Can Passive Leg Raising Be Considered the Gold Standard in Predicting Fluid Responsiveness?

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To the Editor:

We read with great interest the article by Vignon and colleagues (1) [this issue, pp. 1022–1032]. The study is second to none in the fluid responsiveness literature when it comes to number of patients included (540) and particularly when it comes to detailed high-quality echocardiographic evaluation.

Still, the outstanding combination of study size and echocardiographic evaluation merits, or maybe even obliges, additional analyses to be reported, which appear straightforward based on the existing data:

First, the passive leg-raising (PLR) test defined fluid responsiveness in the study because PLR has demonstrated a nearly perfect fluid responsiveness prediction (2).

Two hundred and twenty-nine patients got an evaluated fluid challenge, and the ability of the echocardiographic measures and pulse pressure variation (ΔPP) to predict the *actual* fluid response was reported in the study's supplemental data (Vignon and colleagues' Table E4). However, the authors also had the largest cohort to date to evaluate the prediction ability of PLR. Since metaanalyses are inherently prone to limitations of publication bias and heterogeneity across studies, this unique chance for evaluating the "true" classification performance of PLR should not be missed.

Yet, few data regarding PLR classification were reported: "Mean increase of left ventricular stroke volume induced by fluid loading was markedly higher in patients with PLR, which was indicative of fluid responsiveness (36 ± 26% [n = 161] vs. 5 ± 17% [n = 68]: $P < 0.001$)" (1).

We interpret this as follows: in patients with a PLR response exceeding 10%, the fluid response was on average an increase in stroke volume by 36% (SD, 26%), and in patients with a PLR response of less than 10%, the fluid response was on average a 5% (SD, 17%) increase in stroke volume.

Intuitively imagining these data, classification performance of PLR does not seem in accordance with the above mentioned metaanalyses. Assuming normally distributed data (as reported), we modeled the classification performance of PLR in this subpopulation; doing so, 16% of the 161 PLR responders were not true responders, and 38% of PLR nonresponders were true fluid responders, resulting in an estimated sensitivity of 83.8% and a specificity of 62.1% (Figure 1) (positive and negative predictive values of 84.1% and 61.6%, respectively). We therefore kindly ask the authors to report PLR's ability to predict fluid responsiveness in their study. If our interpretation is correct, this raises two important questions: (*1*) Is PLR as reliable in predicting fluid responsiveness as we thought it was? (*2*) For the analyses in which PLR serves as gold standard, how should we interpret the reported ability to predict fluid responsiveness of the echocardiographic variables and ΔPP? An imagined fluid responsiveness variable that perfectly predicted actual fluid response would be in discordance with PLR in 20–30% of cases. This observation makes the overall study results very

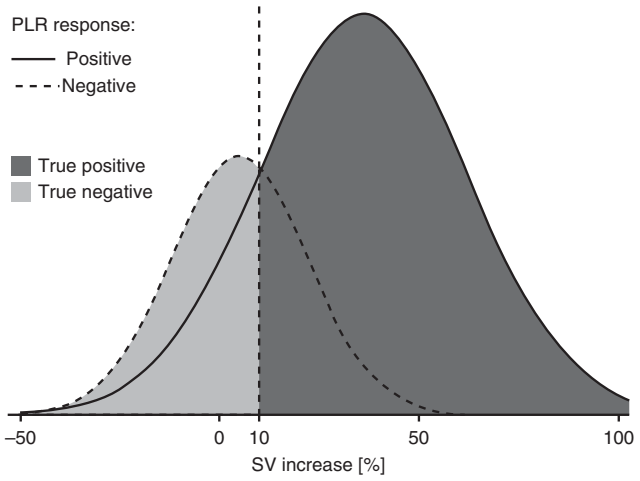

Figure 1. Distributions of stroke volume (SV) increase in the passive leg raising (PLR)-negative and PLR-positive groups according to the reported means and SDs. Distribution areas resemble proportions of reported PLR-negative and PLR-positive cases.

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hard to interpret but could indeed explain the encountered echocardiographic and ΔPP classification results, which we would have expected to be higher, particularly for some of the ΔPP subanalyses.

Second, for ΔPP, we wonder why the authors did not classify patients based on cardiac function (3) and heart rate–to–respiratory rate ratio (4) in the subanalysis with tidal volume above 8 ml/kg, etc. In the subanalysis excluding patients with cardiogenic and obstructive shock, ΔPP had its highest area under the receiver operating characteristics curve of 0.74, emphasizing the importance of cardiac function. Also, it appears that the data set enabled indexing ΔPP to tidal volume or respiratory driving pressure (5, 6), which we suggest to also be reported for a subanalysis, where all known ΔPP limitations are discussed. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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Reply: Dynamic Indices Derived from Heart–Lung Interactions: *Mitis Depone Colla*

From the Authors:

We thank Dr. Lakhal and colleagues, Dr. Myatra and colleagues, and Dr. Vistisen and colleagues for their concise summary of our results and their thoughtful comments. As pointed out by Dr. Lakhal and colleagues, the diagnostic accuracy of commonly used "dynamic" indices was noticeably lower than that reported in pioneer studies, even in the subgroup of patients without respiratory activity, arrhythmia, reduced tidal volume, or elevated intra-abdominal pressure, all factors known to impair the prediction of fluid responsiveness (1). Nevertheless, additional limitations for using "dynamic" parameters such as high heart rate–to–respiratory rate ratio, low total respiratory system compliance, and decreased tricuspid annular peak systolic velocity have not been specifically assessed in our study (2). As anticipated by Lakhal and colleagues, a substantial proportion of our patients (pulse pressure variation: n = 257 [61%]; respiratory variation of the maximal Doppler velocity in left ventricular outflow tract: n = 232 [55%]; respiratory variation of superior vena cava diameter: n = 310 [58%]; respiratory variation of inferior vena cava diameter: n = 217 [51%]) exhibited individual values of "dynamic" parameters within a range of uncertainty; the so-called "gray zone" (3). In these patients, we proposed using distinct cutoff values to optimize either the sensitivity when the benefit of giving fluids exceeds the risk or the specificity when the risk for volume overload exceeds the potential hemodynamic benefit (2). As for any continuous variable, the farther the measured value from the diagnostic threshold, the stronger the accuracy of the prediction of response to fluid loading. However, this tailored approach remains to be validated in specific populations of patients with shock.

We are convinced that the diagnostic ability of "dynamic" parameters to predict fluid responsiveness should not be compared with that of traditional "static" parameters (e.g., central venous pressure), as suggested by Lakhal and colleagues. In a recent review incorporating 1,148 data sets of central venous pressure, most values ranged between 8 and 12 mm Hg, with a large overlap between responders and nonresponders to fluids (4). Accordingly, central venous pressure had low positive and negative predictive values for all specific values assessed in the range of 0–20 mm Hg (4).

As recalled by Dr. Myatra and colleagues, pulse pressure variation is a widely available first-line dynamic parameter that has long been validated to predict fluid responsiveness. As such, it should be used to screen patients who require further hemodynamic assessment, when its value is within the gray zone or when the clinical setting is consistent with a potential false-positive result (5). In these specific patients, critical care echocardiography can then be used to obtain further insights into fluid requirements or right ventricular function (2).

Dr. Vistisen and coworkers challenge the use of passive leg raising as a surrogate of fluid loading to identify fluid responsiveness. Because of the observational nature of our study, patients who received a fluid challenge were highly selected and constituted a biased subset of the cohort (2). Because this study was not aimed at

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