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How Accurate Is Pulse Pressure Variation as a Predictor of Fluid Responsiveness?

To the Editor:

We read with interest the Perioperative Medicine article "Assessing the Diagnostic Accuracy of Pulse Pressure Variations for the Prediction of Fluid Responsiveness: A 'Gray Zone' Approach" by Cannesson *et al.*[1] and its accompanying editorial: "Insights in a 'Gray Zone.'"[2]

Fluid responsiveness is based on the proposition that an increase in cardiac output by at least a certain amount may be achieved by a specific bolus of a specified fluid, whereas nonresponders will require other means to increase the cardiac output. There are a number of limitations with this definition. The type of fluid used will have an impact on the amount of expansion of the intravascular compartment. In the study, iso-oncotic colloid was used, but even the volume effect of this will depend on the volume status of the patient (context sensitive).[3] Associated with this is the fact that the endothelial glycocalyx is degraded by the release of cytokines during surgery or the release of atrial naturietic peptide caused by hypervolemia.[4] The minimally required increase in cardiac output will have a direct impact on the size of the "gray zone," as was demonstrated in the study, and the utility of bolus fluid therapy has been questioned following the publication of the Feast trial.[5] Fluid responsiveness assessed by pulse pressure variation cannot distinguish between an increase in variation caused by fluid loss from that caused by vasodilation.

The concept of pulse pressure variation is closely related to the respiratory cycle and changes in pleural pressure. Pleural pressure changes are impacted by either smaller tidal volumes or poor lung compliance. As an extreme example, high-frequency oscillation ventilation results in minimal pulse pressure variation irrespective of the volume status of the patient. For patients within the "gray zone," increasing the tidal volume may increase the pulse pressure variation indicating fluid responsiveness.

Although it may be reasonable to give a fluid bolus to patients above the upper limit of the gray zone, a knowledge of the cardiac output is extremely useful to make an informed decision on treatment for patients in or below the gray zone and avoid overloading the interstitial space with fluids. Lichtenstein[6] has suggested that transthoracic ultrasound of the lungs may be useful in the early detection of interstitial syndrome (because of fluid overload, cardiac failure, or increased capillary permeability) by observing a change from A-line predominance to B-line predominance.

There are several limitations of the study that may make it difficult to apply to a more general population, including the male predominance in the study (75%) and the selection of mainly cardiac or abdominal aortic surgery (88%) with only 22% being general surgery.

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The "Gray Zone Approach": Assessing the Accuracy of Pulse Pressure Variation without Considering the Prevalence?

To the Editor:

We read with great interest the article of Cannesson *et al.*[1] regarding the accuracy of pulse pressure variation monitoring to predict fluid responsiveness. We applaud the introduction of "misclassification cost" as a novel approach to evaluate the clinical utility of a widely advocated monitoring technique.

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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