Although few people have heard or understand the term “closed-loop control,” it is ubiquitous in modern life. A closed loop is simply a system wherein a controller monitors one or more system variables and adjusts one or more interventions to control that system in response (Fig. 1). A prime example is central air-conditioning: the main unit pumps cool air throughout the house, the temperature is monitored by sensors in the home, and these data are then compared with the settings on the thermostat and used to increase or decrease the cooling so that the temperature hovers near the set point. Although it would be possible to manually adjust the flow of cold air, the odds are that you would often overshoot or undershoot your desired temperature and the system would require many adjustments every hour to even modestly approximate the performance that an automated controller easily achieves. Other common examples are the cruise-control systems in automobiles, electric ovens, and the operation of elevators. Moreover, virtually every system in living organisms is under physiologic closed-loop control. Anesthesiologists themselves constitute closed-loop controllers (Fig. 1): patient output is monitored in the form of vital signs and this information is used to tailor interventions by the practitioner. In control engineering terminology, this arrangement constitutes a closed-loop control system with a human controller in the loop. One noteworthy feature of this particular arrangement is that the attention and actions of the human controller are intermittent.

The benefits of a well-designed automated controller are obvious: automation of previously manual tasks and improvement in stability and accuracy of the controlled variables. Furthermore, a closed-loop system is not distractible from its task and the implemented algorithm is perfectly repeatable, meaning it can be tested and steadily improved upon in practice. A medical example of this behavior is the action of implantable pacemakers and defibrillators, which run for years making decisions without the need for manual validation.

With the benefits of closed-loop systems being what they are, one might question why there are not more used in anesthesia. Obstacles are numerous but include the complexity of biologic systems, uncertainty in measurements and clinical care, regulatory approval and safety, and acceptance by practitioners. The most important element of an effective closed-loop system is the accuracy and validity of the variable(s) monitored by the system; without good feedback, the controller cannot respond appropriately to changes. Nevertheless, this does not mean that closed-loop systems are unrealistic or even impractical.
goals, especially with the rapid advances in monitoring and computing power that we are now witnessing.

Recent improvements in hemodynamic monitoring, and in particular the dynamic variables predictive of fluid responsiveness, suggest that closed-loop management of fluid resuscitation in trauma, operating rooms, and intensive care settings is rapidly becoming an achievable goal. In this article, we review the literature on the predictive dynamic variables of fluid responsiveness, the value of and challenges facing closed-loop controllers in clinical care, and finally suggest approaches in which closed-loop fluid management controllers might be implemented and what features they will likely need to be considered safe, robust, and effective.

**CLOSED-LOOP CONTROLLER: DEFINITION AND DESCRIPTIONS**

Figure 2 illustrates schematically 2 of the most frequently used control methods in clinical devices. Table 1 lists definitions of the most important vocabulary used in control engineering. The type of control method used will have a significant impact on the reliability, benefits, and limitations of the loop, and in large part is dependent on the characteristics of the target system. In the following sections, we describe the most frequently used types of control in health care systems: proportional-integral-derivative (PID), model-based, rule-based, artificial neural networks (ANNs), and fuzzy logic controllers.

The most generic and widely used controller type is the PID controller (Fig. 2A). Differences between the output value and the set point are calculated and used to adjust the input value. Each of the 3 terms in the name accounts for a different component of the error: the present (proportional), past (integral), and future (derivative) error values. To prevent system oscillations, tuning must take place to adjust the individual gains of each of these 3 components.

5–7 PID controllers are often used as the sole control method in clinical applications, particularly in linear systems, but can also be used in combination with other controller types that have further advantages over PID control. In anesthesiology, PID control has frequently been used to control depth of hypnosis.

The model-based approach monitors how accurately a designed model predicts the observed response and uses that information to improve its future processes. Training of the system with simulated data (reference model) or real-time responses (system identification) is required to establish a model’s precision before it can be used in clinical situations.

In medical systems, the model itself is normally based on a combination of established physiologic variables (i.e., pharmacokinetics, circulatory responses, and target site concentrations). Such models help to account for interpatient variability and improve robustness of the controller. Therefore, when a clinical scenario frequently exhibits large differences among patients, a model-based approach is typically advantageous over an exclusively PID-based controller. To improve model parameters from a standard population-based response, a Bayesian approach can also be used to optimize individual parameters within the system.

Model-based approaches have frequently been used for control of neuromuscular blockade and control of hypnosis.

The rule-based controller implements a set of user-defined rules analyzing variables of interest to organize and execute specific controller actions. These rules are generally in an “if-then” format and can be used to interpret quantitative data, qualitative data, or a combination of the two. The manual nature of this design allows for a high level of specification and control, which can be valuable in...
complex systems. Obviously, a rule-based controller is only as effective as the governing rule set and requires extensive testing for stability, but again these controller types are often combined with other control schemes. Combined approaches like these have been used successfully for hemodynamic management and depth of hypnosis.

ANNs are another approach gaining popularity (Fig. 2B). The basis of this approach is to mimic a biologic neural network: there are multiple layers of “neurons” (nodes with individual functions and weights), which manipulate input data into an appropriate output signal. A learning strategy is required to set the various functions and weights to produce a network that correctly interprets specific data. These learning strategies can be automated or supervised, depending on the desired function of the network, but once optimized, these systems can be very robust. An ANN is frequently used when there are multiple inputs and outputs and when a function needs to be inferred from observed data. Simulation and animal studies have demonstrated the feasibility of control of arterial blood pressure (in 6 rabbits and simulation) and sevoflurane concentration using ANNs. The clinical application of ANNs in humans is limited to 7 anesthetized patients, thus the robustness of these controllers in medical care awaits further clinical validation.

Uncertainty and gray areas are both common in medical diagnosis and treatment. Some form of probabilistic decision-making will be required in most systems to account for this fact. “Fuzzy logic,” as Zadeh termed it in 1965, is one mathematical model that allows computer programs to work with uncertainty. Instead of allowing for only the logical values true and false, degrees of truth are allowed. Linguistically, we are used to dealing with these partial truths; clinicians have little trouble understanding what is meant by “his blood pressure is a little low.” Fuzzy logic allows this same approach to be used in computer systems, and because of the utility of this approach, there has been an exponential growth in the medical and bioinformatics literature on fuzzy logic in the past two decades.

One drawback to fuzzy logic is that because of the relation to linguistic thinking, there is a degree of arbitrariness that goes into the design of the controller. Even when experts are used in the design process, there may be some disagreement about set boundaries and significance (for example, what constitutes “significant” hypoxia, a saturation of 90%, 88%, or 86%?). For this reason, fuzzy sets, once designed, need to be rigorously tested to verify their appropriateness across a range of clinical scenarios.

**CLOSED LOOPS IN MEDICINE: HISTORY AND CURRENT TRENDS**

Automated systems offer clear benefits to clinicians. The first, touched on in the introductory text, is the freeing of limited human resources. In medical settings such as surgery, trauma, and intensive care, this typically means the time and attention of the highly trained specialists providing patient care, a scarce resource in the best of times, which becomes less available as the criticality and intensity of the scenario increases. By shifting some of the decision-making to automated systems, particularly systems that have been proven to be effective and reliable, the attention of providers can be focused on other aspects of care.

Additionally, autonomous devices can be used in areas where immediate access to experts may not be available. If a closed-loop controller is shown to be as effective as a clinician in its management of a particular variable, it becomes a sort of portable expert. It can then be deployed in combat zones, remote rural locations, or even outer space if need be, and can act in place of experts until they become available. This does not mean automated systems are not without limitations, however. A brief review of some of the described systems will elucidate the benefits and possibilities of automated systems as well as the challenges faced in their implementation.

**Neuromuscular Blockade**

One requirement of automated controllers is a reliable measure of the system’s desired effect. Neuromuscular blockade is a natural target for closed-loop controllers because the effects of these drugs are relatively easily measured by noninvasive monitors. In 1976, Cass et al. reported on the use of computer-controlled infusions of d-tubocurarine, gallamine, alcuronium, and pancuronium in sheep. After that, the first closed-loop muscle-relaxant
infusion systems were reported on beginning in the mid-1980s, with later comparison studies showing a steadier level of neuromuscular blockade than was achieved with intermittent bolus or manually set infusion. Later systems became more sophisticated, including adaptive elements that could self-adjust in response to patient-specific factors. On the whole, use of closed-loop control of muscle relaxants for surgery has been shown to provide “stable surgical operating conditions over a wide range of patient sensitivities while infusing the minimum amount of drug.”

It should be noted that closed-loop controllers have less utility when overdosing of the controlled treatment carries little risk and the effect can be rapidly reversed. For this reason, the recent availability of drugs such as cyclodextrin that can immediately reverse deep residual blockade now limit the clinical interest of muscle-relaxant closed-loop control.

Insulin Therapy
The chronic nature of diabetes mellitus and the need for continuous real-time adjustment of insulin levels in response to fluctuating glucose levels has made insulin therapy another natural target for closed-loop control systems. Computer-assisted dose calculations and modeling began in the 1980s along with early attempts at closed-loop control. Continuous wearable closed-loop infusion pumps were also first tested in this era. Although truly portable, closed-loop, glucose-sensing insulin infusion pumps are not yet widely available, there is rapid progress in this area as glucose monitoring continues to become more sophisticated.

The safety record of computer-assisted and computer-controlled insulin infusions is very good, with modern systems consistently reporting tighter glycemic control with fewer complications and less hypoglycemia than standard strict protocols. The direct relationship between insulin and glucose levels has been partly responsible for the success of these systems despite the interpersonal and even interdevice response variability encountered. The chief difficulty in creating continuous portable closed-loop insulin management systems is that reliable measurement of blood glucose level still requires invasive testing. This may soon be overcome; a subcutaneous enzymatic sensor is now clinically available, for example, and has been successfully used in a closed-loop insulin controller.

Sedation and Anesthesia
Automated administration of anesthetics began in the United States. Mayo and Bickford developed a prototype automatic anesthetic delivery system that regulated the administration of ether or thiopental using electroencephalographic (EEG) activity. This research group first successfully closed the loop on 50 human patients back in 1950! Closed-loop research continued at the University of Utah during the 1980s and focused on control of respiration and inhaled volatile anesthetics. Moreover, closed-loop systems for nitroprusside infusions, muscle relaxants, and even the first closed-loop fluid-infusion system based on urine output were reported. These early systems, as well as other closed-loop anesthetic delivery systems developed around the same time, were found to be safe and to reliably deliver the desired concentration of anesthetic over long time spans. Different inputs have been used to control anesthetic drugs. Examples include median EEG activity for methohexital administration and auditory evoked potentials for propofol. Interest in closed-loop control was renewed with the introduction of the Bispectral Index (BIS) monitor, which allowed for the continuous monitoring of electrocortical activity in the operating room. Table 2 summarizes studies that included the BIS monitor in the closed-loop controller. Since 1998, approximately 400 patients have been anesthetized using a BIS-propofol closed-loop PID model, rule-based (15%), or neural network controller (2%), demonstrating the feasibility of automated propofol administration during induction and maintenance of general anesthesia.

The BIS monitor has also been used to automate delivery of isoflurane and still other EEG monitors can be used to control depth of hypnosis.

These systems are effective but do have limitations because the target return variables are only moderately accurate surrogates for depth of anesthesia. Even given this limitation, modern closed-loop IV anesthesia infusion systems have been able to outperform anesthesiologists in randomized clinical trials. The selection of the controlled variable remains difficult when discussing automated administration of an opioid. Mean arterial blood pressure and heart rate were previously used to control alfentanil administration, but electrocortical activity has also been used to control alfentanil and remifentanil. Recently, the Sedasys system was made commercially available in Australia and Canada. This controller allows the automated titration of propofol and oxygen using hemodynamic and oxygen saturation variables during endoscopic procedures. Over all, the automated titration of propofol has been shown to be safe in patients with severe comorbidities, to improve hemodynamic stability, and to decrease the time to tracheal extubation without increasing the occurrence of adverse events. Curiously, the only commercial automated propofol administration system currently in use is designed for nonanesthesia providers.

Ventilation and Oxygenation
Ventilator management is an especially advanced area showing great promise for closed-loop systems. The first automatic control of ventilation was described in 1957 by Saxton and Myers, who used a servo to control negative pressure ventilation. Beginning with the description by Hewlett et al. of “mandatory minute ventilation” in 1977, multiple adaptive modes of ventilation and fraction of inspired oxygen titration have been proposed that rely on closed-loop controllers for their operation. A particular focus area of closed-loop ventilators is weaning, with clinical studies showing shorter times to extubation when these modes are used. Some authors have suggested that closed-loop ventilator management has advanced to the point where it may be an emerging standard of care.
Other Systems
Closed-loop systems have been reported for many other clinical applications: induction of labor with Pitocin,116,117 nitroprusside in hypertensive crises,82,83,118 vasopressors drugs,119 phenylephrine during spinal anesthesia for cesarean delivery,120 postoperative autotransfusion,121 and even intraaortic balloon pump function.122

CLOSED-LOOP MANAGEMENT OF FLUID ADMINISTRATION
Goals of Fluid Management and Hemodynamic Optimization
As stated by Arthur Guyton: “The primary function of circulation is to supply body tissues with nutrients, to eliminate waste products, to transfer hormones between circulation is to supply body tissues with nutrients, to eliminate waste products, to transfer hormones between body parts, and, in general to maintain “homeostasis”—an appropriate tissue environment for optimal cell function and survival.”123,124 To achieve this goal, two physiologic objectives are required: adequate perfusion pressure to drive blood into organ capillaries, and adequate cardiac output (CO) to deliver oxygen.123,124 A variety of studies have demonstrated that meeting these goals by CO maximization during high-risk surgery results in an improved postoperative outcome with concomitant savings on costs.125–130 Although the ideal goal of fluid administration would be to perfectly match the oxygen delivery to the oxygen demand (optimization), the lack of clinically reliable oxygen uptake monitoring131 makes CO maximization the most logical approach until such monitoring becomes available.

Historical Approaches to Hemodynamic Optimization
That hypovolemia induces hypotension, oliguria, and tachycardia is obvious. These signs are inadequate in themselves, however, because they only appear in severe hypovolemia132 and are not specific.133–135 Invasive central venous pressure (CVP) and pulmonary capillary wedge pressure have been used for years to monitor patients’ intravascular volume status. However, the assumption that CVP and pulmonary capillary wedge pressure reflect ventricular preload (or preload dependence) is erroneous, and studies have failed to demonstrate any accuracy of these variables for predicting the effects of intravascular volume expansion on CO133,135–137 or to improve patients’ outcomes.138–145

Studies focusing directly on CO optimization use a CO monitor (often esophageal Doppler) to titrate fluid administration to the point at which CO does not further increase after intravascular volume expansion. Reports have shown the clinical benefits of this approach.146,147 Very few centers have adopted goal-directed fluid administration protocols in their daily clinical practice, however, likely because of the traditional difficulty in monitoring CO. The clinical “gold standard” for CO measurement is still an invasive pulmonary artery catheter with intermittent thermocilum.148–151

Table 2. Summary of Studies Using Bispectral Index–Propofol Closed-Loop Controllers for Anesthesia Management

<table>
<thead>
<tr>
<th>Study</th>
<th>Algorithm</th>
<th>Surgery</th>
<th>Induction</th>
<th>Control group</th>
<th>Multicenter</th>
<th>ASA physical status</th>
<th>Age (y)</th>
<th>Duration (min)</th>
<th>Analgesia</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortier et al.10</td>
<td>Model-based</td>
<td>Orthopedic</td>
<td>Manual</td>
<td>No</td>
<td>No</td>
<td>III and IV</td>
<td>48.7 ± 7</td>
<td>28.8 ± 13.3</td>
<td>Spinal</td>
<td>10</td>
</tr>
<tr>
<td>Morley et al.94</td>
<td>PID and TCI</td>
<td>Gynecologic/general</td>
<td>Manual</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>41 (25–60)</td>
<td>87 [35–164]</td>
<td>Mixture propofol/alfentanil</td>
<td>30</td>
</tr>
<tr>
<td>Leslie et al.109</td>
<td>PID</td>
<td>Colonoscopy/sedation</td>
<td>Manual</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>60 ± 16</td>
<td>19 [7–50]</td>
<td>None</td>
<td>16</td>
</tr>
<tr>
<td>Slinys et al.19</td>
<td>Model-based</td>
<td>Gynecoscopic/laparatomy</td>
<td>Manual</td>
<td>No</td>
<td>No</td>
<td>46 ± 4</td>
<td>110</td>
<td></td>
<td>Remifentanil fixed</td>
<td>10</td>
</tr>
<tr>
<td>Absalom et al.9</td>
<td>PID and TCI</td>
<td>Orthopedic</td>
<td>Manual</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>67 ± 11</td>
<td>72 [40–80]</td>
<td>Epidural</td>
<td>10</td>
</tr>
<tr>
<td>Absalom and Kenny200</td>
<td>PID and TCI</td>
<td>Body surface</td>
<td>Manual</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>43 (30–72)</td>
<td>27.5 [12–86]</td>
<td>Remifentanil TCI fixed</td>
<td>20</td>
</tr>
<tr>
<td>Liu et al.8</td>
<td>PID and TCI</td>
<td>General, gynecologic, urology, orthopedic, thoracic ...</td>
<td>Closed-loop</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>58 ± 15</td>
<td>136 ± 86</td>
<td>Remifentanil TCI variable</td>
<td>83</td>
</tr>
<tr>
<td>Liu et al.89</td>
<td>PID and TCI</td>
<td>Lung transplantation</td>
<td>Closed-loop</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>43 ± 14</td>
<td>343 ± 108</td>
<td>Remifentanil TCI</td>
<td>20</td>
</tr>
<tr>
<td>Puri et al.30, Haddad et al.26</td>
<td>PID Neural network</td>
<td>Urology, general, orthopedic, no cardiac surgery</td>
<td>Closed-loop</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>41 ± 16</td>
<td>97 [41–298]</td>
<td>Remifentanil TCI ± TEA</td>
<td>20</td>
</tr>
<tr>
<td>De Smet et al.18</td>
<td>Bayesian-based</td>
<td>Gynecologic/sedation</td>
<td>Closed-loop</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>32 ± 5</td>
<td>17 ± 3</td>
<td>Fentanyl</td>
<td>20</td>
</tr>
<tr>
<td>Agarwal et al.91</td>
<td>PID</td>
<td>Cardiac</td>
<td>Closed-loop</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>41 ± 16</td>
<td>357 ± 103</td>
<td>Fentanyl bolus</td>
<td>19</td>
</tr>
<tr>
<td>Hegde et al.92</td>
<td>PID</td>
<td>Pheochromocytoma/ laparoscopy</td>
<td>Closed-loop</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>38 ± 15</td>
<td>75 [49–255]</td>
<td>Epidual and fentanyl</td>
<td>13</td>
</tr>
<tr>
<td>Méndez et al.203</td>
<td>PID and TCI</td>
<td>General, thoracic, urologic, orthopedic, thoracic, cardiac ...</td>
<td>Closed-loop</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>30–60</td>
<td>143 ± 57</td>
<td>Remifentanil bolus</td>
<td>15</td>
</tr>
<tr>
<td>Hemmetting et al.72</td>
<td>Rule-based</td>
<td>General, thoracic, urologic, orthopedic, thoracic, cardiac ...</td>
<td>Closed-loop</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>54 ± 20</td>
<td>140 ± 78</td>
<td>Remifentanil bolus</td>
<td>20</td>
</tr>
<tr>
<td>Liu et al.202</td>
<td>PID and TCI</td>
<td>General, gynecologic, urologic, orthopedic, thoracic, cardiac ...</td>
<td>Closed-loop</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>57 ± 15</td>
<td>140 ± 78</td>
<td>Remifentanil bolus</td>
<td>83</td>
</tr>
</tbody>
</table>

Closed-loop controllers in Bispectral Index–Propofol studies: data are presented as mean ± SD or median [interquartile range]. PID = proportional-integral-derivative; PI-DTP = proportional integral with death-time compensation; TCI = target-controlled infusion; TEA = thoracic epidural analgesia.
What anesthesiologists and/or intensivists want to know before they administer fluids is: “will my patient’s CO increase in response to intravascular volume expansion?” In other words, is the patient preload dependent? Instead of simply monitoring a given hemodynamic variable, functional hemodynamic monitoring addresses this question by assessing how the system responds to an induced change.

In mechanically ventilated patients under general anesthesia or moderate sedation, the effects of positive pressure ventilation on preload and stroke volume can be used to detect fluid responsiveness: if mechanical ventilation induces respiratory variations in stroke volume or in arterial pulse pressure variation (PPV), it is more likely that the patient is preload dependent and CO will increase if fluid is given. Figure 3 shows the Frank-Starling relationship with the associated arterial waveform tracings, and Figure 4 shows how PPV is calculated.

The functional hemodynamic variables have been developed and validated in clinical practice over the last 4 decades. Respiratory variations in the arterial pressure were found to be related to patients’ fluid status, and systolic pressure variation (SPV) is frequently >10 mm Hg higher in hypovolemic patients compared with normovolemic patients. In 1983, Coyle et al. described the Delta up and Delta down components of SPV in an abstract, but this work was never released as a full paper. In 1987, Perel et al. showed that SPV was related to the intravascular volume status in an animal model, that it was an early detector of hypovolemia, and that it reacted earlier than CVP. Several studies were then able to demonstrate that SPV was an accurate predictor of fluid responsiveness in adult patients undergoing surgery and in patients treated in the intensive care unit (ICU). More recently, PPV has been shown to be superior to SPV in mechanically ventilated patients with septic shock.

In the same time period, noninvasive assessment of fluid responsiveness based on the analysis of respiratory variations using the plethysmographic waveform was investigated. Respiratory variations in the plethysmographic waveform have been shown to be related to the patient’s fluid status, and there is a strong relationship between SPV and respiratory variations in the peak of the plethysmographic waveform before and after hemorrhage. In 2007, a study showed that the respiratory variations of the plethysmographic waveform amplitude were able to predict fluid responsiveness in mechanically ventilated patients. A multitude of other studies have been published demonstrating that the invasively and noninvasively assessed functional hemodynamic variables are useful for the prediction of fluid responsiveness in an operating room and an ICU setting, even after considering their potential limitations.

These dynamic variables have several limitations. First, patients are required to be sedated and their lungs

**Figure 3.** Frank-Starling relationship with corresponding respiratory variations in the arterial pressure waveform. High respiratory variation in the arterial pressure or in the plethysmographic waveforms indicates that the patient is on the steep portion of the Frank-Starling relationship. Low variation indicates that the patient is on the plateau. Cardiac output maximization concepts aim at increasing cardiac output until it reaches the plateau of the Frank-Starling relationship. This goal, as demonstrated on this figure, could be achieved by minimizing respiratory variation in arterial pressure or plethysmographic waveform.

**Figure 4.** Pulse pressure variation (PPV) and systolic pressure variation (SPV) calculation from the arterial pressure waveform. PP_max and PP_min = maximum and minimum arterial pulse pressure over a single respiratory cycle. PPV is then calculated as: (PP_max - PP_min)/((PP_max + PP_min)/2).

**Recent Advances in Perioperative Hemodynamic Monitoring and Fluid Management**

What anesthesiologists and/or intensivists want to know before they administer fluids is: “will my patient’s CO increase in response to intravascular volume expansion?” In other words, is the patient preload dependent? Instead of simply monitoring a given hemodynamic variable, functional hemodynamic monitoring addresses this question by assessing how the system responds to an induced change.

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These dynamic variables have several limitations. First, patients are required to be sedated and their lungs

**Video 1.** Demonstration of the evolution in arterial pressure variation and hemodynamic variables.
mechanically ventilated. Studies have thus far failed to demonstrate that these variables can predict fluid responsiveness in spontaneously breathing patients. Moreover, tidal volume affects the predictive value of the variables. A minimal tidal volume of 8 mL/kg of body weight is necessary. Patients must be in sinus rhythm, the chest and pericardium must be closed, and intraabdominal pressure should be within normal ranges. Apart from these cardiopulmonary limitations that are common to any dynamic variable of fluid responsiveness, variables derived from the plethysmographic waveform have additional limitations. The plethysmographic waveform analysis is limited by vasomotor tone, which strongly affects the waveform. Thus, this technique may only be used during profound general anesthesia and it seems less stable in the ICU setting.

One advantage of the functional variables of fluid responsiveness is that they can be derived from a noninvasive arterial pressure waveform or from the plethysmographic waveform (Video 1, see Supplemental Digital Content 1, http://links.lww.com/AA/A325). Recently, several new methods have been developed to automatically and continuously calculate these indices. These continuous measures make optimization strategies that incorporate them feasible, and studies suggest that this approach has the ability to improve postoperative outcomes.

### From Goal-Directed Fluid Therapy to Closed-Loop Hemodynamic Management

Closed-loop fluid management is in its infancy. Previously, urine output and mean systemic filling pressures were both used as feedback variables for automated fluid administration systems, but beyond the initial study, these systems were not further reported on. More recently, in 2008, Kramer et al. published a series of articles evaluating different aspects of closed-loop resuscitation using arterial blood pressure, CO, or skeletal muscle oxygenation as the feedback variable. Using a PID algorithm, they were able to show more stable urine output rates than were achieved with manual hourly adjustments.

Despite the modest successes of these studies, closed-loop fluid resuscitation has been hampered by the limited quality of measures such as urine output and arterial blood pressure in predicting fluid responsiveness (Table 3). The proliferation of noninvasive CO monitors, along with the development and validation of the dynamic predictors of fluid responsiveness, however, has made closed-loop fluid management truly practical. Because invasive monitors are no longer necessary, CO monitoring can be performed continuously across a broad range of patients. The evidence supporting goal-directed fluid management is strong enough that its routine use should be adopted in moderate- to high-risk patients during both surgery and in the ICU.

The dynamic predictors of fluid responsiveness have made it possible to predict in advance of a bolus whether the volume is likely to improve CO (i.e., whether a patient is preload dependent). Moreover, they also indicate the degree of preload dependence present in a given patient, providing further invaluable information about intravascular volume status. Thus, despite the limitations in the clinical use of these measures (for example, the requirement for mechanical ventilation), they are nevertheless essential measures for automated systems to use in guiding fluid therapy and could be used in up to 40% of all patients undergoing anesthesia. The possible advantage of automated fluid administration is even more pronounced in ICU settings where physician and nursing attention is often spread over the entire unit; a system capable of intelligently and continuously maintaining an optimal CO could have a profound impact on outcomes. Simulation data comparing a novel model- and rule-based closed-loop fluid management system with anesthesiologist management was recently presented showing a higher and steadier CO in the closed-loop group.

As a first step toward clinical application of closed-loop systems, decision support systems may be developed and

### Table 3. Advantages and Limitations of Potential Inputs for a Closed-Loop Fluid Management System

<table>
<thead>
<tr>
<th>Input</th>
<th>Advantages</th>
<th>Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine output</td>
<td>Easy to monitor</td>
<td>Late detector of hypovolemia, relation between</td>
</tr>
<tr>
<td></td>
<td></td>
<td>urine output and volemia is not specific,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>invasive</td>
</tr>
<tr>
<td>Heart rate</td>
<td>Easy to monitor</td>
<td>Nonspecific</td>
</tr>
<tr>
<td>Central venous pressure and</td>
<td>Several positive outcome studies, minimally</td>
<td>Invasive, nonspecific, difficult to monitor</td>
</tr>
<tr>
<td>wedge pressure</td>
<td>invasive and noninvasive monitoring</td>
<td>accurately, poor predictor of fluid</td>
</tr>
<tr>
<td></td>
<td>equipment now available</td>
<td>responsiveness</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>Best predictors of fluid responsiveness,</td>
<td>Low invasive monitoring techniques have their</td>
</tr>
<tr>
<td></td>
<td>outcome studies, can be monitored from a</td>
<td>own intrinsic limitations, no single absolute</td>
</tr>
<tr>
<td></td>
<td>single arterial pressure waveform, easy to</td>
<td>cardiac output target, some monitoring</td>
</tr>
<tr>
<td></td>
<td>monitor</td>
<td>technologies are highly invasive</td>
</tr>
<tr>
<td>PPV/SVV</td>
<td>Same as for PPV/SV, very sensitive to</td>
<td>Requires mechanical ventilation, tidal volume</td>
</tr>
<tr>
<td></td>
<td></td>
<td>at least 6 mL/kg, no arrhythmia, closed chest</td>
</tr>
<tr>
<td>Respiratory variations in the</td>
<td>Good predictor of fluid responsiveness,</td>
<td></td>
</tr>
<tr>
<td>plethysmographic waveform</td>
<td>outcome study, easy to monitor, noninvasive</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Same as for PPV/SV, very sensitive to</td>
</tr>
<tr>
<td></td>
<td></td>
<td>vasomotor tone, which can induce an unstable</td>
</tr>
<tr>
<td></td>
<td></td>
<td>signal over time</td>
</tr>
</tbody>
</table>

PPV = pulse pressure variation; SVV = stroke volume variation.
implemented. Although decision support algorithms also standardize care and make outcome-based analysis more practical, widespread adoption of these protocols is challenging. Clinical protocols require time and often significant effort with frequent interventions from caregivers; thus, the time spent in applying protocols will most likely be the main barrier to implementation. Closed-loop systems can provide a bridge to the acceptance of clinical protocols by performing the many required tasks of the protocol in a less demanding manner.

Despite the potential utility, there are myriad challenges facing the clinical application of closed-loop fluid management. The first and most obvious consideration with all automated systems is safety. Closed loops must be “fail safe”; if they malfunction or receive bad data, they must behave in a way that does not harm the patient. In the case of fluid administration, this means not overloading (or severely underresuscitating) the patient. Similarly, these systems must be tolerant of the artifact and error in clinical monitors and again must be capable of filtering this noise without jeopardizing patient care.1-7 Food and Drug Administration approval and clinician acceptance may also prove difficult.

An important point is that these systems are not meant to run in the absence of a supervising clinician, although the general public and indeed many physicians may believe that these devices will “take over.” It cannot be overstated that this is not the case. Closed-loop systems are meant to be supervised by experts while helping to implement clinical protocols and standardize patient care. In addition, they may help bring the level of safety provided by anesthesiologists to an outside location where no physicians are available, but they will still require oversight by a trained specialist in these settings to be operated safely.

There are challenges with monitoring devices themselves, principally with the fidelity of monitors in measuring the target variable and the ability of the closed-loop controller to account for the uncertainty involved in all monitoring devices. Additionally, there will be tremendous interpatient variability in a given set of monitored values because of disease states, cardiac and pulmonary status, and even baseline physiology. Similarly, a physiologic model may not be applicable to or consider all possible circumstances a controller might encounter. For this reason, a robust and specific measure of the effect is necessary to allow for interpatient or intrapatient variability along with extensive testing in simulation and supervised clinical trials.

Infusion pumps used to administer fluids will have to be precise and will need several layers of fail-safes for use with a closed-loop system should the system malfunction or become disconnected from the pumps. The closed loop itself needs to be intelligent enough to detect situations in which it cannot handle fluid and hemodynamic management on its own. Of course, the supervisor will always have the ability to “open the loop” and take over for the algorithm, providing an important additional layer of protection.

Another challenge may be the complexity of hemodynamic physiology. Unlike insulin systems that target glucose level, or anesthetic closed loops that target BIS, hemodynamic management does not lend itself to management using only a single feedback variable. An ideal closed-loop system for fluid management will use both CO and the dynamic predictors of fluid responsiveness to tailor fluid therapy, along with heart rate and arterial blood pressure at the very minimum. These challenges will, in all probability, require a sophisticated controller algorithm to manage safely.

**CONCLUSION**

Anesthesiologists are often compared to airline pilots: induction, maintenance, and emergence from anesthetics have many parallels with the takeoff, cruising, and landing of aircraft. In aviation, automatic pilots, although unquestionably very sophisticated, are nothing more than closed-loop systems that use data garnered from myriad sensors throughout the aircraft to control engine power and flight controls to provide a safe, stable flight to the destination. Likewise, closed-loop controllers can act as copilots in clinical settings, providing safe and stable control of one or more aspects of care under the supervision of a clinician.

With the development and refinement of the dynamic predictors of fluid responsiveness, fluid management can now be included with hypnosis, ventilation, and a host of other applications for which closed-loop control is feasible. In time, these individual systems will likely be combined into comprehensive controllers capable of fully integrated anesthesia management, with depth of anesthesia, ventilation, temperature, fluid management, and more, all controlled by a single overarching system. This arrangement will allow for cooperation and coordinated action among the various individual components.

We postulate that the future of anesthesia will rely on two separate but interdependent technologies: the sensors and monitors on one side, and the controllers on the other. A great deal of work remains to be done, for example: controller design, clinical application, and outcomes-based research. Nevertheless, if we can build automated systems to reliably keep 350,000-pound aircraft in the air for hours at a time, there should be little doubt we can design automated systems to safely and reliably manage complicated aspects of medical care.

**APPENDIX: VIDEO LEGEND**

**Video 1.** Demonstration of the evolution in arterial pressure variation and hemodynamic variables before and after intravascular volume expansion in an illustrative patient.

**DISCLOSURES**

**Name:** Joseph Rinehart, MD.

**Conflict of Interest:** Dr. Rinehart is coowner and coinventor of US patent serial no. 61/432,081 for intelligent, patient-adaptive, and case-based learning closed-loop fluid administration system based on the dynamic predictors of fluid responsiveness.

**Attestation:** Dr. Rinehart participated in manuscript drafting and final approval of the manuscript.

**Name:** Ngai Liu, MD, PhD.
Conflict of Interest: Dr. Liu is a patent holder in France for the gain constants and control algorithm for a closed-loop anesthesia management system (no. BFF08P669, Institut National de la Propriété Industrielle, France).

Attestation: Dr. Liu participated in manuscript drafting and final approval of the manuscript.

Name: Brenton Alexander, MS.

Conflicts of Interest: Dr. Alexander has no conflicts of interest to declare.

Attestation: Dr. Alexander participated in manuscript drafting and final approval of the manuscript.

Name: Maxime Cannesson, MD, PhD.

Conflict of Interest: Dr. Cannesson is a consultant for Fresenius Kabi, Edwards Lifesciences, Masimo Corp., Coviden, ConMed, BMEye, CNSystem, and Philips Medical Systems. Dr. Cannesson is coowner and coinnventor of US patent serial no. 61/432,081 for intelligent, patient-adaptive, and case-based learning closed-loop fluid administration system based on the dynamic predictors of fluid responsiveness. Dr. Cannesson is inventor and coowner of US patent appl. no. 13/095,827 for assessing fluid responsiveness using the EKG waveform analysis.

Attestation: Dr. Cannesson participated in manuscript drafting and final approval of the manuscript.

This manuscript was handled by: Dwayne R. Westenskow, PhD.

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