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REVIEW ARTICLE/BRIEF REVIEW

Inter-device differences in monitoring for goal-directed fluid therapy

Différences entre dispositifs de monitorage pour la réanimation liquidienne ciblée

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Abstract

Purpose *Goal-directed fluid therapy is an integral component of many Enhanced Recovery After Surgery (ERAS) protocols currently in use. The perioperative clinician is faced with a myriad of devices promising to deliver relevant physiologic data to better guide fluid therapy. The goal of this review is to provide concise information to enable the clinician to make an informed decision when choosing a device to guide goal-directed fluid therapy.*

Principal findings *The focus of many devices used for advanced hemodynamic monitoring is on providing measurements of cardiac output, while other, more recent, devices include estimates of fluid responsiveness based on dynamic indices that better predict an individual's response to a fluid bolus. Currently available technologies include the pulmonary artery catheter, esophageal Doppler, arterial waveform analysis, photoplethysmography, venous oxygen saturation, as well as bioimpedance and bioreactance. The underlying mechanistic principles for each device are presented as well as their performance in clinical trials relevant for goal-directed therapy in ERAS.*

Conclusions *The ERAS protocols typically involve a multipronged regimen to facilitate early recovery after surgery. Optimizing perioperative fluid therapy is a key component of these efforts. While no technology is without limitations, the majority of the currently available literature suggests esophageal Doppler and arterial waveform analysis to be the most desirable choices to guide fluid administration. Their performance is dependent, in part, on the interpretation of dynamic changes resulting from intrathoracic pressure fluctuations encountered during mechanical ventilation. Evolving practice patterns, such as low tidal volume ventilation as well as the necessity to guide fluid therapy in spontaneously breathing patients, will require further investigation.*

Résumé

Objectif *La réanimation liquidienne ciblée fait partie intégrale de nombreux protocoles de récupération rapide après une chirurgie (RRAC ou ERAS: Enhanced Recovery After Surgery) utilisés à l'heure actuelle. Le clinicien en périopératoire est confronté à une myriade de dispositifs promettant de fournir des données physiologiques pertinentes pour mieux guider la réanimation liquidienne. L'objectif de cet exposé de synthèse est de fournir une information concise permettant au clinicien de prendre une décision éclairée sur le choix d'un dispositif devant guider la réanimation liquidienne ciblée.*

Constatations principales *L'objectif de nombreux dispositifs utilisés pour le monitorage avancé de l'hémodynamie consiste à fournir des mesures de débit cardiaque tandis que d'autres, plus récents, incluent une estimation de la réponse liquidienne en fonction d'indices dynamiques qui prédisent mieux la réponse individuelle à un*

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bolus liquidien. Les technologies actuellement disponibles incluent le cathétérisme de l'artère pulmonaire, le Doppler œsophagien, l'analyse de la courbe artérielle, la photopléthysmographie, la saturation veineuse en oxygène, ainsi que la bioimpédance et la bioréactance. Les principes mécanistes sous-jacents de chaque dispositif sont présentés, ainsi que leurs performances au cours d'essais cliniques pertinents pour la réanimation liquidienne ciblée dans le cadre de la RRAC.

Conclusions *Les protocoles RRAC impliquent habituellement un schéma thérapeutique multiaxes pour faciliter la récupération rapide après chirurgie. L'optimisation périopératoire de la réanimation liquidienne est un élément clé de ces efforts. Bien qu'il n'y ait pas de technologies dénuées de limites, l'essentiel des publications actuellement disponibles suggère que le Doppler œsophagien et l'analyse des courbes artérielles sont les choix les plus souhaitables pour guider l'administration de liquides. Leur performance dépend, en partie, de l'interprétation des modifications dynamiques résultant de la fluctuation de la pression intrathoracique observée au cours de la ventilation mécanique. Les schémas évolutifs de pratique, tels que la ventilation à petit volume courant ainsi que la nécessité de guider la thérapie liquidienne chez des patients respirant spontanément, nécessiteront des études complémentaires.*

In the late 1990s, surgeons and anesthesiologists began a critical assessment of the individual components of the perioperative experience in an effort to reduce the time required to recover from surgery.[1] Working together, these physicians challenged the traditional practices of their respective specialties and began to develop comprehensive perioperative protocols based on best available evidence. The results of this undertaking are the Enhanced Recovery After Surgery (ERAS) protocols we know today (Table 1).[2-14]

All ERAS protocols typically share the following features:

1) The patient plays a prominent role in their own care and recovery.
2) Patients are no longer inappropriately fasted before surgery.
3) Multimodal analgesia is utilized in order to minimize intraoperative and postoperative systemic opioid use.
4) Ambulation is initiated on the day of surgery.

While independent examination of the relative value of these four components is difficult, it seems that intraoperative fluid administration has a substantial impact on perioperative outcomes.[15-17] Many, but not all, ERAS protocols utilize goal-directed therapy (GDT) to guide intraoperative fluid administration.

In two meta-analyses, an attempt was made to assess the utility of GDT and/or fluid optimization protocols for the management of patients in the perioperative period (although not specifically limited to ERAS protocols). Gurgel *et al*. examined 32 randomized controlled trials encompassing 5,056 patients and found a significant reduction in mortality (odds ratio [OR] 0.67; 95% confidence interval [CI]: 0.55 to 0.82; $P < 0.001$) in the

Table 1 Enhanced recovery after surgery case control studies

ENHANCED RECOVERY AFTER SURGERY CASE CONTROL STUDIES					
3,028 Subjects, weighted average 3.0-day reduction in LOS					
Year	Author	Patients	*n*	Outcome	Fluids
2000	Porter	Whipple	148	Reduced mean stay 2.9 days	N/A
2007	Kennedy	Whipple	*	Reduced mean stay 3.5 days	N/A
2008	Balzano	Whipple	504	Reduced median stay 2 days	N/A
2008	Reismann	Routine Pediatric Surgery	436	Reduced mean stay 5 days	N/A
2009	Kennedy	Whipple	135	Reduced median stay 6 days	N/A
2011	DiSebastiano	Whipple	145	Reduced mean stay 9 days	N/A
2007	Vanounou	Whipple	209	No difference	N/A
2013	Tang	Esophagectomy	108	Reduced median stay 4 days	"conservative"
2013	Blom	Esophagectomy	181	Reduced median stay 1 day	"restricted"
2013	Connor	Liver Resection	120	Reduced median stay 3 days	"minimized the use of intravenous fluids"
2013	Kalogera	Gynecologic Oncology	476	Reduced median stay 1 day	"decrease crystalloid… increase colloid"
2013	Daneshmand	Bladder Resection	220	Reduced median stay 4 days	N/A
2014	Khreiss	Rectal Cancer	346	Reduced mean stay 2 days	500 $mL \cdot hr^{-1}$

*Additional data published in 2009 by the same group, thus only the second, larger cohort was utilized in the analysis. LOS = length of stay

high-risk (expected mortality > 20%) group.[18] Hamilton *et al.* examined 29 randomized controlled trials encompassing 4,085 patients and found a significant reduction in mortality (OR 0.48; 95% CI: 0.33 to 0.78; $P < 0.001$) and surgical complications (OR 0.43; 95% CI: 0.34 to 0.53; $P < 0.001$) for all patients.[19]

The focus of this manuscript is on understanding both the function of the various devices (i.e., technological assessment) available to guide the anesthesiologist interested in the practice of GDT as well as the clinical evidence base to support various technologies (i.e., clinical data).

Devices

Pulmonary artery catheter

The pulmonary artery catheter (PAC), considered by many to be the clinical *gold standard* for the measurement of cardiac output, has been used in many GDT trials, though primarily in the management of critically ill patients.[18,19] The development of alternative less-invasive means of measuring cardiac output (e.g., esophageal Doppler), a shift of focus from cardiac output to volume status optimization, and a series of prospective randomized controlled trials that failed to show improvements in mortality when applied to critically ill patients,[20-22] have precluded the PAC from use in ERAS protocols. For these reasons, PACs are not further addressed in this review.

Esophageal Doppler

Technological assessment

The esophageal Doppler monitor (EDM) was developed in an effort to measure cardiac output without the requirement for a PAC.[23] The technology is based on the Doppler principle, which relates the velocity (v) of a moving object to the change in frequency that occurs when a sound wave is reflected off the object.[24] This can be described mathematically as:

$$v = \frac{\Delta f \times \mathrm{c}}{2\mathrm{f0} \times \cos\theta}$$

where Δf represents the frequency difference between the emitted and returned (ultra)sound signal, c represents the speed of sound in tissue, f_0 represents the frequency of the incident ultrasound beam, cos represents cosine, θ represents the angle of incidence, and v represents the velocity of a moving reflector. The accuracy of Doppler measurements is dependent on the angle of incidence (θ); accordingly, as θ increases, the Doppler-derived velocity of the object will be increasingly underestimated.

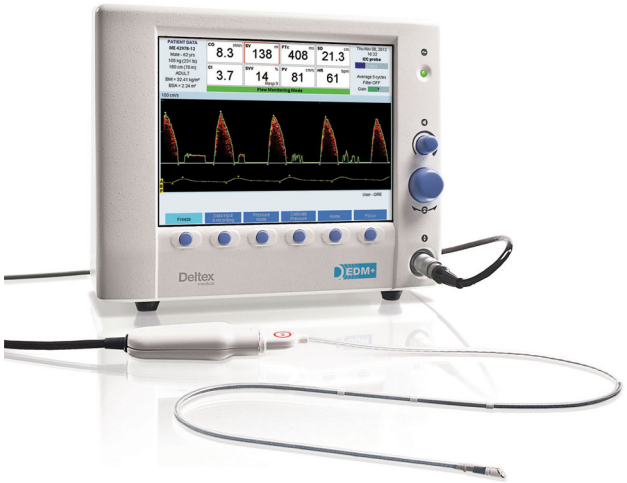

Fig. 1 Deltex CardioQ EDM. EDM = esophageal Doppler monitor

The only currently available clinical device, the CardioQ™ EDM (or ODM in the United Kingdom) is made by Deltex Corporation (Chichester, West Sussex, United Kingdom) (Fig. 1). The CardioQ requires insertion of a small esophageal probe via the nose or mouth to a depth of approximately 35-45 cm. The patient's age, height, and weight are entered into the device's software and the velocity of descending aortic blood flow is converted to an estimate of cardiac output using a nomogram-based estimate of the aortic cross-sectional area.[23] Additionally, measurements are recorded for corrected flow time (FT_c), i.e., the duration of systolic flow divided by the square root of the cardiac cycle time (330-360 msec is considered normal), and for stroke volume variation (SVV) as a surrogate for intravascular volume status.

To guide fluid therapy, the clinician can use FT_c (or SVV) to detect relative hypovolemia. If hypovolemia is suspected based on FT_c or SVV, a fluid challenge is given. If cardiac index or stroke volume increases (e.g., by 10%), the patient is deemed *fluid responsive* and a fluid bolus is re-administered. This process continues until the stroke volume or cardiac index no longer increases with fluid administration, or until FT_c or SVV has normalized (in which case, intravascular volume should be normal).[25]

The CardioQ has several potential sources of error and disadvantages. Measurement of descending aortic blood flow neglects flow to the brain and upper extremities and requires the use of a conversion factor. The area of the descending thoracic aorta is estimated based on the same normative data of height and weight – it is not measured specifically for the patient being monitored. The angle of incidence is also not precisely known. Additionally, the

device is not truly *continuous*, as its position within the esophagus can shift during anesthesia and surgery. Furthermore, it is susceptible to signal artifact during electrocautery and therefore requires periodic operator intervention to ensure a high-quality Doppler signal. Because it is uncomfortable for patients, esophageal Doppler is typically used only in anesthetized or sedated patients.

Despite these potential limitations, the data to support the accuracy of Doppler technology (not limited to esophageal Doppler) are quite strong. Overall, comparisons with invasive technologies (electromagnetic flowmeters[26-29] and transit-time flow probes)[30-32] in animal models and the Fick method in both animals[29,33] and humans[34-47] have been favourable.

Clinical data

Of all devices available to optimize fluid management in the context of ERAS protocols, esophageal Doppler is supported by the largest, most compelling body of evidence. The use of this device for *fluid optimization* has been studied in at least seven prospective randomized controlled trials encompassing 694 subjects undergoing diverse procedures, including orthopedic, abdominal, trauma, and urologic surgery. The mean weighted average of these trials suggests a reduction of 3.7 days in hospital length of stay (LOS) (Table 2).[25,48-53]

In addition to these randomized controlled trials, the United Kingdom's National Health Service Technology Adoption Centre conducted a case study of esophageal Doppler as part of its enhanced recovery effort. Based on the use of EDM in 649 patients undergoing major surgery at three hospitals (as compared with 658 matched patients who did not received EDM in the 12 months prior), the National Health Service (NHS) documented a 3.6-day reduction in hospital LOS.[54]

As a result of the accumulating evidence suggesting improved outcomes with the use of EDM, the NHS and the National Institute for Health and Care Excellence (NICE) group released practice guidelines which state:

> "*The case for adopting the CardioQ-EDM in the NHS is supported by the evidence. There is a reduction in post-operative complications, use of central venous catheters and in-hospital stay (with no increase in the rate of re-admission or repeat surgery) compared with conventional clinical assessment with or without invasive cardiovascular monitoring.*"[55]

Similarly, Centers for Medicare & Medicaid Services (Agency for Healthcare Research and Quality [AHRQ]) in

Table 2 Randomized controlled trials and intraoperative fluid optimization

INTRAOPERATIVE FLUID OPTIMIZATION: RCTs					
Esophoageal Doppler: 694 Subjects, weighted average 3.7-day reduction in LOS					
Year	Author	Patients	*n*	Outcome	Device
1997	Sinclair	Orthopedic surgery	40	Reduced mean stay 9 days	EDM
2002	Gan	Major elective surgery	100	Reduced mean stay 2 days	EDM
2002	Venn	Orthopedic	90	Reduced mean stay 6 days	EDM
2005	Wakening	Colorectal	128	Decreased hospital stay 1.5 days	EDM
2006	Noblett	Colorectal	108	Reduced mean stay 2 days	EDM
2007	Chytra	Trauma	162	Reduced mean stay 5 days	EDM
2011	Pillai	Radical Cystectomy	66	Reduced mean stay 4 days* (*NS)	EDM
Arterial Waveform: 546 Subjects, weighted average 2.2-day reduction in LOS					
2005	Pearse	"High risk" surgery	122	Reduced median stay 3 days	LiDCO (SV)
2007	Lopes	"High risk" surgery	33	Reduced mean stay 10 days	PPV
2008	Buettner	Abdominal	80	No difference in outcomes	SPV
2010	Benes	Abdominal	120	Reduced mean stay 1 day	FloTrac
2010	Forget	Major abdominal surgery	*	Reduced lactate at all time points	PVI
2013	Jones	Liver Resection	91	Reduced mean stay 3 days	LiDCO
2013	Ramsingh	Abdominal	38	Reduced mean stay 2.5 days	FloTrac
2013	Goepfert	Cardiac Surgery	100	Reduced time to hospital discharge criteria 1 day	PiCCO

*Utilized pleth variability index (PVI), not arterial waveform analysis. EDM = esophageal Doppler monitor; LOS = length of stay; PPV = pulse pressure variation; RCTs = randomized controlled trials; SPV = systolic pressure variation; SV = stroke volume

the United States examined the data on esophageal Doppler monitoring, and concluded that:

> "*The addition of esophageal Doppler monitoring for guided fluid replacement to a protocol using CVP [central venous pressure] and conventional clinical assessment during surgery leads to a clinically significant reduction in the rate of major complications and total complications in surgical patients compared to CVP plus conventional clinical assessment. The strength of evidence supporting this finding is strong.*"[56]

Arterial waveform analysis

Technological assessment

Arterial waveform analyzers attempt to estimate stroke volume (and cardiac output) using sophisticated evaluation of the shape of the arterial waveform. The principles of arterial waveform analysis have been extensively reviewed elsewhere,[57] but most devices are based on the Windkessel theory developed by Frank. These devices typically estimate stroke volume using a variation of the following equation:

$$SV = k \times P(1 + A_S/A_D)$$

where k is a constant, P is an estimate of pressure (how this is measured differs in each technique), A_S is the area under the blood pressure waveform during systole, and A_D is the area under the blood pressure waveform during diastole. The major exception to this is the FloTrac Vigileo device made by Edwards Lifesciences (Irvine, CA, USA), which uses a proprietary empirically-derived algorithm to estimate stroke volume.[58]

Broadly, arterial waveform analyzers can be classified as *uncalibrated* or *calibrated* devices. The FloTrac Vigileo, ProAQT (Pulsion, Munich, Germany), MostCare (Vytech, Vygon, Italy), and LiDCOrapid (LiDCO, London, UK) devices do not require calibration. In contrast, the PiCCO (Pulsion, Munich, Germany) and the LiDCO$^+$ (LiDCO, London, UK) are calibrated by transpulmonary thermodilution (which requires a central venous catheter and a brachial or femoral arterial catheter, but not a pulmonary artery catheter) and lithium dilution, respectively (Table 2). The purpose of calibration is to correct the estimate of k for changes in afterload.[57] Because they rely on analysis of a blood pressure tracing, these devices can be used in patients who are fully awake.

The majority of experimental[59-61] and clinical[62-65] data suggests that calibration of arterial waveform analyzers improves accuracy, although this finding is not universal.[64,66-68] The accuracy of these devices generally decreases during periods of hemodynamic instability;[59,60,64,69-71] thus, there appears to be a tradeoff between convenience and reliability, especially in situations in which loading conditions are expected to change.

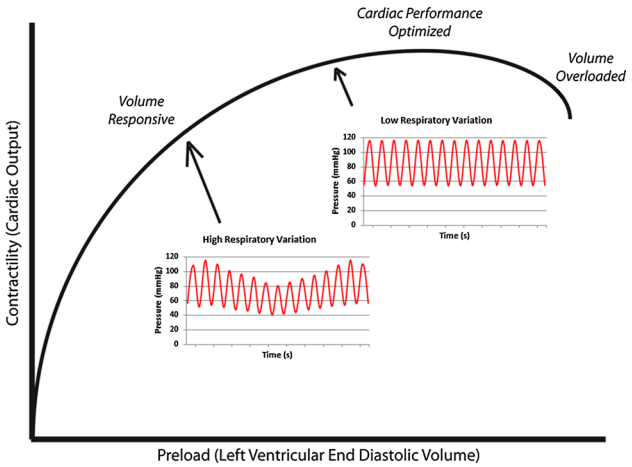

Fig. 2 Frank Starling curve

By measuring the area under the curve (or stroke volume) with each heartbeat, and comparing the minimal *vs* maximal value over one respiratory cycle, arterial waveform analyzers are able to measure SVV, an indication of the patient's location on the Frank-Starling curve (Fig. 2). It is important to point out that, while some arterial waveform analyzers may not measure cardiac output accurately in the setting of extreme hemodynamic conditions, their ability to measure pulse pressure variation (PPV) in response to positive pressure ventilation (hence *fluid responsiveness*) is likely not compromised. Furthermore, the continuous nature of these devices is a significant advantage in a busy operating room environment.

Clinical data

Arterial waveform analyzers have been utilized in many GDT trials, primarily for the care of critically ill patients.[18,19] Compared with esophageal Doppler, they have not been studied as thoroughly in conjunction with ERAS protocols, in part because they have not been commercially available for the same period of time. Anesthesiologists have started to repeat these fluid optimization studies using arterial waveform analyzers as alternatives to EDM (Table 2).[72-77] Five trials[72,73,75-77] documented reductions in LOS as well as an improvement in meaningful clinical outcomes, but not all studies demonstrated a benefit.[74] The mean weighted average reduction in LOS for these trials (2.2 days) is less than the reduction in LOS seen with EDM (3.7 days), but the total

number of studies (11) and subjects (1,018) precludes statistically meaningful comparisons.

Several points are worth mentioning. First, the earliest arterial waveform analyzer trial was published ten years after the first EDM trial, and some of the observed differences with regard to clinical efficacy may be related to other changes in care over this decade. Second, arterial waveform analyzers cannot be used reliably in the setting of aortic insufficiency or an irregular heart rhythm. Lastly, much of the data supporting the ability of SVV to predict fluid responsiveness was conducted using tidal volumes of 8-10 $mL \cdot kg^{-1}$. These devices have not been adequately validated at lower tidal volumes or in subjects with spontaneous ventilation. That being said, estimates of *stroke volume* (as opposed to SVV) should not be affected by these differences in intrathoracic pressure or volume.

Photoplethysmography

Technological assessment

The photoplethysmographic (PPG) waveform is produced by directing red or near-infrared light into a body part (e.g., finger) and plotting the intensity of transmitted radiation as a function of time.[78] Hemoglobin absorbs both red and near-infrared light; therefore, as pulsatile arterial blood enters and leaves the body part, *transmittance* of red and near-infrared light will change accordingly. As one might expect, the raw PPG waveform oscillates with respiration at the respiratory rate. The utility of this information was lost on the developers of pulse oximetry who considered it an "artifact" and went so far as to apply a high-pass filter to PPG waveforms in order to remove this unwanted source of "noise".[79] Indeed, most commercial pulse oximeters filter out low-frequency oscillations.

The Masimo Radical-7® (Masimo Corporation, Irvine, CA, USA) device is a pulse oximeter designed specifically to quantify the amount of low-frequency variation in the PPG tracing, as well as to display the raw waveform in real time (Fig. 3). *Pleth variability index* (PVI®) is the photoplethysmographic analogue of PPV from the arterial line and compares the *largest pulse oximeter pulse pressure* (PP_{max}) with the *smallest pulse oximeter pulse pressure* (PP_{min}) over the course of one breath. PVI is defined as:

$$PVI = PP_{max} - PP_{min}/(\text{Average}[PP_{max}, PP_{min}])$$

where PP is equal to the amplitude of the PPG waveform. Thus, PVI is analogous to PPV[80] from the arterial waveform. Several studies have confirmed that PVI can predict the cardiovascular response to both passive leg raising[81] and fluid administration in patients whose lungs are mechanically ventilated.[82-85] Despite the growing body of data suggesting that PVI is capable of predicting fluid responsiveness, there does not seem to be strong agreement

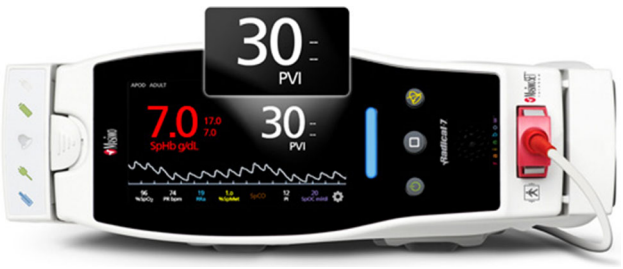

Fig. 3 Masimo Radical-7 device displaying PVI (30) and the raw (unfiltered) PPG tracing in real time. PPG = photoplethysmographic; PVI = pleth variability index

between PVI and PPV.[86-90] The reasons for this paradox (excellent predictor of fluid responsiveness yet not in agreement with arterial-derived metrics) are not clear but may be related to the dependence of PVI on perfusion.[91]

While the Masimo device may not be as effective as its more invasive counterparts during periods of malperfusion, it has three major advantages – relative low cost in comparison with its competitors, the ubiquity of pulse oximetry (which of course is a Canadian Anesthesiologists' Society basic monitoring standard),[92] and ease of use.

Alternatives to the Masimo device include the Edwards ClearSight system™ (Edwards Lifesciences, Irvine, CA, USA) and the CNSystems CNAP (CNSystems, Graz, Austria), both of which utilize the *volume clamp* technique, and the former of which utilizes the *physiocal* technique to reproduce a blood pressure tracing accurately from multiple finger cuffs. The volume clamp technique utilizes an inflatable finger bladder connected to a highly responsive feedback controller that automatically adjusts the bladder pressure to maintain a constant level of infrared transmittance through the finger. As blood volume increases (and transmittance of infrared radiation decreases), the cuff is inflated; conversely, as blood volume decreases (and transmittance of infrared radiation increases), the cuff is deflated. The cuff pressure required to maintain stable transmittance is the same as the arterial blood pressure in the finger, and in this way, arterial finger pressure can be measured continuously.[93] Critical to the success of the volume clamp technique is the ability to keep the peripheral arteries in an *unstretched* state. This is accomplished using the physiocal technique, wherein the finger cuff pressure is increased in stepwise fashion, and pressure is selected at the maximal PPG amplitude – this is the feedback setpoint. Periodically, the volume clamp technique is paused and the physiocal technique reapplied.[94] The NexFin device then applies arterial waveform analysis algorithms (above) to the resultant waveform to estimate stroke volume and SVV.

Clinical data

The Masimo Radical-7 has been utilized in one GDT study to date, though it was not part of a specific ERAS protocol.

Forget *et al*. randomized general surgery patients to fluid management guided by traditional parameters (mean arterial pressure, central venous pressure) or PVI and found lower lactate levels at every time point in the PVI group despite receiving 500 mL less fluid.[95] The NexFin device has not yet been utilized as a GDT device for ERAS, but given the accuracy of its blood pressure measurements[96-98] and its completely non-invasive nature, it is promising.

Venous oxygen saturation

Technological assessment

Mixed venous oxygen saturation (SvO_2) and central venous oxygen saturation ($ScvO_2$) measure the oxygen saturation of pulmonary arterial and central venous blood, respectively, using specially designed oximetry catheters. These devices are based on the premise that inadequate oxygen delivery (as may be seen in shock states) or ineffective consumption of oxygen (as may be seen in sepsis) will manifest as an abnormality in either SvO_2 or $ScvO_2$.[99] Advantages of SvO_2 and $ScvO_2$ include their reliability, continuous nature, and rapid response time. The major disadvantage of this technology is the requirement for central venous catheterization, which incurs several risks, the most important of which may be central line-associated bloodstream infection.[100]

Clinical data

Mixed venous oxygen saturation and $ScvO_2$ have not been used as part of ERAS protocols specifically; thus, their potential utility can be estimated only by extrapolating from published data in the critically ill and other perioperative patient populations. Mixed venous oxygen saturation was used as a therapeutic endpoint in a large multicentre randomized controlled trial of critically ill patients but did not lead to improvements in survival.[101] A smaller single-centre randomized controlled trial of *early GDT* in septic patients found a significant reduction in mortality when hemodynamics were modified to achieve a target $ScvO_2 > 70\%$.[102] A more recent larger multicentre randomized controlled trial designed to confirm these findings found no such difference.[103]

A small randomized controlled trial in patients undergoing major abdominal surgery found that titration of oxygen extraction ratio (O_2ER; based on $ScvO_2$) to $< 27\%$ reduced LOS and organ failure.[104] Importantly, the O_2ER group had lower lactates and higher $ScvO_2$ than the control group at the majority of time points, showing physiologic efficacy. A subsequent larger randomized controlled trial focusing on maintenance of $SvO_2 > 70\%$ (and lactate < 2 mEq·L^{-1} in cardiac surgical patients led to a slight reduction in morbidity and LOS, although SvO_2 and lactate did not appear to be appreciably different between groups, making the result difficult to interpret.[105] A large retrospective observational analysis of SvO_2 catheter use in cardiac surgical patients found no difference on outcomes associated with SvO_2 catheter use.[106]

Tissue oxygen saturation

Technological assessment

Tissue oximetry offers an exciting alternative to SvO_2 and $ScvO_2$ catheterization. Based on the principles of near-infrared spectroscopy (NIRS) – which analyze the non-pulsatile component of electromagnetic radiation capable of penetrating 2-3 cm into tissue – NIRS devices are able to estimate the tissue oxygen saturation (StO_2), i.e., a mixture of arterial (30%) and venous (70%) blood, of brain or muscle.[107,108]

Major advantages of NIRS-based estimates of StO_2 include their reliability in states of low perfusion (as they do not require pulsatility) and the ability to monitor multiple end-organs (as opposed to SvO_2 and $ScvO_2$, which are able to assess only global measures of oxygen supply and demand). The main disadvantages of NIRS technology are cost and the inability to distinguish between arterial and venous blood, i.e., assuming an arterial to venous ratio of 30:70 may lead to erroneous measurements. Published data on cerebral oximetry devices suggest they suffer from some extracranial contamination of their signals[109] and interdevice differences (which complicate interpretation).[110]

Clinical data

There is at least one randomized controlled trial showing the successful use of cerebral oximetry to improve outcomes in patients undergoing cardiac surgery.[111] While there was not a significant difference in the incidence of stroke (the study was not powered to detect this), use of cerebral oximetry led to a reduction in a composite index of overall morbidity. The reasons for this are complex but likely reflect the ability of the brain to autoregulate during cardiopulmonary bypass,[112,113] its position as a *sentinel organ*,[114] as well as the benefits of protocolized oxygen-centric hemodynamic management in terms of organ function, which has been shown in medical[102] as well as both non-cardiac[104] and cardiac[105] surgical patient populations (although it is important to point out that not all studies have been positive).[103] Given the brain's ability to autoregulate, one would expect it to be

highly specific but insensitive for perfusion abnormalities; thus, investigators have sought other organ systems to serve as a more sensitive sign of malperfusion or impending organ injury. There does appear to be a relationship between low muscle StO_2 values (measured in the thenar eminence) and Sequential Organ Failure Assessment (SOFA) and APACHE II scores in critically ill patients.[115] As with SvO_2 and $ScvO_2$ catheterization, StO_2 (brain or muscle) has not (yet) been utilized as an endpoint for therapy in the context of ERAS protocols.

Bioimpedance and bioreactance

Technological assessment

Bioimpedance and bioreactance devices are based on Ohm's law, which relates electrical current (I) to voltage (V) and resistance (R) by the equation:

$$I = V/R$$

The human thorax is made up of various materials, all of which resist the flow of electrical current to different degrees. Over the course of one heartbeat, the volume of intrathoracic fluid changes, and these changes manifest as changes in impedance (resistance to pulsatile flow). Bioimpedance devices apply a small electrical current across the chest and continuously measure impedance, which is related to intrathoracic blood volume. These devices assume that impedance is exclusively a function of changes in intrathoracic blood; they are susceptible to electrical noise, electrode positioning, and pulmonary edema, and are not particularly accurate.[116-124] Bioreactance, in which the phase shift between the applied and measured voltage is correlated to stroke volume, was developed in an effort to reduce the sensitivity to artifact.[125]

Advantages of bioimpedance and bioreactance devices include their completely noninvasive nature as well as their ability to provide continuous measurements.

Clinical data

The NICOM (Cheetah Medical, Newton, MA, USA) device was recently compared with EDM for GDT based on stroke volume in 100 patients undergoing colorectal surgery. There was no difference in LOS between the NICOM-guided and EDM-guided groups, although the study may not have been adequately powered to detect clinically significant differences in LOS. Additionally, there was very poor agreement between NICOM- and EDM-based estimates of stroke volume, with 95% intervals exceeding $\pm$ 50 mL. That said, there were no significant differences between devices with regard to the decision to give intravenous fluids (the fluid management protocol was based on a $\geq$ 10% increase in stroke volume with fluid challenge). This suggests that trending between the two devices is reliable, although the authors did not examine this specifically.[126]

Future directions

The relative contribution of specific intraoperative GDT to ERAS protocols is not known. Because the use of these devices incurs additional cost and, in some cases, risk, future research should focus on the additional value of intraoperative GDT in comparison with the simple *fluid restriction* used in many ERAS protocols. Brandstrup *et al.* attempted to address this question in a single study of 150 patients undergoing colorectal surgery and found no difference in complications or LOS between patients guided by esophageal Doppler and those guided by a more simplistic *fluid restriction* regimen. It would be premature to make practice changes based on this single study, but it is thought provoking and additional work is needed in this area.[127]

Evidence is accumulating that decreasing tidal volumes used for intraoperative mechanical ventilation leads to improved outcomes.[128,129] Many measures of *fluid responsiveness* were validated using 8-10 $mL \cdot kg^{-1}$ tidal volumes, and because they are dependent on intrathoracic pressure changes, they may not be as useful as tidal volumes in contemporary practice which have generally decreased to the 5-6 $mL \cdot kg^{-1}$ range. A reduction in bowel edema does not likely justify an increased risk of pulmonary injury, and future work is needed in this area.

Lastly, many of the monitors designed for intraoperative GDT do not work in patients with spontaneous ventilation.[130] As anesthesiologists become increasingly involved in the perioperative experience, they will find themselves unable to apply their intraoperative fluid management strategies to their postoperative patients until additional means of measuring fluid responsiveness are developed for patients receiving spontaneous ventilation following tracheal extubation. Currently, the only available means of measuring fluid responsiveness in these patients is by performance of a passive leg raising maneuver.[131]

Conclusions

Many, but not all, ERAS protocols utilize intraoperative GDT to optimize fluid management. Most of these devices attempt to assess fluid responsiveness in real time, either by assessing respiratory variation in blood pressure or flow or

by measuring the change in cardiac output that occurs after a fluid bolus is administered. Of all available devices, esophageal Doppler monitors are supported by the largest and most compelling body of data, but they can only be used intraoperatively and are not truly continuous. Arterial waveform analyzers offer a truly continuous estimate of fluid responsiveness but require the placement of an intra-arterial catheter. Their estimates of cardiac output are likely less reliable than those of esophageal Doppler, especially when loading conditions change. Furthermore, arterial waveform analyzers are not supported by as strong an evidence base, but this is primarily because fewer studies have been conducted. The PPG devices cannot be recommended for ERAS protocols based on clinical outcomes data, but the physiologic studies conducted with the PVI, the relatively low cost of the devices, and the fact that all anesthetized patients receive pulse oximetry suggest that the PVI may be an extremely useful intraoperative monitoring tool in relatively healthy patients. Venous oxygen saturation has no established role in ERAS protocols. NIRS-based tissue oximetry may eventually serve as a therapeutic endpoint, although it has not been tested in the context of ERAS. Bioimpedance devices are relatively inaccurate monitors of cardiac output and have not been tested as a therapeutic endpoint in ERAS protocols. Bioreactance devices are relatively new, and a single study suggests very little difference in intraoperative fluid administration as compared with EDM, but additional studies are needed. At this time, we cannot conclude which device has the most beneficial effects on patient outcomes; therefore, future research should include comparisons of the effects of different monitoring devices on meaningful clinical endpoints.

Key points

- Intraoperative fluid management is frequently protocolized in *Enhanced Recovery After Surgery* protocols.
- Available devices to guide fluid therapy differ based on the parameter they measure (e.g., cardiac output *vs* stroke volume variation) as well as their underlying mechanistic principles, level of invasiveness, and cost.
- Devices that integrate the impact of intrathoracic pressure changes during mechanical ventilation on cardiac output likely best predict hemodynamic responses to fluid administration.
- Future research should compare different strategies for fluid management, including goal-directed therapy *vs* fluid restriction, examination of their impact on relevant clinical outcomes and cost, and extension of the fluid responsiveness concept to patients whose lungs are ventilated using low tidal volume lung-protective strategies and to patients with spontaneous breathing.

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