Assessment of Fluid Responsiveness

Insights in a "Gray Zone"

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"The gray zone approach introduces a new conceptual way of looking at PPV [pulse pressure variations] [to guide fluid therapy]."

THE analysis of dynamic changes in hemodynamics during respiration, such as pulse pressure variation (PPV), is now recognized as a reliable predictor of fluid responsiveness in the ventilated patient.[1,2] With the use of specific cutoff values, patient populations are divided into "responders" (patients who will benefit from additional fluid loading) and "nonresponders" (those who will not benefit from additional fluid loading). However, even when using PPV, a correct assessment of fluid responsiveness may remain difficult in a substantial number of patients. Indeed, some patients who are expected (based on PPV analysis) to respond favorably to a fluid challenge will show no improvement in hemodynamics when fluids are actually administered. This problem of diagnostic accuracy of PPV for the prediction of fluid responsiveness is addressed in the current issue of ANESTHESIOLOGY by Cannesson *et al.*[3] They propose an original approach that provides a more realistic interpretation of the clinical reality and takes into account the exact nature of hemodynamic physiology.

Clinical decision-making mostly uses a binary approach, which is to treat a patient or not. Diagnostic tests need to help in this decision-making, so we also expect a binary answer from these tests: the test is positive (so I have to treat the patient) or the test is negative (so I do not need to treat this patient). Because a perfect discrimination between a "positive" and "negative" test result remains beyond possibility, we expect the tests we use to have optimal sensitivity (detect the true positives) but also optimal specificity (detect the true negatives). A system that is too sensitive will identify too many people as positive (false-positive results), leading to the treatment of patients who actually do not need treatment. A system that is too specific will fail to identify people with the disease (false-negative results), leading to the withholding of treatment from patients who actually need it. Receiver operator characteristic methodology has been developed and used for many years as a means to evaluate the sensitivity and specificity of a diagnostic test and to identify the optimal decision point or cutoff value of the test. This diagnostic cutoff point is then used to make a clinical discrimination.

How is the cutoff point actually determined? This can be based on a pure mathematical analysis to either minimize the mathematical distance between the receiver operator characteristic curve and the ideal point (sensitivity = specificity = 1) or to maximize the difference (Youden index) between the receiver operator characteristic curve and the diagonal or chance line (sensitivity + specificity − 1). Whereas the first approach minimizes misclassification, the second one maximizes appropriate classification.[4] An alternative approach will also take into account the cost-benefit ratio of the consequence of having either false-positive or false-negative results. One can easily appreciate that in certain pathologic conditions, treatment of a patient with a false-positive result may be worse than missing a false-negative result or conversely that not treating a patient with a false-negative result may be worse than treating one with a false-positive result. In the case of PPV assessment, a low cutoff value for the diagnosis of fluid responsiveness (*e.g.*, less than 10%) may result in a substantial number of false-positive results and carry the

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risk of applying an inappropriate volume loading in patients for whom this may have deleterious effects. Conversely, a high cutoff value (*e.g.*, more than 20%) may result in a substantial number of false-negative results, in which necessary volume loading is withheld from patients who would actually benefit from fluid administration. One can imagine that, when dealing with a patient population at risk for developing acute lung injury, avoidance of excessive fluid loading is more important than in a normal population. Thus, in such patient population, it might be preferable to avoid the false-positive results at the expense of increasing the false-negative ones.

Another point also deserves attention. The binary approach used for defining the cutoff value for PPV does not take into account the specific nature of the Frank-Starling relationship. According to this relationship, the stroke volume response to a given volume load is not a simple "yes" or "no" phenomenon but instead represents a continuum of values ranging from a large increase in stroke volume to no increase and even a decrease, depending on which point of the Frank-Starling curve the heart is actually working. This point may differ substantially within the same patient and certainly between patients.

For these reasons, the application of a single cutoff value of PPV to assess fluid responsiveness may not be appropriate. Cannesson *et al.* identified these pitfalls and proposed an alternative conceptual approach that allows the use of PPV for the prediction of fluid responsiveness in a way that is more consistent with the actual pathophysiologic reality.[3] Instead of using one single cutoff value of PPV, they applied the "gray zone" approach[5] to assess diagnostic accuracy of PPV for the prediction of fluid responsiveness. This approach uses two cutoffs: one cutoff that with near certainty identifies the nonresponders and another cutoff that with near-certainty identifies the responders. Thus, these cutoffs define on the one hand a lower and a higher cutoff value that allow reliable clinical decision-making on fluid administration, and identify on the other hand a gray zone, in which such decision-making is not possible.

Cannesson *et al.* found that in their particular study population this PPV gray zone ranged between 9 and 13% and that approximately one quarter of the study population was within these limits. Interestingly, the PPV threshold of 12.5 ± 1.6%, defined in the meta-analysis of Marik *et al.*,[1] as having the highest sensitivity and specificity (89% and 88% respectively; area under the receiver operator characteristic curve of 0.94) falls within this gray zone.

The gray zone approach introduces a new conceptual way of looking at PPV that is more in line with the physiologic hemodynamic principles and clinical reality than using a single cutoff value. It is to be expected that this new approach of assessing diagnostic accuracy of dynamic variables of fluid responsiveness will be of great help in future clinical decision-making. Additional studies are needed to explore the best strategies for assessing fluid responsiveness in patients who have PPV in the gray zone. Finally, it needs to be explored how the current findings, obtained in anesthetized ventilated patients in the operating room, translate into other clinical settings.

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