Original Article

Pulse-wave transit time with ventilator-induced variation for the prediction of fluid responsiveness

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Aim: Although pulse pressure variation is a good predictor of fluid responsiveness, its measurement is invasive. Therefore, a technically simple, non-invasive method is needed for evaluating circulatory status to prevent fluid loading and optimize hemodynamic status. We focused in the pulse-wave transit time (PWTT) defined as the time interval between electrocardiogram R wave to plethysmograph upstroke, which has been recently introduced to non-invasively assess cardiovascular response. In the present study, we evaluated the efficacy of pulse-wave transit time (PWTT) with ventilator-induced variation (PWTTV) in predicting fluid responsiveness.

Methods: We evaluated six domestic pigs weighing 46.0 ± 3.5 kg. After anesthesia induction, electrocardiogram, femoral arterial blood pressure, plethysmograph on the tail, and carotid artery blood flow were monitored and hemorrhage was induced by withdrawing 20 mL/kg blood over 20 min; 5 mL/kg blood volume was then autotransfused over 10 min. Then PWTTV and pulse pressure variation were measured at tidal volumes of 6 and 12 mL/kg.

Results: Area under the receiver operating curve values for the prediction of a >10% change in carotid artery blood flow were 0.979 for pulse pressure variation and 0.993 for PWTTV at a tidal volume of 6 mL/kg and 0.979 and 0.979, respectively, at a tidal volume of 12 mL/kg (all P < 0.0001).

Conclusions: Measured non-invasively, PWTTV showed similar utility to pulse pressure variation in predicting >10% changes in carotid artery blood flow induced by autotransfusion.

Key words: Autotransfusion, blood volume, hemodynamic, non-invasive, pulse pressure

INTRODUCTION

FLUID THERAPY DURING surgery is challenging as both hypovolemia and fluid overload could result in circulatory failure, thereby leading to increased mortality. Therefore, the prediction of patient responses to fluid therapy remains a major issue in the optimization of hemodynamic status. However, there had been no apparent hemodynamic parameter to optimize a fluid balance. Cardiac filling pressures are unable to accurately estimate fluid balance in critically ill patients. Recently, dynamic variables, such as systolic pressure variation, pulse pressure variation (PPV), and stroke volume variation, have been used to detect hypovolemia and evaluate fluid responsiveness. Of these parameters, PPV was considered the most accurate predictor of fluid responsiveness. However, it is calculated by invasive measurement of arterial pressure waveforms. Accordingly, there is a clinical need for non-invasive methods of estimating fluid responsiveness.

In an attempt to resolve this challenging clinical problem, we focused on absolutely non-invasive hemodynamic variables measured by pulse-wave transit time (PWTT), that is, the time interval between the detection of a beat on electrocardiogram (ECG) and on photoplethysmography. Pulse-wave transit time is useful in predicting changes in blood pressure, cardiac output (CO), and fluid responsiveness. It consists of two components: the pre-ejection periods and the vascular transit time. Pre-ejection period has a significant correlation with left ventricular contractility and preload, leading to pulse pressure (PP) changes. Vascular transit time, which is calculated from the pulse wave velocity, has a significant correlation with aortic and brachial PP. In addition, PWTT is useful in the assessment of blood pressure variability and rapid blood pressure changes. We therefore thought that PWTT might be able to track changes in PP. Feissel et al. reported that the respiratory
change in the pre-ejection period with an almost identical definition to PWTT with ventilator-induced variation is as accurate as PPV in predicting fluid responsiveness under septic patients, with an area under the receiver operating characteristic curve (AUROC) of 0.94 and the best threshold value of 4%. However, the ventilator-induced variation in PWTT, termed PWTTV, has not been evaluated in predicting fluid responsiveness under hypovolemia secondary to hemorrhage.

In the present study, we hypothesized that PWTTV might be a good marker in predicting fluid responsiveness and evaluated PWTTV in severely hypovolemic ventilated animals.

**METHODS**

The present study was carried out at the Kochi Medical School (Kochi, Japan) and was approved by the Institutional Animal Research Ethics Committee (H-00094). All experiments were undertaken according to the National Institutes of Health guidelines for the use of experimental animals. We studied six domestic pigs (mean weight, 46.0 ± 3.5 kg).

**General procedure**

**Animal preparation**

Six adult domestic pigs were subjected to overnight fasting, with free access to water. Anesthesia was induced with an i.m. injection of midazolam (0.2 mg/kg), ketamine (5 mg/kg), medetomidine hydrochloride (0.04 mg/kg), and atropine sulfate (0.05 mg/kg). Anesthesia was maintained with isoflurane in 0.5 L/min oxygen and 1.5 L/min air, propofol (2 mg/kg/h), ketamine (5 mg/kg/h), and vecuronium bromide (0.2 mg/kg/h). An adequate depth of anesthesia was evaluated by the maintenance of physiological variables (heart rate and arterial pressure). Supplementary boluses of 1 mg/kg ketamine were given if an animal developed unexpected tachycardia or arterial hypertension. All measurements were carried out at least 5 min after anesthesia was given to minimize the effects of drugs on measured parameters.

Tracheostomy and mechanical ventilation was carried out with the following baseline ventilator settings: a tidal volume (TV) of 12 mL/kg with positive end-expiratory pressure of 3 cmH₂O. Ventilatory frequency was adjusted in order to maintain an end-dioxide (EtCO₂) between 35 and 45 mmHg (Ultima; Datex/Instrumentarium, Helsinki, Finland). The inspiratory fraction of oxygen was adjusted to maintain an arterial saturation of greater than 95%. These settings were used for initial ventilation.

Standard three-lead electrocardiography (lead II), airway pressure monitoring, femoral arterial pressure monitoring, and tail photoplethysmograph were carried out using a polygraph system (RMT-1000; Nihon Kohden, Tokyo, Japan) (f = 1 kHz). The left femoral artery was cannulated for arterial pressure measurements (systole, diastole, mean; ART). A left femoral vein cannula was inserted for infusions, bleeding, and transfusions. Vascular pressures were measured using calibrated pressure transducers (Blood Pressure Monitoring Kit SCKD-5005 [S568]; Becton Dickinson Critical Care Systems, Singapore) positioned at the level of the left atrium. A 7-Fr pulmonary artery catheter (774HF75; Edwards Lifescience, Irvine, CA, USA) was inserted by pressure curve visualization through the internal jugular vein. Pulmonary artery pressures (systole, diastole, mean; PAP) and central venous pressures were measured. Cardiac output was measured by the thermodilution method. Ten milliliters of ice-cold saline was injected three times into the proximal port of the pulmonary artery catheter to calculate CO, with mean CO values recorded. Carotid artery blood flow was measured using an ultrasound flow meter (Transit-time Perivascular Flowmeter TS420, T402; Transonic Systems, New York, NY, USA). After surgical preparation, continuous infusion of 2 mL/kg/h lactated Ringer’s solution was given during the entire experiment. After data collection, animals were euthanized by potassium chloride overdose while under deep anesthesia (Fig. 1).

**Signal processing of ECG, blood pressure, and photoplethysmograph curves**

Electrocardiogram, ART, and photoplethysmograph curves were digitally upsampled offline to 1,000 Hz. The up-sampling was performed in order to obtain a temporal resolution of 1 ms in the curves, which is prerequisite regarding some of the investigated hemodynamic variables. All signal processing and subsequent data analysis were carried out in Labchart 7 (ADInstruments, Bella Vista, Australia).

**Calculation of PWTTV**

Pulse-wave transit time was defined as the time interval from the ECG R wave to the pulse photoplethysmography upstroke. The rise point of the pulse wave was defined as the point at which the differentiated pulse wave reached 30% of its peak amplitude according to previous studies. Maximal (PWTTmax), minimal (PWTTmin), and average (PWTTavg) pulse-wave transit time values were determined over the same respiratory cycle.
We defined PWTTV using the following equation:

\[ \text{PWTTV} = \frac{\text{PWTT}_{\text{max}} - \text{PWTT}_{\text{min}}}{\text{PWTT}_{\text{avg}}} \]

**Calculation of PPV**

Pulse pressure was defined as the difference between systolic and diastolic arterial pressure. Maximal (PP\(_{\text{max}}\)), minimal (PP\(_{\text{min}}\)), and average (PP\(_{\text{avg}}\)) PP values were determined over the same respiratory cycle.

We then calculated PPV as follows:

\[ \text{PPV} = \frac{\text{PP}_{\text{max}} - \text{PP}_{\text{min}}}{\text{PP}_{\text{avg}}} \]

**Study protocol**

**To demonstrate fluid responsiveness in PWTTV**

Hemorrhage was induced by the withdrawal of a blood volume (BV) of 20 mL/kg over 20 min. After hemorrhage, autotransfusion was carried out by the step by step addition of a BV of 5 mL/kg. Ventilator settings were changed from a TV of 6–12 mL/kg with a positive end-expiratory pressure of 3 cmH\(_2\)O. Data were collected from five different phases – after hemorrhage (baseline) and after each transfusion – while maintaining hemodynamic stability for 10 min (Fig. 2).

**Statistical analysis**

Data from a previous study where used for the power analysis.\(^{17}\) Using these data (mean PPV, 13%; standard deviation [SD], 6%), six pigs were predicted to be required in order to detect a 10% difference in PPV, considered clinically significant, with \(\alpha = 0.05\) and a power of 80%. Accordingly, six pigs were used in the present study. Hemodynamic values were presented as means ± SD). Spearman’s rank correlation coefficient and fitting to the regression line using the least squares method were applied to evaluate the correlation between PP and PWTT. To confirm the correlation, we compared calculated PP values with measured PP values using Bland–Altman plots.\(^{18}\) The limit of agreement was defined as ± 2 SD. Receiver operating characteristic curves were used to compare the ability of each method to predict a >10% change in CO. The best threshold of a receiver operating characteristic curve was chosen as that which maximized the Youden index (sensitivity + specificity – 1).\(^{19}\) Predictive accuracy was described using standard terms: poor (AUROC, 0.6–0.7), fair (AUROC, 0.7–0.8), good (AUROC, 0.8–0.9), and excellent (AUROC, 0.9–1.0). The AUROC data were presented with 95% confidence intervals (CI). \(P\)-values < 0.05 were considered statistically significant (JMP Sample JSL Scripts 2009 and JMP 11 2014; SAS Institute, Cary, NC, USA).

**RESULTS**

Heart rates significantly increased after hemorrhage compared to after anesthesia induction at a TV

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of both 6 and 12 mL/kg. The ART, PAP, and estimated CO values were significantly decreased after hemorrhage compared to after anesthesia induction at a TV of both 6 and 12 mL/kg. After transfusion, HR gradually decreased and ART, PAP, and carotid artery blood flow gradually increased at a TV of both 6 and 12 mL/kg, although these differences did not reach statistical significance (Table 1).

The AUROC values for PPV and PWTTV under a TV of 6 mL/kg were 0.944 (excellent, $P < 0.0001$; 95% CI, 0.764–0.989) and 0.993 (excellent, $P < 0.0001$; 95% CI, 0.898–0.999), respectively. Threshold values were 15% (sensitivity and specificity of 100% and 83%, respectively) for PPV and 7% (sensitivity and specificity of 83% and 92%, respectively) for PWTTV. The AUROC values for PPV and PWTTV under a TV of 12 mL/kg were 0.979 (excellent, $P < 0.0001$; 95% CI, 0.829–0.998) and 0.997 (excellent, $P < 0.0001$; 95% CI, 0.860–0.997), respectively. Threshold values were 16% (sensitivity and specificity of 92% and 91%, respectively) for PPV and 8% (sensitivity and specificity of 85% and 85%, respectively) for PWTTV (Table 2, Fig. 3).

**DISCUSSION**

In the present study of severely hypovolemic animals, we showed that PWTTV has an excellent (TV of 12 and 6 mL/kg) ability to predict a >10% change in carotid artery blood flow, similar to that of PPV. Because its measurement is non-invasive, PWTTV was considered a superior hemodynamic parameter from a clinical point of view.

First, we planned to be able to detect fluid responsiveness to small transfusion amounts (BV of 5 mL/kg in each phase) as the results derived from the present study could have utility in patients with hemodynamic instability. Therefore, we evaluated small variations in CO. Arterial pulse-wave analysis devices, esophageal Doppler devices, and/or transesophageal echocardiography have been used recently to estimate fluid responsiveness,20 but these devices have >10% internal error when calculating CO.21,22 Therefore, we were unable to detect small changes in CO, particularly on or after a steep portion of the Frank–Starling curve. We used carotid artery blood flow values to distinguish between responders and non-responders. Carotid artery blood flow has been reported to be representative of beat-by-beat CO23 and can be measured without thoracotomy. Hemodynamic variables with ventilator-induced variation have been reported to be influenced by open-chest conditions.24–26 Therefore, we considered carotid artery blood flow as the most reliable marker for estimating fluid responsiveness in order to detect small variations in CO.

Second, we compared PWTTV with PPV to clarify the benefit of PWTTV. Cannesson et al. reported PPV as a superior hemodynamic parameter for the estimation of fluid responsiveness (AUROC, 0.938; cut-off, 12.5%; sensitivity, 87%; specificity, 89%).27 Therefore, among the different methods that are currently available for detecting fluid responsiveness, PPV has received the greatest attention,5,6 and it has been validated under specific conditions, such as controlled ventilation with a TV of at least 8 mL/kg.28 Therefore, we evaluated at both low (6 mL/kg) and conventional (12 mL/kg) TV ventilation. Pulse-wave transit time with ventilator-induced variation had an excellent predictive ability for fluid responsiveness at a TV of 12 mL/kg (AUROC, 0.979; cut-off, 8%; sensitivity, 85%; specificity, 85%) and also excellent at a TV of 6 mL/kg (AUROC, 0.993; cut-off, 7%; sensitivity, 83%; specificity, 92%), in hypovolemic ventilated animals. Therefore, the results of the present study were considered to be reliable. Pulse-wave transit time with ventilator-induced variation was therefore considered a superior dynamic parameter.
### Table 1. Hemodynamic variables under different ventilatory settings before and after volume loading

| TV (mL/kg) | HR (b.p.m.) | ART (mmHg) | PAP (mmHg) | CVP (mmHg) | CO (L/min) | Estimated CO (L/min) | Carotid blood flow (L/min) | PWTTV (%) | PPV (%) |
|------------|-------------|------------|------------|------------|------------|----------------------|---------------------------|-----------|---------|
|            |             | Systole    | Diastole   | Mean       | Systole    | Diastole   | Mean       |           |         |
| 6 mL/kg    | After anesthesia induction | 95 ± 13 | 113 ± 22 | 77 ± 17 | 95 ± 18 | 18 ± 9 | 7 ± 9 | 13 ± 10 | 3 | 6.9 ± 0.3 |
|            | After hemorrhage (20 mL/kg) | 113 ± 29 * | 80 ± 27 * | 50 ± 17 * | 61 ± 20 * | 10 ± 8 * | 0 ± 7 | 4 ± 7 | 0 | 4.3 ± 0.9 * | 0.6 ± 0.3 | 26 ± 13 | 27 ± 5 |
|            | Transfusion 1 (5 mL/kg) | 107 ± 20 | 104 ± 18 | 64 ± 14 | 80 ± 14 | 11 ± 9 | 3 ± 9 | 7 ± 9 | 0 | 5.5 ± 0.9 | 0.8 ± 0.5 | 18 ± 15 | 13 ± 6 |
|            | Transfusion 2 (5 mL/kg) | 101 ± 13 | 107 ± 21 | 67 ± 19 | 83 ± 19 | 14 ± 10 | 5 ± 8 | 9 ± 9 | 0 | 5.9 ± 0.8 | 0.9 ± 0.4 | 13 ± 8 | 9 ± 2 |
|            | Transfusion 3 (5 mL/kg) | 95 ± 12 | 109 ± 20 | 68 ± 20 | 85 ± 20 | 16 ± 9 | 5 ± 9 | 11 ± 9 | 1 | 6.0 ± 0.8 | 0.9 ± 0.5 | 14 ± 10 | 7 ± 2 |
|            | Transfusion 4 (5 mL/kg) | 95 ± 10 | 113 ± 23 | 71 ± 22 | 88 ± 23 | 16 ± 8 | 8 ± 7 | 12 ± 8 | 2 | 6.2 ± 1.0 | 0.8 ± 0.5 | 13 ± 9 | 6 ± 2 |
| 12 mL/kg   | After anesthesia induction | 95 ± 13 | 113 ± 22 | 77 ± 17 | 95 ± 18 | 18 ± 9 | 7 ± 9 | 13 ± 10 | 3 | 6.9 ± 0.3 |
|            | After hemorrhage (20 mL/kg) | 115 ± 26 * | 67 ± 22 * | 41 ± 14 * | 51 ± 16 * | 10 ± 7 * | 0 ± 7 | 5 ± 7 | 0 | 3.8 ± 0.9 * | 0.5 ± 0.2 | 29 ± 15 | 31 ± 7 |
|            | Transfusion 1 (5 mL/kg) | 110 ± 20 | 100 ± 18 | 63 ± 13 | 77 ± 14 | 12 ± 9 | 3 ± 7 | 7 ± 10 | 0 | 5.1 ± 0.8 | 0.8 ± 0.4 | 22 ± 17 | 24 ± 11 |
|            | Transfusion 2 (5 mL/kg) | 103 ± 15 | 106 ± 22 | 67 ± 19 | 83 ± 19 | 12 ± 9 | 5 ± 8 | 8 ± 8 | 0 | 5.8 ± 0.7 | 0.9 ± 0.4 | 19 ± 9 | 19 ± 5 |
|            | Transfusion 3 (5 mL/kg) | 97 ± 12 | 108 ± 22 | 67 ± 20 | 83 ± 21 | 15 ± 9 | 5 ± 9 | 10 ± 9 | 1 | 6.1 ± 0.8 | 0.9 ± 0.4 | 17 ± 9 | 13 ± 4 |
|            | Transfusion 4 (5 mL/kg) | 95 ± 9 | 111 ± 22 | 71 ± 22 | 87 ± 22 | 17 ± 10 | 8 ± 8 | 13 ± 10 | 2 | 6.3 ± 1.2 | 0.8 ± 0.4 | 21 ± 19 | 12 ± 3 |

Values are expressed as means ± standard deviation.
ART, arterial pressure waveform; CO, cardiac output; CVP, central venous pressure; HR, heart rate; PAP, pulmonary artery pressure; PPV, pulse pressure variation; PWTTV, pulse-wave transit time with ventilator-induced variation.

*P < 0.05 vs after anesthesia induction.
LIMITATIONS

THE PRESENT STUDY has some limitations. First, we undertook the present study using young subjects. Cardiac function and vessel reactivity were absolutely normal. Therefore, particularly in elderly subjects and/or subjects with cardiovascular disease, the results might be changed. Second, the present study was designed to evaluate the fluid responsiveness using PWTTV and PPV during severe hypovolemia secondary to hemorrhage. We were unable to ensure that the same volume status was present in all experimental animals as time-dependent compensatory fluid shifts could have interfered with volume status. Therefore, we were unable to evaluate the BV from PWTTV and PPV values. Finally, in the present study, pulmonary conditions in all subjects were thought to be normal. Therefore, under pulmonary insufficiency, PWTTV values might be changed. Further basic and clinical studies are required to determine the reliability of PWTTV for estimating fluid responsiveness.

CONCLUSIONS

PULSE-WAVE TRANSIT time with ventilator-induced variation, which is measured non-invasively, was found to be a good and reliable predictor of >10% changes in carotid artery blood flow induced by transfusion, similar to PPV. We believe this novel non-invasive hemodynamic parameter could be useful in various clinical settings, including the ward, operation room, and emergency room.

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**DISCLOSURE**

Approval of the research protocol: The present study was carried out at the Kochi Medical School (Kochi, Japan) and was approved by the Institutional Animal Research Ethics Committee (H-00094).

Informed consent: N/A.

Registry and the registration no. of the study/trial: N/A.

Animal studies: All animal experiments were undertaken following the national guidelines and the relevant national laws on the protection of animals.

Conflict of interest: None.

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