FLUID MANAGEMENT AND OPTIMIZATION are daily problems in anesthesiology and in the critical care setting. Hemodynamic management is related to the optimization of oxygen delivery to the tissues and has been shown to be able to improve postoperative outcome and to decrease the cost of surgery.1,7 Schematically, in the operating room, the anesthesiologist and his/her patients have to deal with 2 distinct risks: hypovolemia on one side and hypervolemia on the other side. Both risks potentially can lead to a decrease in oxygen delivery to the tissues and to an increase in postoperative morbidity (Fig 1). However, despite evidence showing that organ perfusion requires 2 physiologic objectives, adequate perfusion pressure in order to force blood into the capillaries of all organs and adequate cardiac output to deliver oxygen and substrates and to remove carbon dioxide and other metabolic products,8 and despite data showing the impact of cardiac output optimization on postoperative outcome, cardiac output monitoring rarely is used in the daily anesthesiology practice; clinicians still rely on clinical judgment, blood loss estimates, and the vague concept of third-space losses.9

Since the 1980s, a significant portion of the medical literature focusing on perioperative hemodynamics has been related to the concept of fluid responsiveness that describes the ability of the circulation to increase cardiac output in response to volume expansion.10-23 It now is clear that dynamic parameters of fluid responsiveness, based on cardiopulmonary interactions in patients under general anesthesia and mechanical ventilation, are superior to static indicators (such as central venous pressure).10,24,25 These dynamic indicators can be derived from a single arterial pressure waveform (systolic pressure variations [SPVs] and pulse-pressure variations [PPVs]) (Fig 2) or from the plethysmographic waveform (respiratory variations in the plethysmographic waveform amplitude [ΔPOP] and plethysmographic variability index [PVI]).10,26 Their aim is to predict an increase in cardiac output induced by volume expansion before volume expansion is actually performed. Described more than 40 years ago,27 these dynamic indices have undergone significant improvement of late.28 During the past 2 years, several new software applications and algorithms have been developed to automatically and continuously calculate these indices.17,19,29,33 These new monitoring parameters open the door to the optimization of these dynamic indicators of fluid responsiveness and to an alternative to cardiac output monitoring and optimization.26 Recent studies suggest that this approach has the ability to improve postoperative outcome.34-36 In the present article, how these dynamic parameters may be used in clinical practice as a means to guide fluid management is discussed.

Arterial Pressure Variation and Goal-Directed Fluid Therapy

Maxime Cannesson, MD, PhD

Physiologic Foundations of Arterial Pressure Variation as a Guide to Fluid Management

Volume expansion frequently is used during anesthesiology to improve hemodynamics. The expected hemodynamic responses to volume expansion are increases in right ventricular end-diastolic volume, left ventricular end-diastolic volume, stroke volume, and cardiac output. These responses are expected because there is a positive relationship between ventricular end-diastolic volume and ventricular stroke volume. However, these expected responses to volume expansion actually depend on several sophisticated parameters. For example, the increase in end-diastolic volume induced by volume expansion is related to the partitioning of the fluids into the different cardiovascular compartments organized in series. Additionally, the increase in stroke volume as a response to the increase in end-diastolic volume depends on ventricular function. In clinical practice, the anesthesiologist never knows how fluids are partitioned or how contractile the ventricles of his/her patient are. Therefore, if inappropriately administered, volume expansion does not achieve its main objective: an increase in ventricular stroke volume. More importantly, an inappropriate volume can induce tissue edema and oxygen delivery alteration, working against the original goal of increased oxygen delivery. Therefore, it is of major importance for the anesthesiologist to be able to predict the effects of volume expansion before he/she performs volume expansion.

Ventricular Preload

Ventricular preload is defined as the degree of tension of the cardiac muscle when it begins to contract.37 In clinical practice, it is almost impossible to measure the degree of tension of the cardiac muscle when it begins to contract. Consequently, clinicians use pressure or volume parameters for the assessment of preload.38 The pressure parameters used are left and right ventricular filling pressures, and the volume parameter used is

From the Department of Anesthesiology and Perioperative Care, School of Medicine, University of California, Irvine, Orange, CA.
Conflicts of interest: M.C. is a consultant for ConMed, Covidien, Edwards Lifesciences, Fresenius Kabi, and Masimo Corp.
Address reprint requests to Maxime Cannesson, MD, PhD, Department of Anesthesiology and Perioperative Care, University of California, Irvine, 333 City Boulevard West Side, Orange, CA 92868-3301.
E-mail: maxime_cannesson@uci.edu
Published by Elsevier Inc.
1053-0770/2403-0020$36.00/0
doi:10.1053/j.jvca.2009.10.008
Key words: fluid responsiveness, fluid optimization, cardiac output, outcome
mainly left ventricular end-diastolic volume obtained through left ventricular end-diastolic area. Indices of preload have been used extensively over the past decades to guide volume expansion.38 The rationale behind the use of these indices to predict the effects of volume expansion on stroke volume and cardiac output is related to the Frank-Starling relationship (Fig 3). This relationship describes the intrinsic ability of the heart to adapt to increasing volumes of inflowing blood. In essence, the greater the heart muscle is stretched during filling, the greater is the force of contraction and the greater the quantity of blood pumped into the aorta. Stated another way, “Within physiologic limits, the heart pumps all the blood that returns to it by the way of the veins.”37 The shape of the Frank-Starling relationship is curvilinear (Fig 3). The first portion of this relationship is called the steep portion, and the second portion is called the plateau. If the heart is working on the steep portion (low preload), then an increase in preload (induced by volume expansion) will induce a significant increase in stroke volume (here the heart is said to be preload dependent). If the heart is working on the plateau (elevated preload), then an increase in preload (induced by volume expansion) will not induce any significant increase in stroke volume (here the heart is said to be preload independent). The Frank-Starling relationship does not depend only on preload and stroke volume, but it also depends on ventricular function, and the Frank-Starling curve is flattened when ventricular function is impaired. Consequently, for a given preload value, it is not possible to predict the effects of an increase in preload on stroke volume.

If the heart is working on the steep portion (low preload), then an increase in preload (induced by volume expansion) will induce a significant increase in stroke volume (here the heart is said to be preload dependent, and the patient is a responder to volume expansion). If the heart is working on the plateau (elevated preload), then an increase in preload (induced by volume expansion) will not induce any significant increase in stroke volume (here the heart is said to be preload independent, and the patient is a nonresponder to volume expansion). According to this observation, it becomes apparent that knowing preload will then help to predict fluid responsiveness. However, the Frank-Starling relationship does not depend only on preload and stroke volume, but it also depends on ventricular function because the Frank-Starling curve is flattened when ventricular function is impaired (Fig 3). Consequently, for a given preload value or central venous pressure, it is not possible to predict the effects of an increase in preload on stroke volume.11,20,22,24,39-44 Thus, preload or its surrogates are not accurate predictors of fluid responsiveness.

Preload Dependence

The main question anesthesiologists have to answer before they perform volume expansion is “will my patient’s cardiac output increase after volume expansion?” Embedded in this question is the following question: “is my patient preload dependent or not?” Preload dependence is defined as the ability of the heart to increase stroke volume in response to an increase in preload. As has been seen earlier, preload itself is not
predictive of preload dependence. Recently, the trend in anesthesiology and critical care has been the emergence of parameters able to accurately predict preload dependence, which, based on the analysis of the effects of fluid challenges on stroke volume, appear to be the best predictors of fluid responsiveness. In the anesthesiology setting, cardiopulmonary interactions have been used as a surrogate to assess the effects of a fluid challenge on stroke volume. In patients under general anesthesia, positive-pressure ventilation induces cyclic changes in vena cava blood flow, pulmonary artery flow, and aortic blood flow. During inspiration, vena cava blood flow decreases (venous return decreases) and, according to the Frank-Starling relationship, pulmonary artery flow decreases. Approximately 3 beats later this decrease in pulmonary artery flow is transmitted to the left ventricle, inducing a decrease in aortic stroke volume. Consequently, mechanically ventilated patients under general anesthesia present with cyclic changes in left ventricular stroke volume. When the heart is working on the steep portion of the Frank-Starling relationship, these respiratory variations are important because slight changes in right ventricular preload induced by mechanical ventilation will induce significant changes in stroke volume (Frank-Starling) (Fig 4); whereas when the heart is working on the plateau of this relationship, respiratory variations are small because changes in right ventricular preload induced by mechanical ventilation have no impact on stroke volume (Fig 4). Because arterial pressure parameters are related to stroke volume and arterial compliance, respiratory variations in arterial pressure parameters reflect respiratory variations in left ventricular stroke volume if arterial compliance is considered stable during a single respiratory cycle.

In 1978, Rick and Burke showed that respiratory variations in the arterial pressure were related to the patient’s fluid status and that SPV was frequently more than 10 mmHg in hypovolemic patients. In 1983, Coyle et al described the delta-up and delta-down components of SPV in an abstract presented at the American Society of Anesthesiologists annual meeting but never released as a full paper. In 1987, Perel et al showed that SPV was related to volume status in an animal model, and in the 1990s several studies showed that SPV was an accurate predictor of fluid responsiveness in adult patients undergoing surgery and in the intensive care unit. In 2000, Michard et al showed that PPV was superior to SPV for the assessment of fluid responsiveness in mechanically ventilated patients with septic shock. In parallel, noninvasive assessment of fluid responsiveness based on the analysis of the respiratory variations in the plethysmographic waveform was studied. The first study suggesting that the respiratory variations in the plethysmographic waveform were related to the patient’s fluid status was published by Partridge in 1987, the same year the article from Perel et al focusing on SPV was published. In 1999, Pizov et al showed the close relationship between SPV and respiratory variations in the peak of the plethysmographic waveform at baseline and after hemorrhage. Finally, in 2007, the present author’s team showed that the respiratory variations in the amplitude of the plethysmographic waveform are able to predict fluid responsiveness in mechanically ventilated patients. Today, several studies have shown that this parameter is useful for the purpose of fluid responsiveness prediction in anesthesiology and in intensive care.

Limits of the Dynamic Parameters of Fluid Responsiveness

Dynamic parameters of fluid responsiveness based on cardiopulmonary interactions have several limitations that need to be stated clearly before they can be used adequately in the clinical setting. First, these parameters have to be used in mechanically ventilated patients under general anesthesia. Until now, studies have failed to show that PPV, SPV, or ΔPOP can predict fluid responsiveness in spontaneously breathing patients. Moreover, tidal volume affects the predictive value of dynamic parameters so a tidal volume of 8 mL/kg of body weight with a positive end-expiratory pressure between 0 and 5 cmH₂O is required to use the indices. A significant weakness in the current literature on arterial pressure variation is a lack of control or documentation of intrathoracic pressure when the measurements are made. Any patient can appear “fluid responsive” with enough pressure in the chest. Because many sicker patients have variable lung compliance, the intrathoracic pressure that results from a given tidal volume is unpredictable. This is especially true in the operating room where surgical position or other factors such as laparoscopy can significantly influence effective lung compliance. Previous studies are limited by the fact that they typically use volume ventilation, and pressure in the chest (plateau pressure) is not reported. In general, patients have to be in sinus rhythm, the chest must be closed (open chest as well as an open pericardium strongly modify the cardiopulmonary interactions), and intra-abdominal pressure has to be within normal ranges. These dynamic indicators need to be explored further in children and in the setting of left ventricular failure and acute respiratory distress syndrome. Apart from these limitations...
caused by cardiopulmonary interactions that are common to any dynamic parameters, indices derived from the plethysmographic waveform have additional specific limitations. The plethysmographic waveform analysis is limited by the vasomotor tone that strongly impacts the waveform. Consequently, patients have to be studied during profound general anesthesia, and it seems that ΔPOP is less stable in the intensive care unit setting than in the anesthesiology setting.

When one or several limitations preclude the use of these indices, it is possible to use other dynamic parameters that do not rely on respiratory variations in stroke volume. Respiratory variations in the inferior vena cava diameter or collapsibility of the superior vena cava can be measured by using echocardiography. The effects of a passive leg raising on stroke volume can be used as well as an end-expiratory occlusion to obtain information regarding preload dependence. However, these indices are more likely to be used in the intensive care unit rather than in the operating rooms.

Fluid Optimization: From Cardiac Output to Pulse-Pressure Variations Monitoring

Fluid optimization concepts have changed dramatically over the past 10 years. A recent review article by Chappell et al described a rational approach for fluid management during anesthesia. In this article, the author claimed that using the right kind of fluid in the appropriate amounts at the right time may improve patient outcome. They declared that it is erroneous to compare 2 classes of fluids (crystalloids vs colloids) and that instead discussion should focus on the use of crystalloids and colloids in different situations.

The goal of perioperative fluid optimization is the same as that of the cardiovascular system under normal conditions: an adequate blood flow in vital organs and in traumatized tissues so as not to compromise the first and to enable effective wound healing in the latter. Hence, a rational substitution therapy accounts for crystalloids and iso-oncotic colloids in balanced preparations. Perioperative fluid losses should be replaced according to the physiologic background; crystalloids serve to replace extracellular losses, whereas colloids should serve to restore cardiac preload in order to optimize cardiac output. The current trend is to restrict crystalloids administration and to optimize cardiac output using colloids.

Impact of Cardiac Output Optimization on Postoperative Outcome

Several studies have shown that cardiac output optimization using colloids is able to improve postoperative outcome and to decrease the cost of surgery. Cardiac output optimization aims to optimize oxygen delivery in a way that is proportional to cardiac output, hemoglobin, and arterial oxygen saturation.

As has been shown earlier, cardiac output can be optimized by bringing the patient to the plateau of the Frank-Starling relationship. Most studies focusing on cardiac output optimization used a cardiac output monitor to titrate colloids administration in order to reach the plateau of the Frank-Starling curve when cardiac output does not increase anymore after volume expansion. Several positive studies were conducted by using esophageal Doppler. However, very few centers use esophageal Doppler and have yet to adopt goal-directed fluid administration protocols in their daily clinical practice. This is probably related to the changes in how cardiac output is measured in daily clinical anesthesia practice. The gold standard for cardiac output measurement still remains the pulmonary artery catheter with intermittent thermodilution. However, in the clinical setting, the use of the pulmonary artery catheter has dramatically decreased because several studies have suggested that the use of pulmonary artery catheterization does not improve outcome and, in some cases, even worsens patients’ outcomes. Thus, there has been a decrease in invasive monitoring and a trend toward increased use of less-invasive monitoring.

Numerous clinical trials have documented improved outcome and decreased costs when early goal-directed protocolized therapies are used in appropriate patient populations, such as patients with septic shock presenting to emergency departments and high-risk surgical patients before surgery (preoptimization) and immediately after surgery (postoptimization). This combination of the importance of cardiac output monitoring and decrease in the use of pulmonary artery catheter to measure cardiac output is reflected by the huge industrial interest in the development of alternative cardiac output monitoring and the large number of publications and of scientific sessions dedicated to this topic. However, there is still a gap between clinical practice in which cardiac output is rarely monitored and scientific publications.

Respiratory Variations in Arterial Pulse Pressure: From Manual Calculation to Automated Assessment

Recently, 2 major advances have occurred in dynamic parameters of fluid responsiveness: first, they can be obtained noninvasively using the plethysmographic waveform; and, second, they can be automatically and continuously monitored. This second advance will obviously open the door to the concept of their optimization and, consequently, to the concept of indirect cardiac output optimization using these parameters. As has been seen in the preceding sections, respiratory variations in the arterial pulse pressure can inform clinicians about a patient’s status on the Frank-Starling relationship (assuming there is no clinical limitation to the use of PPV). High respiratory variations (>15%) mean that the patient is on the steep portion. Low respiratory variations (<10%) mean that the patient is on the plateau.

Several devices displaying automated and continuous PPV, stroke volume variations (SVVs), and ΔPOP monitoring are now available. Some display dynamic parameters in association with cardiac output monitoring, and some display them alone. Some devices are invasive, and some are noninvasive. Some algorithms are proprietary, whereas some have been published. Interestingly, some are commercially available despite a lack of clinical validation of the algorithms used for their calculation.

An ideal device allowing for monitoring of these dynamic parameters of fluid responsiveness should present the following characteristics: it should be accurate, it should be reproducible, it should be inexpensive, it should be validated in clinical...
practice, it should be known, it should be able to detect artifacts, it should be able to work independently from the ventilator, and it should be noninvasive.

**How To Test a New Device Allowing for Preload-Dependence Monitoring With Potential Interest for Perioperative Fluid Optimization**

The accuracy of the algorithm has to be tested in clinical practice. Most of the previously published studies evaluating these devices compared manual calculation (manual point-and-click method) with automated values. The statistical analysis of dynamic indices requires a linear regression followed by a Bland-Altman analysis. However, because many studies performed multiple measurements in the same patients, the classic Bland-Altman analysis should now be replaced by a specific technique dedicated to the evaluation of the agreement between methods of measurement with multiple observations per individual. The aim of these devices is to provide a diagnostic tool for fluid responsiveness prediction in a clinical setting. Up to now, the classic methodology used for testing a parameter of fluid responsiveness was as follows. The algorithm had to be tested in patients under general anesthesia and mechanical ventilation. Hemodynamic data were collected at baseline, before volume expansion. Collected hemodynamic data included dynamic parameters of fluid responsiveness (including the tested algorithm and manually calculated respiratory variations in arterial pulse pressure) and static parameters of fluid responsiveness (central venous pressure, pulmonary capillary wedge pressure, and/or left ventricular end-diastolic area) because they reflect the current clinical practice and cardiac output. Then, a volume expansion was performed, and hemodynamic data were collected at the end of this volume expansion. Cardiac output must be measured by using a validated method allowing for less than 10% internal error because fluid responsiveness is defined as a more than 15% increase in cardiac output induced by volume expansion. The most consistent technique is still considered to be the pulmonary artery catheter with intermittent thermodilution. Volume expansion has to be great enough to induce fluid responsiveness. Most of the studies focusing on this topic used 500 mL of hydroxyethyl starch 6%.

Once data are collected, the patients are divided into 2 groups: responders to volume expansion and nonresponders to volume expansion according to the change in cardiac output induced by volume expansion. To be an accurate predictor of fluid responsiveness, the tested index has to be significantly different between responders and nonresponders (higher in responders than in nonresponders for PPV), it must be impacted by volume expansion according to the change in cardiac output induced by volume expansion (higher PPV at baseline, the higher the increase in cardiac output induced by volume expansion), it must be an accurate predictor of fluid responsiveness (area under the receiver operating characteristic (ROC) curve has to be significantly different from 0.5), and its accuracy must be superior to the accuracy of static parameters (comparison of areas under the ROC curves) (Fig 5). The best threshold value for the tested index is defined as the threshold allowing for the maximum specificity plus sensitivity. In the clinical setting, threshold values for PPV, SVV, ΔPOP, and PVI always have been found to be between 10% and 15%, meaning that a PPV, SVV, ΔPOP, and/or PVI value greater than 15% is predictive of fluid responsiveness. This observation is of major importance because fluid optimization based on these parameters will probably aim at keeping the patient under this threshold. Finally, because the aim of these studies is to test the accuracy of a diagnostic tool, they should all refer to the STARD statement. This statement has been developed in order to improve reporting of studies focusing on diagnostic tools. It consists of a checklist of 25 items and flow diagram that authors can use to ensure that all relevant information is present. It has been developed because it previously has been observed that the quality of reporting of studies of diagnostic accuracy has been less than optimal. A question that will have to be explored is the following: should an algorithm proposed for fluid responsiveness monitoring be associated with other hemodynamic parameters such as cardiac output? Because PPV and any other derived parameters have been designed to help clinicians to know where their patient is on the Frank Starling curve, clinicians may wonder whether cardiac output monitoring is still of any value when PPV is monitored. In the same idea, it may be claimed that cardiac output absolute value is not important for conducting fluid optimization and that it is of utmost importance to track relative changes in cardiac output in order to know the patient’s position on the Frank Starling relationship. PPV may achieve this goal even in the absence of cardiac output monitoring. Today, most of the new devices offering cardiac output monitoring have implemented algorithms allowing for PPV and/or SVV monitoring including pulse contour analysis, transpulmonary thermodilution, esophageal Doppler, bioimpedance, and

**Fig 5. Sample ROC curves comparing ΔPP, CVP, and PCWP for predicting fluid responsiveness.**

The predictive values of the tested parameters are compared by comparing the area under the ROC curves. In this illustrative figure, area under the curve for ΔPP is superior to areas under the curves for CVP and for PCWP. ΔPP, respiratory variation in arterial pulse pressure; CVP, central venous pressure; PCWP, pulmonary capillary wedge pressure.
bioreactance. Most of these algorithms are proprietary. On the other hand, some algorithms for PPV monitoring are proposed alone. This is the case for an algorithm proposed by Aboy et al.\textsuperscript{29} that is implemented on Philips Intellivue MP 70 monitors (Philips, Suresnes, France).\textsuperscript{31} The main interest of this algorithm is that it can be obtained from a single arterial pressure, it does not require any specific material, and it has been published and tested in the clinical anesthesia setting.\textsuperscript{31} Two other algorithms have been proposed for PPV monitoring and have been published: one is from Auler et al.,\textsuperscript{121} and the other one is from Pestel et al.\textsuperscript{122} The main limitation of the first one is that it needs to be connected to the capnograph in order to detect the respiratory cycle. The second one has been partially validated in the clinical setting (no volume expansion and no ROC curve analysis). More recently, an algorithm, the PVI, has been proposed for the automatic and continuous monitoring of ΔPOP from a single pulse oximeter.\textsuperscript{17,30} The main interest of this device is that it is completely noninvasive. The main limitation is that, as for any other parameter derived from the plethysmographic waveform, it also depends on vasomotor tone.\textsuperscript{62}

Globally, no currently available device allowing for PPV and/or SVV monitoring presents all the parameters requested to be considered as ideal. Table 1 summarizes interests and limits of the different algorithms available.

### Pulse-Pressure Variations–Guided Fluid Management: From Theory to Practice

Today, only 3 published studies have evaluated the impact of a pulse-pressure-variations–guided fluid management on perioperative outcome,\textsuperscript{34-36} and 5 abstracts have been presented recently at the American Society of Anesthesiologists and at the European Society of Anesthesiologists annual meetings.\textsuperscript{123-127} So far, results are inconclusive, and further studies are required to better explore this topic.

The first study to assess the ability of PPV-guided fluid management to impact postoperative outcome in high-risk surgery patients was published by Lopes et al.\textsuperscript{34} in 2007 and was conducted in Brazil. In this study, the aim of the authors was to minimize PPV to 10% in the intervention group using volume expansion (hydroxyethyl starch 6%), whereas the control group received fluid intraoperatively at the discretion of the anesthesiologist. The software used for PPV monitoring in the control group was published by Auler et al.\textsuperscript{121} Only 16 patients were enrolled in the control group and 17 in the intervention group. The length of mechanical ventilation was significantly de-

<table>
<thead>
<tr>
<th>Device</th>
<th>Main Advantages</th>
<th>Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>PiCCO</td>
<td>Several clinical validations</td>
<td>Invasive</td>
</tr>
<tr>
<td></td>
<td>Stroke-volume variations</td>
<td>Requires specific material</td>
</tr>
<tr>
<td></td>
<td>Pulse-pressure variations</td>
<td>Calibration</td>
</tr>
<tr>
<td></td>
<td>Multimodal monitoring (cardiac output,</td>
<td>No artifact detection</td>
</tr>
<tr>
<td></td>
<td>vascular resistances, etc</td>
<td>Proprietary algorithm</td>
</tr>
<tr>
<td>Vigileo-FloTrac</td>
<td>Multimodal monitoring (cardiac output,</td>
<td>Semi-invasive</td>
</tr>
<tr>
<td></td>
<td>vascular resistances, etc</td>
<td>Requires specific material</td>
</tr>
<tr>
<td></td>
<td>No calibration</td>
<td>No artifact detection</td>
</tr>
<tr>
<td></td>
<td>Semi-invasive</td>
<td>Divergent data regarding cardiac output</td>
</tr>
<tr>
<td></td>
<td>Several clinical validations</td>
<td>determination</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Proprietary algorithm</td>
</tr>
<tr>
<td>Aboy’s algorithm</td>
<td>Algorithm has been published</td>
<td>No multimodal monitoring</td>
</tr>
<tr>
<td></td>
<td>No specific material</td>
<td>Semi-invasive</td>
</tr>
<tr>
<td></td>
<td>No added cost</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Artifact detection</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clinical validation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No calibration</td>
<td></td>
</tr>
<tr>
<td>PVI</td>
<td>Noninvasive</td>
<td>Vasomotor tone</td>
</tr>
<tr>
<td></td>
<td>Multimodal monitoring (hemoglobin)</td>
<td>No artifact detection</td>
</tr>
<tr>
<td></td>
<td>No calibration</td>
<td>Proprietary algorithm</td>
</tr>
<tr>
<td>Others</td>
<td>Clinical validation</td>
<td>Needs to be connected to the ventilator</td>
</tr>
<tr>
<td></td>
<td>Semi-invasive</td>
<td>No distribution</td>
</tr>
<tr>
<td></td>
<td>No calibration</td>
<td>Semi-invasive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Artifact detection?</td>
</tr>
<tr>
<td>Auler’s algorithm</td>
<td>Clinical validation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Semi-invasive</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No calibration</td>
<td></td>
</tr>
<tr>
<td>Pestel’s algorithm</td>
<td>Semi-invasive</td>
<td>No extensive clinical validation</td>
</tr>
<tr>
<td></td>
<td>No calibration</td>
<td>No distribution</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Semi-invasive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Artifact detection?</td>
</tr>
<tr>
<td>Bioimpedance</td>
<td>Noninvasive</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Multimodal monitoring (hemoglobin)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No calibration</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clinical validation</td>
<td></td>
</tr>
<tr>
<td>LidCo</td>
<td>Semi-invasive</td>
<td>No clinical validation</td>
</tr>
<tr>
<td></td>
<td>Multimodal monitoring (hemoglobin)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No calibration</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clinical validation</td>
<td></td>
</tr>
</tbody>
</table>

Table 1. Main Advantages and Limits of Currently Available Devices Allowing for Monitoring of Dynamic Parameters of Preload Dependence
creased in the intervention group (1 v 5 days, \( p < 0.05 \)), the length of stay in the intensive care unit was decreased (3 v 9 days, \( p < 0.01 \)), the length of stay in the hospital was decreased (7 v 17 days, \( p < 0.01 \)), and the number of postoperative complications per patient were decreased (1.4 v 3.9, \( p < 0.05 \)). While interesting, these results are not strong enough to sustain the use of PPV-based protocols for fluid management in the operating room. Several limitations strongly impact the conclusions of this study. First, PPV at baseline in the control group was 22%, reflecting severe hypovolemia. Moreover, although the intervention group received 2,250 mL of colloids and 2,200 mL of crystalloids during surgery, the control group received 1,560 mL of crystalloids and no colloids at all. Consequently, the study seems to compare a severely hypovolemic group (control) with a standard group (intervention), and the results cannot be extrapolated to the current clinical practice. Second, the number of patients in this study was too small to draw conclusions.

A more recent study was published by Buettner et al\(^3\) in 2008. This study evaluated the influence of systolic pressure variation–guided intraoperative fluid management on organ function and oxygen transport. Eighty patients undergoing major abdominal surgery were studied. Forty patients were randomized to the control group, and 40 were randomized to the intervention group in which fluid management was guided by systolic pressure variation with a trigger at 10% for volume expansion. The algorithm used for SPV monitoring was developed by the authors. The duration of mechanical ventilation, length of stay in the intensive care unit, length of stay in the hospital, and mortality were comparable between both groups. Moreover, in comparison with routine care, intraoperative SPV-guided treatment was associated with slightly increased fluid administration, whereas organ perfusion and function parameters were identical between both groups. Interestingly, in this study, SPV values at baseline were identical in both groups (6% v 7%) and were far lower than PPV in the Auler et al study. SPV in this study was kept below 15% in both groups.

Finally, a study was published in 2008 by Kobayashi et al\(^6\) of patients undergoing esophageal surgery. Only 9 patients were enrolled in the study, and there was no randomization and no goal-directed protocol. Consequently, the results from this study cannot be considered as significant.

To the best of our knowledge, 5 recent abstracts focusing on PPV or SVV intraoperative-guided fluid optimization recently have been presented at international meetings. Results from these preliminary studies are not conclusive yet but are clearly encouraging. Because the studies are not released yet and the data are not complete, the results are not discussed further.

**FUTURE RESEARCH TOPICS**

As has been seen, it is too early to draw conclusions regarding the ability of PPV-guided fluid management to improve patient outcome. However, it is tempting to postulate that knowing that cardiac output optimization (maximization) is able to improve patient outcome, PPV optimization (minimization) also should improve patient outcome. The main draw of PPV-guided fluid management is that it is an individualized approach and that it may help to give the appropriate amount of fluid to the patient rather than to overload the patient. However, further studies are required to clearly answer this question and to better define the use of PPV and other dynamic parameters in the clinical settings.

In the following section, future research topics related to these parameters are discussed. First, as discussed in the previous section focusing on cardiac output, despite evidence that cardiac output–guided fluid management can improve outcome, it appears that cardiac output is rarely used in clinical practice. In the same area, central venous pressure is still widely used for fluid responsiveness despite many studies showing that it is a poor predictor of response to volume expansion. Also, despite evidence showing that PPV and SVV are the best predictors of fluid responsiveness, dynamic indices still are rarely calculated in the clinical setting. The author does not have a clear picture regarding how clinicians conduct hemodynamic monitoring in daily practice. Thus, the present author strongly believes that a survey focusing on perioperative hemodynamic monitoring and fluid optimization should be conducted to better understand the full picture and whether or not clinicians adopt new hemodynamic concepts.

Second, it is unclear whether PPV and/or other dynamic parameters should be used alone or in combination with other hemodynamic parameters such as cardiac output or central venous oxygen saturation to guide fluid management.\(^7\) This is of major importance because the timing of use of dynamic parameters needs further exploration. Apart from intraoperative and preoperative hemodynamic optimization, pre- and postoperative optimization periods may be of importance. However, in the postoperative period, dynamic parameters of fluid responsiveness may be useless because many patients are spontaneously breathing. The question is as follows: is PPV optimization alone enough or do clinicians need to monitor cardiac output or central venous oxygenation at the same time?

Third, even if PPV and SVV have been studied for many years, there are still unresolved questions that should be answered before they are finally implemented into clinical protocols for hemodynamic optimization. For example, the relationship between PPV and systolic pressure variations (Δup and Δdown) should be further explored because in some situations PPV may reflect a Δup component, whereas in some other situations it may reflect a Δdown component.

Fourth, methodology evaluating dynamic parameters of fluid responsiveness should be improved to better reflect the clinical practice. Most of the previously published studies compared dynamic parameters with static parameters. However, the medical decision-making process is much more complicated than that. Rather than comparing dynamic parameters with other indices, a Bayesian inference, integrating several parameters together, may improve the accuracy of these indices. In the same area, alternative techniques to ROC curve approach should be proposed. This approach was described during World War II but is still used to evaluate a diagnostic tool despite major recent advances in statistics. The ROC curve approach considers that clinical practice is a “black or white” situation in which patients are either responders or nonresponders. From this approach, a threshold value is proposed for the tested index. This threshold is supposed to provide acceptable sensitivity and specificity for fluid responsiveness prediction. However, clinical practice is not a “black or white” event, and every
clinician knows that some patients are responders to volume expansion despite a PPV at baseline around 9%, whereas some patients are nonresponders to volume expansion despite PPV at baseline at 15%. Thus, most quantitative tests do not perfectly discriminate between subjects with and without a given characteristic. New statistical approaches propose methods to construct a 3-zone partition for a quantitative test to avoid the binary constraint of a “black or white” decision that often does not fit the reality of clinical or screening practice. This approach intentionally includes a gray zone between positive and negative conclusions.123 This approach has been used to define the predictive value of brain natriuretic peptide in the emergency department setting.129 The author believes that this approach should be used for dynamic parameters of fluid responsiveness, and, that instead of choosing a single threshold (13% for example), authors should report data using a gray zone with a upper limit allowing for optimal positive likelihood ratio and a lower limit allowing for optimal negative likelihood ratio. The gray zone between these 2 values would be an inconclusive zone in which patients can be either responders or nonresponders. More importantly, this approach would allow knowing how many patients are included inside the gray zone and, consequently, whether or not the tested index is useful in clinical practice.123 This approach would also be important in order to define what threshold should be used for PPV-guided fluid management protocols and whether a gray zone approach would be more appropriate than a single threshold approach.

Fifth, PPV and/or SVV still require an invasive intra-arterial catheter. Obviously, the author cannot support the concept of an increase in invasive monitoring for fluid optimization management when noninvasive monitoring provides the same information. Future studies will have to investigate what hemodynamic monitoring has to be used in which patients and when. Because noninvasive monitoring will still be used for moderate-risk surgery, plethysmographic waveform analysis,26 noninvasive arterial pressure monitoring,21 and bioimpedance and bioreactance will have particular uses in such a setting.

Finally, clinicians will need strong outcome studies before these parameters are implemented in clinical practice. Just like any other monitoring devices, automatic and continuous monitoring of these parameters has a cost. This cost can only be justified if it is shown that the protocols based on these devices can improve patients’ health. Outcome studies are complicated to run and are very expensive, and their results are not predictable. In countries where the quality of care is high and poor postoperative outcome is rare, a large number of patients are required in order to show a difference in morbidity and/or mortality induced by a protocol based on a monitoring parameter. Moreover, as shown with studies based on cardiac output optimization, even if the results of the outcome studies are positive, clinicians have the final decision on whether or not to use the protocols in their clinical practice.

CONCLUSION

PPV is superior to static parameters for fluid responsiveness prediction. This parameter has the ability to be used for hemodynamic management and fluid optimization in patients under general anesthesia and mechanical ventilation. However, very few studies have evaluated the influence of PPV- or SPV-guided intraoperative fluid management on postoperative outcome, and their results are inconclusive. Further studies are required to better define how these parameters can be implemented in clinical protocols for perioperative fluid management.130,131

ACKNOWLEDGMENTS

The author thanks Prof Jean-Jacques Lehot, Prof Vincent Piriou, Dr Olivier Desebbe (CHU de Lyon, France), Prof Jean-Louis Teboul (Kremnic Bicetre,France), Prof Jean-Yves Lefrant (CHU de Nimes, France), Prof Benoit Tavernier (CHU de Lille, France), Prof Bruno Riou (Pitié Salpêtrière, France), Prof Kirk Shelley (Yale, USA), and Prof Michael Pinsky (University of Pittsburgh Medical Center, USA) for their teaching and for insightful discussions about cardiopulmonary interactions, perioperative fluid optimization, plethysmography, and research methodology. Also, the author thanks Dr Max Cho for English editing.

REFERENCES

15. Feissel M, Teboul JL, Merlani P, et al: Plethysmographic dy-
1111, 2007
variability index indicate the respiratory induced variation in the ple-
thsymogram and arterial pressure waveforms? Anesth Analg 106:
1189-1194, 2008
18. Cannesson M, Desebbe O: Using ventilation induced plethys-
mographic waveform variations to optimize patient fluid status. Curr
Opin Anaesthesiol 21:772-778, 2008
volume variations obtained with Vigileo/FloTrac system to monitor
fluid responsiveness in mechanically ventilated patients. Anesth Analg
108:513-517, 2009
variation as a guide to fluid therapy in patients with sepsis-induced
prediction of fluid responsiveness during major hepatic surgery. Br J
Anesth 97:808-816, 2006
22. Perel P, Pizov R, Cotev S: Systolic blood pressure variation is
a sensitive indicator of hypovolemia in ventilated dogs subjected to
blood pressure variations and echocardiographic estimates of end-
diastolic left ventricular size in patients after aortic surgery. Anesth
Analg 78:46-53, 1994
24. Marik PE, Baram M, Vahid B: Does central venous pressure
predict fluid responsiveness? A systematic review of the literature and
rrial waveform derived variables and fluid responsiveness in me-
chanically ventilated patients: A systematic review of the literature.
Crit Care Med 37:2642-2647, 2009
26. Desebbe O, Cannesson M: Using ventilation induced plethys-
mographic variations to optimize patient fluid status. Curr Opin An-
aesthesiol 21:772-778, 2008
27. Morgan BC, Martin WE, Hornbein TF, et al: Hemodynamic ef-
fects of intermittent positive pressure respiration. Anesthesiology
27:584-590, 1966
systemic arterial pressure as an indicator of volume status. Anesthesi-
ology 59:A53, 1983
estimate the pulse pressure variation index deltaPP. IEEE Trans
Biomed Eng 51:2198-2203, 2004
index to monitor the respiratory variations in the pulse oximeter ple-
thysmographic waveform amplitude and predict fluid responsiveness in
algorithm for automatic estimation of the respiratory variations in
arterial pulse pressure to monitor fluid responsiveness in the operating
puls wave-form derived stroke volume variation predicts fluid respon-
siveness in mechanically ventilated patients undergoing liver transplan-
33. Reuter DA, Kirchner A, Felbinger TW, et al: Usefulness of left
ventricular stroke volume variation to assess fluid responsiveness in
patients with reduced cardiac function. Crit Care Med 31:1399-1404,
2003
34. Lopes MR, Oliveira MA, Pereira VO, et al: Goal-directed fluid
management based on pulse pressure variation monitoring during high-
risk surgery: A pilot randomized controlled trial. Crit Care 11:R100,
2007
systolic-pressure-variation-guided intraoperative fluid management on
fluid responsiveness after esophageal surgery using stroke volume
37. Guyton AH, Hall JE: Heart muscle: The Heart as a pump and
function of the heart valves, in Elsevier S (ed): Textbook of Medical
on intensive care units: Results from a postal survey. Intensive Care
39. Michard F, Reuter DA: Assessing cardiac preload or fluid re-
sponsiveness? It depends on the question we want to answer. Intensive
Care Med 29:1396, 2003; author reply 1397
40. Michard F, Ruscio L, Teboul JL: Clinical prediction of fluid
responsiveness in acute circulatory failure related to sepsis. Intensive
Care Med 27:1238, 2001
41. Michard F, Teboul JL: Using heart-lung interactions to assess
fluid responsiveness during mechanical ventilation. Crit Care 4:282-
289, 2000
42. Michard F, Teboul JL: Predicting fluid responsiveness in ICU
2002
volume index as an indicator of fluid responsiveness in critically ill
patients with acute circulatory failure: A comparison with central
44. Osman D, Ridel C, Ray P, et al: Cardiac filling pressures are not
appropriate to predict hemodynamic response to volume challenge. Crit
Care Med 35:64-68, 2007
45. Bendjelid K, Romand JA: Fluid responsiveness in mechanically
ventilated patients: A review of indices used in intensive care. Intensive
Care Med 29:352-360, 2003
46. Rick JJ, Burke SS: Respirator paradox. South Med J 71:1376-
1378, 1382, 1978
47. Partridge BL: Use of pulse oximetry as a noninvasive indicator
48. Pizov R, Ya’ari Y, Perel A: The arterial pressure waveform
during acute ventricular failure and synchronized external chest com-
arterial blood pressure and photoplethysmography during mechanical
mographic dynamic indices to test responsiveness for testing fluid
administration in hypotensive patients: A clinical trial. Anesth Analg
103:1478-1484, 2006
duced plethysmographic variations predict fluid responsiveness in
ventilated postoperative cardiac surgery patients. Anesth Analg
105:448-452, 2007
52. De Backer D, Pinsky MR: Can one predict fluid responsiveness
in spontaneously breathing patients? Intensive Care Med 33:1111-
1113, 2007
prediction of volume responsiveness in critically ill patients with spon-