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Applied physiology at the bedside to drive resuscitation algorithms

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Abstract

Hemodynamic instability is associated with significant morbidity and mortality. Goal-directed therapeutic algorithms have been used in various clinical settings to reverse or prevent organ damage and death that could occur with a low oxygen delivery state. Most current resuscitative algorithms use static physiologic measures to determine if a patient will respond to proven therapies. While static parameters are useful in identifying the potential for clinical instability, they cannot tell us how patients will respond to an intervention. Applied physiology, through the use of functional hemodynamic monitoring can predict the body's reaction to therapy because they are based on cardiovascular dynamics. A growing body of evidence supports the use of applied physiologic principles in goal directed therapeutic algorithms for appropriate and effective resuscitation/optimization. Over time, applied physiology should be incorporated into standardized protocol-driven care to improve outcomes in patients experiencing, or at risk for hemodynamic instability.

Introduction

Patients who are at risk for clinical decompensation should be identified as early as possible to prevent subsequent morbidity and mortality. Many of the available tools and parameters that could be used to identify and manage instability do not take the dynamic nature of disease into account. The use of applied physiologic techniques allows clinicians to perform an intervention in an unstable patient and follow the changes in bedside hemodynamics.

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This is possible by identifying each of the components of cardiovascular function that may be contributing to clinical instability, including volume responsiveness, vasomotor tone and contractility. The practice of applied physiology also requires a framework to maximize clinical utility; goal-directed therapeutic algorithms can provide such a framework. In this review, our objectives are the following: (1) to demonstrate that static physiologic indices are good diagnostic tools to identify occult organ hypoperfusion and hemodynamic compromise, but they have limited utility in subsequent management; (2) to summarize existing applied physiologic techniques, the principles behind their utility, and discuss advantages and disadvantages of each; (3) to show that goal-directed therapeutic algorithms for addressing imminent or existing hemodynamic compromise can be a useful tool in the management of the critically ill; and (4) to demonstrate that the integration of applied physiologic techniques into goal-directed therapy can improve the implementation of those algorithms, and together they can improve outcomes in those experiencing, and at risk for clinical instability. Although this discussion can be applied to any condition that causes imminent or existing hemodynamic instability like sepsis or trauma, we will focus on perioperative care.

Static variables are needed to diagnosis instability early, but have limited roles in subsequent management: the $v\text{-}a\text{pCO}_2$ gap and other surrogates of tissue hypoperfusion

Timely identification of clinical instability is always the first step in correcting the pathophysiology that leads to tissue hypoperfusion and end-organ damage. Many studies have shown that early diagnosis of cardiovascular instability leads to early interventions and better outcomes.¹⁻⁴ A number of variables are already in use in the operating room (OR) and intensive care unit (ICU) setting that function as surrogates for end organ perfusion and measures of oxygen delivery. Lactate, base deficit, cardiac output (CO), stroke volume (SV), mixed venous (SvO_2) and central venous oxygen saturation (ScvO_2), are all examples of established static variables that can reliably diagnose impending cardiovascular stress. These variables are quite familiar to anesthesiology practice. However, what may not be familiar to bedside clinicians is the use of the veno-arterial pCO_2 gap ($v\text{-}a\text{pCO}_2$ gap). This parameter is used to summarize the balance between global tissue metabolic supply and demand.

The $v\text{-}a\text{pCO}_2$ gap is unlike most other static variables used to diagnose hemodynamic compromise; instead of assessing global cardiovascular function, the $v\text{-}a\text{pCO}_2$ gap reflects the balance between global tissue flow and metabolic activity.^{5,6} CO_2 is an end product of both aerobic and anaerobic metabolism. As tissue perfusion decreases, metabolism remains constant so tissue CO_2 levels increase, causing venous pCO_2 to increase.⁷ Anaerobic metabolism generates less CO_2 than aerobic metabolism, so in the setting of reduced tissue blood flow and impaired mitochondrial function pCO_2 measured within a particular tissue bed may not increase. Therefore, in the setting of severe organ failure, venous CO_2 levels may be low even in low flow states. The difference between the arterial pCO_2 and the central venous (or mixed venous) pCO_2 can be a surrogate marker for impaired tissue blood flow and correlates very well with cardiac index.⁸ Moreover, a persistently large $v\text{-}a\text{pCO}_2$ gap is predictive of mortality.⁹

Static variable measurements are useful for timely identification of impending hemodynamic compromise, but they have a very limited role in the reversal of cardiovascular instability. For instance, the $v\text{-}a\text{pCO}_2$ gap can identify tissue hypoperfusion even after global markers of oxygen extraction such as ScvO_2 have been corrected because CO_2 is more diffusible than O_2 ; CO_2 can follow tissue metabolism better in heterogeneous flow states. However, isolated measures of tissue hypoperfusion cannot inform clinicians about the appropriate therapy to administer. Other static parameters such as central venous pressure (CVP) or pulmonary artery occlusion pressure (P_{pao}) are mistakenly used in the OR and ICU settings to determine if patients will respond to a fluid bolus in the setting of hypoperfusion. However, isolated CVP and P_{pao} measurements cannot be used to identify patients who are fluid responsive.^{10–12} Moreover, CVP is not a measure of preload (a volume) but the back pressure to it. CVP is also affected by other factors, including intrathoracic pressure.¹³ Single static measurements cannot be used to assess dynamic processes such as fluid responsiveness. Static parameter measures are sometimes repeated during management to judge the adequacy of resuscitation; lactate clearance is one example cited in the literature.^{14,15} Management decisions for hemodynamic optimization should be made based on the body's response to a physiologic challenge prior to therapeutic intervention. Fortunately, there are many techniques that can be applied to assess dynamic changes important in the management of impending hemodynamic compromise.

Functional hemodynamic monitoring: Applied physiology at the bedside

The goal in cardiovascular monitoring is not just to identify a problematic process, but to predict how patients would respond to a therapeutic action. The best way to predict how the body will adapt to an intervention is not from an instantaneous view of hemodynamics, as is the case with static measures, but to see how the body changes when the system is disturbed. Functional hemodynamic monitoring involves repeated measurement of cardiovascular variables in response to a defined and quantifiable physiological perturbation. A summary of existing applied physiologic techniques is found in table 1. The physiologic disturbance can be induced, as is the case with a fluid challenge, passive leg raising maneuver or vascular occlusion test. The disturbance could also be related to the interactions between heart and lung physiology; examples of these techniques include positive pressure ventilation-induced changes in arterial pulse pressure and left-ventricular (LV) stroke volume, and respiratory variation in superior vena cava or inferior vena cava diameter. These techniques can identify the intervention(s) necessary to reverse clinical decompensation when the following are used: (1) a dynamic output parameter measurement that can quantify the physiologic effects of the intervention (column 2 in table 1); and (2) a means to display and quantify those output measures, such as echocardiography or a hemodynamic monitoring device (column 3 in table 1). We will discuss each of the available applied physiologic tests in detail in the next few sections.

The fluid challenge

The traditional approach to assess volume responsiveness is to infuse a small fluid bolus rapidly and see if the cardiovascular response is positive. The main goal in the fluid

challenge is to see if blood flow improves with volume loading. If this occurs in an unstable patient then one must resuscitate with fluids.

There is no standard approach to administer a fluid bolus, therefore the following details must be considered that may affect the outcome of this test: (1) the nature of the fluid; (2) the rate of infusion; (3) the volume of infusion; (4) the prespecified targets for output measures that would suggest volume responsiveness, and (5) potential for harm with further bolus infusion. Although the use of albumin provides no added advantage over crystalloids during resuscitation^{15–17}, it may be an important consideration when one decides on the rate of fluid infusion. To assess fluid responsiveness, crystalloids should be infused as quickly as possible. However, some animal studies suggest that maximum volume loading occurs with colloids when they are infused at a slower rate.¹⁸ This may be due to the simultaneous transient increases in systemic arterial pressure, decrease in precapillary resistance, and hemodilution, all of which cause increased capillary hydrostatic pressure and therefore capillary leak. These effects are not as prominent from crystalloid infusion probably because of the already low oncotic pressure and high propensity toward capillary leak. Further study in patients is needed to confirm these observations.

The amount of fluid used to identify volume responsiveness is another point to consider. While there is no consensus on how much to give, crystalloids are often given in increments of 500–1000 mL of crystalloid.¹⁹ However, this must be adjusted depending on whether patients have met certain prespecified targets for output parameters, and whether additional volume may cause harm. If a patient is volume responsive, one would expect mean arterial pressure (MAP), CO or SvO₂ to increase, or lactate or HR to decrease.

Once a parameter(s) is selected to determine whether a patient is volume responsive, one must define what that means with respect to the parameter(s) chosen. For instance, once a volume load is given, many studies have defined volume responsiveness as a percent increase in CO of more than 12–15%.²⁰ Once the CO no longer increases by this amount, one can cease the volume load. If ScvO₂ is the parameter chosen, one might define volume responsiveness as an increase in SvO₂/ScvO₂ up to an absolute value of 60–70%.²¹ These “stop” parameters can interrupt volume loading trials when there is potential for volume overload and patient harm.

There are disadvantages in using fluid challenges to identify volume responsiveness. First, only half of all hemodynamically unstable patients will be responders.²² To administer the fluid challenge would delay appropriate therapy in half of all patients who receive them. Furthermore, it may also be detrimental if fluid infusion promotes right heart failure or edema formation. For these reasons it would be preferable to have a simple and rapid way of assessing volume responsiveness without giving a fluid challenge. The remainder of our discussion on fluid responsiveness and applied physiology will focus on techniques that do not require volume loading.

Passive leg raise maneuver

Passive leg raising (PLR) is a maneuver that causes stored venous blood in the lower extremities to be transferred into the central compartment. If the subject is volume

responsive then CO will increase, otherwise it will not. The maneuver is illustrated in figure 1: the trial starts with the subject supine (approach “A”), at which time baseline CO, SV, or an alternate measure of systemic blood flow is taken. The legs are passively raised to 30° above the chest and held there for 1 minute. This approximates a 300 ml fluid bolus in a 70 kg man. The increased preload lasts for about 2 to 3 minutes, during which time repeated flow measurements are taken. After 3 minutes, blood volume is redistributed back to the venous circuit. An easier alternative involves elevating the head 30–45°, then rotating the bed so that the head is supine and the legs are elevated (approach “B”, figure 1). This approach has the advantage of not altering intra-abdominal pressure or causing patient discomfort. Regardless of the preferred method, PLR is relatively easy to perform, it is reversible and therefore imposes no harm from excess fluids, and it can be repeated as many times as necessary to determine the appropriate time to cease volume resuscitation.²³

Many of the same methods used to detect an appropriate response to a fluid bolus can be used with PLR (table 1). SV/CO calculated from arterial waveform analysis, or esophageal/trans thoracic Doppler can identify volume responsiveness after PLR.^{24–29} Monge et al.³⁰ found that if CO derived from esophageal Doppler changed >12% after PLR, it had sensitivity of 95% and specificity of 94% to predict fluid responsiveness in a multidisciplinary ICU patient population with acute circulatory failure. Other PLR studies have demonstrated a range of sensitivities (77–97%) and specificities (83–100%) to predict equally varied definitions of volume responsiveness related to increases in SV, mainly in medical ICU patients.^{25–29} Maizel et al.³¹ showed that among a mixed MICU population PLR-induced changes in CO measured by esophageal Doppler can predict volume responsiveness well (AUC 0.95), but has very different sensitivities and specificities depending on the cutoff value chosen. A change of >5% had a sensitivity and specificity of 94% and 83%, respectively, but they become 63% and 89% if the cutoff >12% change. This may not be surprising since they used a bolus of 500 mL to determine volume responsiveness, a much smaller volume than is released into systemic circulation from PLR, assuming a weight of 70 kg.

PLR is a very useful applied physiologic technique when employed in the appropriate context. It can be implemented reliably regardless of whether the patient is breathing spontaneously or on full mechanical ventilatory support. However, if intra-abdominal hypertension co-exists, then the CO response to PLR may be misleading because the shift of fluid may be limited even if the subject would respond to fluid.³²

Increases in CO or SV are the most commonly used output measures to determine volume responsiveness with PLR; one must be mindful of the conditions in which SV/CO may be inaccurate. In recent years, inpatient clinical practice has shifted towards minimally invasive means of determining blood flow measures like SV and CO. Pulse contour analysis of the arterial waveform are often used to achieve continuous measurements of flow. However, changes in vasomotor tone will render any calculations of SV by pulse contour analysis inaccurate.^{33–35} The Pulse index Continuous Cardiac Output, or PiCCO (Pulsion Medical Systems; Germany), and Flotrac/Vigileo (Edwards Lifesciences; Irvine, CA) are two monitoring systems that infer stroke volume from the pulse contour. The PiCCO integrates the systolic portion of the arterial waveform and divides that by aortic compliance.³⁶ The

Flotrac/Vigileo monitor measures pulsatility of the arterial waveform by calculating the standard deviation of the pressure over 20 seconds, then multiplies it by a constant meant to characterize arterial impedance based on patient demographic data. The PiCCO is a more reliable device in cases of vasoplegia or changes in vasomotor tone because it is a calibrated system, it can be recalibrated when these changes occur. One study showed that the PiCCO device is reliable during hemorrhage with administration of vasopressors only when it is frequently recalibrated.³³ The same is true in severe aortic valvular disease; aortic stenosis and insufficiency both alter the contour of the pressure waveform, confounding pulse contour analysis. Only a direct measurement of SV/CO through a dilutional technique would be accurate in this setting.³⁷ By contrast, the PulseCO algorithm used by the Lithium dilution cardiac output, or LiDCO device (LiDCO, Ltd; Cambridge, UK) calculates stroke volume from a power analysis of the pulsatile change in the arterial waveform. In theory, this makes the LiDCO less sensitive to changes in the arterial wave shape induced by fluctuations in vasomotor tone because a power analysis of the wave is minimally affected by changes in the pulse contour.^{38,39} Though one study has demonstrated that beat-to-beat cardiac output in patients after cardiac surgery are reliably measured up to 8 hours without recalibration,³⁹ further clinical studies are needed to confirm these claims.

Arterial pressure variation: an assessment of heart-lung interaction

Ventilated patients experience normal variations in CO during the respiratory cycle that can be exaggerated under hypovolemic conditions. Arterial pressure variation from respiration predicts volume responsiveness, making it an applied physiologic tool that can be used in functional hemodynamic monitoring. During positive pressure inspiration there is an increase in intrathoracic pressure which causes CVP to increase, and the pressure gradient for venous return decreases. This causes a decrease in venous return to the right heart that diminishes right-sided preload and SV. The lower blood volume ejected from the right heart takes about three or four heartbeats to reach the left heart, resulting in a decrease in left sided SV. The arterial pressure waveform will constantly fluctuate in amplitude reflecting the positive pressure-induced variations in systolic blood pressure, pulse pressure (PP) and SV, as shown in figure 2. The degree to which systolic blood pressure, PP and SV vary will depend on the tidal volume, chest wall compliance and biventricular preload responsiveness.⁴⁰ Increasing tidal volume will increase respiratory variation of the arterial waveform.^{41,42} When the tidal volume is kept constant, the extent to which systolic pressure⁴³, PP⁴⁴⁻⁴⁶, and left ventricular SV⁴⁷⁻⁵⁰ change will reflect volume responsiveness. Marik et al.⁵¹ performed a systematic review of both medical and surgical patients and found that pulse pressure variation (PPV) >13%, or stroke volume variation (SVV) >12% identified preload responsiveness with an area under the receiver operator characteristic (AUC), sensitivity, and specificity of 0.94, 89%, 88%, and 0.84, 82% and 86%, respectively. SPV had an AUC of 0.85. (Most patients received tidal volumes of 8–10 mL/kg.)

In addition to identifying response to fluid administration, PPV and SVV taken as a ratio can identify the need for vasopressor therapy in the setting of hemodynamic compromise. Hadian et al.⁵² studied 15 post-cardiac patients and found that vasodilator therapy increased PPV and SVV, but decreased PPV/SVV ratio. By contrast, administration of norepinephrine did not change PPV or SVV, but it increased the PPV/SVV ratio. A decrease in central

arterial compliance causes a decrease in PPV/SVV ratio. Furthermore, Monge et al.⁵³ showed that critically ill patients who were both volume responsive (defined as a PPV > 15% or SVV > 10%) and hypotensive had a PPV/SVV ratio of at least 0.9. When these patients were given a fluid challenge they remained hypotensive despite an increase in cardiac output. A low PPV/SVV ratio can therefore identify distributive shock caused by decreased vasomotor tone, even in a hypovolemic state.

Measurements of arterial pressure variation should not be interpreted under certain conditions. For instance, irregularly irregular rhythms such as atrial fibrillation will not produce the expected stroke volume since there is no atrial kick. Any measurements of variation in SV produced by heartbeats that were not triggered by the sinus node may be difficult to interpret, and therefore shouldn't be used to determine volume responsiveness.⁵⁴ Similarly, arterial pressure variation cannot determine how a patient will respond to fluid under open-chest conditions,⁵⁵ making it unusable during many types of cardiac and thoracic surgeries. In order to maintain consistently administered tidal volumes, patients should not be breathing spontaneously. In addition, forced expiration from abdominal muscle use can cause an artificial rise in arterial pressure during expiration, potentially causing larger PPV or SVV values independent of stroke volume. Patients should be on complete mechanical ventilation without ventilator dyssynchrony. PPV and SVV also should not be interpreted in the setting of increased intra-abdominal pressure. This can decrease chest wall compliance and allow for greater changes in pleural pressure for a given tidal volume, which will cause artificially elevated measurements.⁵⁶

In other scenarios, arterial pressure variation should be interpreted with caution. Smaller tidal volumes may diminish the SVV and PPV in volume responsive patients and produce a false negative result. De Backer et al.⁵⁷ found that PPV is only a reliable predictor of volume responsiveness when the tidal volume is at least 8 mL/kg. However, Huang et al.⁵⁸ showed that when these patients received tidal volumes less than 6 mL/kg and PEEP values of 12 or more, PPV could predict volume responsiveness among the ICU patient population, though with diminished accuracy (AUC 0.77; sensitivity 68%; specificity 100%).⁵⁸ There are potential explanations for the discrepancy in results between the study by Huang et al. and that of De Backer et al. The higher PEEP levels in the Huang study translate to lower preload and higher afterload during inspiration, exaggerating the respiratory variation in PPV than would have been measured at the lower PEEP levels seen in the De Backer study. Furthermore, De Backer et al. enrolled a heterogeneous population while Huang studied only severe ARDS patients (mean PaO₂/FiO₂ ratio of 140 mmHg and compliance of 26.2 mL/cm H₂O).⁵⁸ It could be that the low compliance seen in ARDS elevated the intrathoracic pressures which exaggerated the PPV in the Huang study. When patients are on low tidal volume ventilation, an alternative applied physiologic technique may need to be used.

It is important to know the method by which devices calculate stroke volume variation because this will also determine the accuracy of that measurement in a particular clinical scenario. In an earlier section, we discussed the effects that changes to vasomotor tone will have on beat-to-beat estimates of SV taken from pulse contour analysis. Changes in vasomotor tone will also affect the accuracy of SVV in an uncalibrated system. Therefore, frequent calibration of a system that allows for thermodilution- such as the PiCCO and

calibrated LiDCO devices- may provide more reliable estimates of SVV when clinicians suspect changes in vasomotor tone.^{35,59} Though newer versions of the FloTrac software (an uncalibrated system) may accurately measure SV, and therefore SVV in vasoplegic patients,⁶⁰ further studies are needed before its use can be advocated in this setting.

Noninvasive assessment of heart-lung interaction

The principles of arterial pressure waveform analysis can be extended to two noninvasive assessments of respiratory variation on arterial pressure: (1) Finger plethysmography, a nonintrusive means of reproducing arterial waveforms; and (2) pleth variability from a pulse oximetry waveform. Finger plethysmography obtains continuous arterial waveform data through volume clamping of the finger; pressure from a finger cuff is applied such that blood volume flowing through the digital arteries is held constant at all times. Once a scaling function is applied (usually against the brachial artery from a sphygmomanometer) the noninvasive arterial pressures correspond to those in the brachial artery and can be converted into a waveform. Noninvasive measurement of the arterial waveform is reasonably accurate when compared to intra-arterial catheter-derived waveforms,^{61–63} and can predict fluid responsiveness using respiratory variation.⁶³ Respiratory-induced changes in the pulse oximetry pleth waveform is also a reliable means for predicting patient response to volume.^{64–66} One meta-analysis among adults in the ICU and OR showed that both pleth variability index and variation in the plethysmograph waveform amplitude were good at differentiating volume responders from nonresponders (pooled AUC 0.85).⁶⁷ The best cutoffs ranged from 9.5 to 15%, depending on the study. By contrast, a meta-analysis of pediatric patients showed that pleth variability was not a good measure of fluid responsiveness.⁶⁸ The reasons for this are likely due to differences in physiology than in the ineffectiveness of the parameters. Children have more compliant arteries than adults; since pulse pressure is inversely dependent on arterial compliance, these more compliant vessels will be less affected by respiratory variation in stroke volume. In addition, immature ventricles are less compliant, minimizing the end diastolic volume in children. This also could decrease the expected PPV and SVV in children and negate their effectiveness.

If used in the right patient population, noninvasive waveform variation analyses can be applied outside of acute care areas, where the placement of an arterial catheter is either cumbersome (emergency department or labor and delivery suite) or impractical (medical/surgical ward or step down unit). However, finger plethysmograph-derived arterial pressure variation and pulse oximetry plethysmograph variation require further study before more widespread use, particularly in the setting of non-distributive shock with compensatory peripheral arterial vasoconstriction. In addition, noninvasive measures of respiratory variation may suffer from many of the same issues that their invasive counterparts face, including limited interpretation in the setting of dysrhythmias and low tidal volume ventilation.

Respiratory variation of echocardiographic parameters

Ventilatory-dependent changes can be visualized using echocardiography, just as arterial pressure exhibits changes with inspiration and expiration. We will discuss three different

techniques to assess respiratory variation: changes to aortic blood flow, ventricular area, and vena cava collapsibility indices.

Aortic blood flow and peak velocity. Just as stroke volume exhibits changes with inspiration, so does blood flow in the descending aorta. Through the use of esophageal Doppler, aortic blood flow can determine volume responsiveness with reasonable accuracy. Monnet et al.⁶⁹ studied a cohort of mechanically ventilated MICU patients and found that the change in aortic blood flow during respiration was a good predictor of volume responsiveness. (AUC of 0.93). A change in aortic blood flow of 18% or more predicted response to fluid infusion with a sensitivity of 90% and a specificity of 94%. Furthermore, as volume responders were given fluid, the change in aortic blood flow during respiration decreased.

The peak velocity can be derived from the time integral of aortic flow. Studies have been done to assess its ability to predict volume responsiveness in adults, but the data is inconclusive. Feissel et al.⁷⁰ showed that respiratory variation in peak aortic flow velocity of 12% or more was able to accurately identify volume responsiveness- the latter defined as an increase in cardiac index of 15% or more after bolus of 8 mL/kg of synthetic colloid- with a sensitivity of 100% and specificity of 89%. Cardiac index-induced changes with volume expansion were closely correlated to respiratory variation in peak aortic flow velocity. Guinot et al. were unable to replicate these findings in a mixed surgical population.⁷¹ It is possible that the correlation found by Feissel et al. was caused by a mathematical commonality between aortic velocity and cardiac output; they are both derived from esophageal Doppler and require a velocity time integral for calculation. Monnet et al.⁶⁹ showed that respiratory variation in peak velocity can identify fluid responsiveness, but it was not as good as respiratory variation in aortic blood flow (AUC of 0.82 and 0.93, respectively).

Respiratory variation in aortic blood flow and peak velocity can identify volume responsiveness in pediatric patients. One study on mechanically ventilated pediatric patients showed that respiratory changes in peak velocity outperformed SVV in identifying those who were volume responsive, with an AUC of 0.95.⁷² These findings were confirmed in two other studies on a similar patient population.^{73,74}

Left ventricular stroke area. During inspiration in mechanically ventilated patients the positive intrathoracic pressure causes a decrease venous return and ultimately a decrease in left ventricular preload and area, which increases again after spontaneous expiration. Cannesson et al.⁷⁵ used automated border detection to calculate real-time left ventricular changes in stroke area on a beat-to-beat basis. Using esophageal echocardiography they visualized the heart in a short axis view; during diastole the area of the left ventricular chamber was manually traced to identify the endocardial border of the left ventricle. Subsequently, the left ventricular area was displayed automatically on a beat-to-beat basis. With this technique, Cannesson et al. showed that respiratory variation of left ventricular stroke area was higher in a cohort of volume responsive mechanically ventilated patients undergoing coronary artery bypass grafting, compared with non-responders. That variation

decreased with volume expansion. A cutoff of 16% change in stroke area predicted fluid responsiveness with a sensitivity of 92% and a specificity of 83%.

Vena cava collapsibility indices. Inspiration during spontaneous breathing increases venous return by making intrathoracic pressure more negative, causing inferior vena cava (IVC) and superior vena cava (SVC) collapse. The vessels then re-expand with spontaneous unforced expiration. The respiratory effects on the IVC during mechanical ventilated patients are opposite; the IVC will dilate with inspiration because the positive intrathoracic pressure serves as a back-pressure to venous return in the extrathoracic IVC. The ratio between inspiratory and expiratory diameters provides an estimate of the variation during the respiratory cycle.

Superior or inferior vena cava variation with respiration is a good noninvasive determinant of volume responsiveness. Juhl-Olsen et al.⁷⁶ found that spontaneously breathing patient volunteers who were subjected to slow hemorrhage from blood donation had a statistically significant increase in IVC collapsibility index from 10.3 to 24.8%. They found no association between this and the expected hemodynamic response, as measured by CO from transthoracic echocardiography. Feissel et al.⁷⁷ assessed performance of IVC respiratory variation in a cohort of mechanically ventilated MICU patients; they found that an IVC distensibility index of 12% not only identified volume responders (defined as an increase in CO >15% with 8 mL/kg of colloid) with a positive predictive value and negative predictive value both >92%, but it also correlated highly with CO. Machare-Delgado et al.³⁴ demonstrated that a >12% respiratory variation in IVC was able to identify volume responsiveness (defined as a >10% increase in stroke volume index, the stroke volume divided by body surface area) with a sensitivity of 100% and specificity of 53%. (The investigators did not use airway pressure to gauge the appropriate measurement times for expiration and inspiration, potentially accounting for the low specificity.) About half of these patients were on mechanical ventilation with ARDS with a mean tidal volume of 8.1 mL/kg, showing that the technique can be applied to patients with pulmonary pathology. Another study in a similar patient population showed a sensitivity and specificity of 90% when the IVC distensibility index cutoff was 18%.⁷⁸ Vieillard-Baron et al.⁷⁹ showed that an SVC collapsibility index of 36% was able to accurately identify volume responders (sensitivity of 90%; specificity of 100%) amongst a population of MICU patients in septic shock. The authors note that the clinicians in their ICU routinely use transesophageal echocardiography (TEE) and therefore these results may not be completely generalizable to other ICU settings.

There are advantages and disadvantages of using respiratory variations in SVC or IVC diameter to measure volume responsiveness. SVC collapse can only be measured with TEE; it is therefore reserved for patients on mechanical ventilation in the OR or ICU setting. IVC variation can be assessed in both mechanically ventilated and spontaneously breathing patients. However, SVC variation directly mirrors the antagonistic relationship between central blood volume and intrathoracic pressure, a driving force behind heart-lung interaction. As such, SVC variation is considered superior to IVC variation for assessing fluid responsiveness.⁸⁰

There are some additional disadvantages to using echocardiography, whether it is used to detect respiratory changes, or as a means of assessing output changes to a physiologic perturbation like PLR or fluid challenge. The placement of an esophageal echocardiographic probe is contraindicated in patients with esophageal injury or surgery. Moreover, the standard esophageal probe is quite large and is not designed to be retained in the esophagus for prolonged periods of time. Smaller probes are currently on the market for this use, providing the opportunity for frequent reassessment of hemodynamic changes.⁸¹ In situations where prolonged TEE probe placement is not practical, transthoracic echocardiographic approaches to measure many of the same parameters is equally as effective at predicting volume responsiveness.²⁰ Lastly, echocardiography is operator dependent; special training is needed to be able to reliably, and accurately acquire the data necessary to apply transthoracic or esophageal echocardiography.

Vascular occlusion test

The applied physiologic techniques mentioned thus far are used to target adequate global oxygen delivery. However, depending on the integrity of local autoregulatory mechanisms, attaining adequate global perfusion does not necessarily equate to better regional or tissue perfusion.⁸² Microcirculatory dysfunction is more prevalent among nonsurvivors than survivors of septic shock.⁸³ Tissue oxygen saturation (StO_2) is an indicator of microcirculatory oxygen saturation in the organ of interest, measured by near-infrared spectroscopy. It is a validated method of assessing microcirculatory status, especially in septic and trauma patients.⁸⁴

StO_2 can be coupled with a vascular occlusion test (VOT), a technique that uses dynamic physiology to identify local tissue metabolic rate. VOT-induced StO_2 changes in the thenar eminence of the hand may identify occult hypoperfusion despite adequate CO, and therefore could help guide resuscitation. To perform a vascular occlusion test, a sphygmomanometer cuff is inflated on the arm to 30 mmHg above systolic pressure for 3 minutes or until the StO_2 decreases to 40%.⁸⁵ Figure 3 highlights the expected changes in StO_2 throughout the maneuver: the decline in StO_2 (DeO_2) reflects local metabolic rate and mitochondrial function. The recovery of StO_2 after cuff deflation (ReO_2) is a surrogate for local cardiovascular reserve and microcirculatory flow.⁸⁴ StO_2 changes seen with vascular occlusion can identify patients who will respond to a volume challenge. Futier et al.⁸⁶ conducted a prospective study in which they gave 42 fluid challenges to patients undergoing major abdominal surgery with signs of hypovolemia, defined by elevated pulse pressure variation or stroke volume variation. All StO_2 measurements were taken after anesthesia induction. Hypovolemia developed intraoperatively and patients were given a 500 mL bolus of synthetic colloid. Patients were separated into those who appeared fluid responsive- defined as an increase in SV > 15% after colloid infusion- and fluid nonresponsive. They found a statistically significant reduction in the StO_2 recovery slope (ReO_2) with hypovolemia relative to baseline (5.1%/sec vs. 3.57%/sec; $p < 0.01$). More importantly, there was a statistically significant difference in the ReO_2 before volume expansion between fluid responders and nonresponders. When patients are loaded with volume, the ReO_2 improved without a change in systemic hemodynamics.⁸⁶ This is not surprising since cardiovascular reserve is lost with hypovolemia, and recovers after fluid replacement. It

should be noted that StO_2 levels prior to vascular occlusion were similar before and after volume loading, and between fluid responders and non-responders. The vascular occlusion test provides dynamic parameters like ReO_2 that can identify volume responsiveness when static StO_2 fail to do so.

The StO_2 desaturation and recovery slopes can predict patient outcome. DeO_2 and ReO_2 are both associated with commonly-used hemodynamic and metabolic parameters,^{87–88} and can discriminate between survivors and nonsurvivors in the ICU.^{89–91} ReO_2 is associated with subsequent organ failure and mortality.⁹² Furthermore, the ReO_2 improves outcome prediction of the simplified acute physiology score II (SAPS II) and sequential organ failure assessment (SOFA) score.⁹³ VOT-induced change in StO_2 provides information about organ function independent of global hemodynamic parameters and common laboratory measures of organ integrity like serum creatinine.

StO_2 changes during a vascular occlusion test can be reliably measured when patients are under the effects of general anesthesia, and can be used to identify volume responsiveness during surgery. Patients under general anesthesia may have changes to their desaturation and recovery curves compared to their baseline values without sedation. Bernet et al.⁹⁴ studied 15 cardiac surgery patients before and after general anesthesia and found a statistically significant decrease in the desaturation slope and in the recovery slope. The former change reflects the decrease in overall metabolic rate induced by anesthesia; the latter demonstrates that anesthesia decreases local cardiovascular reserve by microcirculatory vasodilation, limiting the effects of further reperfusion-induced vasodilation. Despite these changes, Futier et al.⁸⁶ showed that clinicians can still identify volume responsiveness in patients under anesthesia.

Other clinical scenarios could make it difficult to interpret StO_2 changes induced by a vascular occlusion test. Muscle relaxants markedly diminish local metabolic rates, making any StO_2 measurements at the thenar eminence uninterpretable.⁹⁵ The same may be true of hypothermic patients, but this requires further study. Darker skin, thick or edematous connective tissue, and low hemoglobin levels can make StO_2 measurements inaccurate.⁹⁵ Further study is needed in these patient populations to assess the reliability and accuracy of StO_2 measurements, and whether dynamic changes caused by vascular occlusion testing can be used in these scenarios to determine volume responsiveness and guide hemodynamic management.

Though vascular occlusion targeted to a pre-specified StO_2 threshold used by Gomez et al.⁸⁵ yields more reproducible effects compared to other methods,⁷⁶ there is no accepted standard. Also, there are no studies to date that assess the use of a cutoff value for the recovery slope to identify volume responsiveness. These issues must be addressed before this promising technique can be applied in routine clinical practice.

Goal-directed therapeutic algorithms are useful, but need to be improved

The primary goal of resuscitation or hemodynamic optimization is to restore or maintain adequate oxygen delivery. Goal-directed therapy seeks to do so by individualizing treatment according to a patient's needs at any given time. The concept of using hemodynamic

monitoring to guide goal-directed therapy has been successfully applied for quite some time.¹ Existing studies apply some combination of therapeutic targets for preload (inferred from CVP or pulmonary artery occlusion pressure), CO, or oxygen delivery. A number of meta-analyses have shown that these algorithms improved outcomes in various surgical populations, but mainly among those with the highest disease burden or risk of mortality. Brienza et al.⁹⁷ reviewed perioperative goal-directed therapies in high-risk patients undergoing cardiac and non-cardiac surgery, and showed a reduction in post-operative renal injury (OR = 0.64). (High-risk surgical patients were defined by ASA status, age and comorbid disease burden.) In another meta-analysis of thirty-two clinical trials with a total of 5056 patients, a statistically significant decrease in mortality with perioperative goal-directed therapy was only found in patients with a baseline mortality >20% (OR 0.32).⁹⁸ Aya et al.⁹⁹ reviewed only those studies that assessed the benefits of perioperative hemodynamic optimization in the cardiac surgery population. They found five studies with a combined total of 699 patients that used fluids, inotropes, blood, and nitrates to reach goal targets for a number of static hemodynamic parameters, including lactate, cardiac index and central venous oxygen saturation (ScvO₂). Goal-directed therapy decreased both postoperative complications (OR 0.33) and hospital length of stay (mean difference -2.44), but there was no decrease in mortality. (Only three of the five studies reported mortality, which could explain the lack of an observed mortality benefit.) There were several mythological flaws in this meta-analysis: it only included five randomized controlled trials, definitions of therapeutic goals varied across studies, and complication outcomes of interest were variably reported. Finally, funnel plot analysis showed that there might be publication bias, though attempts were made by the investigators to retrieve all relevant unpublished data.⁹⁹

Cardiovascular optimization before the surgical insult is an effective means of minimizing tissue hypoperfusion and organ injury. This form of goal-directed therapy is referred to as pre-optimization. Preoptimization goal-directed strategies generally target resuscitation to some threshold of oxygen delivery. These O₂ delivery levels are supra-physiologic for resting metabolic requirements and require good cardiovascular reserve to achieve these targets. Thus, many patients in these studies required supplemental inotropic drug infusions. Wilson et al.¹⁰¹ studied the effects of preoptimization of high-risk patients undergoing elective vascular, urologic, or general surgery by randomization to either dopexamine (an inotrope and vasodilator) or epinephrine, or aggressive preoperative care. The intervention arms targeted oxygen delivery >600 mL/min/m². The investigators demonstrated a 14% absolute reduction in mortality in those who received either intervention. The protocol required the placement of a pulmonary artery catheter to measure CO, so patients were admitted to the ICU after surgery. Since only a small number of the patients were routinely admitted preoperatively for these surgeries this approach could increase the healthcare cost. However, a cost-effectiveness analysis showed that when surgical preoptimization was compared to non-protocolized perioperative care, mean total costs decreased by more than €5000 (\$7,000).¹⁰¹ The additional cost of preoperative inpatient stay and aggressive care in the intervention groups were offset by much longer postoperative stays and higher associated use of therapies-fluid infusions and drugs- in the usual care group.

Goal-directed therapeutic options, whether preoperative (preoptimization), intraoperative, or postoperative can be implemented collectively to improve outcome. Boyd et al.¹⁰² studied 107 high-risk surgical patients admitted to the ICU preoperatively to reach certain target treatment goals such as a MAP between 80–110 mmHg, and a pulmonary artery occlusion pressure of 12–14 mmHg. Patients were randomized to two arms: a protocol arm where they received a dopexamine infusion with an additional preoperative oxygen delivery target of $>600\text{ mL/min/m}^2$, or a control arm without supranormal oxygen delivery goals. In the intervention group, dopexamine infusion was continued postoperatively and adjusted to target a lactate level $<1.5\text{ mmol/L}$, and the same oxygen delivery goal. The investigators found statistically significant reductions in mortality (22.2% to 5.7%) and the mean number of postoperative complications (1.35 to 0.68).¹⁰² More recently, Pearse et al.¹⁰³ evaluated whether a perioperative hemodynamic algorithm targeting cardiac output could improve postoperative outcomes. Over 700 high-risk patients aged 50 and older undergoing major gastrointestinal surgery were randomized to either usual care or a cardiac output-guided goal-directed protocol in which fluids and/or dopexamine infusion was given during, and six hours following surgery. The composite primary outcome of 30-day postoperative mortality and surgical complications was decreased by 6.8% in the intervention group (36.6% vs. 43.4%). However, this did not reach statistical significance ($p=0.07$), probably because the study was powered to a higher effect size. Pearse et al included their trial in their own meta-analysis. They confirmed an improvement in complication rates with perioperative goal-directed therapy, though there was no improvement in mortality.¹⁰³

Patients receive the most benefit from goal-directed therapy when the intervention uses some combination of fluid, inotrope, or vasopressor therapy to address potential causes of low oxygen delivery. Existing studies on goal-directed therapy have used targets of certain static parameters, such as CVP and pulmonary artery occlusion pressure, to assess volume status, cardiac output and ScvO_2 or SvO_2 to identify need for inotropes, and still other parameters such as MAP and systemic vascular resistance to identify those who may be vasopressor responsive.^{104–106}

While some studies show that goal-directed therapeutic strategies can be effective using static variables, a few studies demonstrate no benefit,^{107–109} including a recent large multicenter randomized controlled trial.¹¹⁰ The ProCESS investigators¹¹⁰ randomized emergency department patients with severe sepsis or septic shock to: (1) early goal-directed therapy as defined by Rivers et al.¹ with protocols that used target CVP, MAP, and ScvO_2 values to guide therapy; (2) protocol-based “standard” ED care which gave fluids and vasopressors only based on noninvasive vital signs measurements; or (3) usual care. No benefits were seen with the use of early goal-directed therapy or protocol-based standard care over usual care (21.0%, 18.2%, and 18.9%, respectively).¹¹⁰ “Negative” studies may highlight the inadequacies of static indices to identify dynamic processes like volume responsiveness, indicating the need to improve goal-directed algorithms and their ability to effectively individualize the care of the critically ill.

Improving goal-directed therapeutic outcomes with applied physiologic techniques

Using applied physiology to determine volume responsiveness would be an important addition to goal-directed algorithms. Lopes et al.¹¹¹ showed that a pulse pressure variation-driven fluid management algorithm decreased the number of postoperative complications, duration of mechanical ventilation, ICU length of stay and hospital length of stay among high-risk surgical patients, compared to usual care. Salzwedel et al.¹¹² studied the use of PPV in a more comprehensive goal-directed approach that included vasopressor and inotropic therapy guided by MAP and cardiac index, respectively. This multicenter study of 160 elective surgery patients demonstrated a decrease in postoperative infections using goal-directed therapy, compared with usual practice.

Few studies in the literature incorporate systolic pressure variation and its derivatives into goal-directed algorithms. Buettner et al.¹¹³ studied eighty patients undergoing elective major surgery and randomized them to either an SPV-guided intraoperative fluid management strategy (the intervention group) or a control group. Those in the intervention group were given volume if the SPV was >10%. They noted a statistically significant increase over time in SPV and one of its derivatives in the control group, suggesting a hypovolemic state. In theory, since patients in the control group had evidence of hypovolemia by SPV despite usual care, and this parameter was corrected in the intervention group, one would expect to see better organ perfusion in the intervention group. However, there was no difference in organ perfusion parameters between the control and intervention groups, even though intervention patients received more fluid on average than their control counterparts. Patients in this study were relatively healthy- indicated by normal ScvO₂, v-a pCO₂ gap and lactate levels- so there may not have been any reversible organ ischemia to begin with. Further studies will need to be done on SPV-driven fluid management, and in the context of other goal-directed therapeutic parameters like SV or CVP to determine its impact on patient outcome.

There are a number of studies on stroke volume variation (SVV)-directed fluid resuscitation under different conditions.^{114–117} Schereen et al.¹¹⁴ conducted a pilot multicenter study in high-risk surgical patients that compared an intraoperative fluid optimization protocol driven by SVV and SV to usual care. The intervention group experienced fewer postoperative infections. The authors showed a trend toward decreased organ dysfunction in the treatment group, but the study was underpowered to address this outcome. Ramsingh et al.¹¹⁵ studied an intraoperative SVV-driven fluid management protocol in low- and moderate-risk patients undergoing high-risk abdominal surgery. They demonstrated a decrease in bowel recovery time and hospital length of stay with the intervention group compared to usual care. Benes et al.¹¹⁶ incorporated pressure measures of preload (CVP), and CO to get a more comprehensive picture of hemodynamics since many factors can confound SVV independent of volume responsiveness. In their study, the goal-directed therapy group demonstrated more intraoperative hemodynamic stability, lower postoperative lactate levels (used as a surrogate for global oxygen delivery), and a consequently lower incidence of organ dysfunction compared with controls. Perhaps the most compelling study of SVV

comes from Mayer et al.¹¹⁷ They compared a goal-directed protocol of SVV in a flow-targeted algorithm (the intervention group) to a protocol that used static measures of preload targeted to MAP and urine output (the control group). Not only did they demonstrate a decrease in length of hospital stay with the protocol incorporating SVV, but the intervention group also experienced less perioperative complications. There was no statistically significant difference in ICU length of stay or mortality, but the study was not powered for this outcome.

Some authors have proposed recommendations on the use of applied physiology at the bedside to drive resuscitation and hemodynamic optimization. McGee et al.¹¹⁸ demonstrated that functional hemodynamic monitoring can be used in many settings for patients at risk of decline. The first step is to determine if a patient is volume responsive (i.e. SVV >10% or PPV >13%). If he/she is not, then stroke volume index can be used to determine the need for a vasopressor (for decreased vasomotor tone), inotropic support (in a low output state), or a diuretic (for volume overload or acute lung injury).

A more robust algorithm can be constructed using a functional hemodynamic monitoring protocol designed by Pinsky.¹¹⁹ By incorporating indicators of preload-responsiveness, vasomotor tone, and (indirectly) contractility we will integrate many of the applied physiologic techniques that were discussed earlier (see figure 4): The first step is to identify if a patient is hemodynamically stable, defined by normotension, a normal serum lactate level, and no signs of new end organ injury. If so, and the patient is under preoperative care they may benefit from a preoptimization strategy prior to surgery. Patients would benefit most if they are high surgical risks because of significant comorbidity such as severe chronic obstructive pulmonary disease, or if they are going to have high-risk surgery such as cardiac bypass. If patients are unstable or scheduled for high-risk surgery that would benefit from preoptimization, then they are grouped with the unstable population and treated accordingly. Clinicians treating patients in low acuity settings, such as a medical/surgical ward, or areas in which quick assessment is necessary, such as in the Emergency Department or Labor and Delivery suite, then less invasive monitoring should be used initially to assess stability and guide resuscitation. Patients in high acuity areas wherein the potential for rapid deterioration is more likely, like the OR and ICU, may benefit from more invasive monitoring because of the greater degree of signal stability related to invasive monitoring techniques.

Similar to the McGee algorithm, one must first ask if the patient is preload responsive. Depending on the clinical setting and patient situation, a number of applied physiologic techniques are available (figure 4). For instance, if a patient on a medical or surgical ward has no intra-abdominal hypertension, the treating clinician can perform a passive leg raise, in conjunction with a transthoracic echocardiogram or a noninvasive finger cuff monitoring system to assess changes in CO. If the patient has frequent dysrhythmias, then the echocardiogram would be preferable because it allows direct assessment of inferior vena cava collapse during ventilation. Alternatively, one can use pleth variability or a vascular occlusion test. If the patient is in the OR or ICU then any of the aforementioned techniques can be used, but there are other options. If the patient has no dysrhythmias and is on mechanical ventilation, one can use arterial pressure variation measures such as SVV, PPV, and SPV to determine preload responsiveness. If the patient is on low tidal volume

ventilation (<6 mL/kg) then SPV, PPV and SVV are still excellent predictors of volume responsiveness, but their negative predictive value is degraded. If sepsis is suspected, then a calibrated pulse contour system such as PiCCO or the LiDCO device should be used to measure CO and SVV because uncalibrated devices may have larger degrees of measurement error. Alternatively, any of the echocardiographic techniques can be used to identify the degree of respiratory variation in flow, ventricular area, IVC or SVC diameter.

The measures of preload responsiveness can also be used to assess vasomotor tone through the dynamic central arterial elastance (Ea'), the ratio of PPV/SVV. Normal Ea' values range from 2.0 to 1.2. If Ea' is <0.9 then vasomotor tone is markedly reduced. If patients also have hypotension causing decreased organ perfusion then a vasopressor may be indicated independent of the need for fluid resuscitation. An $Ea' > 2.0$ reflects increased vasomotor tone and in an otherwise stable patient suggests occult cardiovascular compromise, although this specific construct has not been prospectively validated. If either PPV or SVV are unavailable, and applied physiology identified volume nonresponsiveness in a hypotensive patient, then vasopressor therapy is indicated to sustain vital organ perfusion pressures. Finally, if the patient is not volume responsive, vasomotor tone is adequate, and the patient is still hemodynamically unstable or showing signs of end organ injury, then the etiology is loss of cardiovascular reserve. This can be due to heart failure, obstructive etiologies (i.e. pulmonary embolism or tamponade) or pulmonary hypertension. Initially, one can add an inotrope to increase cardiac contractility, however these patients need further evaluation and presently that requires echocardiography to ascertain the anatomical etiology of the decreased cardiac reserve.

At the conclusion of the algorithm, it is important to reassess changes in patient status. After implementation of an intervention (green boxes in figure 4) one must determine if it had an effect. Patient's clinical status may also have decompensated in spite of the management path chosen. Also, changes may have been made in patient care independent of these interventions that might affect subsequent management. For instance, if a patient's anesthesia dose is increased, then the subsequent decrease in stressed volume will cause patients to become preload responsive even if they were not before. Clinicians should repeat the algorithm frequently since there are many factors that could influence patient status and response to therapy.

There are two major differences in the approach by McGee et al.¹¹⁸ and the modified functional hemodynamic monitoring algorithm we have just described. First, the latter allows one to choose the best applied physiologic technique to use depending on the specific patient type, and clinical scenario. For instance, it would be inappropriate to use SVV to determine preload responsiveness in a patient with atrial fibrillation or undergoing open cardiac surgery. If the patient is hypothermic or receiving paralytic agents and StO_2 changes caused by the VOT are altered, then a different maneuver or technique should be chosen. The McGee et al. algorithm does not allow for much flexibility since the only applied physiologic measurement used is SVV. Second, the functional hemodynamic monitoring algorithm takes the clinical setting into account, providing a determination of the feasibility of a given applied physiologic technique. It would be impractical to use transesophageal echocardiography to assess and reassess respiratory variations in aortic flow in a non-

intubated spontaneously breathing patient, but TEE would be feasible and often preferable in the OR and occasionally in the ICU.

Goal-directed therapy need not only be performed with applied physiologic techniques; one can incorporate static parameters. Repeated measures of oxygen extraction such as $ScvO_2$, complimented by measures of tissue blood flow such as veno-arterial pCO_2 gap can refine treatment by identifying when resuscitation measures have reversed tissue hypoperfusion. Vallee et al.¹²⁰ found that a large $v-a pCO_2$ gap correlated with lower lactate clearance and cardiac index during fluid administration in a cohort of septic shock patients. A targeted $v-a pCO_2$ gap of <6 mmHg could be used in conjunction with lactate clearance and changes in $ScvO_2$ to refine inotrope titration and the choice between blood products or crystalloids during resuscitation.¹²⁰ Thus, algorithms guided by applied physiologic principles can be refined with repeated measures of static parameters to address the adequacy of tissue blood flow and metabolic need.

Challenges

Before applied physiologic techniques can be incorporated into existing goal-directed therapeutic interventions, certain challenges exist. Many functional hemodynamic monitoring techniques may seem cumbersome to perform. For example, echocardiographic measures of IVC or SVC variation cannot be measured continuously. Minimally invasive monitoring to acquire CO, SV, SVV, or PPV measures often requires insertion of an arterial catheter and periodic recalibrations. Echocardiography is especially problematic because quality images depend on the operator and patient anatomy. Often multiple cardiac views are needed to confirm specific cardiac abnormalities, depending on image quality. Aortic flow measures require proper alignment of the Doppler sensor to the aortic valve. Similarly, the vascular occlusion test takes minutes to perform, particularly if one uses a predefined StO_2 value, and not an absolute elapsed time to stop the occlusion (figure 3). Furthermore, these functional measures need to be periodically reassessed after every intervention or change in patient status. Clinicians may find certain techniques burdensome. However, we submit that use of these techniques are necessary to prevent patients from receiving therapies inappropriately that may lead to patient harm, such as excess fluid resuscitation. There are a number of applied physiologic techniques available, and clinicians can use those that are appropriate to the demands of their practice. Finally, there are a large number of applied physiologic techniques that determine preload responsiveness, but few assess vasomotor tone and the need for inotropic support. In many cases, these can be inferred if a goal-directed therapeutic algorithm is followed (figure 4). However, clinicians would benefit from direct assessment of inotropic need through applied physiologic principles. Wall motion assessment through echocardiography is one available option, but new methods should be developed and validated to increase the robustness of available dynamic monitoring.

There are likely a set of patients that will maximally benefit from goal-directed therapy because of their intrinsic instability or the nature of the surgical stress. Clearly, patient selection will play an important role in defining the effectiveness of these interventions. Resuscitative algorithms will only improve outcomes if the resuscitation targets prevent or

minimize tissue ischemia to improve outcomes. Much of the literature on hemodynamic preoptimization focuses on moderate-to-high risk surgical patients undergoing equally risky surgery. Subjecting low-risk patients to inotropes that will drive their oxygen delivery to supranormal levels may cause harm, and could impose unnecessary cost to the healthcare system. Moreover, supranormal oxygen delivery is harmful in medical conditions such as sepsis,^{3,4,121} where high metabolic rate and cardiac oxygen consumption could make unnecessary inotropic support problematic. Careful patient selection will be necessary for researchers to design better studies, and for clinicians to treat patients more effectively.

Data output from a goal-directed approach may occasionally differ from the clinical picture. The challenge for the clinician is to identify when and why data is erroneous and what the correct monitoring management action should be under those circumstances. A goal-directed algorithm is only as good as its component parts, and the therapeutic targets that guide management are not without their limitations and errors. Moreover, patients may show signs of hemodynamic improvement though certain artificial targets, such as reaching a SVV < 13%, were not reached. If a patient undergoing resuscitation recovers signs of adequate tissue perfusion and there is no evidence of tissue ischemia then further resuscitation may not be indicated. In these situations, rigid protocol application should not replace sound clinical judgment. Personalizing care based on functional hemodynamic monitoring guidelines rather than strict adherence to a defined protocol presently seems the most reasonable approach to support. This may be difficult to craft into a prospective clinical trial, but not impossible.

Conclusions

Goal-directed therapeutic algorithms seek to deal with hemodynamic derangements in a comprehensive and systematic way, and have demonstrated decreased morbidity and mortality in high-risk surgery and high-risk patients based on defined targets for physiologic variables and parameters. Most algorithms currently applied in clinical practice use static metrics to determine appropriate therapy. They do not provide clinicians with the answer to the real management question about how a patient will respond to a certain therapy. Applied physiology creates functional hemodynamic monitoring parameters that provide measures of those dynamics and gives real-time bedside assessment, allowing personalized therapeutic guidance. Applied physiologic techniques can be incorporated into goal-directed algorithms through the use of functional hemodynamic monitoring and may improve the performance of this approach to manage existing, or imminent critically illness. Present literature demonstrates that this is feasible and necessary as a change to the practice of goal-directed therapy based on static parameters. Resuscitative algorithms driven by applied physiologic techniques can simultaneously standardize and individualize patient care, and improve the outcomes of those with, and those at risk for instability.

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Figure 1.

The passive-leg raising (PLR) maneuver to predict preload responsiveness. There are two acceptable approaches to PLR. The first (top half of figure) begins with the patient supine, at which time baseline measurements of systemic blood flow (CO, SV, etc.). The legs are elevated 30° above the chest and held there for 1 minute. The patient is placed once again in the supine position and systemic blood flow measurements are again taken within 2–3 minutes of completion of the maneuver. An alternative approach (bottom half of figure) starts with the head of the patient's bed elevated to 30–45°. Baseline flow is documented, then the bed is rotated until the head is supine and legs are elevated above chest. The patient is again placed in the starting position and flow measurements are retaken. Abbreviations: cardiac output, CO; stroke volume, SV.

Figure 2.

Respiratory variation in pulse pressure, stroke volume, and systolic pressure. Top graph: Pulse pressure variation (PPV) is calculated by finding the difference in the maximum (PP_{max}) and minimum (PP_{min}) pulse pressures over a respiratory cycle and dividing that by the average of those values. Stroke volume variation (SVV) is calculated in a similar way, but estimates of stroke volume are commonly made by computing the area under the systolic portion of the arterial waveform (pulse contour analysis). Bottom graph: Systolic pressure variation (SPV) is also calculated similar to PPV, but other derivative variables may be used as well. The Δ_{Up} assesses the difference between maximum systolic blood pressure (SBP) and the mean SBP for a given respiratory cycle. The Δ_{Down} quantifies the difference between mean SBP and minimum SBP over one respiratory cycle. The data output for PPV, SVV and SPV that comes from commercially available monitors is usually an average of more than one respiratory cycle. Abbreviations: maximum pulse pressure over 3–5 respiratory cycles, PP_{max}; the minimum pulse pressure over the same series of respiratory cycles, PP_{min}; the maximum stroke volume over 3–5 respiratory cycles, SV_{max}; the minimum stroke volume over 3–5 respiratory cycles, SV_{min}; systolic pressure variation, SPV.

Figure 3.

Tissue oxygen saturation in response to a vascular occlusion test. Tissue oxygen saturation (StO_2) is measured on the thenar eminence of the hand using near-infrared spectroscopy. Baseline values are determined, and a proximal sphygmomanometer cuff on the ipsilateral arm (forearm) is inflated to >30 mmHg above systolic blood pressure, causing distal ischemia resulting in StO_2 to decrease. The sphygmomanometer remains inflated until either a pre-specified amount of time has elapsed (e.g. 3 minutes), or when the $StO_2 < 30\%$. The sphygmomanometer is then deflated, and the downstream reperfusion causes StO_2 to rapidly increase. Because the tissues experience maximal microcirculatory vasodilation during the ischemic period (desaturation), the tissue oxygen saturation may go above its baseline for a period of time before returning back to baseline, i.e. the hyperemic response. Once the changes in StO_2 are plotted on a graph, the slopes of the desaturation and recovery portions of the curve (DeO_2 and ReO_2 , respectively) can be used to make inferences about local metabolic rate, local cardiovascular reserve and microcirculatory flow.

Figure 4.

An applied physiology-based goal-directed therapeutic algorithm to treat/prevent hemodynamic instability. The brown boxes highlight the three critical questions that must be asked every time the algorithm is applied to guide therapy (the green boxes): First, one must ask if the patient is stable. If so, and he/she is not a high risk surgical candidate, then there is no need to proceed (the red box). If the patient will benefit from preoptimization goal-directed therapy, or is unstable (i.e. hypotensive or has signs of hypoperfusion) then one must identify the setting to determine the appropriate applied physiologic technique to use that will answer the next critical question of volume responsiveness. If the patient is in a setting where invasive monitoring isn't practical, then one has a limited number of applied physiologic techniques to choose from to identify any benefit with fluid therapy (middle of figure, left of orange dashed line). If the patient is in a place where invasive monitoring is practical and may be beneficial, then there are many options for functional hemodynamic monitoring (middle of figure, right of orange dashed line). Once patients are identified as volume responsive (bottom half of diagram, left of dashed blue line) or not (bottom half of diagram, right of dashed blue line) one must answer the last critical question regarding changes in vasomotor tone. If PPV or SVV were used to identify volume responsiveness and both were reliably measured, then one can use the ratio of PPV to SVV, to identify decreased dynamic central arterial elastance (Ea') and thus the need for vasopressors. If either PPV or SVV are not available or invalid, then one could give vasopressors in addition to volume (bottom of diagram, left of dashed blue line). If Ea' is normal in a volume nonresponsive patient who is either unstable or may benefit from surgical preoptimization, or Ea' cannot be interpreted in a hypotensive patient that is not responsive to volume, then inotropic support may be needed (bottom of diagram, right of dashed blue line). A high Ea' in an unstable patient who is not volume responsive suggests cardiovascular compromise, in which case inotropic support may be warranted (blue box with "?"). In order to get maximum benefit, this algorithm should be repeated after every therapeutic intervention,

when there is a change in patient management independent of these therapies, or if there are signs of changing clinical status.

Abbreviations: passive leg raise, PLR; inferior vena cava, IVC; pulse pressure variation, PPV; stroke volume variation, SVV; systolic pressure variation, SPV; superior vena cava, SVC; dynamic central arterial elastance, Ea'.

a-Normal blood pressure, normal lactate, and no signs of end-organ injury

b-Hi-risk preoperative surgical patients undergoing high-risk surgery

c-Settings with either limited monitoring capabilities (medical and surgical units) or limited time to do invasive monitoring (emergency department, labor and delivery suite)

d-Operating room or intensive care unit

e-Threshold should be adjusted if tidal volume <8 mL/kg or >10 mL/kg

f-This applies to spontaneously breathing patients. For those on mechanical ventilation, the appropriate IVC distensibility index cutoff may be 18%

g-Threshold value for vascular occlusion test currently unavailable

Table 1

Summary of existing applied physiologic techniques

Technique	Output measure	Methods of output detection	Physiologic assessment	Advantages	Disadvantages
Fluid bolus	•Increase in SV/CO	•Monitor output ^a	•Volume responsiveness	•Gold standard for identifying volume responders	•Caution with volume overload
	•High lactate clearance	•TTE/TEE (Doppler)			•No standard approach
	•Increase in SvO ₂				
	•Increase in blood pressure				
	•Decrease in HR				
PLR	•Increase in ABF				
	•Increase in SV/CO	•Monitor output ^a	•Volume responsiveness	•No added volume if patient is volume overloaded	•Caution with intra-abdominal hypertension
	•Increase in blood pressure	•TTE/TEE (Doppler)		•Spontaneous breathing or mechanical ventilation	
	•Decrease in HR				
	•Increase in ABF				
Arterial pressure variation ^b	•svv	•Direct visualization	•Volume responsiveness	•Immediately available data; no maneuvers	•Unreliable in spontaneously breathing patient, those with dysrhythmias or open chest
	•PPV	•Monitor output ^a	•Vasomotor tone ^c		•Caution when applied to those ventilated with low V _t
	•SPV				•Accuracy of each output measure depends on monitor ^d
Pleth variability	•PVI	•Direct visualization	•Volume responsiveness	•Immediately available data; no maneuvers	•Unclear utility with peripheral vasoconstriction
	• POP			•Noninvasive	•May not be effective in children
Respiratory changes in aortic blood flow	• ABF	•TEE/TTE (doppler)	•Volume responsiveness	•Can use in spontaneously breathing or mechanically ventilated pt ^e	•Operator dependent
	• PV		•Contractility		•Cumbersome to measure
Respiratory changes in LV stroke area	• LV stroke area	•TTE/TEE	•Volume responsiveness	•Can use in spontaneously breathing or mechanically ventilated pt ^e	•Operator dependent
			•Contractility		•Cumbersome to measure
Vena cava collapsibility with respiration	•SVC collapsibility index	•TEE/TTE ^f	•Volume responsiveness	•Can use in spontaneously breathing or	•Operator dependent

Technique	Output measure	Methods of output detection	Physiologic assessment	Advantages	Disadvantages
				mechanically ventilated pt ^e	
	•IVC collapsibility/distensibility index ^g		•Contractility		
VOT	•StO ₂ recovery slope (ReO ₂)	•Near infrared spectroscopy	•Volume responsiveness	•Provides info on microcirculatory metabolism and function •Predictability not affected by anesthesia ^h	•No standardized approach •No accepted cutoff of ReO ₂ •Cumbersome to measure •May not be generalizeable to all vascular beds •Cannot use with paralytic agents

SV=stroke volume; CO=cardiac output; SvO₂=mixed venous oxygen saturation; HR=heart rate; pt=patient; TTE=transthoracic echocardiography; TEE=transesophageal echocardiography; SVV=stroke volume variation; PPV=pulse pressure variation; SPV=systolic pressure variation; Vt=tidal volume; PVI=pleth variability index; POP=respiratory variation in the pulse oximetry plethysmographic waveform amplitude; CVP=central venous pressure; PAC=pulmonary artery catheter; ABF=respiratory variation in aortic blood flow; PV=respiratory variation in peak blood velocity; LV=left ventricle; SVC=superior vena cava; IVC=inferior vena cava; StO₂=oxygen saturation in peripheral muscle

^a Many commercially available devices provide numerical output for PPV, SVV, and SPV, which are more accurate than direct visualization of the arterial waveform

^b Derived from waveforms via intra-arterial catheterization, or noninvasive recreations of arterial pressure waves via finger plethysmography

^c Inferred by the relationship between PPV/SVV, a measure of dynamic central arterial elastance

^d See text for further details

^e Transthoracic echocardiography only. Transesophageal echocardiography performed preferably in mechanically ventilated patients

^f SVC collapsibility index can only be measured via transesophageal echocardiography; IVC indices can only be measured via transthoracic echocardiography

^g Termed the IVC collapsibility index when performed on spontaneously breathing patients, and IVC distensibility index in patients on mechanical ventilation

^h There is a change in the properties of curves with anesthesia, but the basic morphology of the StO₂ curve in response to a vascular occlusion test is unchanged and still can be used to successfully predict volume responsiveness