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Plethysmography Variation Index (PVI) Utility In Guiding Goal-Directed Fluid Therapy During Major Abdominal Surgery

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Abstract

When considering intra-operative MAP maintenance, preload is a significant driving factor of stroke volume and therefore cardiac output. In major abdominal surgeries, large fluid shifts are common and accurate fluid resuscitation is extremely important to maintain hemodynamic stability and promote optimal patient outcomes. Invasive methods of measuring fluid status range from esophageal doppler derived flow time (FTc) and arterial line-derived metrics such as stroke volume variation (SVV) and pulse pressure variation (PPV). However, invasive means are not always warranted for every surgical procedure or patient and there is a higher potential risk for complication. Plethysmography Variation Index (PVI) has been introduced as a non-invasive alternative to gauge preload status, predict fluid responsiveness, and guide goal-directed fluid therapy. The success of PVI during major abdominal surgery is mixed. Significant predictive ability to determine fluid responsiveness exists and compares well to invasive techniques. However, the ability to track dynamic stroke volume (SV) changes correlates poorly with fluid bolus administration and PVI tracings. Overall, the total volume of fluid administered and post-operative patient outcomes all compare favorably with PPV, SVV, and FTc. Ultimately, the use of PVI during major abdominal surgery can be useful if fluid management is considered and approached in at least two distinct parts: first, recognition of hypovolemia and fluid responsiveness, to which PVI can accurately provide data; second, continued tracking of hemodynamic changes post bolus and the warranting of subsequent boluses, to which PVI is not well suited to direct.

Keywords: Plethysmography Variation Index, fluid management, non-invasive, major abdominal surgery, intravenous fluid volume, pulse pressure variation, stroke volume variation, esophageal doppler, flow time corrected.

Plethysmography Variation Index (PVI) Utility in Guiding Goal-Directed Fluid Therapy During Major Abdominal Surgery

Recently, there is a renewed focus on the importance of maintaining adequate mean arterial pressure (MAP) peri-operatively. Studies have shown brief periods of MAP below 65 mmHg significantly increase the risk of post-operative morbidity and mortality (Hu & Lim, 2022). MAP can be manipulated via various interventions: the balancing of anesthetic depth, vasopressor use, and intravascular volume augmentation. The latter is of particular interest as the optimization of preload is critical to improving and maintaining peri-operative hemodynamics (Gregory, 2020). Although common NPO times rarely dehydrate patients clinically, the combination of mild volume depletion and vasodilatory anesthetics increases the incidence of hypotensive periods (Weber et al., 2020). However, the determination of a patient's fluid status remains of continued debate and without a systematic approach, subsequent decisions regarding fluid resuscitation lack accuracy. Administration of boluses to the fluid unresponsive—defined as no change in cardiac output post fluid bolus—may cause fluid overload and lead to deleterious effects such as acute heart failure, pulmonary edema, and peripheral edema that interferes with surgical wound healing and end-organ function. Without explicitly discussing best fluid management practices, the essence of the decision-making process lies within an initial accurate gauge of fluid status.

Invasive methods of determining fluid status have been successfully implemented and proven to predict fluid responsiveness and track hemodynamic changes (Rathore et al., 2017). However, not all surgeries or patient populations require the application of arterial lines, central venous catheters, or trans-esophageal echocardiograms (TEE). In the last decade, application of non-invasive peripheral monitors to determine fluid status and track subsequent hemodynamic

change has occurred. Of interest, Masimo's PVi ®, which stands for plethysmograph variability index, utilizes a pulse oximeter plethysmographic tracing to measure the dynamic volume change between pulsatile and non-pulsatile flow in the capillary bed during a full respiratory cycle. This differs from arterial waveform analyses which measure pressure waveform changes (Masimo - Pleth Variability Index (PVi), n.d.).

This literature review seeks to investigate the application, success, and limitations of non-invasive PVI device-guided fluid therapy during major open abdominal surgery. This surgery is of interest due to the inherent presence of large intra-operative fluid shifts, hemodynamic instability, and the need for regular fluid replacement. The literature review will investigate studies comparing pulse pressure variation (PPV), stroke volume variation (SVV), and esophageal doppler corrected flow times (FTc) to plethysmography variation index (PVI) monitoring during major abdominal surgeries. Primary outcomes are not solely judged by the accuracy and agreement of measurements concerning fluid responsiveness, but by overall improvement of hemodynamics such as stroke volume (SV). Secondary points of comparison note total fluid volume administration and post-operative outcomes trends.

Background

The importance of guided fluid therapy during the peri-operative period does not merely revolve around MAP maintenance with fluid resuscitation, but accurate recognition and delivery of such boluses to the correct patient population. The balance between under-resuscitation and fluid overload can be fine and it requires accurate assessment to optimize hemodynamics and maintain homeostatic intravascular volume and oxygen delivery (Singh et al., 2011).

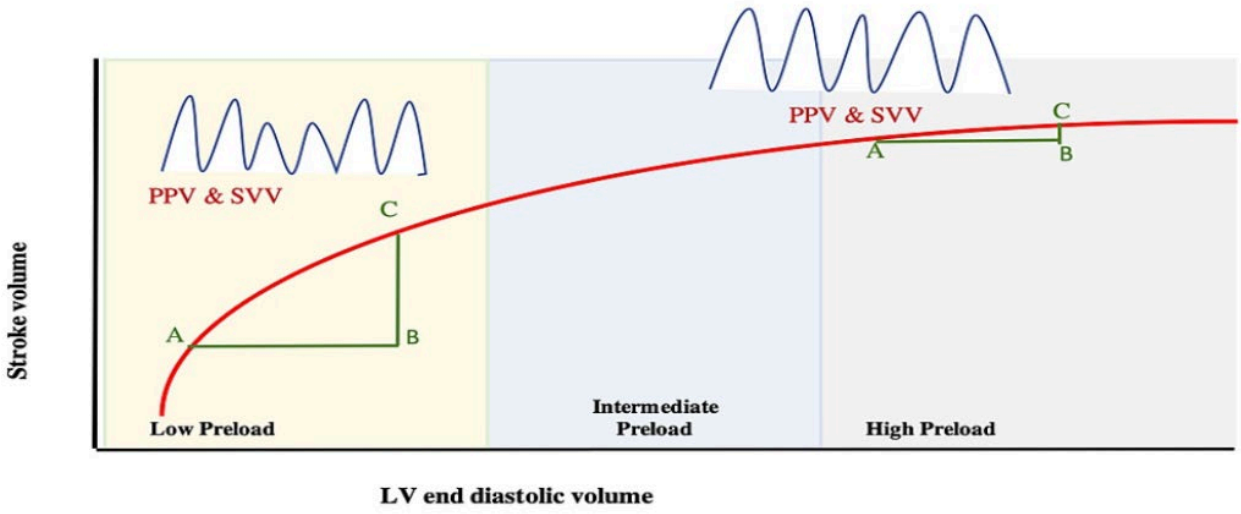
Euvolemia describes a state in which the preload delivered to the left ventricle is an appropriate volume to support adequate cardiac output but isn't overloaded whereby cardiac

chambers become overfilled, distended, and unable to maintain meaningful forward ejection (Singh et al., 2011). A productive way to visualize the balance between hypovolemia and hypervolemia is to reference the Frank-Starling curve (see Figure 1), which relates venous return (preload) to SV and ultimately cardiac output (CO). The premise is that a continuous increase in preload will elevate CO until a plateau is reached. When the operating point on the curve is shifted left in response to a decrease in preload, overall cardiac performance declines and is reflective of a hypovolemic state. Conversely, as the operating point shifts right, in response to increased preload, there is increased cardiac output. However, increasing cardiac output is not limitless and overfilling of the left ventricle can occur. Upon this plateau, CO ceases to increase and back pressure from the left ventricle can lead to pulmonary and peripheral edema which represents a hypervolemic state (Hall, 2015).

The process of modulating cardiac output via increased stroke volume at the conclusion of a fluid bolus is termed, fluid responsiveness (Singh et. Al., 2011). As noted in Figure 1, patients positioned on the steeper slope (low preload) respond vigorously to a fluid challenge with a subsequent increase in SV. Conversely, a patient positioned on the upper plateau does not respond to a fluid challenge with an increased SV, and therefore is considered fluid non-responsive (Megri et. Al., 2022). Recognition of this population differentiation is crucial before further fluid resuscitation is provided. Repeated fluid boluses to the non-responder would overload the left ventricle and produce pulmonary edema, V/Q mismatch, and end-organ dysfunction. This determination of fluid responsiveness is essentially the first step in the clinical decision-making process for augmenting MAP with fluid boluses.

Figure 1

Frank-Starling Curve



Note: The Frank-Starling curve displays the relationship between left ventricular (LV) SV and LV end-diastolic volume (EDV), which is synonymous with preload. To the left of the curve, which corresponds to low preload or hypovolemic states, SV is initially low; however, increases in preload lead to marked increases in SV. Conversely, the right portion of the curve, which corresponds to high preload or hypervolemic states, displays that SV does not change significantly when preload is increased and a plateau has been reached (Vos et. Al., 2013).

The influence of positive pressure ventilation on the cardiovascular system serves as the basis for the following methods of predicting fluid responsiveness. Cyclical changes in cardiac chamber loading occur during every respiratory cycle. As positive inspiratory pressure is applied, left ventricular (LV) preload is initially augmented by an increased delivery of pulmonary vascular blood. This positive pressure simultaneously alters LV and aortic transmural pressure, creating a reduced after-load. As a result of this physiology, LV stroke volume is augmented (Megri et. Al., 2022).

Simultaneously, the right ventricular (RV) SV is reduced as a product of two ongoing factors: first, right heart preload is diminished because the passive filling gradient is reduced

between the inferior vena cava (IVC) and the right atrium (RA). This occurs due to a multifactorial increase in right atrial pressure (RAP). Secondly, ejection of RV SV is hindered by increased pulmonary vasculature resistance caused by positive pressure placed on alveoli (Megri, et. Al., 2022). This lack of RV preload consequently affects the following cardiac cycle with reduced LV filling and ultimately a reduced CO. This phenomenon, pulsus paradoxus, is defined by large swings in systolic blood pressure during inspiration. When this is observed, there is a greater likelihood of intravascular volume deficit and therefore responsiveness to fluid boluses (Singh et. Al., 2011).

Mechanisms used to determine eligibility for fluid resuscitation primarily rely upon invasive methods that measure arterial pressure waveforms. Of the methods compared to PVI , PPV and SVV were the most utilized. Pulse pressure variation is a displayed percentage derived from the difference between max pulse pressure and minimum pulse pressure noted during a single respiratory cycle. The maximum and minimum points correlate to the apex of a pulse pressure waveform on the largest and smallest amplitudes, respectively (Sondergaard, 2013). Typically, a calculated value of 14% infers a threshold indicative of fluid responsiveness. Following a fluid bolus, if the PPV decreases below 10%, two assumptions are allowed: the patient was fluid responsive and cardiac output was augmented via increased stroke volume (Sondergaard, 2013). Similarly, SVV is derived by the same equation as PPV but uses the volume contained within each pulse pressure waveform. Both metrics are categorized as dynamic because waveform variation is a direct product of cardiovascular change elicited during a respiratory cycle. In contrast, the use of central venous pressure (CVP) as a fluid status marker is considered static because it measures only a single point in time (Jozwiak et al., 2018).

A more direct measurement of preload and fluid responsiveness is derived from doppler analysis of aortic root blood flow by trans-esophageal echocardiogram. As LV ejected stroke volumes are measured, from the upstroke of a waveform to its return to baseline, a flow time is created. To adjust for variations in heart rate, corrected flow times (FTc) are derived and utilized in the creation of a volume curve. Ultimately, this is combined with other TEE measurements to produce an accurate SV utilized to calculate CO, assess preload, and fluid status (Jozwiak et al., 2018).

Utilizing the exact same principles of physics, PVI notes perfusion indices (PI) within peripheral capillary beds throughout the respiratory cycle. PI compares the maximum flow volume to the minimum volume during pulsatile and non-pulsatile blood flow. Both volumes are calculated as a percentage to be utilized as a threshold for fluid resuscitation, in a similar manner as prior invasive techniques (Vos et. Al., 2013). The primary difference is this technique is derived from non-invasive application of a pulse oximeter specifically calibrated to PVI algorithms.

By nature of easy implementation, non-invasive devices broaden a clinician's ability to predict which patients need fluid resuscitation and tailor therapy by accurate, guided methods. As such, the focus of this literature review is to investigate the utility of a non-invasive method in determining fluid responsiveness and correlating fluid resuscitation to hemodynamic improvement. In doing so, an articulated framework to procure the most relevant evidence is facilitated by utilizing the PICOT format as follows:

In the adult surgical population, can the utilization of a non-invasive plethysmography variation index (PVI) gauge dynamic fluid status and responsiveness as accurately as invasive methods in goal-directed fluid therapy for major abdominal surgery?

Literature Review

Search Methods

Sources selected for this literature review were obtained from Google Scholar, Pubmed, Scopus, MEDLINE, and CINAHL Complete. Initial queries were directed via the University of New England's library services. Search terms were as follows: plethysmography variation index, PVI, goal-directed fluid therapy, fluid management, abdominal surgery, pulse pressure variation, PPV, PVI vs PPV, non-invasive, stroke volume, and fluid responsiveness.

Article selection was based on the type of study performed, with special attention and preference given to randomized control trials (RCTs), systematic reviews of RCTs, prospective experimental studies, quasi-experimental, observational studies, and case reports. The publish date range window was ten years. Although Masimo's PVi device was recently approved by the FDA, the bulk of clinical studies regarding this technology seemed to occur in the early 2010s (Businesswire, 2020). Ultimately, twenty articles were accepted. The rejection of articles was based upon the presence of confounding clinical variables known to skew data (pneumoperitoneum, continued vasopressor use) and lack of focus directed to major abdominal surgery.

Although there lacked a single, common point of comparison between PVI and invasive methods, common themes arose and served as an axis for this literature review. Statistical accuracy of fluid responsiveness predictability, correlation of bolus administration to changes in SV, total amounts of intravenous fluids administered, and observed clinical impacts, such as length of stay (LOS), complication rates, and lab values were notable points of comparison between studies. Studies with clinical outcomes as endpoints appeared to associate successful outcomes to properly executed, accurately guided fluid therapy. Thus, the purpose of this review

is to create a more comprehensive study of PVI's potential utility within abdominal surgery compared to established invasive methods.

Study Methods

Surgeries

Major abdominal surgeries included in the reviewed studies were Whipple procedures, hemicolectomies, bowel resections, liver transplants, and open laparotomies. These types of surgeries were of interest due to large fluid shifts and the need for accurate and guided intra-operative fluid resuscitation (Prabhu et al., 2019). Laparoscopic procedures were excluded due to the significant impact of pneumoperitoneum on ventilation and venous return, which would skew data points (Warnakulasuriya et al., 2016).

Invasive Methods

Historically, methods such as Ftc, SVV, and PPV have accurately measured fluid responsiveness and guided directed fluid therapy in a variety of critical care and surgical applications (Hofer et al., 2008). All three of these methods are invasive, which confers an inherent risk of complication and additional needed resources. Moreover, these methods may not be warranted in many surgeries due to such invasiveness or technical skill required. However, it is valuable to compare these widely accepted invasive methods to a newer, non-invasive method in predicting fluid responsiveness.

Inclusion and Exclusion Criteria

Inclusion criteria for the reviewed studies included non-emergent, ASA 1-3 adult patients. All were mechanically ventilated for the entirety of surgery with a mean surgical time ≥

90 minutes. Epidural adjuncts were considered, but the primary anesthetic was general anesthesia maintained with inhaled volatile agents. More importantly, exclusion criteria focused on patients not in sinus rhythm, the presence of advanced cardiac disease, valvular disease, intracardiac shunts, low ejection fraction (EF), uncontrolled hypertension, significant peripheral vascular disease, spontaneous ventilation, and the presence of pneumoperitoneum in laparoscopic procedures; as the above conditions all drastically alter the accuracy of waveform variability, whether arterial or plethysmographic (Sondergaard, 2013).

Comparative Methods

Sixteen studies directly compared PVI to an invasive form of monitoring fluid responsiveness. Metrics were obtained and correlation was extrapolated between the comparison groups. Five studies compared PVI to peri-operative use of "conventional" fluid management techniques, which base the need for fluid resuscitation on static measurements such as heart rate, MAP, urine output, or central venous pressure (CVP). Although not exactly the focus of this literature review, these studies serve as another comparative marker of the outcomes of PVI directed peri-operative fluid management.

In all studies, baseline hemodynamics were obtained after the induction of general anesthesia and establishment of a stable steady state where broad swings in heart rate or MAP were no longer occurring. This was a universal method, which allowed a controlled starting point before the occurrence of fluid challenges, surgical influences, and the observation and tracking of the studies' variables. (Essam, 2016, Zimmermann 2010).

Studies utilized a range of methods that provided baseline fluid boluses and maintenance infusion rates, which were predetermined and not administered according to PVI or hemodynamic changes. Seven accepted studies provided a post-induction bolus, typically

averaging 250-500ml, whether a set volume and/or weight-based bolus dose. Another nine studies utilized continuous maintenance infusions ranging from 2-4ml/kg/hr starting immediately post-induction. The reasoning and impact of this technique were not entirely clear. It should be noted all studies provided additional fluid boluses when hemodynamic changes or decreases in SV occurred.

The majority of studies (sixteen) provided boluses when PVI, PPV, or stroke volume index (SVI) thresholds were reached. The determined PVI threshold ranged from 10-20% with the mean, median, and mode residing around 13%. Upon reaching this value, a fluid bolus was provided to reduce said measurement, reflecting less waveform variability between heartbeats and within respiratory cycles. The variety of invasive metrics had their own predetermined threshold, typically based on prior studies with defined percentages deemed sensitive and reliable. The majority of administered crystalloid boluses were 250ml.

The primary hemodynamic measurement utilized to gauge responsiveness was stroke volume or stroke volume index, which was monitored either by esophageal doppler or invasive catheter modalities. Typically, boluses were prompted when SV decreased by ten percent. “Fluid responders” were denoted by increases in SV of approximately ten percent, post bolus. All studies using this technique eliminated participants if there was no response in SV following bolus dosing.

Rarely did these studies utilize hemodynamic instability, defined by a change in systolic blood pressure or heart rate by 20%, as a prompt for fluid boluses. Additionally, a minority of studies determined successful fluid responsiveness by a 10-15% increase in cardiac index (CI). The studies utilizing such techniques were screened for study rigor and quality, as well as proper statistical analysis of findings prior to inclusion in this literature review.

Statistical Analysis

If primary endpoints revolved around the predictability of fluid responsiveness or overall correlation to SV change, studies often employed receiver operative characteristic (ROC) curves, correlation coefficients (r), Cohen's kappa concordance, and p-values reflecting statistical significance. ROC curves and subsequent areas under the curve (AUC) were utilized to gauge predictive ability, with higher AUC values signifying a greater ability to differentiate fluid responders. Higher correlation coefficients also indicated greater positive relation between a PVI threshold percentage, fluid boluses administered, and subsequent SV changes; reflecting the ability to track hemodynamic changes post-fluid challenges. An (r) < 0.4 indicated poor correlation and conversely (r) >0.7 indicated excellent correlation (Prabu et al., 2019). P-values, with results < 0.05, signified greater statistical significance, that the null hypothesis should be rejected, and that a strong relationship between the observed dependent variable and the study's independent variables was present.

Results

Fluid Responsiveness and Hemodynamic Tracking

The process of determining fluid responsiveness is a crucial aspect of goal-directed intra-operative fluid therapy. The predictive value of a technique helps the clinician understand whether the metrics observed (ie PVI thresholds) can accurately determine fluid responsiveness and provide sensitivity and specificity to which patients should receive fluid boluses. Further correlation between administered boluses and improved SV is of equal importance in guiding future resuscitation, which equates with accurate hemodynamic tracking.

PVI vs FTc. Balhmann et al. (2015) utilized ROC curves to assess sensitivity and specificity of PVI's predictive ability for fluid responsiveness. In 31% of scenarios when doppler

studies indicated a bolus (sensitivity), PVI also did; moreover, when 72% of doppler studies did not indicate a bolus (specificity), PVI also did not prompt fluid administration, this ultimately lent a ROC score of 0.55 (Bahlmann et al., 2015). Further, Cohen's kappa coefficient was used to determine concordance between PVI and esophageal doppler algorithms in the ability to track hemodynamic improvement, which was reflected by an SV increase of > 10% post-bolus. Only 51% of PVI fluid boluses resulted in SV increases, allocating an overall kappa value of 0.11 (Bahlmann et al., 2015). Ultimately, this lent poor concordance between PVI and FTc for fluid responsiveness discrimination and the ability to track hemodynamic changes.

In a study by Essam et al., (2016) hemodynamic variables (FTc, SV, PVI, HR and MAP) were all recorded in post-inductive steady state and then after a fluid bolus. Readings were recorded again when SV decreases prompted fluid resuscitation during the peri-operative period. Ultimately, during steady state, PVI had weak predictive ability of fluid responsiveness with a ROC of 0.623, CI 95%, p-value of 0.0155; however, when dynamic changes occurred (ie surgical events or hemodynamic changes), PVI predictive ability increased to a ROC value of 0.877 with 95% confidence interval and a p-value of < 0.0001 (Essam et al., 2016). Physiological reasons as to why a marked improvement occurred in a dynamic state versus steady state were not elaborated upon. This conclusion essentially contradicts the above findings from the 2015 work by Balhmann et, al.

Similarly, Hood and Wilson (2011), utilized an approach that recorded esophageal SV and peripheral (earlobe and fingertip) PVI measurements after a 500ml bolus during post-induction steady state. Intra-operatively, boluses were also administered when SV decreased by 10% with a serial recording ten minutes afterward. Predictive ability of determining fluid responsiveness in the steady state was high with an AUC of 0.96, (95% CI, P < 0.001) (Hood &

Wilson, 2011). Intra-operatively, ROC analysis lent significant predictive ability with an AUC of 0.71 (95% CI, p = 0.006). PVI was 65% sensitive for responsiveness and 67% specific for non-responders (Hood & Wilson, 2011). In a similar study, utilizing a PVI threshold of 8%, Lahner et. al. (2012), reported 100% sensitivity and 44% specificity. After 250ml boluses were delivered prompted by SV decreases, the AUC for PVI was 0.67 (Lahner et. Al., 2012). These two studies support the notion that PVI can predict fluid responsiveness well but did not determine whether PVI tracks hemodynamic changes well.

PVI vs PPV, SVV. Although an older study, the 2006 work by Solus-Biguenet et. al., compared PVI (referred to as PPVfina in the study) to PPV. Comparing another invasive metric to PVI, this citation serves as an important segue into the following comparisons of PVI vs PPV and SVV. Ultimately, Solus-Biguenet et. al., produced similar results to the previous studies with a PVI AUC of 0.81 ($p < 0.001$), post 250ml boluses (Solus-Biguenet et al., 2006).

Prabu et al. (2019), utilized SVV to monitor and guide ongoing peri-operative fluid therapy while simultaneously recording PVI measurements. All data were compared using correlation coefficients (*r*). PVI readings consistently reported 2-3% higher than SVV, and with an (r) of 0.3742, displayed a weak positive correlation. Furthermore, when both data were entered into a scatter plot, the variation was wide and conferred a lack of agreement (Prabhu et al., 2019). This reflected an inability of PVI to accurately track ongoing hemodynamic changes.

Hoiseth et. al. (2011), separately guided fluid management by TEE SV measurements, but focused the study on comparing PVI (referred to as ΔPOP) to PPV (referred to as ΔPP) for predictive ability. Utilizing ROC curves, a PVI threshold of 11.4% yielded an AUC of 0.72, $p < 0.001$ and 86% sensitivity (Hoiseth et al., 2011). This result displayed PVI's ability to predict fluid responsiveness well.

Vos et. al. (2013), created an interesting amalgamation of the above studies, simultaneously comparing PVI, SVV, and PPV, reporting the predictive ability of fluid responsiveness (ROC curves) and then tracking the hemodynamic changes with subsequent interclass correlation (*r*). There was little difference in AUC: 0.78, 0.81, 0.77 for PVI, SVV, and PPV respectively. PVI also had 82% sensitivity and 77% specificity. Pre-bolus correlation of PVI to SVV and PPV was r = 0.71 and 0.8, respectively. However, a surprising change occurred post-bolus, which reflected hemodynamic tracking: PVI greatly lost correlation with SVV and PPV with r = 0.11 and 0.41, respectively (Vos et al., 2013).

Konur et. al. (2016), followed liver transplant r**ec**ipients and marked PVI, PPV, and SVV during dissection and anhepatic phases. ROC results for predictive ability were low with an AUC of 0.56 and 0.55 for dissection and anhepatic phase respectively. Correlation coefficients, to SVV and PPV, were high however with $r = 0.63$, $p = 0.001$ and $r = 0.77$, $p < 0.001$.(Konur et. Al., 2016).

Zimmerman et al. (2010), in addition to comparing predictive abilities and hemodynamic change correlation of SVV and PVI, also included CVP data. SVV had a high correlation with hemodynamic change, r = 0.80 (P < 0.001) and PVI followed with r = 0.61 (P<0.004). ROC curves denoted both SVV and PVI as highly predictive of fluid responsiveness (SVV AUC 0.993, PVI AUC 0.973). The notion that CVP is a static, unreliable marking for hemodynamic tracking was reflected by r = 0.18 (P = 0.45). This continues to support evidence that PVI predicts responsiveness well but then wanes in the ability to track changes; additionally, it reinforces the notion that dynamic modes of measurement outperform static hemodynamic markers such as CVP.

In a study performed by Lee et. al. (2016), PVI was compared to right ventricular end-diastolic volume index (RVEDVI) during liver transplantation. RVEDVI is derived from the placement of a pulmonary artery catheter and despite appearing as a static marker such as CVP and PAOP, RVEDVI has been correlated well to SVV, a dynamic metric as previously mentioned (Kim et al., 2013). With that, ROC values were utilized in addition to correlation coefficients. PVI predicted fluid responsiveness with an AUC of 0.745 and PVI correlated with RVEDVI changes post-fluid bolus with an r = 0.492 (Lee et. Al., 2016). Again, PVI predicts responsiveness well yet fails to track ongoing hemodynamic change.

A comprehensive assessment of PVI's ability to gauge fluid responsiveness and track hemodynamic change is found in a 2012 meta-analysis by Sandroni et. al. This study wasn't entirely focused to major abdominal surgeries yet possessed a meaningful account of PVI utility in major surgeries and utilized parameters closely shared by the previous studies. Using ROC for fluid responsiveness and correlation coefficients for hemodynamic tracking, pooled data displayed a similar AUC of 0.85, sensitivity and specificity of 80% and 76%, respectively, and a correlation coefficient of 0.58, all with 95% CI (Sandroni et. Al., 2012). This meta-analysis ranks PVI's ability to predict responsiveness and track hemodynamic changes similar to the prior RCTs.

Total Volume Crystalloid Administered

PVI vs FTc. In seven of the selected articles, the total crystalloid volume administered was the primary endpoint. These studies compared therapies guided either by PVI or FTc-derived algorithms to gauge fluid responsiveness and subsequently prompt bolus administration.

Abdullah et al. (2012), found no significant difference in volume delivered between the two groups. FTc guided therapy delivered 2670ml crystalloid and PVI delivered 2730ml crystalloid.

This finding was replicated by Bahlmann et al. (2015) in an RCT that compared PVI to doppler-guided open abdominal surgery in 75 participants. Volumes of crystalloid administered during optimization rounds were found to have minimal difference. Average total fluid balances at end of surgery were strikingly close with doppler crystalloid volumes of 1335ml and PVI-guided administration of 1395ml (Bahlmann et al., 2015).

In their 2018 follow-up study, Bahlmann et. al. primarily focused on clinical outcomes for 150 participants managed by PVI and doppler FTc methods during open abdominal surgery. As a secondary endpoint however, total volumes of both crystalloid and colloid were noted and found to be similar between the two groups. Finally, with similar results, Warnakulasuriya et. al (2016), observed an overall lower mean intra-operative fluid balance for PVI when compared to FTc (PVI 838ml; FTc 1144ml) with a p-value of 0.150 (Warnakulasuriya et al., 2016).

PVI vs PPV. Employing a different comparison method—PVI vs PPV guided delivery—one RCT of seventy-six participants reported similar total volumes administered. The study's method consisted of a baseline infusion of 2ml/kg/hr and then 250ml boluses if PVI or PPV thresholds were reached. Coeckelenbergh et. Al. (2019), reported an average of 500ml for PVI and 550ml for PPV with a p-value of 0.458 (2019).

PVI vs Conventional. For the sake of comprehensiveness, total fluid volumes were compared between PVI-directed therapy and "conventional fluid management," (CFM) which guides fluid delivery via static markers like MAP and HR. Utilizing similar PVI thresholds to prompt fluid resuscitation, crystalloid volumes administered were significantly lower with a p-value of < 0.001 (PVI: 900ml, CFM: 1946ml) (Cesur et al., 2018). These results were

comparatively echoed in findings by Yu et al. (2013), with a p-value < 0.05 (PVI: 1918ml, CFM: 2346ml) (2013). This reflects the utility and benefit of dynamic modes of fluid-guided therapy over static markers.

Secondary Endpoints

The total fluid volume administered along with the accuracy and ability of PVI to predict fluid responsiveness is of primary importance for this literature review; however, when considering a change of practice, the implementation of a chosen technique and how it affects a patient is of great interest. Secondary endpoints focused on intra-operative and postoperative lactate levels, the overall length of stay (LOS), and the incidence of complications. Comparison between PVI and invasive methods are of primary interest; however, PVI will again be compared to conventional fluid management for comprehensiveness.

PVI vs FTc. Warnakulasuriya et. al. (2016), in a study of forty colorectal surgical patients, chose to compare all of the three above outcomes between esophageal doppler and PVI managed cases. Upon arrival to PACU, initial PVI lactate levels were higher than esophageal doppler (1.98 vs 1.21, p = 0.007); however, levels were statistically similar intra-operatively and ultimately of no difference come post-op day one. Similarly, both the rate of complications and median hospital stays were found to be of no significant difference, with a rate of major complications being 11% and a median stay of seven days (Warnakulasuriya et al., 2016).

Bahlmann et. al. (2018), in a large RCT of 150 patients, additionally found that there was no statistically significant difference in the length of stay, which averaged eight days for both groups p = 0.57, and no difference in the number of post-operative complications. A total of 64 complications occurred in the PVI group, which equates to 51%, and 70 in the esophageal doppler group, equating to 49%. Balhmann et. al., provided an exhaustive list of qualifying

complications, which ranged from major complications such as sepsis, myocardial infarction, and stroke to minor complications such as superficial wound dehiscence, severe PONV, and superficial wound infections. Ultimately, each group contributed two patients with complications to the ICU, $p = 0.57$ (Bahlmann, 2018).

Abdullah et. al. (2011), mirrored the above two studies, comparing PVI to FTc guided management, using primary endpoints of serum lactate, overall morbidity, and LOS. Additional measures were employed to ensure that extraneous co-morbidities or intra-operative influences did not skew study results. In total, immediate postoperative and 24 hr ICU data displayed no difference in serum lactate or hemodynamic parameters, and overall morbidity and LOS were nearly identical (p value < 0.05) (Abdullah et. al., 2011).

PVI vs PPV. In a moderately sized RCT of 76 patients, Coeckelenbergh et. al. (2019), used LOS as their primary endpoint in the comparison of PVI or PPV-guided fluid therapy. This appears to be vulnerable to extraneous variables such as the presence of co-morbidities and intraoperative influences as reflected in the reported p-values. Nonetheless, LOS was comparable with little difference ($p = 0.230$, 95% CI) and post-operative complications were of similar rate, $p = 0.395$ (Coeckelenbergh et al., 2019).

PVI vs Conventional. Nethan et al. (2017), in an RCT of one hundred patients undergoing a range of abdominal surgeries, noted that PVI-guided therapy had a significantly faster post-operative return of gastrointestinal function versus conventional fluid management and LOS was also noted to be shorter, ($p < 0.001$). Forget el. al. (2010), utilized a moderately sized RCT of 87 patients, to display similar findings. PVI lactate levels were found to be significantly lower intra-operatively, at 24 hours, and 48 hours post-operatively with p values of 0.04, 0.02, and 0.03, respectively.

Discussion

Evaluation

Given the majority of the reviewed studies are RCTs, a certain level of confidence is permitted when interpreting and evaluating the data because observer bias and confounding variables are inherently minimized by design (Siepmann et al., 2016). When synthesizing findings, PVI has mixed success when considering the ability to predict fluid responsiveness and correlate readings with hemodynamic changes. Consistently, PVI can accurately and comparably predict which patients will respond to fluid boluses when a threshold percentage is reached. However, the continued correlation of bolus administration with predictable change in SV does not maintain accuracy. As seen with the secondary endpoints, PVI is as successful as invasive methods in maintaining comparable total volume of crystalloid administered, lactate levels, LOS, and post-operative outcomes; furthermore, PVI far outperforms CFM in these same metrics.

Despite being non-invasive, PVI utilizes the same physiological principles as PPV and SVV to gauge patients' fluid status. Per Vos et.al. (2013), PVI predicts fluid responsiveness as well as invasive techniques in major abdominal surgery. Thus, when a PVI threshold is crossed, for example, 13%, there is statistically significant ability to gauge where on the Frank-Starling curve a patient may be and therefore predict their response to fluid challenge.

However, PVI consistently fails to compare with invasive methods in the ability to track hemodynamic change post-fluid administration . Despite the ability to gauge initial responsiveness, the continued association between the bolus administration and SV improvement is low. The average correlation coefficient (r) reported was 0.45, which classifies PVI's ability to track SV changes and therefore hemodynamics as weak.

Implications

With the ability to predict fluid responsiveness yet the inability to track subsequent hemodynamic change, it is difficult to solely rely upon PVI as a tool to guide goal-directed fluid therapy. When PVI changes do not correlate accurately with hemodynamic changes, the patient's interpreted position on the Frank-Starling curve ultimately becomes a mystery again despite an accurate first assessment. It can be appreciated that if fluid administration continues under the assumption that SV augmentation has not occurred—reflected by persistently high PVI readings—the patient may quickly enter the plateau on the Frank-Starling curve and experience the deleterious effects of hypervolemia. However, this does not ultimately categorize PVI as completely useless. If fluid resuscitation can be approached, at minimum, as a two-part process, then PVI may be a productive tool in the initial recognition of patients that need fluid resuscitation. Knowing that further tracking may be inaccurate, a clinician may incorporate this into the comprehensive clinical picture and utilize other methods for continued fluid resuscitation. Also, if it's simply a case that may not need prolonged, continued fluid administration, then PVI guidance may be deemed safe and sufficient.

Limitations & Future Direction

Ultimately, the majority of studies utilized an RCT design, analyzed data with appropriately selected statistics, and employed clinical scoring systems that reduced potentially confounding variables. However, all studies were subject to limitations, which prompt consideration of the impact on the data displayed. Limitations included:

Baseline fluid boluses and maintenance infusion rates varied greatly between studies. Seven studies provided a baseline, post-induction bolus, typically averaging 250-500ml, based upon a predetermined volume or a weight-based dose. Another nine studies utilized continuous maintenance infusions ranging from 2-4ml/kg/hr starting immediately after induction. A few

studies mention, in their own discussion on limitations, that the administered bolus size (250ml vs 500ml) could have an impact on the sensitivity of PVI readings, with better quality readings associated with larger bolus sizes (Hoiseth et. Al., 2011).

Alteration of vasomotor tone was another significant limitation in studies. Influenced by a myriad of physiological, surgical, and pharmacological variables during surgery, regardless of etiology, the consensus is that PVI reliability is deeply affected by changes in vasomotor tone and subsequent reduction of blood flow in distal capillary beds (Perel, 2020, Monnet et. Al., 2013). A common source of deleterious change to vasomotor tone is vasopressor use, especially norepinephrine (Vos et. al., 2013). The study conducted by Prabhu et. al. (2019), displayed how distal digits are affected to a greater extent than more central areas of measurement such as earlobes or the forehead with the use of vasopressors. As such, studies with overt and regular use of norepinephrine were excluded from this literature review; however, some of the aforementioned studies did utilize infrequent boluses of norepinephrine.

Another significant limitation includes the delivered tidal volume (VT). Since the basis of PVI measurement is dependent on positive pressure ventilation, a 6ml/kg vs 8ml/kg VT can potentially make a difference in the recording quality of PVI (Bahlmann et. al., 2018). Thus, further studies are warranted to dictate and guide optimal ventilation strategies.

As for PVI itself, thresholds higher or lower than 13%, may elicit alterations in the predictability of fluid responsiveness (Hood & Wilson, 2011). Within this review, the vast majority of cases utilized 13% as the treatment threshold so this is a theoretical limitation within this specific literature review. Additionally, PVI tracings based on raw pulse oximetry data instead of the specific Masimo PVI algorithm run the risk of skewed tracing analysis (Hoiseth et. Al., 2011).

Conclusion

Considering the multifactorial approaches in controlling and optimizing peri-operative MAP, fluid balance remains an important cornerstone. Goal-directed fluid therapy is proven to safely achieve euvolemia and improve patient outcomes. However, the decision-making tree that leads to accurate and appropriate fluid resuscitation is not universally agreed upon. Invasive methods that gauge preload status have been used for decades with accurate results but not all surgeries or patient populations demand such invasive techniques. PVI is offered as a non-invasive alternative to gauge pre-load status and fluid responsiveness. As such, this review appears to confirm that PVI is an accurate gauge of fluid responsiveness and is an acceptable tool to guide goal-directed fluid therapy in major abdominal surgeries. However, the use of PVI for precise, continued tracking of SV changes after bolus administration is deemed less accurate. If utilizing PVI as a sole method to guide fluid resuscitation, anesthesia providers must be aware of its limitations. The value of predicting fluid responsiveness is clear in the initial stages of fluid resuscitation; however, the subsequent process, which consists of dynamic tracking, should be accomplished by other monitoring methods or through greater clinical contextualization. Appreciating the comprehensive clinical picture, which includes dynamic patient and surgical influences, can highlight the benefits of PVI while simultaneously achieving euvolemia in patients undergoing major abdominal surgery. Ultimately, despite the lack of strong association between fluid boluses administered and SV augmentation, the total volume of fluid administered and post-operative patient outcomes remain similar in both PVI and invasive monitoring cohorts.

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