Original Article

Prediction of Intraoperative Pressure Responsiveness by Dynamic Arterial Elastance in Patients Undergoing Major Abdominal Surgery

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ABSTRACT

Introduction: Optimal arterial load is crucial to the simultaneous achievement of adequate oxygen delivery and perfusion pressure. Dynamic arterial elastance (Eadyn) has been proposed to represent arterial load. This study aimed to examine the ability of Eadyn to predict pressure responsiveness during major abdominal surgery.

Methods: In this analysis, we used hemodynamic data obtained from our observational study assessing the volume effect of various fluids during goal-directed fluid management in patients undergoing major gastrointestinal surgery. Stroke volume variation (SVV) and pulse pressure variation (PPV) were continuously monitored via the non-calibrating arterial pulse contour method, and Eadyn (PPV/SVV) was calculated offline. The presence of pressure responsiveness was assumed if the mean arterial pressure increased by more than 10% after fluid challenges, with a 15% or more increase in stroke volume. The predictive ability of Eadyn was assessed with receiver operator characteristics analysis.

Results: Positive pressure response was found in 34 of 50 fluid challenges in 33 patients. The area under the ROC curve of Eadyn for the prediction of pressure responsiveness was 0.80, suggesting the good diagnostic ability for Eadyn. The sensitivity and specificity were 0.82 and 0.63, respectively, with the best cutoff point at 1.20. The gray zone was calculated as Eadyn of 1.05-1.37, and 42% of measurements fell into this zone.

Conclusions: Eadyn showed moderate accuracy for the prediction of pressure responsiveness after the fluid challenge. However, a considerable fraction of the fluid challenges with positive fluid responsiveness fell within the gray zone.

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KEYWORDS: goal-directed fluid management, preload, dynamic parameter, pressure responsiveness, arterial elastance

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Introduction

Ensuring adequate oxygen delivery is one of the key elements of perioperative management. A decrease in cardiac output or stroke volume is more common when oxygen delivery is decreased. Because the reduction of preload due to preoperative dehydration, sympathetic blockade, inflammatory edema, and surgical blood loss is common, maintaining adequate preload is crucial. In this respect, goal-directed fluid management, which comprises the evaluation of preload responsiveness and timely fluid challenge, has been advocated.[1–5]

To ensure oxygen delivery to the peripheral tissues, adequate perfusion pressure is necessary and is as important as oxygen delivery. This is reflected by the fact that intraoperative hypotension is repeatedly accompanied by increased postoperative morbidities and mortality.[6–10] Since cardiac performance is relatively stable during anesthesia, cardiac output is typically dependent on the preload. To achieve adequate cardiac output/stroke volume and perfusion pressure, parameters which reliably predict simultaneous increase of both cardiac output/stroke volume and arterial pressure after a fluid challenge should be helpful.

In this context, arterial load evaluation may aid the assessment of the change in arterial pressure in response to the change of stroke volume. Among the several parameters used to describe arterial load, dynamic arterial elastance (Eadyn) has drawn attention.[11–13] Eadyn is the ratio of pulse pressure variation (PPV) to stroke volume variation (SVV), and its ability to predict pressure responsiveness, which is broadly defined as a simultaneous positive response of both stroke volume and arterial pressure after fluid challenge, has been reported with mixed results.[14–20] In particular, most of these previous reports collected data in certain contexts such as before surgery,[19, 20] after major intervention during surgery,[16] or in the ICU.[14, 15, 17, 18] In this regard, currently available evidences have limited generalizability since these data did not account for significant change of preload and arterial load during major abdominal surgery. Thus, it is necessary to further evaluate Eadyn as an indicator of pressure responsiveness in various contexts during extensive surgery. Additionally, gray zone approach has become increasingly popular to account for the conclusiveness of such parameters as PPV, SVV, and Eadyn.[21] This study aimed to investigate whether Eadyn can reliably predict pressure responsiveness during major abdominal surgery using gray zone approach.

Methods

Study design

This analysis was based on an observational study that was designed to compare the volume effects of crystalloid and colloid after a fluid challenge in patients undergoing major abdominal surgery. The primary results are under consideration for publication (Toyoda D, Maki Y, Sakamoto Y, Yamamoto T, Kotake Y. Comparison of volume and hemodynamic effects between colloid and crystalloid in patients undergoing major abdominal surgery with goal-directed fluid management). The original study protocol was approved by the Ethics Committee of Toho University Ohashi Medical Center (No. Ohashi 14-13), and written informed consent was obtained at the preoperative clinic.

Patients undergoing major intra-abdominal surgery with indications for both invasive arterial cannulation and central venous catheter insertion from October 2014 to February 2017 at Toho University Ohashi Medical Center were enrolled in this study. Patients who were younger than 20 years, pregnant, undergoing laparoscopic surgery, had a persistent atrial flutter or arterial fibrillation, had more than mild aortic regurgitation preoperatively, and with the presence of distorted arterial wave were excluded from this analysis.

Intraoperative management and data collection

All the subjects were anesthetized with sevoflurane in combination with a continuous thoracic epidural block and mechanical ventilation. The tidal volume was fixed at 8 ml/kg predicted body weight, and respiratory rate was adjusted to maintain $PetCO_2$ between 35 mmHg and 40 mmHg. The PEEP level was fixed at 5 cmH_2O throughout the study period. Either the left or right radial artery was cannulated with a 22-G catheter (Introcan, B. Braun, Melsungen, Germany), and arterial pressure, stroke volume index (SVI), and SVV were continuously monitored with FloTrac sensor and Vigileo monitor (ver 3.04, Edwards Lifesciences, Irvine, CA, USA). Other standard monitors were also applied, and all the physiological data were stored in the anesthesia information management software (CAP-2000, Nihon Kohden Corp, Tokyo, Japan). Additionally, arterial, photoplethysmographic, and airway pressure waveforms were digitally sampled at a rate of 125 Hz and stored in a personal computer. PPV was determined

Table 1 Patient demographics (n = 33)

Age (y/o)	68 ± 11
Gender (male/female)	23/10
Height (cm)	161 ± 10
Weight (kg)	57 ± 12
BMI (kg/m^2)	22.0 ± 3.6
ASA PS (1/2/3)	1/19/13
Comorbidities	
Hypertension/coronary artery disease/valvular heart disease/congestive heart failure	14
Chronic obstructive lung disease	1
Diabetes	9
Surgical specialties	
Upper gastrointestinal	3
Hepatobiliary	25
Gynecological	1
Urological	4
Total amount of intravenous fluid (ml/kg/hr)	6.9 [5.4-7.7]
Number of patients who received blood products intraoperatively (packed red cells/fresh frozen plasma/platelet concentrate)	12/5/1
Estimated blood loss (g)	415 [165-782]
Urine output (ml/kg/hr)	0.53 [0.36-0.89]

Data are presented as number, mean ± SD, or median [IQR] when appropriate.

offline every 10 seconds with MATLAB software (R2014, MathWorks, Natick, MA, USA) using the standard formula, and SVV was determined every 20 seconds with the algorithm in the Vigileo monitor. The averaged value for a 1-min interval was used as a representative value for SVV and PPV.

Protocolized intraoperative goal-directed fluid management was applied to the participants of this analysis. Briefly, bicarbonate Ringer's solution (BRS; Otsuka Pharmaceutical Factory, Japan) was administered at a rate of 1.5 ml/kg/hr, and 250 ml of fluid challenge either with BRS, 6% HES 130/0.4 (hereafter HES; Voluven, Fresenius-Kabi, Germany), or 5% albumin (hereafter Alb; Japan Blood Product Organization, Tokyo, Japan) was provided under SVI monitoring. The decision to provide a fluid challenge was at the discretion of the attending anesthesiologists, and each fluid challenge consisted of a manual rapid injection of 250 ml fluid using a 50-ml syringe.[22] Basically, BRS and HES were alternatively used as fluid challenges throughout the anesthesia, and Alb was used in selected cases involving a prolonged procedure or significant blood loss.

Analysis

To correctly assess pressure responsiveness, we analyzed hemodynamic change only when the fluid status and vascular tone were supposedly stable during the 30-min span from the onset of a fluid challenge. Thus, any fluid challenge, which occurred less than 60 min after the epidural administration of local anesthetics or during measurable blood loss, administration of bolus vasoactive agents, or change of the dose of continuously administered vasoactive drugs, was excluded from the analysis. In this study, positive fluid responsiveness was defined an SVI increase of 15% or more after a fluid challenge.[21] Among the fluid challenges with a positive fluid response, the presence of pressure responsiveness was defined as when the mean arterial pressure increased by more than 10% before the fluid challenge.[18] In this study, we also evaluated several parameters such as systemic vascular resistance (SVR), net arterial compliance (C),[23] and effective arterial elastance (Ea)[24] in addition to Eadyn for the accuracy of evaluating pressure responsiveness. SVR, C, and Ea were defined as MAP/CO*80, stroke volume/arterial pulse pressure, and 0.9*systolic arterial pressure/stroke volume, respectively.[17,18]

Data were analyzed with Stata/SE (ver. 14.2, Stata Corp, College Station, TX) and R (ver. 3.3.0, R Project, Vienna, Austria). The normality of data was examined with the Shapiro-Wilk test. Normally distributed data are expressed as mean ± SD, while non-normal data are expressed as median [IQR] in Table 1 and Table 2. First, the differences in several indices between pressure responsive

Table 2 Effects of fluid challenge on variables of arterial load according to positive and negative pressure responsiveness

	Positive pressure responsiveness (n = 34)		Negative pressure responsiveness (n = 16)	
	Before fluid challenge	Maximal response	Before fluid challenge	Maximal response
HR (/min)	66 (12)	67 (15)	70 (12)	67 (11)
MAP (mmHg)	54 (12)	64 (12)	64 (13)	66 (11)
SVI (ml/m^2)	37 (7)	48 (8)	38 (8)	47 (8)
PPV (%)	21.3 (13.4-26.2)	14.7 (11.4-18.9) *	14.9 (12.4-17.1)	11.7 (10.1-17.2)
SVV (%)	12.3 (9.8-19.0)	9.5 (6.2-11.4)	12.9 (11.8-14.8)	9.9 (8.5-11.7)
Dynamic arterial elastance	1.37 (1.23-1.75) *	1.51 (1.34-2.02)	1.07 (0.96-1.33)	1.36 (0.97-1.84)
Total systemic vascular resistance (dyn·s·cm^5)	1147 (974-1380)	1083 (1009-1221)	1175 (1090-1374)	1002 (906-1192)
Net arterial compliance (ml/mmHg)	1.47 (1.18-1.61)	1.36 (1.20-1.64)	1.41 (1.21-1.57)	1.55 (1.40-1.87)
Effective arterial elastance (mmHg/ml)	1.27 (1.08-1.46)	1.19 (1.06-1.38)	1.36 (1.16-1.47)	1.08 (1.02-1.33)

Hemodynamic data are presented as mean (SD), while arterial load parameters are presented as median (IQR). Positive pressure responsiveness is defined as 10% or more increase in MAP when SVI increases by ≥15% after a fluid challenge. *$P < 0.05$ vs. pre-fluid challenge value in negative pressure responsive situations via the Mann-Whitney test.

and nonpressure responsive situations immediately before a fluid challenge were compared with the parametric unpaired t-test or nonparametric Mann-Whitney test. Second, we analyzed the relationship between Eadyn immediately before the fluid challenge and the percent change of MAP with either Pearson's correlation coefficient or Spearman's correlation coefficient, depending on the distribution. Third, the predictive ability of several arterial load parameters including Eadyn immediately before the fluid challenge for positive pressure responsiveness was analyzed with receiver operating characteristic (ROC) analysis. The best cutoff value of Eadyn for positive pressure responsiveness was determined to maximize the Youden index (sensitivity + specificity − 1). Fourth, the gray zone was determined for Eadyn where either sensitivity or specificity was lower than 90%.[21, 25] The 95% confidence interval of area under the ROC curve (AUROC) and the gray zone were calculated using a bootstrap method with a 2,000 resampling. $P < 0.05$ was considered to indicate statistical significance. We used the same power calculation as a previous report where 48 instances with a positive fluid response would provide an adequate power of beta = 0.2 at an alpha of 0.05 to detect an area under the curve difference of 0.1.[17]

Results

Forty-nine patients matched the inclusion criteria and were enrolled in this study. Sixteen patients were excluded from the analysis because of unsuccessful epidural catheterization (n = 1), change to palliative procedure (n = 1), and failure of the data recording system (n = 14). Consequently, data from 33 patients were analyzed. The demographic and surgical data of these subjects are summarized in Table 1. During the anesthetic care of these subjects, 345 fluid challenges were performed and further evaluated (Fig. 1). Among these fluid challenges, 220 were excluded from the analysis because of possible interferences by epidural block, active hemorrhage, vasoactive drug administration, and vascular clamp/declamp. Ultimately, 125 fluid challenges were analyzed. Among them, 50 fluid challenges were classified as having a positive fluid response since these fluid challenges were accompanied with a greater than 15% increase in stroke volume. These fluid challenges with a positive fluid response were further divided into two subsets: positive pressure responsiveness (MAP increase exceeding 10%, n = 34) and negative pressure responsiveness (n = 16). The hemodynamic data before the fluid challenge and at the time of peak stroke volume response are summarized in Table 2. Several parameters including PPV and Eadyn were not normally distributed, and significant differences in pre-fluid challenge PPV and Eadyn were found between positive and negative pressure responsive situations. Additionally, a significant correlation was found between Eadyn before fluid challenge and percentage MAP change via Spearman's correlation ($r = 0.492$, $P < 0.001$). On the contrary, both absolute value and percentage change of heart rate did not correlate with Eadyn before fluid challenge.

The result of the ROC analysis regarding Eadyn and other parameters as predictors of positive pressure re-

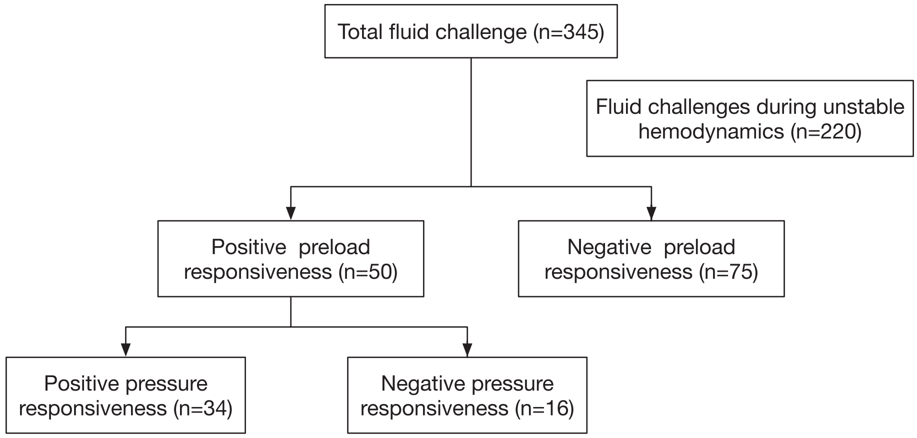

Fig. 1 Summary of fluid responsiveness and pressure responsiveness in the study cohort
Positive fluid responsiveness was defined as 15% or more increase in the stroke volume index after a fluid challenge. Positive pressure responsiveness was defined as 10% or more increase in mean arterial pressure, in addition to positive fluid responsiveness.

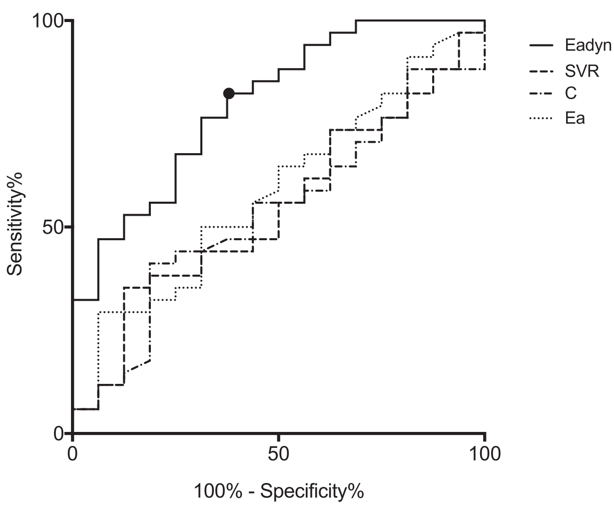

Fig. 2 ROC curve of dynamic arterial elastance, total systemic vascular resistance, net arterial compliance, and effective arterial elastance for predicting positive pressure responsiveness. The closed circle on the ROC curve of dynamic elastance represents the best cutoff value.
Eadyn dynamic arterial elastance, *SVR* total systemic vascular resistance, *C* net arterial compliance, *Ea* effective arterial elastance

sponsiveness is demonstrated in Fig. 2. The area under the ROC curve (AUROC; 95% confidence interval) of Eadyn was 0.80 (0.67-0.93), indicating that Eadyn has moderate accuracy and good diagnostic value.[26] However, the AUROC (95% confidence interval) of SVR, C, and Ea was 0.45 (0.29-0.63), 0.53 (0.39-0.70), and 0.41 (0.25-0.58), respectively (Fig. 2). Thus, the AUROC of Eadyn was significantly higher than that of other arterial load parameters. Eadyn at 1.20 provided the best combination of sensitivity 0.82 and specificity 0.63. The gray zone was calculated as between 1.05 and 1.37, and 21 measurements (42%) fell into this zone.

Discussion

We found that Eadyn before a fluid challenge has moderate accuracy and good predictive ability for intraoperative pressure responsiveness in patients undergoing major intra-abdominal surgery. However, a considerable proportion of the fluid challenges with positive fluid responsiveness fell within the gray zone. On the contrary, other arterial load parameters such as SVR, C, and Ea failed to meaningfully predict the presence of pressure responsiveness.

Recently, the interaction between perioperative fluid management and patient outcome has been repeatedly demonstrated, especially showing that providing an optimal amount of fluid is important. To achieve such an objective, goal-directed fluid management has been advocated and has achieved a mostly favorable outcome.[1,3,5] Regarding this paradigm, stroke volume is optimally maintained by a repeated fluid challenge if the patient is fluid responsive.[27] Although blood pressure received less attention compared to stroke volume in earlier studies, recent studies have clearly demonstrated that hypotension is an independent and significant risk factor for postoperative complications.[6–10] Thus, modern hemodynamic management simultaneously aims to maintain both stroke volume and MAP with fluid challenge and vasopressor administration.[3, 28] Because the response of blood pressure after a notable increase in stroke volume depends on the arterial load, the assessment of arterial load can provide important information during goal-directed fluid management. Several parameters such as SVR, C, and Ea have been proposed as indicators of arterial load.[13] Recently, Pinsky proposed the use of Eadyn to predict pressure responsiveness.[11, 12] Since either PPV or SVV has been used to predict fluid responsiveness, the measurement of PPV and SVV and the calculation of Eadyn enable the simultaneous assessment of both fluid and pressure responsiveness. Pinsky also predicted that an Eadyn between 0.8 and 1.2 represents the normal arterial load. Based on this, several studies investigated the validity of Eadyn as a predictor of pressure responsiveness with mixed results. While favorable results are reported from most studies using postoperative or critically ill patients in the intensive care unit (ICU),[14, 15, 17, 18] studies assessing pressure responsiveness in anesthetized patients found that Eadyn is not useful for predicting the presence of fluid challenge-induced pressure responsiveness.[10, 16, 19] Additionally, the assessment of arterial load with Eadyn may be useful for predicting successful weaning from norepinephrine in patients with hepatic ischemia-reperfusion-induced hypotension,[16] septic shock,[29] and vasoplegic syndrome after cardiopulmonary bypass.[30]

In the current study, the AUROC of Eadyn was 0.8, suggesting that Eadyn has moderate accuracy and a good diagnostic ability for identifying intraoperative pressure responsiveness under various clinical contexts other than active bleeding or neuraxial block-induced sympathetic blockade. Several previous studies reported even higher Eadyn AUROCs for pressure responsiveness in ICU patients. For example, Monge Garcia et al. reported an AUROC of 0.98 in critically ill patients with circulatory failure and hypotension using the same hemodynamic monitor as ours.[14] In their study, both sensitivity and specificity were higher than 90%, with the best cutoff value of 0.89. The same authors reported a similarly high AUROC at 0.94 by independently measuring SVV and PPV with a transesophageal Doppler and arterial pressure.[17] In that study, the sensitivity and specificity were 90.9% and 91.5%, respectively, at the threshold of 0.94. Cecconi et al. also found that Eadyn had a good diagnostic ability, with an AUROC of 0.92 and best cutoff value of 1.06 in postoperative patients with spontaneous breathing activity.[18]

Our data basically agree with the results of these previous reports, but the best cutoff value was relatively higher as compared with Pinsky's original prediction. The underlying mechanisms behind the discrepancy in the best cutoff values between our report and theirs remain unclear. We hypothesize that exposure to anesthetic agents may alter the arterial load and affect the relationship between stroke volume and MAP. This hypothesis warrants further investigation.

We also found that the gray zone of Eadyn was between 1.05 and 1.37, and 42% of the measurements fell within this inconclusive zone. The gray zone approach has been applied to assess the fluid responsiveness, but to our knowledge, the gray zone of Eadyn was only determined by Cecconi et al.[18] They reported that the gray zone of Eadyn was between 0.9 and 1.15, and 35% of the measurements fell within this range in postoperative patients. These data collectively suggest that caution should be exercised concerning the interpretation of Eadyn because of the considerably wide gray zone.

This study has several limitations. First, the clinical context of the fluid challenges in this study may not have been identical. To limit the variation of the clinical context, we excluded the data during epidural block-induced vasodilation, hemorrhage-related hypovolemia, hemodynamic change due to vascular clamp/declamp, and vasoactive agent-related hemodynamic change. Thus, we assume that our results are applicable to the intraoperative hemodynamic change due to the surgical manipulation-induced inflammatory response. However, such context may significantly vary compared with previous investigations, which collected data during more standardized conditions. This may be the reason some of the data were not normally distributed. Second, three different fluids were used for fluid challenges, and the combined data were used for the analysis. Since colloid solutions such as HES and albumin have a larger volume effect compared with crystalloids, the presence or absence of fluid responsiveness may be affected by the fluid type. However, since the analysis was limited to occasions with positive fluid responsiveness, we believe that the types of the fluid used in the fluid challenge had little, if any, effect on the interpretation of the current data. Third, several data points used in this analysis were obtained from the same subject. However, we believe that our results remain valid and do not need statistical compensation since the context of each fluid challenge was more significantly affected by intraoperative conditions such as fluid status and sympathetic tone than by the individual vascular status. Fourth, mathematical coupling between SVV and PPV may exist since both SVV used in this study and PPV were derived from the same arterial pulse contour.[31] This issue remains inconclusive at this time, and further evaluation is necessary. Despite these limitations, this investigation provides clinically relevant data about the prediction of pressure responsiveness during major intra-abdominal surgery.

Conclusions

Eadyn was moderately accurate in predicting the simultaneous increase of MAP when fluid challenge produced a positive increase in stroke volume in larger contexts during major abdominal surgery as compared with the currently available data. We also found that considerable data fell into gray zone. The impact of hemodynamic management including Eadyn should be examined in future clinical trials.

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