluid challenge during neurosurgery. In line with previous mini-fluid challenge research,[2–4] the mini-fluid challenge predicted fluid responsiveness with compelling accuracy.[1] Still, we feel there are some very important methodologic aspects to highlight for the existing mini-fluid challenge results: predictor and outcome variables being calculated from the same baseline.

Except for Guinot *et al.*'s study,[4] all existing studies[1–3] calculated their predictor and outcome variables as follows: the predictor variable is based on a change from baseline to after the mini-fluid challenge —in the present study, a $\Delta SVI_{100}$ variable was calculated, see the study's figure 1.[1] The outcome variable (defining the fluid response) has been calculated as a change *also* from baseline (before the mini-fluid challenge) to after the full fluid challenge—in the present study, a $\Delta SVI_{250}$ variable was calculated. Now, $\Delta SVI_{100}$ and $\Delta SVI_{250}$ are mathematically coupled *via* the baseline value ($\Delta SVI_{100} = [SV_{afterMFC,\ 100ml} - SV_{baseline}]/SV_{baseline}$ and $\Delta SVI_{250} = [SV_{afterFC,\ 250\ ml} - SV_{baseline}]/SV_{baseline}$). Unfortunately, this means that the high predictive power of the mini-fluid challenge approach can be explained by not only one but by three reasons: (1) A true predictive power of the mini-fluid challenge (which we would all love to believe); (2) A statistical phenomenon (see below), or (3) A combination of 1 and 2 (most likely the case). To understand the statistical phenomenon, let's imagine the case where the mini-fluid challenge itself induces a significant increase in stroke volume, say $\Delta SVI_{100}$ is 10%. If stroke volume stays unaltered when infusing the remaining 150 ml, this would give rise to a $\Delta SVI_{250}$ of still 10%, defining a positive fluid response—even though stroke volume has not changed at all with the second infusion. In other words, $\Delta SVI_{100}$ and $\Delta SVI_{250}$ are likely to agree (even when they don't) simply because they have been calculated based on the same *baseline* value, whose random measurement error and/or physiologic variation (which is present in any measurement) is carried over in calculations of both $\Delta SVI_{100}$ and $\Delta SVI_{250}$. The problem is even demonstrated in figure 2,[1] where some *responders* (as defined by $\Delta SVI_{250}$) experience status quo or even reductions in stroke volume during the last part of the 250 ml infusion, *i.e.* $\Delta SVI_{100}$ is higher than $\Delta SVI_{250}$. To take this down to a clinical everyday level, consider our standard fluid challenge approach in most goal-directed therapy applications: We usually administer a first fluid challenge of 250 ml and evaluate the stroke volume response: Let's say we encounter a stroke volume increase of 20%. Afterward, we give a second fluid challenge (as merited by our goal-directed therapy protocols) and stroke volume stays the same—we have reached the Frank-Starling curve plateau, and we now consider our patient unresponsive to fluids. According to the mini-fluid challenge design described earlier, however, this second fluid challenge would be considered a positive fluid response, because stroke volume is still 20% higher than the baseline value before the first fluid challenge. This obviously makes no sense. Note that the only difference in this example is that we replaced 100 + 150 ml infusions with 250 + 250 ml infusions, and it should be clear that in future mini-fluid challenge studies, the outcome/response variables must be independent of the predictor variables. It could be suggested to use the stroke volume value after the mini-fluid challenge as a new baseline for the subsequent fluid challenge, but that approach also creates a mathematical coupling, which theoretically *reduces* the predictive power of the mini-fluid challenge because the outcome, $\Delta SVI_{250}$, is then defined as $\Delta SVI_{250} = (SV_{afterFC,\ 250ml} - SV_{afterMFC,\ 100ml})/SV_{afterMFC,\ 100ml}$. The $SV_{afterMFC,\ 100ml}$ measurement would then be part of both predictor ($\Delta SVI_{100}$, described above) and outcome calculations. Because $SV_{afterMFC,\ 100ml}$ is a positive term in the $\Delta SVI_{100}$ calculation and a negative term (being subtracted) in the $\Delta SVI_{250}$ calculation, the random variation in $SV_{afterMFC,\ 100ml}$ would drag $\Delta SVI_{100}$ *and* $\Delta SVI_{250}$ in "opposite" directions and thus make $\Delta SVI_{100}$ *and* $\Delta SVI_{250}$ *less likely* to agree (as opposed to the design with a common baseline value). In that sense, we strongly encourage following the design suggested by Guinot *et al.*,[4] who had a new baseline measurement 5 min after the mini-fluid challenge, or at least keeping baseline variables "separated" as Mallat *et al.*[3] did (*i.e.* by measuring pulse pressure variation changes after the mini-fluid challenge and relating that to stroke volume changes after the fluid challenge—changes in two different variables). Otherwise, the study design itself may artificially boost the true predictive power of the mini-fluid challenge and result in a self-fulfilling prophecy, and we would have no means to evaluate how big the boost had been. So, even though it might be argued that we are not far from recommending that clinicians start getting familiar with and gathering experience with this simple, low-dose-fluid approach, we believe that the next step is to settle optimal methodology for this otherwise compelling approach.

## Competing Interests

The authors declare no competing interests.

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*In Reply:*

We sincerely thank Drs. Vistisen and Scheeren for their insightful comments regarding our recent article.[1] The authors pinpointed that calculating predictor and outcome variables from the same baseline may induce theoretical methodologic misinterpretations. Even though we agree with their point of view, we are convinced that it has less impact on our results.

Vistisen and Scheeren claimed that Guinot *et al.*'s study[2] was the only work that addressed the mini-fluid approach with good methodology because it had a new baseline measurement five minutes after each mini-fluid challenge. Interestingly, the results from this study are very close to ours. The area under the receiver operating curve of that study was 0.93 (95% CI, 0.8 to 0.97) and 0.95 (95% CI, 0.90 to 0.99) in our study. The best cut-off value was 7% (6% in our study), gray zone ranged between 3 and 8% including 14% of patients (4 to 7% including 19% of patients in our study). This highlights similarity of the results observed whether we use the methodology recommended by Vistisen and Scheeren or ours. The potential "artificial boost of predictive power of the mini-fluid challenge," induced by our methodology, claimed by Vistisen and Scheeren, is clearly not obvious.

The concept of mini-fluid introduced by Muller *et al.*[3] is to infuse a small quantity of fluid to test whether stroke volume will increase. The major advantage of this concept is to stop fluid administration when stroke volume does not increase after a small fluid infusion, thereby reducing ineffective volume administration. The mini-fluid challenge helps the physician to predict fluid responsiveness and fluid unresponsiveness. We fully agree that standard strategies based on international recommendations and cited by Vistisen and Scheeren improve patient outcome. In two thirds of cases, however, these strategies lead to ineffective fluid administration.[4] A mini-fluid approach could decrease the rate of unnecessary fluid administration and consequently increase the benefit of fluid optimization. Further studies are warranted to investigate this issue.

To conclude, we agree that mathematical coupling exists between the effects of mini-fluid challenge and volume expansion. However, based on previous studies and ours, with all due respect, we completely disagree that mini-fluid challenge resembles a self-fulfilling prophecy design. A fluid challenge can be looked at as a bet; if we have to lose this bet, let's make sure to lose as little as possible!

## Competing Interests

Dr. Biais received honoraria from Edwards Lifesciences (Irvine, California) and Pulsion Medical System (Feldkirchen, Germany) for lecturers. The other authors declare no competing interests.

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# Assessing Glucose Meter Accuracy: The Details Matter!

*To the Editor:*

We read with great interest the recent article by Dr. Karon *et al.* titled "Accuracy of Capillary and Arterial Whole Blood Glucose Measurements Using a Glucose Meter in Patients under General Anesthesia in the Operating Room."[1] We congratulate the authors on identifying a glucose meter potentially safe for insulin dosing in the perioperative environment using both capillary and arterial samples, given that no glucose meter is currently approved by the U.S. Food and Drug Administration for use with capillary (fingerstick) samples in critically ill patients.[2] Using this meter may offer