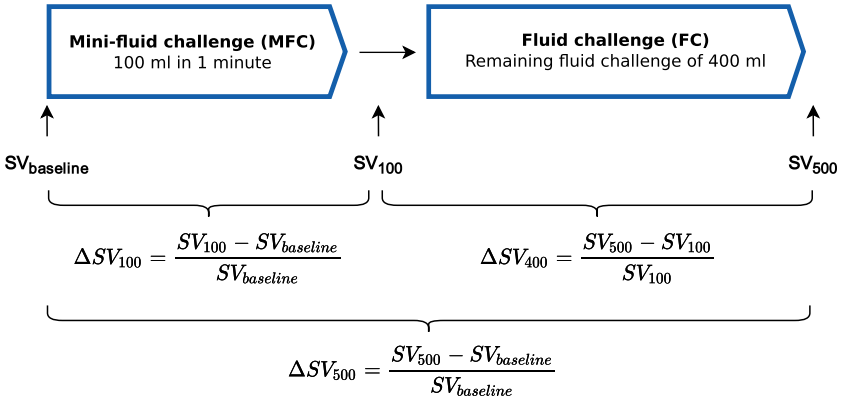

FIGURE 1 Representation of the design used in most mini-fluid challenge (MFC) studies. In this design, stroke volume (SV) is measured three times: (1) At baseline, (2) after the MFC and (3) after the full fluid challenge

when evaluating the accuracy of the MFC as a predictor of fluid responsiveness, only the effect of the last 400 ml should define the outcome. The naive solution would be to use the MFC (ΔSV_{100}) to predict ΔSV_{400} (see Figure 1). Unfortunately, this does not solve the shared error problem. The random variation of the SV_{100} measurement will introduce a similar problem, since that variable is now a constituent of both the predictor (ΔSV_{100}) and outcome (ΔSV_{400}) variables (see Figure 1). In this case, the random variation in SV_{100} will make the predictor and outcome variables *less likely* to agree, by creating a spurious, negative, correlation, leading to an underestimation of the true classification accuracy.

Both the problems described above arise from *mathematical coupling* of the predictor and outcome.[20,21]

2.3 | Secondary analysis of an existing study

To illustrate what happens with classification, if we try to predict ΔSV_{400} instead of ΔSV_{500}, we extracted ΔSV_{100} and ΔSV_{500} from plot 3A in the pioneering study by Muller et al and calculated the corresponding ΔSV_{400}.[1] Data were captured using DataThief III (version 1.7, datathief.org). Although the study reported relative VTI changes (ΔVTI), we will continue to use the SV term for consistency.

ΔSV_{400} is defined as

$$\Delta SV_{400} = \frac{SV_{500} - SV_{100}}{SV_{100}}.$$

If ΔSV_{100} and ΔSV_{500} are known, we can calculate ΔSV_{400}:

$$\Delta SV_{500} + 1 = (\Delta SV_{100} + 1) \cdot (\Delta SV_{400} + 1).$$

Therefore,

$$\Delta SV_{400} = \frac{\Delta SV_{500} + 1}{\Delta SV_{100} + 1} - 1.$$

We then analysed ΔSV_{100}'s (MFC) ability to predict $\Delta SV_{400} > 15\%$.

2.4 | Simulations

Simulations can reveal how shared error can introduce a significant bias to the result of MFC studies. The magnitude of the problem in existing studies is impossible to calculate exactly, since some relevant variables have to be estimated, but a simulation can provide a ballpark estimate.

Using R (4.0.4) and R packages, *pROC* and *Tidyverse*,[22–24] we simulated SV measurements at all three measurement points in Figure 1 (baseline, after 100 ml and after 500 ml fluid) for 2000 subjects. Annotated code generating the simulations is available from the digital Supplementary Material S1, and an interactive tool that allows changing simulation parameters is available from https://johannesne.shinyapps.io/mini-fluid-challenge-simulation/.

2.4.1 | Simulation 1

First, we simulated how the MFC methodology performs in virtual patients whose SV are entirely unresponsive to fluid, but with random variation in SV measurements. Since there is nothing to predict, any apparent predictive ability is a statistical artefact. Each patient was assigned a constant 'true' SV for all three windows (mean = 75 ml, SD = 10 ml), with an additional random variation (mean = 0, SD = 3 ml) that was independent between time windows (see Figure 2). A random error with a SD of 3 ml gives an 8% precision at 75 ml SV. This was chosen to match the between examination variability in VTI measurements performed by the same observer (although the magnitude of this variation will only effect the results of simulation 2).[25] From these three simulated measurements of a 'constant' SV (but with random measurement error added), we calculated ΔSV_{100}, ΔSV_{400} and ΔSV_{500}. We also simulated a second independent SV_{100} measurement ($SV_{100}b$) to serve as the reference for an independent outcome measure ($\Delta SV_{400}b = (SV_{500} - SV_{100}b)/SV_{100}b$). In this initial simulation, we regarded any increase in SV as a positive fluid response. Using ROC analysis, we showed how well ΔSV_{100} predicted an increase in SV with either ΔSV_{500}, ΔSV_{400} or $\Delta SV_{400}b > 0\%$ as the outcome measure. Since SV varies randomly, half of patients should be responders by this definition, and because the variation is independent between the time windows, it should