Using Dynamic Variables to Guide Perioperative Fluid Management

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Intravenous fluid administration is an integral part of patient management during anesthesia. This practice has a strong clinical rationale since a decrease in blood volume, either present before or developing during surgery, is a major cause of morbidity and mortality. In order to preempt the risk of such hypovolemia large amounts of intravenous fluids are frequently administered, especially during major surgery. However, accumulating evidence in recent years has suggested that a too "liberal" approach to perioperative fluid management may lead to increased complications and worse patient outcome.[1] On the other hand, a "restrictive" strategy designed to achieve zero fluid balance following major abdominal surgery may result in a higher rate of acute kidney injury.[2] Both the "liberal" and the "restrictive" approaches to intraoperative fluid management seem to be equally associated with acute kidney injury, increased morbidity, 30-day mortality, cost, and postoperative length of stay.[3] These recent studies led to the recommendation, repeated in a clinically focused review on perioperative fluid therapy published recently in Anesthesiology,[4] that perioperative fluid regimen should be kept "moderately liberal."

While recommendations regarding the general principles of perioperative fluid management do provide useful overall guidance, they may not necessarily be helpful in determining individual patient needs at any specific moment. This may partially explain the observed marked variability in the intraoperative fluid administration across individual anesthesia providers.[3,5] The fact that this marked variability is driven more by the individual provider's preferences than by patient and procedural characteristics[3,5] seems to highlight the need for more physiologically based variables that may individualize perioperative fluid administration and make it more precise.

Concept of Fluid Responsiveness

Fluid administration is indicated in the presence of the two following conditions: (a) the patient requires augmentation of his perfusion; and (b) the patient is going to increase his cardiac output (CO) in response to fluid administration ("fluid responsive").[6] However, the sobering reality, demonstrated repeatedly and consistently, is that fluid administration is associated with an increase in CO in only about 50% of high-risk surgical and critically ill patients.[7] It seems, therefore, that we routinely administer unnecessary and potentially detrimental fluids to about half of the patients in our care. It also means that the traditional tools that we have been using as conceptual surrogates of the elusive left ventricular preload to guide fluid management, cannot accurately identify individual fluids needs. These needs may be better assessed by the determination of the patient's "fluid responsiveness" status. Fluid responsiveness is the degree by which a modification of preload affects the stroke volume (SV) and is best described by the slope of the individual left ventricular function curve (fig. 1). Fluid administration is expected to increase SV when the patient is on the steep portion of the curve ("responder"). However, when the patient is on the flat portion of that curve ("nonresponder"), fluids are not going to be effective and other forms of cardiovascular support should be applied in order to improve hemodynamic stability.

Fluid responsiveness is best determined by measuring the change in CO after the administration of a fluid challenge. A fluid challenge may include varying fluid types (colloids or crystalloids) and volumes (500, 250, and 100 ml), with either 10 or 15% change in CO or SV being considered as a positive test. These marked variabilities may affect the definition of a "responder" or a "nonresponder." Furthermore, using a fluid challenge to determine fluid responsiveness has some other shortcomings: (a) it requires the use of a (preferably continuous) CO monitor; (b) in 50% of the cases the test will be negative and, when frequently repeated, may lead to unintended fluid overload; (c) when administered to a "nonresponder" it may result in an unidentified decrease in oxygen delivery due to hemodilution[8]; and (d) it has to be proactively initiated and offers only intermittent information. Having other variables that can accurately predict fluid responsiveness by modifying preload without the actual administration of fluids is obviously of great clinical value.

Dynamic Variables of Fluid Responsiveness

Variables that describe fluid responsiveness are termed "dynamic" since they result from a combination of a

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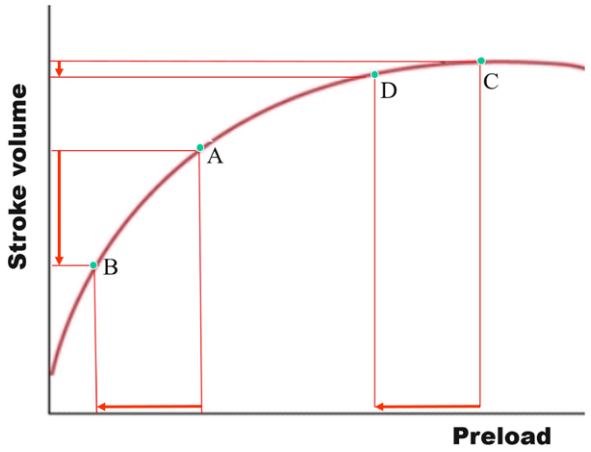


Fig. 1. The left ventricular function curve describes the effect of a change in preload on the stroke volume. The decrease in venous return during the mechanical breath will cause a significant change in stroke volume (*A* to *B*) when the patient is on the steep portion of the curve ("responder"), and a small change (*C* to *D*) in a "nonresponder."

preload-modifying maneuver (*e.g.*, mechanical breath) and the measurement of its immediate hemodynamic response (*e.g.*, change in SV).

Dynamic Variables Induced by Mechanical Ventilation

The increase in intrathoracic pressure during a mechanical breath has direct effects on all heart chambers (for more information, see Michard,[9] Perel *et al.*,[10] and Teboul *et al.*[11]). Prominent among these effects is the transient decrease in venous return that may be regarded as a preload-modifying test of fluid responsiveness. In a patient who is on the steep portion of the left ventricular function curve ("responder"), a mechanical breath will be associated with a transient reduction in venous return and an eventual decrease in left ventricular SV (fig. 1). However, in a patient who is on the flat portion of the left ventricular function curve ("nonresponder") the mechanical breath will not produce any significant reduction in the left ventricular SV (fig. 1). The magnitude of the respiratory-induced changes in the SV is reflected by the respective variations in the arterial blood pressure and the plethysmographic waveforms, which have become the source of the most widely used dynamic variables.[9,10,12,13] The graphic depiction of these variables and the way they are calculated are shown in figure 2. Before describing these variables in more detail, it is important to bear in mind that all have been repeatedly demonstrated to be better predictors of fluid responsiveness compared with any of the commonly used static preload variables like central venous pressure, pulmonary artery occlusion, and left ventricular end-diastolic area.[9,10,12,14]

Pulse Pressure Variation

The pulse pressure variation (PPV) reflects the changes that occur in the pulse pressure (systolic minus diastolic pressure) during one mechanical breath (fig. 2). Among the dynamic variables that are induced by mechanical ventilation, the pulse pressure variation is considered to be the most accurate and frequently serves as a gold standard in the evaluation of new dynamic variables.[9,11–13] A pulse pressure variation threshold value of about 12% has been shown by numerous studies to accurately predict fluid responsiveness in surgical and in critically ill patients.[12] These threshold values are valid only for patients who have sinus rhythm and are ventilated with tidal volumes of 8 to 10 ml/kg with no spontaneous breathing activity. A significant (greater than or equal to 3%) decrease in the pulse pressure variation value following fluid loading is highly indicative of an associated significant increase in the CO.[15] However, a pulse pressure variation value in the range of 9 to 13%, termed the "gray zone," was found to be inconclusive in approximately 25% of patients during general anesthesia.[16]

Stroke Volume Variation

The SV variation (SVV) reflects the respiratory-induced changes in the left ventricular SV during one mechanical breath (fig. 2). The automatic measurement of the SV variation has become available with the introduction of pulse contour analysis for the continuous measurement of CO. An SV variation threshold value of 10% has been originally described in neurosurgical patients,[17] but more recently reported threshold values for the SV variation included 9 to 12%[18] and 14%.[19] The SV variation is somewhat less accurate than the pulse pressure variation[12] due, most probably, to the computational limitations of the pulse contour method in measuring individual SVs in real time.

Systolic Pressure Variation

The systolic pressure variation (SPV) which is the difference between the maximal and minimal values of the systolic arterial pressure during one mechanical breath (fig. 2), was the first dynamic parameter to undergo extensive experimental and clinical validation.[10,20,21] The systolic pressure variation is normally about 8 to 10 mmHg in normotensive anesthetized patients who are ventilated with tidal volume of 8 ml/kg.[22] The systolic pressure variation is somewhat less accurate than the pulse pressure variation, but equally accurate to the SV variation.[9,11,12] When the automatic measurement of dynamic variables is unavailable, the detection of increased respiratory variations in the arterial pressure waveform may be the first sign of developing hypovolemia. These variations are easier to quantify by visually assessing the systolic pressure variation than the pulse pressure variation.[23,24]

Plethysmographic Variability Index

The respiratory variations in the plethysmographic waveform that is displayed by most pulse oximeters present the

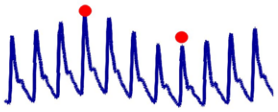
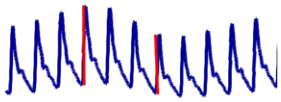
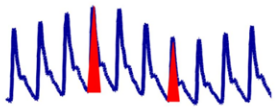
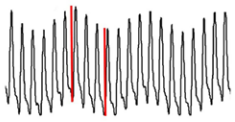
Systolic Pressure Variation		SPmax- SPmin
Pulse Pressure Variation		(PPmax - PPmin) / [(PPmax + PP min)/2]
Stroke Volume Variation		(SVmax - SVmin) / SVmean
Plethysmographic Variability Index		[(PImax − PImin) / PImax] × 100

Fig. 2. Graphic display and formulas of the main dynamic variables that are derived from the respiratory changes in the arterial pressure and plethysmographic waveform during mechanical ventilation. PImax, maximal perfusion index; PImin, minimal perfusion index; PPmax, maximal pulse pressure; PPmin, minimal pulse pressure; SPmax, maximal arterial systolic pressure; SPmin, minimal arterial systolic pressure; SVmax, maximal stroke volume; SVmean, mean stroke volume; SVmin, minimal stroke volume.

most available dynamic parameter in mechanically ventilated anesthetized patients.[25] The plethysmographic variability index (PVI) is calculated as the difference between the maximal and minimal values of the perfusion index (the ratio between pulsatile and nonpulsatile infrared light absorption) during one mechanical breath divided by the maximal perfusion index (fig. 2).[26] The plethysmographic variability index has been shown to be a good predictor of fluid responsiveness, with an originally reported cut-off value of 14%,[27] although other cut-off values have been reported as well. The plethysmographic variability index may be significantly affected by a changing vasomotor tone (*e.g.*, hypothermia, vasoconstriction). However, it is able to reflect even mild decreases in circulating blood volume intraoperatively,[21] and may be the only source of information on fluid responsiveness during low and medium risk surgery.

Limitations of Ventilation-induced Dynamic Variables. The limitations and confounding factors of ventilation-induced dynamic variables have been extensively described and should be well recognized.[9,11,13,28]

Spontaneous Ventilation. The hemodynamic effects of a spontaneous breath are very different than those that occur during mechanical ventilation, include an increase rather than a decrease in venous return, and may vary from one breath to another.[29] As a result, dynamic variables poorly predict fluid responsiveness during spontaneous breathing. Many small studies that examined the utility of dynamic variables during spontaneous breathing had either negative or inconclusive results, and in many of them attempts were made to intentionally augment spontaneous respiratory efforts.[29] Of note, when blood volume is severely reduced, a deep spontaneous breath may collapse the very compliant venae cavae, cause a sudden significant decrease in the venous return and CO, and produce large variations in the systolic blood pressure (pulsus paradoxus).[30]

Dynamic variables during spontaneous breathing do, however, reflect true hemodynamic events and therefore should not be automatically discarded as meaningless or artefactual.[29] During spontaneous breathing these variables may be used to monitor respiratory rate, respiratory effort, pulsus paradoxus (*e.g.* asthma, cardiac tamponade), and, most importantly, upper airway obstruction.[29,31] Spontaneous breathing efforts during patient–ventilator asynchronies may exaggerate dynamic variables and decrease their predictive accuracy.[32] The potential ability of these variables to serve as an alert to the appearance of such asynchronies and to estimate their severity is obvious yet unexplored.

Size of Tidal Volume/Inflation Pressures during Mechanical Ventilation. Dynamic variables predict fluid responsiveness best when the tidal volume is at least 8 ml/kg.[28,33] Lower tidal volumes (*e.g.*, 6 ml/kg) used during protective lung ventilation, may produce inadequate changes in the CO and reduce the accuracy of dynamic variables. However, hypovolemia may produce high values of dynamic variables even under such circumstances.[11] Excessively high tidal volumes,

inflation pressures and positive end-expiratory pressure levels, air-trapping, reduced lung and chest wall compliance, prone position, and increased intraabdominal pressure may all increase the numerical value of dynamic variables in the absence of fluid responsiveness (false positive), while open-chest conditions (*e.g.*, cardiac surgery) decrease the predictive ability of dynamic variables.[9,11,28]

Nonsinus rhythm. Arrhythmias cause increased variability of the SV and therefore decrease the usability and accuracy of respiratory-induced dynamic variables.

Right heart failure. The output of the failing right heart may be further decreased by the increase in its afterload during the mechanical breath. The resulting increased respiratory variations may be erroneously attributed to increased fluid responsiveness.

Early inspiratory SV augmentation. During early inspiration, the mechanical breath squeezes the pulmonary blood volume into the left side of the heart, which, in turn, leads to an early augmentation of left ventricular ejection.[9,10] This augmentation, also termed delta Up, is further facilitated by the simultaneous decrease in left ventricular afterload, is more prominent during hypervolemia or congestive heart failure, and may decrease the accuracy of dynamic variables.

Other Dynamic (Intermittent) Variables. When ventilation-induced dynamic variables are unavailable or deemed inaccurate, and when clinical circumstances demand a more precise fluid administration, other dynamic variables may be helpful in the assessment of fluid responsiveness. It is important to realize, however, that nearly all of these other variables are measured *intermittently,* as opposed to the pulse pressure, SV and systolic pressure variations, and the plethysmographic variability index, which are all measured *continuously*. Obviously, *continuous* dynamic variables may identify hemodynamic changes much earlier than *intermittent* ones. Studies that compare various dynamic variables focus mostly on their performance as predictors of fluid responsiveness but disregard this major difference in their clinical utility.

Passive Leg Raising. The response to the passive leg raising maneuver has gained growing recognition as a reliable dynamic parameter that can be used even in the presence of spontaneous breathing.[4,34] The effect of passive leg raising has to be immediately assessed by a continuous measurement of CO, since relying on the changes in blood pressure alone may be misleading.[34] Since it is recommended that passive leg raising should start from the semi-recumbent and not from the supine position,[34] the execution of such a major positional change makes passive leg raising less practical intraoperatively.

Echocardiographic Dynamic Variables. Respiratory variations of the superior and inferior vena cava diameter and of Doppler velocity in the left ventricular outflow tract are examples of dynamic variables that can be intermittently measured by echocardiography in mechanically ventilated patients.[35] Of note, the collapsibility index of the inferior vena cava that has been claimed to reflect fluid responsiveness in spontaneously breathing patients is greatly affected by the magnitude the inspiratory effort.[36]

New Dynamic Variables. The end-expiratory occlusion test is performed by interrupting the ventilator at end-expiration for 15 to 30 s and assessing the resulting changes in CO.[37] The physiologic rationale of this test is that as ventilation is stopped in expiration, the cyclic impediment to venous return is interrupted leading to an eventual increase in left ventricular preload and increase CO in "responders." Another new test, designed especially for the determination of fluid responsiveness during mechanical ventilation with low tidal volumes, is the "tidal volume challenge" which introduces a transient 1-min increase in tidal volume from 6 to 8 ml/kg predicted body weight.[33]

Dynamic Variables and Perioperative Goal-directed Therapy. There seems to be a growing consensus that perioperative goal-directed therapy is associated with decreased mortality and morbidity especially in high-risk surgical patients undergoing noncardiac surgery.[4,38,39] However, this consensus embraces a variety of strategies,[39] some of which may have opposing impact on fluid balance.[40] The "classic" strategy, which advocates the administration of fluid challenges as long as the SV increases by more than 10%, or when the SV decreases by more than 10%,[39] frequently leads to many ineffective fluid challenges and to more fluids being administered compared with standard care.[39,40] The administration of consecutive fluid challenges during goal-directed therapy may also result in iatrogenic hemodilution and a paradoxical decrease in oxygen delivery.[8] In contrast, protocols that use SV variation greater than 12% or plethysmographic variability index greater than 13% as triggers for fluid administration have been repeatedly shown to result in *less* fluids being administered and in better outcome compared with standard care.[41–43] This under-recognized, yet most important, value of dynamic variables stems from their ability to identify "nonresponders" and to prevent the administration of ineffective fluid challenges.[40] This advantage has been recognized by the investigators of the large contemporary trial that is aimed at reexamining the effectiveness CO-guided goal-directed therapy.[44] According to the trial's amended protocol, a fluid challenge is to be repeated only if the SV increased by more than 10% in response to the previous challenge *and* only if the SV variation is at least 5%.[44] This significant addition to the protocol may improve the results of the original study and decrease the number of ineffective fluid challenges.[39]

Although goal-directed therapy that is based on dynamic variables has been reported to decrease postsurgical morbidity and intensive care unit length of stay,[45] its impact on patient outcome may be significantly affected by the specific values that are applied in the protocol. Using inconclusive values that are well within the "gray zone" (*e.g.*, SV

variation greater than 10%) may in fact lead to the administration of more fluids compared with standard care.[46] New "closed-loop" systems provide the ability to preset the level of pulse pressure variation that will trigger a fluid challenge, and thus may be helpful in achieving the optimal net overall fluid balance.[47]

Clinical Context and Application. Appropriate conditions for the determination of fluid responsiveness from the respiratory variations of the plethysmographic and arterial pressure waveforms are present in many surgical patients.[25] Anesthesia providers should regularly inspect these analog waveforms and assess the magnitude of their respiratory variations, as these may precede any change in vital signs. However, the correct interpretation and clinical application of dynamic variables require some preliminary important considerations. The first is familiarity with the basic principles of heart–lung interaction during mechanical ventilation and the physiologic significance of these variables. The second is the ability to identify the various confounding factors that may limit the accuracy and usefulness of dynamic variables. The interpretation of dynamic variables should then take into account the actual clinical situation. High values of dynamic variables may indeed be a sign of developing hypovolemia that needs to be corrected by fluid administration. However, a high SV variation value that accompanies hypotension soon after the induction of anesthesia may be due to vasodilation and may be best addressed by the administration of a vasoconstrictor rather than bolus fluid therapy.[48] Of note, a recently published study demonstrated that when preload dependence (pulse pressure variation greater than 13%) is accompanied by hypotension during abdominal surgery, it may also be associated with a low SV and reduced sublingual microcirculation, both of which can improve after fluid administration.[49]

The correct interpretation of dynamic variables may benefit from their integration with information provided by other available sources, such as physical examination, echocardiography, filling pressures, the amplitude of the plethysmographic perfusion index, and changes in the partial pressure of end-tidal carbon dioxide that may reflect changes in CO.[50] Such a multiparametric approach may complement dynamic variables in determining context-specific fluid needs (*e.g.*, vasodilation, increased risk of fluid administration) or when their values seem inconclusive.

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