Journal of Pediatric Intensive Care 3 (2014) 35–40
DOI 10.3233/PIC-14084
IOS Press

Plethysmography variability index response to isovolemic hemodilution in children prior to surgery for congenital heart disease

Brian Schloss[a,*], Aymen Naguib[a], Bruno Bissonnette[a], Peter Winch[a], Julie Rice[a], Mark Galantowicz[b], Yongjie Miao[c] and Joseph D. Tobias[a]
[a]*Department of Anesthesiology & Pain Medicine, Nationwide Children's Hospital, Columbus, OH, USA*
[b]*Department of Pediatric Cardiothoracic Surgery, Nationwide Children's Hospital, Columbus, OH, USA*
[c]*Department of Cardiovascular and Pulmonary Research, Nationwide Children's Hospital, Columbus, OH, USA*

Received 19 June 2014
Revised 2 July 2014
Accepted 5 July 2014

Abstract. The aim of this study was to evaluate the response of pleth variability index (PVI) to phlebotomy in anesthetized children prior to surgery for congenital heart disease. After induction of general anesthesia and prior to surgical incision, approximately 10 mL/kg of blood was removed from 40 mechanically ventilated children over a 5–10 min period. The PVI was continuously monitored. Additionally, the volume of crystalloid required to ensure hemodynamic and near infrared spectroscopy stability was recorded. There was no difference between the pre-phlebotomy PVI ($13\% \pm 6.2$) and the post-phlebotomy PVI ($16.4\% \pm 9.6$) ($P = 0.55$). Patients who had a starting PVI $\leq$14% had a significant increase in PVI after phlebotomy from $9.1\% \pm 3$ to $14.3\% \pm 7.2$ ($P = 0.0014$). Although, patients with a pre-phlebotomy PVI of >14% required more crystalloid replacement (11 ± 9.4 mL/kg) than those with a PVI $\leq$14% (5.3 ± 4.7 mL/kg), this was not significant ($P = 0.06$). In patients who received less crystalloid replacement during phlebotomy, PVI did show a significant increase. Additionally, the data suggests that patients with a pre-phlebotomy PVI >14% required greater fluid replacement than those with a PVI < 14%. Further research is needed to better delineate the utility of PVI in this unique group of patients.

Keywords: Pleth variability index, fluid responsiveness, plethysmography

1. Introduction

Dynamic parameters of fluid responsiveness, such as pulse pressure variation (PPV) and stroke volume variation (SVV), reflect hemodynamic changes secondary to intermittent positive pressure ventilation [1]. These indices have proven to be superior to static measures of preload in predicting stroke volume increases in response to fluid challenges [2]. Furthermore, the use of these dynamic parameters in a goal-directed fashion has been shown to improve outcomes in high risk, adult surgical patients [3–6]. As such, there is increasing interest in the use of a goal directed fluid strategy for a broader array of surgical patients. In addition, evidence regarding the validity of PPV and SVV in pediatric patients is mixed [7].

The use of plethysmography waveform analysis to predict fluid responsiveness was suggested

*Corresponding author: Dr. Brian Schloss, MD, Department of Anesthesiology & Pain Medicine, Nationwide Children's Hospital, 700 Children's Drive, Columbus, OH 43205, USA. Tel.: +1 614 722 4200; Fax: +1 614 722 4203; E-mail: Brian.Schloss@Nationwidechildrens.org.

in 1999 [8], and further advancements in signal processing technology have linked changes in plethysmography waveform amplitude to PPV [9] and fluid responsiveness [10–13]. The plethysmography waveform amplitude; however, is not easily monitored and therefore holds little clinical utility.

Another measure of plethysmography variation has been developed and incorporated into a new generation of pulse oximetry (Radical 7 pulse oximeter, Masimo Corporation, Irvine CA) and deemed the pleth variability index (PVI). A recent meta-analysis in adults [14], and three recent pediatric studies have shown PVI to accurately predict fluid responsiveness [15–17].

At our institution, it is current practice to remove approximately 10–20 mL/kg of blood with minimal crystalloid replacement prior to surgery for congenital heart defects. This phlebotomy is this clinical practice avoids an unacceptable drop in hemoglobin during the initiation of cardiopulmonary bypass (CPB) [18]. This practice of preoperative phlebotomy provides the unique opportunity to study monitors of fluid balance and intravascular volume alterations without significantly affecting anesthesia practice. Motivated by the lack of data in pediatric patients, the aim of the present study was to prospectively examine the response of PVI to preoperative phlebotomy in children prior to surgery for congenital heart disease (CHD). While this clinical situation does not allow us to test fluid responsiveness per se, it does give us the opportunity to observe PVI changes under conditions of acute intravascular volume changes associated with intraoperative phlebotomy.

Our primary outcome variable was post-phlebotomy PVI, as our hypothesis was that PVI after phlebotomy would be higher than PVI prior to phlebotomy. Our secondary outcome variable was total fluid volume administered to maintain hemodynamic stability. We hypothesized that those with higher starting PVI would require more fluid resuscitation.

2. Materials and methods

After institutional board (IRB) review and approval, a total of 40 patients who were scheduled for surgery for CHD using CPB were enrolled (Table 1). Following the induction of general anesthesia with standard monitoring according to the standards of the American Society of Anesthesiologists, the Masimo pulse co-oximeter (Radical 7, software 7.6.2.1, Masimo Corporation, Irvine CA) was applied to the patient's finger using a disposable probe (adult & pediatric Resposable Rev E R2-20 & R2-25, and Adhesive Rev E R1- 20 L). The probe was placed on the ring or index finger. Perfusion index (PI) is calculated as the ratio between constant and intermittently absorbed light by the pulse oximeter probe. PVI is then automatically calculated based on the dynamic change in PI throughout a respiratory cycle with the formula $[(PI_{max} - PI_{min})/PI_{max}], \times 100$ [19].

Body temperature was continuously monitored and maintained at 36–37°C during data collection. Anesthesia was maintained with 2% sevoflurane in oxygen. Phlebotomy was performed over a 5–10 min period through a central venous catheter or an arterial cannula. The volume of blood removed was calculated based on the patient's weight, starting hematocrit, and a target hematocrit after the initiation of CPB of 24–28%. Prior to the start of phlebotomy, the PVI was recorded during a hemodynamically stable period with minimal stimulation. Hemodynamic values including mean arterial pressure and heart rate, as well as cerebral oxygenation measured by near infrared spectroscopy (NIRS) were monitored during phlebotomy. A greater than 20% change from baseline in these parameters was remedied by volume replacement with crystalloid, the administration of phenylephrine or temporary cessation of phlebotomy. These interventions were left at the discretion of the anesthesiologist. PVI data was collected by a third party and blinded to the anesthesia team during data collection. Additional data collected included patient's age, weight, drugs used during the case, lactate, blood pressure, total pre-CPB crystalloid administered and cerebral oxygen saturation. The crystalloid replacement is the total amount of fluid given prior to initiation of CPB. While our practice is to minimize fluid administration during active phlebotomy, the anesthetic records do not allow us to report how much fluid was given specifically during phlebotomy.

Descriptive statistics were computed to summarize all variables of interest. For continuous variables, mean and standard deviation or median and interquartile rages are provided where appropriate. Student unpaired *t*-test or Wilcoxon rank sum test, where appropriate, was used to compare fluid replacement between pre-phlebotomy PVI >14% group and pre-phlebotomy PVI >14%. Paired *t*-test or non-parametric Wilcoxon singed-rank test was used to test the difference between pre-PVI and post-PVI groups. A P value of less than 0.05 was considered significant. The

data were analyzed using the statistical software SAS version 9.2 (SAS Institute, Cary, NC).

Institutional Review Board approval was obtained prior to this study.

3. Results

A total of 31 of the 40 enrolled patients were included in the final cohort following the exclusion of nine patients due to incomplete data sets. A list of surgeries and their individual fluid requirements are described in Table 1. Ages ranged from 0.25 yr to 19 yr. No arrhythmias were noted during phlebotomy on continuous electrocardiography. All patients were mechanically ventilated during data collection with an average tidal volume of 8.4 ± 1.8 mL/kg. An average of 9.2 ± 3.2 mL/kg of blood was removed during phlebotomy. The average crystalloid replacement prior to initiation of CPB was 7.3 ± 7.1 mL/kg. There was no statistical difference between the pre-phlebotomy PVI ($13 \pm 6.2\%$) and the post-phlebotomy PVI ($16.4 \pm 9.6\%$) ($P = 0.55$). The PI decreased significantly from $6.1 \pm 4.5\%$ to $4.1 \pm 2.9\%$ after phlebotomy ($P = 0.019$).

Of the 31 patients, 20 had a PVI of $\leq 14\%$ (Group 1) while 11 had a PVI >14% prior to phlebotomy (Group 2). There were no significant differences between groups with respect to age, weight, pre-phlebotomy blood pressure, or volume of blood removed during phlebotomy (Table 2). The average crystalloid replacement in group 1 (5.3 ± 4.7 mL/kg) was smaller than crystalloid replacement in group 2 (11 ± 9.4 mL/kg), though this was not a significant difference ($P = 0.06$). Additionally, hemoglobin decreased from 13.3 ± 2.4 g/dL to 12.2 ± 2.3 g/dL ($P = 0.08$), hematocrit decreased from $39.1 \pm 7\%$ to $36 \pm 6.9\%$ ($P = 0.78$), systolic blood pressure decreased from 96.6 ± 18.1 mmHg to 82.4 ± 23.6 mmHg ($P = 0.001$), mean arterial pressure decreased from 69 ± 18 mmHg to 60.1 ± 14.5 mmHg ($P = 0.017$), heart rate changed insignificantly from 103 ± 33.1/min to 100.8 ± 35.5/min ($P = 0.29$), and cerebral saturation decreased from $76 \pm 7.6\%$ to $68.2 \pm 9.4\%$ ($P = 0.005$) (Table 3).

The 20 patients in group 1 (PVI of $\leq 14\%$) had a significantly higher post-phlebotomy PVI ($14.3 \pm 7.2\%$) compared with pre-phlebotomy PVI ($9.1 \pm 3\%$) ($P = 0.0014$). The 11 patients in group 2 (PVI >14%) had a significantly lower post-phlebotomy PVI ($13.7 \pm 9.6\%$) compared with pre-phlebotomy PVI ($20.2 \pm 3.5\%$).

A total of three patients received one time doses of phenylephrine during phlebotomy. Their doses of phenylephrine were 1.4 μg/kg, 2.7 μg/kg, and 1 μg/kg respectively. Their pre-phlebotomy PVI readings were 6%, 17%, and 19%. Their post-phlebotomy PVI readings were 12%, 10%, 19%. Their pre-CPB fluid replacements were 14.5 mL/kg, 14.4 mL/kg, 10.8 mL/kg. One of these same patients required a 7 min pause in phlebotomy. No other patients required vasopressors or phlebotomy pauses.

4. Discussion

The PVI is a novel method of measuring plethysmography variation in response to intermittent positive pressure ventilation (Radical 7 pulse oximeter, Masimo Corporation, Irvine CA). Because the use of dynamic fluid responsiveness parameters are becoming more commonplace in patient monitoring [20], the PVI offers a uniquely non-invasive method of measuring fluid balance in patients undergoing intermittent positive pressure ventilation. Data recorded in the adult population suggest that PVI predicts fluid responsiveness [14]. Similarly, encouraging data has emerged in the pediatric population as well [15–17]. In the present study, there were no significant changes in the PVI following phlebotomy when the cohort was analyzed as a whole. However, when examining the groups separately, PVI did change significantly after phlebotomy.

Given that blood was removed with minimal volume replacement, it is hypothesized that the PVI would increase after the removal of approximately 10 mL/kg of blood. While a small volume of crystalloid (7.3 mL/kg) was administered to replace the whole blood that was removed, only a fraction (30–40%) of this crystalloid volume would remain in the intravascular space [21]. Thus, given their preoperative fasting time and the phlebotomy, it is likely that the patients had a significant decrease in their intravascular status at the time of the post-PVI recording. Our traditional hemodynamic variables such as mean arterial pressure and cerebral saturation did indeed show significant decreases post-phlebotomy. However, when the group was examined as a whole, the PVI increase after phlebotomy was not significant. While unexpected, we postulate that the PVI was not sensitive enough to determine the change in intravascular volume given

a whole blood removal 9.2 mL/kg in the setting of 7.3 mL/kg crystalloid replacement. In important consideration, however, is the internal recruitment of fluid into the intravascular space that occurs during phlebotomy [22]. While difficult to clinically quantify, this may have played a role in augmenting the small amount of crystalloid that was administered.

While no change in PVI was noted in the cohort as a whole, significant changes in PVI were found when examining the two groups separately. Those patients whose pre-phlebotomy PVI values were $\leq$14% had a significant increase in PVI after completion of phlebotomy (9.1% to 14.3%). These patients had an average crystalloid replacement of 5.3 mL/kg. Interestingly, those who had a pre-phlebotomy PVI of >14% had a significant decrease in PVI after completion of phlebotomy (20.2% to 13.7%). These patients received an average crystalloid replacement of 11 mL/kg. A decrease in PVI may not be expected after removal of 9.7 mL/kg of blood; however, this decrease is likely secondary to the larger fluid resuscitation in this group. Patients in group 1, who received a limited fluid resuscitation, had a significant increase in PVI after phlebotomy.

When analyzing fluid requirements between the two groups, a correlation between the amount of fluid administered prior to CPB and the pre-phlebotomy PVI was noted. Those with a pre-phlebotomy PVI of $\leq$14% received an average of 5.3 mL/kg crystalloid replacement in order to maintain hemodynamics, whereas those with a pre-phlebotomy PVI of >14% received an average of 11 mL/kg replacement. This difference, while not significant, suggests the potential utility of PVI given that higher PVI values are indicative of vascular depletion. It is also possible that an association might exist but our study was not powered well enough to detect it.

Given that it was intended as a preliminary trial to evaluate the feasibility of studying this and other monitors which may non-invasively provide insight into hemodynamic function, it is possible that our study may have been underpowered thereby explaining the negative results. However, we believe that a true power calculation would not have been feasible. This was a preliminary study and there are no data on the behavior of PVI during this type of hemodynamic challenge. Additionally, our phlebotomy volumes and resuscitation volumes could not be controlled as we based these on our usual clinical practice where the amount of blood withdrawn is primarily controlled by the starting hematocrit and the patient's hemodynamic stability during phlebotomy. Given these factors, the variables required for a power analysis were not readily known. Additionally, tidal volumes also play an important role when considering the ability of PVI to predict intravascular depletion and fluid responsiveness. Our cohort had an average tidal volume of 8.3 mL/kg with little variation among the cohort. A minimum tidal volume of 8 mL/kg has been shown to be necessary to accurately assess fluid responsiveness in adults [23]. However, higher chest wall and lung compliance in children may necessitate higher tidal volumes in order to properly manifest these dynamic parameters such as PPV, SVV and PVI. Indeed most prospective studies of fluid responsiveness in children have used tidal volumes of 10 mL/kg [23]. Other variables which may affect the utility of PVI include altered right ventricular function, pulmonary hypertension or the type of congenital heart (cyanotic versus non-cyanotic). In general, none of the patients in the current cohort had significant concerns of right ventricular failure or pulmonary hypertension during their preoperative evaluation; however, the presence of right heart strain or acute pulmonary hypertension cannot be completely ruled out during the time of phlebotomy. Given the heterogeneous nature of patient cohort, we did not have ample numbers to identify the impact of these factors in particular the type of CHD on the PVI responsiveness. Future studies are needed to more clearly define this relationship in the pediatric population.

PI is an important consideration when interpreting PVI. Depending on the clinical circumstance, PI may either act as an adjunct to determining fluid responsiveness or may derange the PVI value. Variables such as surgical stress, adrenergic agonists, and temperature can alter PI, and thus, PVI [24]. Under these circumstances, PVI likely becomes less useful as a measure of fluid status. However, when these confounders are absent, the change in PI may increase the sensitivity of PVI as a measure of fluid responsiveness [25]. This study did show a significant decrease in PI, which we attribute to intravascular depletion. Measurements during this study were taken during a time of minimal nociceptive stimulation, a deep level of anesthesia, and constant temperature. Additional considerations include the study population, as well as our PVI cutoff value of 14%. This study was done in pediatric patients with varying forms of CHD. While this heterogeneous group of patients is not the ideal cohort to study a marker of fluid responsiveness, this study would not

be ethically feasible in any other group of patients. Regarding our PVI cutoff, values of 9.5% to 17% have been reported in the literature [26]. Our cutoff of 14% was chosen after taking many of these previous studies into account. Other cutoff values could have been justified however.

In this institution, the clinical practice for perioperative phlebotomy differs somewhat from which is classically described in the literature. Blood removed during isovolemic hemodilution is generally replaced in a 3:1 ratio. When large volumes of crystalloids are administered, the secondary dilution induced by the initiation of CPB may result in an unacceptably low hematocrit during CPB and the need for allogeneic blood transfusion. In our practice, the amount of crystalloid administered is based on cerebral oxygenation, as assessed by NIRS, and monitoring of vital signs [16]. As such, the amount of crystalloid given is often far less than the traditional 3:1 ratio would suggest. In those patients who successfully adhered to our fluid restriction, the PVI did increase in an expected manner. Similarly, those with a higher starting PVI tended to require more fluid based on hemodynamic and NIRS trends.

In conclusion, the present data suggest that patients with a pre-phlebotomy PVI > 14% required greater fluid replacement than those with a PVI $\leq$14%. Those who successfully adhered to our desired fluid restriction did have a significant increase in PVI after phlebotomy of approximately 10 mL/kg of blood. While it's difficult to draw definitive conclusions from this observational study, our data suggest potential for PVI to help guide our phlebotomy practice prior to congenital cardiac surgery. Although we did not assess stroke volume and true fluid responsiveness, our results do support the need for further studies of PVI in pediatric patients. Continued research is needed to better delineate the utility of PVI in this unique group of patients.

References

[1] Cavallaro F, Sandroni C, Antonelli M. Functional hemodynamic monitoring and dynamic indices of fluid responsiveness. Minerva Anestesiol 2008;74(4):123-35.

[2] Michard F, Teboul JL. Predicting fluid responsiveness in ICU patients: A critical analysis of the evidence. Chest 2002;121(6):2000-8.

[3] Donati A, Loggi S, Preiser JC, Orsetti G, Münch C, Gabbanelli V, et al. Goal-directed intraoperative therapy reduces morbidity and length of hospital stay in high-risk surgical patients. Chest 2007;132(6):1817-24.

[4] Gan TJ, Soppitt A, Maroof M, El-Moalem H, Robertson KM, Moretti E, et al. Goal-directed intraoperative fluid administration reduces length of hospital stay after major surgery. Anesthesiology 2002;97(4):820-6.

[5] Grocott MP, Mythen MG, Gan TJ. Perioperative fluid management and clinical outcomes in adults. Anesth Analg 2005;100(4):1093-106.

[6] Lopes MR, Oliveira MA, Pereira VO, Lemos IP, Auler JO Jr, Michard F. Goal-directed fluid management based on pulse pressure variation monitoring during high-risk surgery: A pilot randomized controlled trial. Crit Care 2007;11(5):R100.

[7] Chung E, Cannesson M. Using non invasive dynamic parameters of fluid responsiveness in children: There is still much to learn. J Clin Monit Comput 2012;26(3):153-5.

[8] Shamir M, Eidelman LA, Floman Y, Kaplan L, Pizov R. Pulse oximetry plethysmographic waveform during changes in blood volume. Br J Anaesth 1999;82(2):178-81.

[9] Cannesson M, Besnard C, Durand PG, Bohé J, Jacques D. Relation between respiratory variations in pulse oximetry plethysmographic waveform amplitude and arterial pulse pressure in ventilated patients. Crit Care 2005;9(5):R562-8.

[10] Natalini G, Rosano A, Taranto M, Faggian B, Vittorielli E, Bernardini A. Arterial versus plethysmographic dynamic indices to test responsiveness for testing fluid administration in hypotensive patients: A clinical trial. Anesth Analg 2006;103(6):1478-84.

[11] Solus-Biguenet H, Fleyfel M, Tavernier B, Kipnis E, Onimus J, Robin E, et al. Non-invasive prediction of fluid responsiveness during major hepatic surgery. Br J Anaesth 2006;97(6):808-16.

[12] Feissel M, Teboul JL, Merlani P, Badie J, Faller JP, Bendjelid K. Plethysmographic dynamic indices predict fluid responsiveness in septic ventilated patients. Intensive Care Med 2007;33(6):993-9.

[13] Desebbe O, Cannesson M. Using ventilation-induced plethysmographic variations to optimize patient fluid status. Curr Opin Anaesthesiol 2008;21(6):772-8.

[14] Sandroni C, Cavallaro F, Marano C, Falcone C, De Santis P, Antonelli M. Accuracy of plethysmographic indices as predictors of fluid responsiveness in mechanically ventilated adults: A systematic review and meta-analysis. Intensive Care Med 2012;38(9):1429-37.

[15] Julien F, Hilly J, Sallah TB, Skhiri A, Michelet D, Brasher C, et al. Plethysmographic variability index (PVI) accuracy in predicting fluid responsiveness in anesthetized children. Paediatr Anaesth 2013;23(6):536-46.

[16] Renner J, Broch O, Gruenewald M, Scheewe J, Francksen H, Jung O, et al. Non-invasive prediction of fluid responsiveness in infants using pleth variability index. Anaesthesia 2011;66(7):582-9.

[17] Byon HJ, Lim CW, Lee JH, Park YH, Kim HS, Kim CS, et al. Prediction of fluid responsiveness in mechanically ventilated children undergoing neurosurgery. Br J Anaesth 2013;110(4):586-91.

[18] Dewhirst E, Winch P, Naguib A, Galantowicz M, Tobias JD. Cerebral oximetry monitoring during preoperative phlebotomy to limit allogeneic blood use in patients undergoing cardiac surgery. Pediatr Cardiol 2013;34(1):75-80.

[19] Cannesson M, Desebbe O, Rosamel P, Delannoy B, Robin J, Bastien O, et al. Pleth variability index to monitor the respiratory variations in the pulse oximeter plethysmographic waveform amplitude and predict fluid responsiveness in the operating theatre. Br J Anaesth 2008;101(2):200-6.

[20] Knott A, Pathak S, McGrath JS, Kennedy R, Horgan A, Mythen M, et al. Consensus views on implementation and measurement of enhanced recovery after surgery in England: Delphi study. BMJ Open 2012;2(6). pii: e001878.
[21] Lobo DN, Stanga Z, Aloysius MM, Wicks C, Nunes QM, Ingram KL, et al. Effect of volume loading with 1 liter intravenous infusions of 0.9% saline, 4% succinylated gelatine (Gelofusine) and 6% hydroxyethyl starch (Voluven) on blood volume and endocrine responses: A randomized, three-way crossover study in healthy volunteers. Crit Care Med 2010;38(2):464-70.
[22] Janetzko K, Klüter H, Kirchner H, Klotz KF. The effect of moderate hypovolaemia on microcirculation in healthy older blood donors. Anaesthesia 2001;56(2):103-7.
[23] Gan H, Cannesson M, Chandler JR, Ansermino JM. Predicting fluid responsiveness in children: A systematic review. Anesth Analg 2013;117(6):1380-92.
[24] Takeyama M, Matsunaga A, Kakihana Y, Masuda M, Kuniyoshi T, Kanmura Y. Impact of skin incision on the pleth variability index. J Clin Monit Comput 2011;25(4):215-21.
[25] Desgranges FP, Desebbe O, Ghazouani A, Gilbert K, Keller G, Chiari P, et al. Influence of the site of measurement on the ability of plethysmographic variability index to predict fluid responsiveness. Br J Anaesth 2011;107(3):329-35.
[26] Nilsson LM. Respiration signals from photoplethysmography. Anesth Analg 2013;117(4):859-65.