However, we feel that the authors may have overlooked an important factor in their analysis. It has been clearly shown that the prevalence of a disease significantly impacts the predictive value as well as the calculated costs of a diagnostic test in a specific population.[2]

From the description in the Materials and Methods section and the illustrations in figures 2 and 4, it appears that Cannesson *et al.* defined their "explicit cost" for a given Cost Ratio [R = Cost False Positives (FP)/Cost False Negatives (FN)] as follows:

$$\text{Explicit Cost} = \text{FP Fraction} \times \text{cost FP} + \text{FN fraction} \times \text{cost FN}$$

This formula can be rewritten as:

$$\text{Explicit Cost} = (1 - \text{Prevalence}) \times (1 - \text{Specificity}) \times \text{cost FP} + \text{Prevalence} \times (1 - \text{Sensitivity}) \times \text{cost FN}.$$

The formula above indicates that there are three primary determinants of explicit cost including the cost ratio used, the discriminatory power of pulse pressure variation, and the prevalence of the responders. The same applies for the determination of an optimal threshold. To our opinion, there are two important implications that should be taken into account when interpreting the results of Canneson *et al.*:

1. Using a bootstrap method to determine the confidence intervals of an optimal threshold will cause resampling of 1,000 populations with varying prevalence, as well as different optimal thresholds. The incorporation of a statistical variance to account for uncertainty of prevalence (rather than to use the measured prevalence) falsely elevates the confidence intervals for optimal threshold in all three "misclassification cost" scenarios.
2. Using the Youden index to determine the threshold when R = 1 is incorrect. Smits[3] recently showed that the Youden index implicitly changes its cost ratio in function of prevalence of the studied population.

These considerations may not completely invalidate the conclusion of Cannesson *et al.* but at least question the accuracy of the data. We believe that the confidence intervals for accuracy of pulse pressure variation are being overestimated and the validity of the technique underrated because the authors did not control for the prevalence of responders in their study population(s).

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In Reply:

Using a gray zone approach to evaluate the accuracy of a diagnostic tool is not new but had never been used before for the evaluation of a hemodynamic parameter such as pulse pressure variation. We are delighted to see that our recently published paper focusing on this specific topic[1] induced so much discussion because it was our goal to bring some provocative thinking regarding the way we approach medical decision-making in the perioperative environment. Consequently, we warmly thank Drs. Bloomstone, Verniquet, and Wyffels and their colleagues for the positive comments on our work.

Dr. Bloomstone and colleagues pointed out that the gray zone for pulse pressure variation (PPV) and stroke volume variation (SVV) may be different and that this may be an issue because SVV is more widely used than PPV in the United States. First, it is not correct that SVV is used more frequently than PPV. In a recently published survey, we showed that PPV is used by 15% of U.S. anesthesiologists *versus* only 6% using SVV.[2] Second, SVV is far more complicated to measure than PPV in the clinical practice. Only the use of specific monitors (with an associated cost) can provide such information. In the United States, and based on the survey mentioned, the first monitor to be used in terms of frequency is the Vigileo monitor (Edwards Lifesciences, Irvine, CA).[2] Even if it would be interesting to assess the gray zone of SVV, one has to remember that the calculation of SVV from the Vigileo monitor is actually a simple arterial-pressure–derived calculation, as has been described recently in a letter cosigned by Dr. Michard, an Edwards employee.[3] Consequently, the pertinence of assessing SVV *versus* PPV only makes sense if the true SVV is measured and not a computation of SVV based on the arterial pressure waveform analysis. Finally, we agree with Dr. Bloomstone that the goals for PPV may vary with the clinical situation. That is exactly what we expressed when we divided the decision-making into two scenarios: liberal *versus* tight fluid control.[1] The idea was to emphasize that the gray zone shifts with clinical goals.

Dr. Verniquet and colleagues ask a very important question: does fluid responsiveness mean that a patient must be

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given fluids? Again, this strongly depends on the decision-making process. If the clinician wants to conduct a goal-directed cardiac output optimization in a high-risk surgery setting (as recently recommended by the National Health Service in the United Kingdom), she or he will have to maximize cardiac output until cardiac output stops increasing after a fluid bolus. In this case, fluid responsiveness will be interpreted as "my patient must be given fluid." On the contrary, if the clinical setting is in favor of a more restrictive approach, the opposite approach should be applied.

Finally, the comments of Dr. Wyffels and colleagues include different concerns. First, they ask whether varying the prevalence of responders across the 1,000 subsamples might have biased the estimation of the gray zones. The definition of explicit costs using the prevalence reported by Dr. Wyffels and colleagues suggests that prevalence affects this estimation. However, we used a random sampling with replacement, and the variation of prevalence of responders across the 1,000 subsamples cannot be large enough to affect the estimation of the confidence interval. In fact, the mean of the prevalence of responders was 50.6% (*i.e.*, equal to the prevalence observed in the original population), and the SD was only 2.4%. According to these results, we have to assume that this theoretically could have biased the results, but we do not think that this systematic error could have any clinical relevance regarding the rounding that has been conducted in the next step of the analysis. However, this point could be a relevant concern when using our approach in smaller populations or with rare endpoint. Consequently, although not relevant for the current study, this comment has to be taken into account in additional studies using this approach.

The next concern underlined by Dr. Wyffels and colleagues was that the cost ratio is affected by the prevalence of the responders in the original population. This suggests that the gray zone in the two unbalanced scenarios would have been different if the prevalences of the responders were different. We should have emphasized this consideration in our discussion. The prevalence of the responders in the population has to be taken into account. The criticism of the Youden's index is similar to the previous comments because it underlines that the prevalence of the responders affects the value of the optimal threshold when a cost ratio is applied. This suggests that the use of our results, when cost ratio is different from 1, might not be adapted if the rates of responders or nonresponders were significantly different from the one reported in our study. Nevertheless, the aims of these subanalyses were not to provide definitive results but to show that the PPV threshold might be different when considering different clinical settings.[4]

Finally, these comments did not modify our conclusions about the optimal threshold and its gray zone in the balanced scenario (R = 1), but they limit the generalization of our results regarding the two unbalanced scenarios to a population with very different rates of responders.

In this study, we were able to show that the gray zone was smaller when the threshold for the definition of fluid responsiveness was set at 15%.[1] Again, this is an important point because clinicians have to understand that if they want to predict an increase in cardiac output of more than 10% after volume expansion, the gray zone is going to be wider than if the threshold is set at 15%, with the reasons being the intrinsic lack of accuracy of most cardiac output monitors to detect such a small change in cardiac output[5] and the change in the prevalence of fluid responsiveness based on its definition.

We know that cardiac output monitoring is useful for evaluating the impact of volume expansion and that it has been used for intraoperative goal-directed therapy with positive results.[6] However, one has to remember a practical fact: cardiac output monitors are not cheap (and we know that the cost of this technology could be overcome by the improvement in postoperative outcome). Not all practitioners, departments, institutions, or countries can afford such devices, especially when their accuracy is so disappointing.[2,5] Companies obviously are promoting the use of cardiac output monitors against the use of PPV or SVV alone because this is where the money is (PPV monitoring can be done for free[7]). However, the real impact in terms of outcome has the potential to be made in countries where accurate, physiologically sound, and inexpensive monitoring solutions such as PPV can be implemented easily. Conducting cardiac output maximization using cardiac output monitors, which have a more than 40% mean error,[5] could easily be achieved by conducting PPV minimization using a cheap, public domain, and accurate physiologic parameter such as PPV. This has been suggested and shown recently.[8,9]

In summary, we are delighted with this opportunity to emphasize some of the most important points of our recently published manuscript. Until recently, studies focusing on dynamic parameters of fluid responsiveness such as PPV or SVV included only a few tens of patients and used a single threshold for the prediction of fluid responsiveness. This study included more than 400 patients in various clinical settings. The letters from Drs. Bloomstone, Verniquet, and Wyffels and their colleagues actually echo our main messages: the meaning of a high or low PPV has to be interpreted within the context; the accuracy of this physiologic parameter is not perfect but seems more satisfying than those of most commercially available cardiac output monitors; and finally, clinical decision-making is not a black-or-white world, and any decision has to be balanced in terms of risk and benefits. We hope this study opens the door to many others on this topic and is another brick in the wall leading to better outcomes for patients.

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