The effects of hemodynamic management using the trend of the perfusion index and pulse pressure variation on tissue perfusion: a randomized clinical trial

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Abstract

Background: Intraoperative hemodynamic management is challenging because precise assessment of the adequacy of the intravascular volume is difficult during surgery. Perfusion index (PI) has been shown to reflect changes in peripheral circulation perfusion. Pulse pressure variation (PPV) reflects the preload responsiveness. The hypothesis of this study was that hemodynamic management using the trend of the PI and PPV would improve tissue perfusion.

Methods: This was a prospective, randomized, parallel design, single-blind, single-center clinical trial. Patients undergoing elective open gynecological surgery requiring a direct arterial line were included. The patients were randomly allocated to two groups. The intervention group received hemodynamic management using the trend of the PI and PPV in an effort to improve tissue perfusion when the mean arterial pressure was <60 mmHg. The control group received hemodynamic management at the discretion of the anesthesia care provider. The primary outcome was the peak lactate level during surgery. The secondary outcomes were the duration of hypotension, intraoperative fluid balance, intraoperative urine output, and postoperative complication rate. Statistical analysis was performed using Student’s t-test and Fisher’s exact test. A P value of <0.05 was considered statistically significant.

Results: Although the intervention significantly decreased the duration of hypotension and intraoperative fluid balance, the peak lactate level was not different between the intervention group and the control group. Intraoperative urine output and postoperative complication rate were not different between the groups.

Conclusion: Hemodynamic management using the trend of the PI and PPV does not improve tissue perfusion in patients undergoing open gynecological surgery.

Trial registration: This trial was prospectively registered on a publicly accessible database (UMIN Clinical Trials Registry ID: UMIN 000026957).

Background

Intraoperative hemodynamic management is challenging because precise assessment of the adequacy of the intravascular volume is difficult during surgery.[1] Dynamic indices based on heart–lung interactions have been increasingly used to guide perioperative fluid resuscitation.[2] Although goal-directed fluid therapy (GDFT) has been shown to reduce perioperative complications in high-risk patients, some studies have shown conflicting results; i.e., GDFT did not reduce complications.[3-5] Challand et al. showed that stroke volume (SV) optimization using colloid bolus administration without vasopressors increased the length of hospital stay.[4] These studies have indicated that GDFT alone is insufficient for optimizing the hemodynamic status during surgery. To ensure adequate tissue perfusion, maintaining appropriate perfusion pressure by methods other than alterations in cardiac output (CO) is also crucial. Hypotension is reportedly associated with adverse perioperative outcomes.[6-8] Walsh et al. showed that
an intraoperative mean arterial pressure (MAP) of <55 mmHg was associated with perioperative acute kidney injury and acute myocardial injury.[6]

The perfusion index (PI) is calculated from the infrared signal using the following formula: PI = (pulsatile signal / nonpulsatile signal) × 100. The PI reflects the amplitude of the pulse oximeter waveform.[9] The PI has been shown to reflect changes in peripheral circulation perfusion.[10] Peripheral perfusion is influenced by CO and peripheral vasomotor tone[11] and is sensitive to sympathetic vasoconstriction and skin temperature.[12, 13] The PI might be used as a surrogate of CO if sympathetic tone and skin temperature are kept stable. The pulse pressure variation (PPV) is calculated from the arterial waveform using the following formula: PPV = [(maximum pulse pressure) − (minimum pulse pressure)] / [(maximum pulse pressure) + (minimum pulse pressure)] × 2⁻¹ × 100 and reflects the preload responsiveness.[14] A PPV of <13% during mechanical ventilation using a tidal volume of 8 mL kg⁻¹ reliably predicts preload responsiveness.[15] A low PPV indicates that the patient’s left ventricle is positioned at the “steep” part of the Frank–Starling curve.[14] Lactate is one of the end products of anaerobic glycolysis. The serum lactate level is considered a surrogate of tissue perfusion because the lactate level increases in states of low peripheral perfusion.[16]

Although the SV and CO can be measured intraoperatively with several devices such as esophageal Doppler or pulse contour analysis, the cost of these devices may impede widespread use of SV/CO measurement.[17] The anesthetic monitor Life Scope J (Nihon Kohden, Tokyo, Japan) provides PI and PPV measurements without any other devices. Anesthesiologists can evaluate the PI and PPV if a pulse oximeter and direct arterial line are placed in the patient. We considered that a hemodynamic protocol that uses the PI and PPV might improve patient safety in hospitals where expensive devices are not feasible because the Life Scope J monitor does not require expensive devices. We developed a hemodynamic protocol using the trend of the PI and PPV to maintain adequate tissue perfusion. The hypothesis of this study was that hemodynamic management using the trend of the PI and PPV would improve tissue perfusion.

Methods

This manuscript adheres to the applicable CONSORT guidelines. The supporting CONSORT checklist is available as Additional File 1. This prospective, randomized, parallel design, single-blind, single-center clinical trial was approved by the ethics committee of Kagoshima University Hospital and was conducted from May 2017 to November 2018 at Kagoshima University Hospital. This trial was prospectively registered on a publicly accessible database (UMIN Clinical Trials Registry ID: UMIN 000026957). Written informed consent was obtained from all participants.

The inclusion criteria were an American Society of Anesthesiologists physical status of I to III and performance of elective open gynecological surgery requiring a direct arterial line. The exclusion criteria were a history of uncompensated cardiac disease, stroke, arrhythmias, and severe liver/renal dysfunction.
Protocol

Before induction of general anesthesia, a thoracic or lumbar epidural catheter (17G Tuohy needle, Hakko disposable epidural catheter; Hakko, Nagano, Japan) was placed at T10 to L1 according to the incision level, and 3 mL of 1% mepivacaine without epinephrine was administered. General anesthesia was induced with target-controlled infusion of propofol (1.0–2.0 mg kg\(^{-1}\)), remifentanil (0.3–0.5 \(\mu\)g kg\(^{-1}\) min\(^{-1}\)), and rocuronium (0.6–1.0 mg kg\(^{-1}\)). Anesthesia was maintained with desflurane (0.6–0.7 age-adjusted minimum alveolar concentration) and remifentanil (0.05–0.5 \(\mu\)g kg\(^{-1}\) min\(^{-1}\)) and intermittent bolus administration of rocuronium (10 mg) and fentanyl (2–10 \(\mu\)g kg\(^{-1}\)). The rate of remifentanil infusion was tailored to control hemodynamic responses. Rocuronium was used to maintain a train-of-four ratio of \(\leq 1\) (TOF-Watch SX; Organon, Dublin, Ireland). The Life Scope J was used to continuously monitor the heart rate, direct arterial blood pressure, electrocardiogram, peripheral oxygen saturation, end-tidal carbon dioxide tension (ETCO\(_2\)), PPV, PI derived from the pulse oximeter plethysmographic waveform, bladder temperature, and skin temperature of the hand. To assess the hemodynamic effects of the intervention, we continuously monitored the cardiac index (CI) and SV variation (SVV) with a high-fidelity dedicated pressure transducer (FloTrac sensor; Edwards Lifesciences, Irvine, CA, USA) and the Vigileo monitor, software version 3.01 (Edwards Lifesciences). The CI was calculated based on real-time analysis of the arterial waveform during a 20-second period. This calculation was performed at a sample rate of 100 Hz without the need for prior calibration using a proprietary algorithm based on the principle that the aortic pulse pressure is proportional to the SV. Dynamic arterial elastance (Ea\(_{\text{dyn}}\)), which represents the arterial load, was calculated as the ratio between the PPV and SVV.

The patients’ lungs were ventilated with an inspired oxygen fraction of 0.4 and tidal volume of 8 mL kg\(^{-1}\) of ideal body weight, and the respiratory rate was adjusted to maintain an ETCO\(_2\) of 35 to 45 mmHg and a positive end-expiratory pressure of 5 to 8 cmH\(_2\)O. The patients were randomly allocated to one of two groups with an allocation ratio of 1:1 using Internet-based software in a complete randomization manner (Research Randomizer version 4.0, retrieved on October 13, 2016 from http://www.randomizer.org/). The patients were blinded to the allocation. In the intervention group, 250 mL of colloid (Voluven; Otsuka Pharmaceutical, Tokyo, Japan) was infused during induction, followed by continuous infusion of a balanced crystalloid (Bicanate; Otsuka Pharmaceutical) at a rate of 2 mL kg\(^{-1}\) h\(^{-1}\). In addition to the balanced crystalloid, 4.3% dextrose solution (Soldem 3A; Terumo, Tokyo, Japan) was administered at a rate of 20 mL h\(^{-1}\). If the MAP was <60 mmHg, the trend of the PI was evaluated (Figure 1). If the PI increased by >5% of previous value in 15 minutes, we considered that the hypotension was due to afterload reduction and administered a 0.1-mg bolus of phenylephrine followed by continuous infusion of phenylephrine at rate of 1.0 mg/h. The infusion rate of phenylephrine was adjusted every 10 minutes (0.1–2.0 mg h\(^{-1}\)) to maintain the MAP within 60 to 90 mmHg. If the PI did not increase by >5% of previous value in 15 minutes, we evaluated the PPV. If the PPV was <13%, we considered that the hypotension was due to reduced contractility and administered a continuous infusion of dobutamine at a rate of 3 \(\mu\)g kg\(^{-1}\) min\(^{-1}\). The infusion rate of dobutamine was adjusted every 10 minutes (1–5 \(\mu\)g kg\(^{-1}\)}
to maintain the MAP within 60 to 90 mmHg. If the PPV was \(\geq 13\%\), we considered that the hypotension was due to preload reduction and administered a 250-mL bolus of colloid (Voluven; Otsuka Pharmaceutical). In the control group, the hemodynamic management was performed at the discretion of the anesthesia care provider. Red blood cells were transfused when the hemoglobin level was \(<7\text{ g dL}^{-1}\). Arterial blood samples were taken at the time of skin incision, every 2 hours during surgery, and at the end of surgery. The lactate concentration was measured using an ABL 620 analyzer (Radiometer, Copenhagen, Denmark). Postoperative complications were recorded during the first 30 days after surgery; these included pulmonary infection and infection of other organs as well as leakage at the anastomosis site.

### Data Analysis

The primary outcome was the peak lactate level during surgery. The secondary outcomes were the duration of hypotension (MAP of \(<60\text{ mmHg}\) or 30% below the value measured the day before surgery while the patient was resting quietly for at least 15 minutes), intraoperative fluid balance, intraoperative urine output, and postoperative complication rate. To detect a 0.5-mmol L\(^{-1}\) difference in the peak lactate level with a two-sided approximation while accepting an a error of 5% and b error of 20%, the required study size was calculated as 34 patients based on the preliminary data using Power and Sample Size Calculation version 3.1.2 (Dupont WD and Plummer WD, Vanderbilt University, Nashville, TN). To account for patient dropout, 20% more patients were added, giving a final sample size of 40 patients. All data were expressed as mean with standard deviation or 95% confidence interval. The statistical analysis was performed using Student’s t-test and Fisher’s exact test (GraphPad Prism 5.0; GraphPad Software, La Jolla, CA, USA). A \(P\) value of \(<0.05\) was considered statistically significant.

### Results

The CONSORT diagram is shown in Figure 2. Of 41 patients considered eligible for the study, 1 patient declined to participate. Thus, 40 patients were included in the study. Three patients did not receive their allocated intervention because of a changed surgical plan and protocol violations. Another three patients’ data were not analyzed because of a protocol violation. Therefore, the data from 34 patients were analyzed. Table 1 shows the patients’ characteristics. Most patients underwent radical hysterectomy. No patient had severe respiratory dysfunction, received preoperative b-blocker medications, or was transfused preoperatively. Table 2 shows the primary and secondary outcomes. Although the intervention significantly decreased the duration of hypotension and intraoperative fluid balance, the peak lactate level was not different between the intervention group and control group. The number of patients whose peak lactate level was \(>2.0\text{ mmol L}^{-1}\) was two in the intervention group and three in the control group (\(P > 0.99\)).

Table 3 shows the intraoperative data. The MAP and SVV were significantly higher in the intervention group than control group. The intervention significantly decreased \(E_{a\text{, dyn}}\). Patients in the intervention group were given less crystalloid intraoperatively than patients in the control group. Although the number
of patients who received a vasopressor was not different between the groups, the dose of phenylephrine was higher in the intervention group. The number of patients whose mean PI was <1.4% was five in the intervention group and three in the control group \((P = 0.69)\). There was no difference in the respiratory parameters between the groups. There was no important harm in either group.

**Discussion**

Hemodynamic management using the trend of the PI and PPV did not decrease the intraoperative peak lactate level. Among the secondary outcomes, the intervention significantly decreased the duration of hypotension and intraoperative fluid balance. The MAP and SVV were higher in the intervention group than control group, although less crystalloid was infused in the intervention group. The intervention significantly decreased \(E_{a_{dyne}}\).

Our hypothesis that hemodynamic management using the trend of the PI and PPV would improve tissue perfusion was not confirmed in this study. There are several possible explanations for why our hypothesis failed to be confirmed. One simple explanation is that the hemodynamic management did not decrease the intraoperative lactate level because the intervention did not improve tissue perfusion. Another explanation is that the intraoperative lactate level did not differ between the groups because tissue perfusion was not decreased in either group. Actually, the lactate levels were not considered to be increased because the peak lactate level in both groups was <2.0 mmol L\(^{-1}\).[18] In addition, the CI and SVI were within the reference range in both groups.[19] Forget et al. reported that GDFT using the pleth variability index reduced the lactate level in patients undergoing major abdominal surgery.[20] The differences in these results might be due to different hemodynamic management protocols and different patient characteristics. We selected open gynecological surgery to reduce variability. Because the PI is sensitive to sympathetic vasoconstriction and skin temperature, we maintained normothermia.[12] A PI of <1.4% has been reported to represent poor peripheral perfusion in clinically ill patients.[10] The number of patients whose mean PI was <1.4% was not different between the groups. Because the PI reportedly has considerable inter-individual variability, we used the trend of the PI.

The intervention significantly decreased \(E_{a_{dyne}}\). \(E_{a_{dyne}}\) is reported to represent the arterial load.[21] The intervention group received larger doses of phenylephrine than did the control group. Monge García et al. showed that increasing the arterial load using phenylephrine infusion significantly decreased \(E_{a_{dyne}}\) in a rabbit model.[22] We have shown that phenylephrine infusion significantly decreased the PPV during one-lung ventilation.[23] In this study, although the doses of phenylephrine were higher in the intervention group than control group, PPV was not different between the groups. The differences between the results of our previous study and current study may be due to the concomitant colloid bolus or dobutamine infusion. No serious adverse events occurred during this study.

Our study has several limitations. First, we included female patients only. Our results cannot be generalized to male patients. Second, the group allocation was only blinded to the patients. Hence, this could have produced bias. However, we believe that our strict protocol minimized the effects of this
potential bias. Third, we used the peak lactate level as a surrogate of tissue perfusion. Because we did not measure tissue perfusion directly using ultrasound or near-infrared spectroscopy, the actual tissue perfusion cannot be assessed.

Conclusions

In conclusion, although hemodynamic management using the trend of the PI and PPV significantly decreased the duration of hypotension and intraoperative fluid balance, the intervention did not decrease the intraoperative peak lactate level. These results indicate that hemodynamic management using the trend of the PI and PPV does not improve tissue perfusion in patients undergoing open gynecological surgery.

Abbreviations

CI, cardiac index; CO, cardiac output; \(Ea_{\text{dyn}}\), dynamic arterial elastance; ETCO\(_2\), end-tidal carbon dioxide tension; GDFT, goal-directed fluid therapy; MAP, mean arterial pressure; PI, perfusion index; PPV, pulse pressure variation; SV, stroke volume; SVV, stroke volume variation

Declarations

Ethics approval and consent to participate

This clinical trial was approved by the ethics committee of Kagoshima University Hospital. This trial was prospectively registered on a publicly accessible database (UMIN Clinical Trials Registry ID: UMIN 000026957). Written informed consent was obtained from all participants.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

KG conceptualized and designed the study; acquired, analyzed, and interpreted the patient data; and wrote the manuscript.

AM helped conceptualize and design the study and critically revised the manuscript.

YK supervised the conduction of the study and critically revised the manuscript.

All authors read and approved the final manuscript.

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Tables

**Table 1.** Patient characteristics
|                                | Intervention Group | Control Group |
|--------------------------------|--------------------|---------------|
|                                | \( n = 17 \)       | \( n = 17 \)  |
| Age (years)                    | 49 ± 11            | 53 ± 17       |
| Height (cm)                    | 156 ± 6            | 157 ± 6       |
| Weight (kg)                    | 61 ± 13            | 55 ± 12       |
| ASA-PS                         |                    |               |
| 1                              | 4 (24)             | 6 (35)        |
| 2                              | 13 (76)            | 11 (65)       |
| Comorbidities                  |                    |               |
| Obesity                        | 3 (18)             | 1 (6)         |
| Smoking                        | 1 (6)              | 1 (6)         |
| Hypertension                   | 5 (29)             | 6 (35)        |
| Anemia                         | 5 (29)             | 3 (18)        |
| Asthma                         | 2 (12)             | 0 (0)         |
| Diabetes mellitus              | 4 (24)             | 1 (6)         |
| Types of surgery               |                    |               |
| Radical hysterectomy           | 12 (71)            | 14 (82)       |
| Radical trachelectomy          | 2 (12)             | 0 (0)         |
| Salpingo-oophorectomy          | 3 (18)             | 3 (18)        |

Abbreviation: ASA-PS, American Society of Anesthesiologists physical status.

Values are expressed as mean ± standard deviation or number and percentage.

**Table 2.** Primary and secondary outcomes
|                              | Intervention Group (n = 17) | Control Group (n = 17) | P value |
|------------------------------|-----------------------------|------------------------|---------|
| Peak lactate levels (mmol/L) | 1.4 ± 1.0                   | 1.2 ± 0.5              | 0.45\textsuperscript{a} |
| Duration of hypotension (min/h) | 7.7 ± 5.0                   | 17.1 ± 10.6            | 0.003\textsuperscript{a} |
| Intraoperative fluid balance (mL/kg/h) | 4.3 ± 1.3                   | 7.2 ± 3.3              | 0.002\textsuperscript{a} |
| Intraoperative urine output (mL/kg/h) | 0.9 ± 0.8                   | 1.2 ± 1.0              | 0.42\textsuperscript{a} |
| Postoperative complication rate (%) | 0                          | 0                      | >0.99\textsuperscript{b} |

Values are expressed as mean ± standard deviation or percentage.

\textsuperscript{a}P values were calculated using Student’s \textit{t}-test. \textsuperscript{b}P values were calculated using Fisher’s exact test.

\textbf{Table 3.} Intraoperative data
|                          | Intervention Group (n = 17) | Control Group (n = 17) | P value |
|--------------------------|-----------------------------|------------------------|---------|
| Duration of anesthesia (min) | 342 ± 96                    | 332 ± 85               | 0.74a   |
| Duration of surgery (min)  | 238 ± 89                    | 239 ± 85               | 0.98a   |
| Intraoperative blood loss (mL) | 468 ± 466                  | 485 ± 407              | 0.91a   |
| HR (beats/min)            | 71 ± 11                     | 75 ± 11                | 0.30a   |
| MAP (mmHg)                | 74 ± 6                      | 69 ± 7                 | 0.04a   |
| PI (%)                    | 2.4 ± 1.6                   | 2.8 ± 1.5              | 0.45a   |
| PPV (%)                   | 9.8 ± 3.8                   | 8.8 ± 2.7              | 0.39a   |
| SVV (%)                   | 12.1 ± 3.8                  | 9.6 ± 2.2              | 0.02a   |
| Ea_{dyn}                  | 0.79 ± 0.09                 | 0.89 ± 0.17            | 0.04a   |
| CI (L/min/m$^2$)          | 2.9 ± 0.7                   | 3.3 ± 1.0              | 0.27a   |
| SVI (mL/m$^2$)            | 41 ± 11                     | 42 ± 8                 | 0.90a   |
| Crystallloid (mL/kg/h)     | 3.8 ± 1.1                   | 6.2 ± 2.1              | 0.0002a |
| Colloid (mL/kg/h)         | 2.3 ± 1.2                   | 3.3 ± 3.0              | 0.23a   |
| Number of patients transfused with RBC (n) | 4                         | 5                      | >0.99b  |
| RBC transfusion (mL)      | 135 ± 256                   | 112 ± 203              | 0.77a   |
| Number of patients used ephedrine (n) | 15                        | 13                     | 0.66b   |
| Ephedrine (mg/h)          | 1.5 ± 1.1                   | 2.1 ± 1.7              | 0.31a   |
| Number of patients used phenylephrine (n) | 16                       | 14                     | 0.60b   |
| Phenylephrine (mg/h)      | 0.73 ± 0.44                 | 0.22 ± 0.32            | 0.0006a |
| Number of patients used dobutamine (n) | 3                         | 0                      | 0.23b   |
| Dobutamine (mg/kg/min)    | 0.14 ± 0.49                 | 0.00 ± 0.00            | 0.24a   |
| ETCO$_2$ (mmHg)           | 37 ± 1.4                    | 37 ± 1.4               | 0.39a   |
| TV (mL/kg of IBW)         | 8.2 ± 0.4                   | 8.3 ± 0.8              | 0.64a   |
| Ppeak (cmH$_2$O)          | 18 ± 2.7                    | 17 ± 1.8               | 0.07a   |
| PEEP (cmH$_2$O)           | 5.1 ± 0.86                  | 4.7 ± 0.7              | 0.11a   |
| ETDes (%)                 | 3.7 ± 0.3                   | 3.5 ± 0.5              | 0.25a   |
| Tblad (°C) | 36.9 ± 0.6 | 36.6 ± 0.6 | 0.18<sup>a</sup> |
| Tskin (°C) | 36.1 ± 0.5 | 35.9 ± 1.1 | 0.44<sup>a</sup> |

Abbreviations: CI, cardiac index; Ea<sub>dy</sub>n, dynamic arterial elastance; ETCO<sub>2</sub>, end-tidal carbon dioxide tension; ETD<sub>e</sub>, end-tidal desflurane concentration; HR, heart rate; IBW, ideal body weight; MAP, mean arterial pressure; PEEP, positive end-expiratory pressure; PI, perfusion index; Ppeak, peak inspiratory pressure; PPV, pulse pressure variation; RBC, red blood cell; SVI, stroke volume index; SVV, stroke volume variation; Tblad, bladder temperature; Tskin, skin temperature of the hand; TV, tidal volume.

Values are expressed as mean ± standard deviation or number.

<sup>a</sup>P values were calculated using Student’s t-test. <sup>b</sup>P values were calculated using Fisher’s exact test.

**Figures**
Figure 1

Hemodynamic management protocol using the trend of the perfusion index and pulse pressure variation. Abbreviations: MAP, mean arterial pressure; PI, perfusion index; PPV, pulse pressure variation.
Figure 2

The CONSORT diagram.

Supplementary Files

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