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ORIGINAL ARTICLE

Low molecular weight pentastarch is more effective than crystalloid solution in goal-directed fluid management in patients undergoing major gastrointestinal surgery

Yoshifumi Kotake · Mitsue Fukuda · Aya Yamagata · Ririko Iwasaki · Daisuke Toyoda · Nobukazu Sato · Ryoichi Ochiai

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Abstract
Background This prospective observational study compared the volume effect between hydroxyethyl starch (HES) and crystalloid solution and its context dependency in intraoperative goal-directed fluid management.
Methods With institutional review board (IRB) approval, 35 patients undergoing major gastrointestinal surgery were enrolled. Fluid challenge consisting of 250 ml of either bicarbonate Ringer solution (BRS) or low molecular weight pentastarch (HES 70/0.5) was given to maintain stroke volume index >35 ml/m^2. The context of fluid challenge was classified as related to either epidural block (EB) or blood loss (BL) or as nonspecific. The primary end point was the interval between index fluid challenge and the next fluid challenge, and the secondary end point was the hemodynamic parameter at the end of fluid challenge. Differences in these parameters in each clinical context were compared between BRS and HES 70/0.5. A p value <0.05 was considered statistically significant.
Results Eighty-eight, 77, and 127 fluid challenges were classified as related to EB and BL and as nonspecific, respectively. In the nonspecific condition, the median (range) interval after fluid challenge with HES 70/0.5 and BRS was 45 (11–162) min and 18 (8–44) min, respectively, and the difference was statistically significant. Also, mean arterial pressure and stroke volume index significantly increased, whereas stroke volume variation significantly decreased after fluid challenge with HES 70/0.5 compared with BRS. Such differences were not observed in the other situations.
Conclusions HES 70/0.5 exerted larger volume effects than did crystalloid under nonspecific conditions. However, similar volume effects were observed during volume loss and extensive sympathetic blockade.

Keywords Goal-directed fluid management · Hydroxyethyl starch · Crystalloid · Stroke volume · Gastrointestinal surgery

Y. Kotake (✉) · D. Toyoda
Department of Anesthesiology, Toho University Ohashi Medical Center, 2-17-6, Ohashi, Meguro, Tokyo 153-8515, Japan
e-mail: ykotake@med.toho-u.ac.jp

M. Fukuda · A. Yamagata · R. Iwasaki · N. Sato · R. Ochiai
Department of Anesthesiology, Toho University Omori Medical Center, 6-11-1, Omori-nishi, Ohta, Tokyo 143-8541, Japan

Introduction

Goal-directed fluid management is recommended to facilitate early recovery after surgery [1, 2]. Although not explicitly defined, it consists of a combination of restrictive crystalloid administration and fluid challenge of hydroxyethyl starch (HES) solution to achieve a hemodynamic goal [3, 4]. However, the rationale for the use of HES has not been established [5, 6]. Intraoperatively, fluid challenge may be indicated due to BL, sympathetic blockade, or other reasons. In each condition, the effects of HES and bicarbonate Ringer's solution (BRS) may also be different, as the efficacy of fluid administration is reported to be context sensitive [7–9]. However, to our knowledge, these possibilities have not been extensively studied. We hypothesized that the efficacy of HES and crystalloid in maintaining a hemodynamic goal was dependent on the context of intraoperative fluid status, such as acute BL and EB-induced sympathetic blockade. The purpose of this prospective observational study was to compare volume effects and context sensitivity of low molecular weight pentastarch (HES 70/0.5) and crystalloid solution in

patients undergoing goal-directed fluid management during open gastrointestinal surgery.

Methods

The study protocol was approved by the institutional review board, and informed consent was obtained from each participant. Inclusion criteria consisted of patients undergoing surgical treatment of esophageal, gastric, pancreatic, or colorectal malignancies. Exclusion criteria consisted of patients <20 years, undergoing laparoscopic surgery, known history of arrhythmia, contraindication of arterial cannulation, and known conditions that affect the reliability of the cardiac output monitor using the arterial pulse contour analysis method.

Patients were anesthetized with a combination of sevoflurane inhalation and EB and were mechanically ventilated with the tidal volume of 8 ml/kg. Respiratory rate was adjusted to maintain end-tidal carbon dioxide (CO_2) between 30–40 mmHg. The left radial artery was cannulated with a 22-gauge plastic needle (Introcan Safety, Braun, Melsungen, Germany), and stroke volume index (SVI) and stroke volume variation (SVV) were monitored with a FloTrac/Vigileo monitor (Ver. 3.02, Edwards Lifesciences, Irvine, CA, USA). The indication of central venous catheterization was at the discretion of the attending anesthesiologists, and if indicated, a 7-F central venous catheter equipped with central venous oxygen ($ScvO_2$) monitoring capability (Presep, Edwards Lifesciences) was inserted. Both central venous pressure (CVP) and $ScvO_2$ were continuously monitored.

The fluid protocol is illustrated in the Fig. 1. During the induction period, 500 ml of BRS (Bicarbon, Ajinomoto Pharma, Tokyo, Japan) consisting of sodium ((Na) 135 mEq/l, potassium (K) 4 mEq/l, calcium (Ca) 3 mEq/l, magnesium (Mg) 1 mEq/l, chloride (Cl) 113 mEq/l, bicarbonate (HCO_3^-) 25 mEq/l, and citrate 5 mEq/l, was administered [10]. Additionally, cephazolin sodium dissolved in 100 ml of normal saline was administered every 3 h. After the monitor setup, the rate of BRS administration was fixed at 1.5 ml/kg per hour. Additionally, 250 ml of either low molecular weight HES 70/0.5 (Salinehes, Fresenius-Kabi, Japan) or BRS was rapidly infused for 15 min when fluid administration was deemed necessary by the attending anesthesiologist to maintain SVI >35 ml/m^2 [11]. The sequence of fluid type was predetermined as described in the Fig. 1, and fluid challenge was repeated as needed throughout the surgical procedure. Administration of blood products and vasoactive agents were at the discretion of the attending anesthesiologist. Arterial blood gas was analyzed before the study started and at least every 2 h intraoperatively with a standard blood gas analyzer (ABL 725, Radiometer, Copenhagen, Denmark).

Postoperatively, the decision to remove the endotracheal tube was at the discretion of the attending anesthesiologists, and patients were transferred to the multidisciplinary intensive care unit (ICU) or surgical high-care unit.

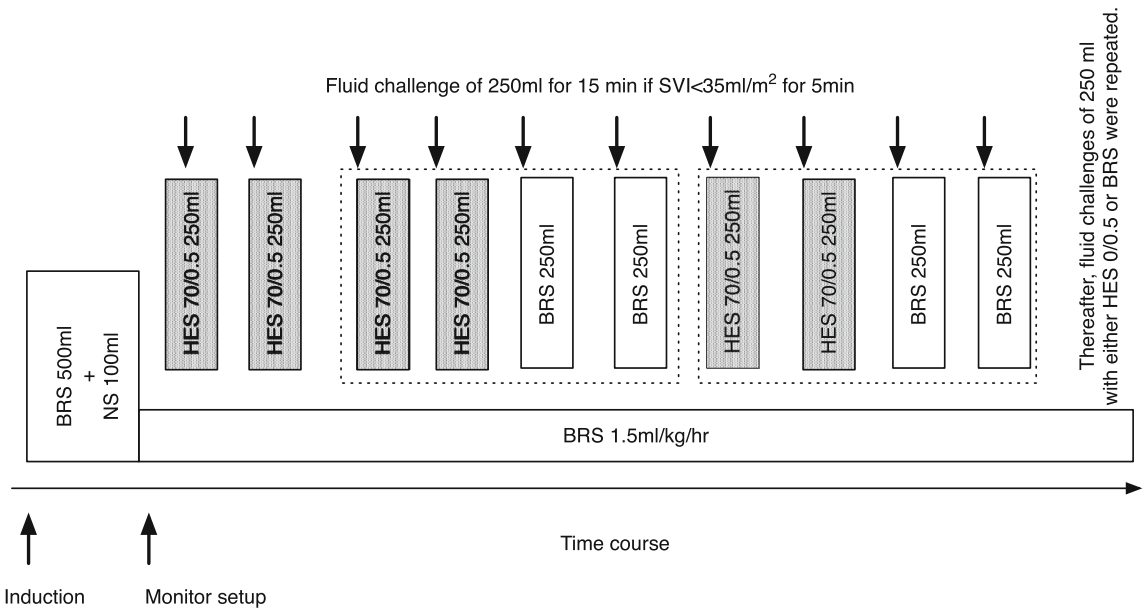

Fig. 1 Protocol of goal-directed fluid management. Two hundred and fifty microliter of pentastarch [6 % saline-based hydroxyethyl starch (HES) 70/0.5 or bicarbonate Ringer's solution (BRS) were rapidly administered to maintain stroke volume index (SVI) >35 ml/m^2. Briefly, after two consecutive fluid challenges with HES 70/0.5, the predetermined sequence, bracketed by the *dashed line*, was repeated until the end of the surgical procedure

Modality of postoperative monitoring and timing of laboratory data collection were at the discretion of surgical team.

All hemodynamic data were retrieved from the electronic anesthesia-record-keeping system. The timing of fluid challenge was also recorded. Additionally, the context of fluid challenge was arbitrarily defined as either related to EB or BL or as nonspecific by a researcher (MF) who was not involved in intraoperative management. Basically, the context of fluid challenge was categorized as BL-related when ongoing BL was >100 ml during the previous 15-min period or within 30 min after active bleeding stopped. The context of fluid challenge was categorized as EB-related when local anesthetics were epidurally injected as a bolus within the previous 60-min period and hypotension and bradycardia was noted. Otherwise, the context was categorized as nonspecific.

The distribution of these parameters was examined with the Shapiro–Wilkes test. If data were normally distributed, they were expressed as mean ± standard deviation (SD), and were analyzed with either Student's *t* test or one-way analysis of variance (ANOVA). If data were not normally distributed, they were expressed as median (range) and analyzed with either the Mann–Whitney *U* test or Friedman test. Additionally, the interval between challenges was compared in order to assess the effective duration of each fluid in maintaining SVI >35 ml/m^2.

To evaluate possible side effects on the renal and coagulation system, the relationship between HES dose and perioperative change of serum creatinine concentration (S_{Cr}), and activated partial thromboplastin time (aPTT) was examined with multivariate regression analysis. For S_{Cr}, age, amount of HES, preoperative S_{Cr}, and intraoperative urine output were selected as explanatory variables. For aPTT analysis, age, amount of HES, preoperative aPTT, and lowest postoperative platelet count were selected as explanatory variables. The amount of BL was not included as an explanatory variable because HES dose and BL amount were correlated with each other. Prism (ver. 5, Graphpad Software, San Diego, CA, USA) and PASW statistics 18 (SPSS Corp., Chicago, IL, USA) were used for statistical analysis; $p < 0.05$ indicated statistical significance.

Results

Thirty-five patients enrolled in this study, and data from all patients were included in the analysis. Among them, 19 patients underwent continuous CVP and $ScvO_2$ monitoring. Demographic and operative data are summarized in Tables 1 and 2. The amount and types of infused fluid during the study period are summarized in Table 2. Fluid challenge was attempted 292 times in these patients.

Table 1 Patient demographic and operative data

Variables	Statistics
Age (years)	65 ± 11
Gender (male/female)	25/10
Height (cm)	163 ± 9
Weight (kg)	58 ± 12
Anesthesia duration (min)	418 ± 188
Surgical procedure (*n*)	
Esophagectomy	6
Gastrectomy	4
Pancreaticoduodenectomy	3
Resection of colon/rectum	22
ASA PS (1/2/3)	12/23/0
Preoperative morbidity[a]	
Cardiovascular	16
Pulmonary	5
Renal	6
Cerebrovascular	8

Data are expressed as mean ± standard deviation or number

ASA PS American Society of Anesthesiologists physical status classification

[a] Multiple comorbidities may be applied to each individual

Table 2 Fluid balance

Variables	Statistics
Total amount of bicarbonate Ringer solution (ml/kg)	25 (12.8–70.3)
Rate of bicarbonate Ringer solution administration (ml/kg/h)	5.0 (2.6–9.5)
Total amount of normal saline (ml/kg)	7.0 (1.5–43.8)
Rate of normal saline administration (ml/kg/h)	1.2 (0.2–2.7)
Total amount of crystalloid (ml/kg)	35.6 (19.1–96.4)
Rate of crystalloid administration (ml/kg/h)	6.2 (3.8–10.6)
Total amount of HES 70/0.5 (ml/kg)	25.0 (12.8–70.3)
Rate of HES 70/0.5 administration (ml/kg/h)	4.4 (2.1–7.9)
RBC transfusion (units)	1.5 (0–8)
FFP administration (units)	0.6 (0–8)
Rate of total fluid administration (ml/kg/h)	10.5 (6.4–16.8)
Blood loss (g)	890 (60–5,640)
Urine output (ml/kg/h)	1.3 (0.3–4.3)

Data are expressed as mean (range). Anesthesia duration was used to calculate per-hour value. In Japan, 1 U of RBC and FFP is prepared from 200 ml of donated blood

HES 70/0.5 hydroxyethyl starch/pentastarch, *RBC* red blood cells, *FFP* fresh–frozen plasma

Among them, 88 were classified as EB related, 77 as BL related, and 127 as nonspecific. Hemodynamic parameters at the start of fluid challenge in each context are summarized in Table 3. Heart rate (HR), SVV, and CVP were

Table 3 Hemodynamic parameters at the start of fluid challenge in each clinical context

Context	EB related ($n = 88$)	BL related ($n = 77$)	Nonspecific ($n = 127$)
HR (min)	69 ± 12	82 ± 19*; **	71 ± 11
MAP (mmHg)	60 ± 15*	64 ± 12	66 ± 14
SVI (ml/m^2)	35 ± 3	33 ± 5*	36 ± 2
SVV (%)	12 ± 7	14 ± 10*	9 ± 7
CVP (mmHg)	6 ± 4 ($n = 36$)	8 ± 2 ($n = 53$)**	7 ± 4 ($n = 66$)
$ScvO_2$ (%)	81 ± 7 ($n = 36$)	74 ± 5 ($n = 53$)*; **	80 ± 7 ($n = 66$)

Data are expressed as mean ± standard deviation. Number of fluid challenges with CVP and $ScvO_2$ monitoring are separately demonstrated in the parenthesis

EB epidural block, *BL* blood loss, *HR* heart rate, *MAP* mean arterial pressure, *CVP* central venous pressure, *$ScvO_2$* central venous oxygen, *SVI* stroke volume index, *SVV* stroke volume variation

* $p < 0.05$ vs. nonspecific, ** $p < 0.05$ vs. EB related

Table 4 Change of hemodynamic parameters between the start and after fluid challenge in each clinical context

	Type of fluid	EB related	BL related	Nonspecific
HR (/min)	HES	2.9 ± 15.3 ($n = 67$)	−1.3 ± 9.2 ($n = 32$)	0.6 ± 6.1 ($n = 67$)
	BRS	3.0 ± 12.9 ($n = 6$)	3.2 ± 8.3 ($n = 34$)	−0.4 ± 5.3 ($n = 38$)
MAP (mmHg)	HES	5.9 ± 15.6 ($n = 67$)	5.9 ± 13.8 ($n = 32$)	4.4 ± 11.9* ($n = 67$)
	BRS	2.0 ± 12.7 ($n = 6$)	3.1 ± 13.2 ($n = 34$)	1.9 ± 11.5 ($n = 38$)
SVI (ml/m^2)	HES	5.3 ± 6.6 ($n = 67$)	2.8 ± 5.5 ($n = 32$)	4.3 ± 6.1* ($n = 67$)
	BRS	3.0 ± 4.3 ($n = 6$)	2.3 ± 6.6 ($n = 34$)	2.1 ± 4.7 ($n = 38$)
SVV (%)	HES	−3.2 ± 6.5 ($n = 67$)	−2.7 ± 7.4 ($n = 32$)	−2.2 ± 4.3* ($n = 67$)
	BRS	−2.5 ± 5.5 ($n = 6$)	−0.6 ± 14.6 ($n = 34$)	−0.3 ± 3.1 ($n = 38$)
CVP (mmHg)	HES	3.9 ± 4.2 ($n = 29$)	0.8 ± 2.7 ($n = 23$)	2.3 ± 4.5 ($n = 40$)
	BRS	0.0 ± 3.2 ($n = 3$)	0.4 ± 2.8 ($n = 22$)	1.1 ± 1.9 ($n = 18$)
$ScvO_2$ (%)	HES	−0.8 ± 3.1 ($n = 29$)	−1.8 ± 4.0 ($n = 23$)	0.7 ± 7.6 ($n = 40$)
	BRS	−1.6 ± 7.7 ($n = 3$)	1.3 ± 3.8 ($n = 22$)	−0.4 ± 2.4 ($n = 18$)

Data are expressed as mean ± SD. Number of fluid challenges are also expressed in parenthesis

EB epidural block, *BL* blood loss, *HR* heart rate, *MAP* mean arterial pressure, *CVP* central venous pressure, *$ScvO_2$* central venous oxygen, *SVI* stroke volume index, *SVV* stroke volume variation

HES hydroxyethyl starch/pentastarch, *BRS* bicarbonate Ringer's solution

* $p < 0.05$ vs. BRS

significantly higher and $ScvO_2$ was significantly lower at the start of BL-related fluid challenge compared with other conditions.

The effects of HES 70/0.5 and BRS on hemodynamics at the end of fluid challenge are summarized in Table 4. After the challenge with HES, mean arterial pressure (MAP), and SVI significantly increased and SVV significantly decreased compared with BRS in the nonspecific condition. The interval between fluid challenges in each context is summarized in Fig. 2. In the nonspecific condition, the median (range) of the interval between the end of index fluid challenge and the start of the next challenge was 45 (11–162) min and 18 (8–44) min after HES 70/0.5 and BRS, respectively, and the difference was statistically significant ($p < 0.001$). The intervals were not statistically different in EB-related and BL-related conditions.

Results of intraoperative electrolyte and acid–base status as well as perioperative laboratory analysis are summarized in Tables 5 and 6, respectively. Intraoperatively, we found significantly increased blood chloride and decreased arterial pH and bicarbonate. These changes correspond to hyperchloremic acidosis, but there was no significant correlation between the dose of HES plus saline and either blood chloride or bicarbonate concentration. White blood cell and platelet counts, prothrombin time International Normalized Ratio (PT-INR), and aPTT significantly changed postoperatively, but S_{Cr} and blood urea did not change significantly. Multivariate regression analysis revealed that there was no significant relationship between HES dose and S_{Cr} increase. Analysis revealed that the increase in aPTT correlated with the change in platelet count and HES dose administered.

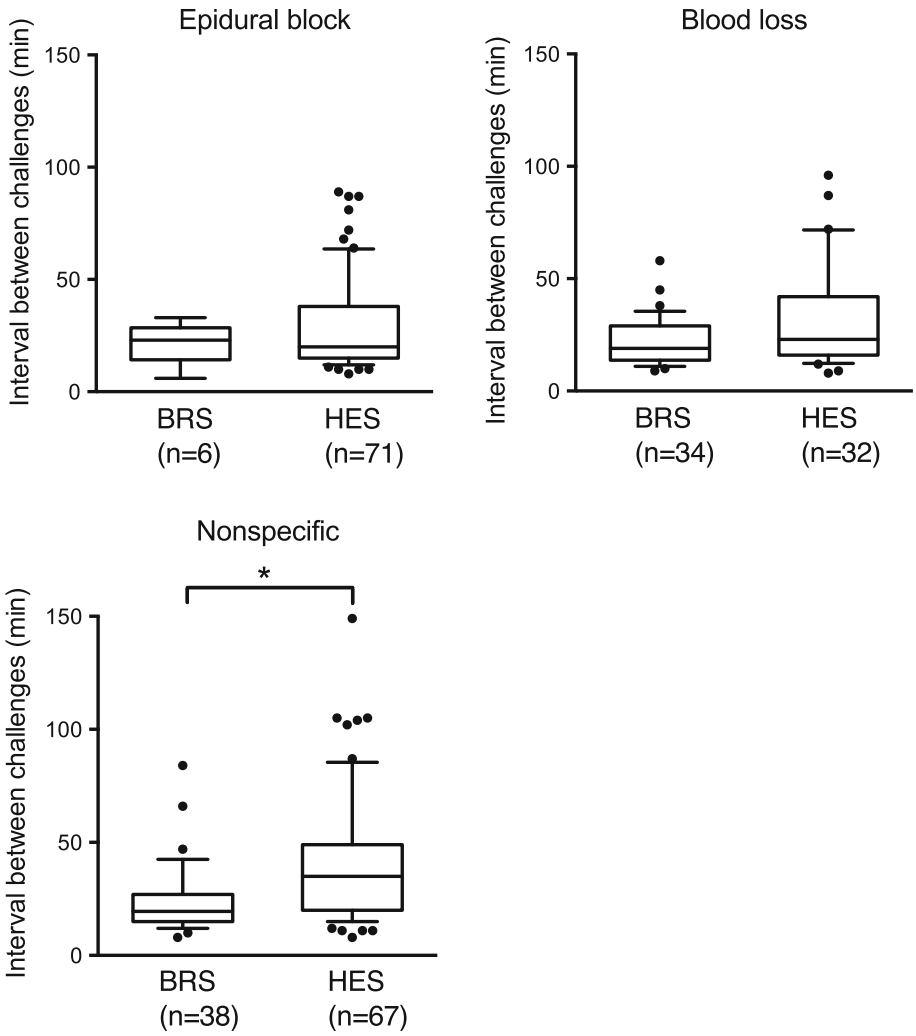

Fig. 2 Interval between index fluid challenge and subsequent challenge in each clinical context. The *box–whisker plot* represents median, 25th–75th percentile, and 10th–90th percentile, respectively. *HES* 6 % saline-based HES 70/0.5 (hydroxyethyl starch/pentastarch)solution, *BRS* bicarbonate Ringer's solution; *$p < 0.05$, Mann–Whitney test

Discussion

The major findings of this study can be summarized as follows: First, hemodynamic parameters, such as SVV, CVP, and $ScvO_2$, when fluid challenge was indicated to maintain SVI >35 ml/m^2 is dependent on the context of the fluid-related intraoperative event, such as BL- or EB-induced sympathetic blockade. Second, in conditions without ongoing BL or anesthesia-induced vasodilation, the fluid challenge of low molecular weight pentastarch exerts significantly larger and more sustained volume effects than does the crystalloid solution in goal-directed fluid management. Goal-directed fluid management presumably represents the combination of crystalloid solution restriction and goal-directed fluid challenge to avoid both excess fluid administration and occult hypoperfusion, which enhances postoperative recovery [2]. The clinical advantages of each component of goal-directed fluid management are demonstrated in several meta-analyses [12–16], and several studies confirm that goal-directed fluid management reduces postoperative morbidity [3, 4]. Most goal-directed protocols using HES successfully achieved clinically relevant outcomes, whereas a study assessing crystalloid solution failed to achieve more favorable outcomes compared with the standard fluid regimen [17]. These findings collectively suggest that HES is the logical choice for fluid challenge in goal-directed fluid

Table 5 Intraoperative electrolyte and acid-base status

	After anesthetic induction	Intraoperative nadir or peak value
Blood sodium concentration (mEq/l)	140 ± 3	139 ± 3
Blood chloride concentration (mEq/l)	107 ± 3	112 ± 3*
Blood pH	7.41 ± 0.04	7.35 ± 0.05*
Blood HCO_3^- (mEq/l)	26.9 ± 2.4	23.4 ± 2.9*

Data are expressed as mean ± standard deviation

HCO_3^- bicarbonate

* $p < 0.05$ vs. preoperative value with paired Student's t test

Table 6 Perioperative laboratory data

	Preoperative value	Postoperative nadir or peak value
Hemoglobin concentration (g/dl)	12.3 ± 2.0	11.1 ± 1.3
WBC count (×1,000/mm^3)	5.6 ± 1.8	9.9 ± 3.5*
Platelet count (×1,000/mm^3)	231 ± 77	173 ± 62*
Serum urea concentration (mg/dl)	13 ± 4	15 ± 4
Serum creatinine concentration (mg/dl)	1.0 ± 0.8	0.9 ± 0.2
aPTT (s)	28.5 ± 3.8	35.2 ± 5.6*
PT-INR	1.0 ± 0.1	1.3 ± 0.2*
Plasma albumin concentration (g/dl)	3.6 ± 0.6	2.4 ± 0.3*

Data are expressed as mean ± standard deviation

WBC white blood cell, *aPTT* activated partial thromboplastin time, *PT-INR* prothrombin time International Normalized Ratio

* $p < 0.05$ vs. preoperative value with paired Student's *t* test

management. However, the advantage of HES was not demonstrated in recent meta-analyses [5, 6].

We believe that our study may provide some relevant information regarding this issue. We used SVI >35 ml/m^2, measured by the noncalibrated arterial-pulse-contour method, as a goal of fluid challenge. Most SVI-oriented goal-directed fluid management empirically applies and repeats fluid challenge as long as the fluid-challenge-induced SVI increase is >10 % of the prechallenge value [18, 19]. Although this approach presumably enables achievement of maximum cardiac output by fluid loading, it is not straightforward and may contradict application of a restrictive fluid strategy. Alternatively, maintaining SVI >35 ml/m^2 improved outcome in patients after cardiac surgery and is more easily applicable to a restrictive fluid strategy [11]. Although our study was not designed to investigate the appropriateness of the goal, we believe our approach may be applicable to goal-directed fluid management in the future.

We found that several hemodynamic parameters differed between each clinical context when fluid challenge was indicated in order to maintain SVI >35 ml/m^2. We assume that fluid challenge categorized as a nonspecific condition represents part of the restrictive maintenance fluid, as the baseline infusion of 1.5 ml/kg per hour was below the infusion rate typically used in the restrictive fluid regimen [20]. HR, SVV, and CVP were all higher, whereas SVI and $ScvO_2$ were lower in the BL-related condition compared with the nonspecific condition. We presume that the low SVI in the BL-related condition reflects that fluid challenge sometimes failed to adequately counteract ongoing BL. We believe increased sympathetic tone may be responsible for the increase in HR and CVP in the BL-related condition compared with the EB-related condition.

It is interesting that SVV was significantly higher at the start of BL-related SVI decrease than at in the other contexts. Dynamic indices are known to better predict fluid responsiveness [21–23], and several studies used respiratory variation of systolic pressure, pulse pressure, or plethysmographic waveform for guidance of intraoperative fluid management [3, 24, 25]. However, the threshold of fluid responsiveness is often derived from the observation of ICU patients without ongoing BL or sympathetic blockade, and our data suggest that using a context-dependent threshold may provide more stable intraoperative hemodynamics.

We found larger and more sustained volume effects after HES infusion than BRS infusion. In volunteers, crystalloid solution quickly equilibrates within extracellular fluid space, and about 25 % of the infused volume remains within intravascular space [26]. Conversely, a hydroxyethyl starch molecule exerts colloid osmotic pressure that is directly dependent on the number of HES molecules in the vasculature. HES 70/0.5 is characterized by its low molecular weight and intermediate degree of substitution. These characteristics refer to the equipotent or slightly smaller volume effect at the onset and rapid dissipation of the volume effect due to its rapid metabolism [27, 28]. Despite these limitations, several studies report a larger volume effect of HES 70/0.5 compared with crystalloid. Ueyama et al. [29] report that HES 70/0.5 significantly increases blood volume and cardiac output and reduces the need for vasopressor compared with lactate Ringer's solution in patients undergoing cesarean section. Tamilselvan et al. [30] found a larger increase in cardiac output and corrected flow time after HES 70/0.5 infusion compared with crystalloid solution in patients undergoing cesarean section. Conversely, McDonald et al. [31] found no significant advantage of using HES 70/0.5 over crystalloid solution in the same patient population. It is probable that these differences may be derived from the difference in the underlying mechanism that requires fluid challenge or the evaluation method for effectiveness. Our data support the advantage of HES over crystalloid solution to maintain increased intravascular volume, venous return, and stroke volume after fluid challenge.

There are several possibilities as to why there was no difference between HES and crystalloid solution in BL- and EB-related conditions. First, either loss of intravascular volume due to hemorrhage or increase of capacitance in the venous system induced by sympathetic blockade might be so large that the difference between HES and crystalloid solution was obscured. Second, there might be context sensitivity for the volume effect of the crystalloid solution. For example, both animal and simulation studies demonstrate that rapid infusion of crystalloid solution transiently but effectively increases blood volume [32, 33]. This

dynamic characteristic of crystalloid solution may contribute to our finding here [34].

Renal injury and hemostatic impairment are the major concerns of HES use [35–38]. However, our finding agrees with the previous report that found no relationship between the amount of HES and postoperative renal function, despite the use of a relatively large dose of HES 70/0.5 [39]. Furthermore, no patient showed signs of postoperative renal injury. Despite recent reports demonstrating increased risk of renal injury after HES administration in different circumstances [40–43], liberal use of HES during surgery may not increase the risk of renal dysfunction [44, 45]. Conversely, a mild but significant relationship between the amount of HES administered and postoperative aPTT was demonstrated. There are several possibilities for the underlying mechanisms of this finding. First, intraoperative BL and dilution of coagulation factors may contribute, as there is an evident linear relationship between the amount of HES administered and BL. Second, there are conflicting reports about the intrinsic effects of HES 70/0.5. Several reports demonstrate minimal effects of HES 70/0.5 on conventional coagulation parameters, such as aPTT and PT [46, 47], and more recent studies that analyzed platelet function or clot formation revealed significant impairment of coagulation function [48, 49]. From these perspectives, more studies are obviously needed to determine the risks and benefits of liberal use of HES 70/0.5 in gastrointestinal surgery.

Another concern about the liberal use of saline-based HES is the relatively large load of chloride ions and the resultant hyperchloremic acidosis [50]. We used BRS as the crystalloid solution to attenuate acidosis progression because it directly supplies bicarbonate to counteract acidosis. However, mild hyperchloremic acidosis was noted during surgery. Clinical implication of this finding remains to be determined, but a negative impact of saline administration on renal function was demonstrated in recent clinical investigations [51, 52].

Based on these concerns, we intended to balance the amount of HES and BRS in this study. Although this protocol precluded direct comparison between HES and BRS, such a strategy regarding the amount of synthetic colloid and crystalloid solution may achieve adequate balance between the benefits and potential risks of colloid solution. Furthermore, possible advantages of balanced solution-based HES preparation in goal-directed fluid management should be evaluated in future studies [53, 54].

This study has several limitations. First, the advantage of HES over crystalloid solution found in this study does not necessarily mean better patient outcome. A prospective randomized study is definitely warranted to evaluate the optimal choice of fluid used in goal-directed fluid management in order to promote early recovery after surgery. Second, the molecular weight of the HES preparation used in this study is lower than the more frequently used HES 130/0.4. Larger volume effect and subsequent longer interval can be anticipated with intermediate molecular weight HES preparation [55]. Actually, the average amount of HES 130/0.4 in the similar goal-directed fluid management protocol was 890 ml during a 295-min operation in patients with an average body weight of 71 kg and roughly corresponds to 50 % of the HES 70/0.5 used in this study [3]. Although the other protocol differences, including our hemodynamic goal, may also be responsible for this difference, the molecular weight of the HES may contribute to that difference. Third, the sequence of fluid was predetermined for practical reasons and to ensure balance between the amount of HES and BRS. We believe the bias introduced by this protocol is negligible, as adequate data points were available for the analysis. Fourth, the hemodynamic change during hemorrhage or EB-induced vasodilation may significantly differ in each episode, and results should be interpreted with caution. Our findings—that there was no statistical difference between HES and crystalloid solution administration during BL- and EB-induced SV decrease—simply reflect the heterogeneity of the condition. We believe that HES remains a viable option to resuscitate intraoperative BL- and EB-induced vasodilation.

In conclusion, our study clearly demonstrates that HES can maintain SVI for a more extended period than can crystalloid solution during the stable condition. This characteristic is evidently advantageous as a supplemental fluid during restrictive fluid strategy. However, the advantage of HES during acute BL or extensive sympathetic EB remains equivocal.

Conflict of interest Dr. Kotake receives consulting fees from Edwards Lifesciences and speaker fees from Fresenius-Kabi Japan.

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