Journal of Anesthesia (2019) 33:656–664
https://doi.org/10.1007/s00540-019-02688-4

ORIGINAL ARTICLE

Two-stage goal-directed therapy protocol for non-donor open hepatectomy: an interventional before–after study

Kazuyuki Mizunoya[1] · Tomoaki Fujii[1] · Masataka Yamamoto[1] · Nobuhiro Tanaka[1] · Yuji Morimoto[1]

Received: 21 January 2019 / Accepted: 23 September 2019 / Published online: 3 October 2019

Abstract

Purpose Hemodynamic management during low central venous pressure (L-CVP)-assisted hepatectomy involves fluid restriction during resection and fluid resuscitation after resection. Recently, high stroke volume variation (SVV) has been reported as an alternative to L-CVP for reducing blood loss during a hepatectomy. The current study evaluated the impact of a newly implemented SVV-based goal-directed therapy (GDT) protocol on blood loss during hepatectomy.

Methods We conducted a before–after comparative study, which included L-CVP-assisted hepatectomy cases (control group) and GDT-assisted hepatectomy cases (intervention group). The GDT protocol included SVV, cardiac index, and mean arterial pressure as hemodynamic parameters. The target SVV ranges were ≥ 13% and ≤ 12% before and after the resection, respectively. The primary endpoint was the proportion of patients whose blood loss was < 400 mL (median of our hepatectomy cases) in the GDT group, and it was compared to a predefined threshold of 50%. We also investigated factors associated with blood loss using multiple regression analysis.

Results We included 66 patients in the control group and 50 in the GDT group. In the GDT group, the median blood loss was 220 mL and 36 patients (72%) lost < 400 mL blood. This was significantly greater than 50% ($P < 0.001$). Post-resection GDT-guided fluid optimization reduced positive intraoperative fluid balance compared to that achieved by the conventional fluid therapy used in the control. Multiple regression analysis showed that GDT application, epidural anesthesia, operative time, and hydroxyethyl-starch infusion volume were associated with blood loss.

Conclusion Compared to conventional management, SVV-guided GDT may reduce blood loss during hepatectomies.

Keywords Hepatectomy · Goal-directed therapy · Stroke volume variation · Central venous pressure

Introduction

Intraoperative blood loss and subsequent allogeneic blood transfusion during hepatectomy have been associated with increased postoperative morbidity and mortality [1, 2]. Therefore, surgical teams should adopt surgical and anesthetic strategies that reduce intraoperative bleeding and blood transfusions [3]. During parenchymal transection under hepatic inflow occlusion, backflow bleeding from the hepatic vein, which correlates with the central venous pressure (CVP), is considered the main source of blood loss. Thus, low CVP (L-CVP [<5 mmHg]) anesthesia is the preferred method to reduce blood loss [4–6]. However, the efficacy of this technique remains controversial due to the conflicting results of previous studies [7].

Stroke volume variation (SVV), a dynamic index derived from arterial pressure waveform analysis, is a reliable indicator of fluid responsiveness. Recently, high SVV has been used as an alternative to L-CVP to reduce blood loss during parenchymal liver transection, especially in living donor hepatectomies [8, 9]. Additionally, unlike CVP, SVV can also be used to guide fluid resuscitation following hepatic resection. SVV-guided goal-directed therapy (GDT) after L-CVP-assisted hepatectomy is a reportedly safe management strategy to optimize fluid status and avoid unnecessary fluid overload [10]. However, the effect of GDT applied throughout a liver surgery has not been evaluated.

Thus, we introduced a new GDT protocol based on FloTrac system (Edwards Lifesciences, Irvine, CA, USA) measurements of SVV, the arterial pressure-derived cardiac index, and the mean arterial pressure (MAP) for hepatectomy

✉ Kazuyuki Mizunoya
kmizunoya201338@gmail.com

[1] Department of Anesthesiology, Hokkaido University Hospital, N14, W5, Kita-ku, Sapporo 060-8648, Japan

cases instead of conventional L-CVP anesthesia. The SVV target value was changed according to the phase of the hepatectomy, with a high SVV target for fluid restriction before the liver parenchymal transection was complete and a low SVV target for fluid resuscitation in the post-resection phase. We hypothesized that, compared to L-CVP management, high SVV (13–18%)-guided GDT would reduce intraoperative blood loss. To test this hypothesis, we compared the intraoperative blood loss during hepatectomies before and after the implementation of our GDT protocol.

Methods

The present interventional before–after study was compared the intraoperative variables of cases before and after GDT implementation using retrospective control data (April 2014 to March 2015) and prospectively collected data. All patients underwent open non-donor hepatectomy at the Department of Gastroenterological Surgery I at the Hokkaido University Hospital. The Hokkaido University Hospital Institutional Review Board (IRB) approved the prospective study protocol (August 2016, 015-0462) and the use of retrospective control data (May 2019, 018-0385). Written informed consent was obtained from all patients in the prospective group (GDT group) and was waived by the IRB in the control. This study is registered at the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (trial ID: 000022403).

Subjects were selected using the following inclusion and exclusion criteria: adult patients who underwent elective open hepatectomy (subsegmental or more extensive resection) were eligible for this trial. The exclusion criteria were as follows: hepatectomy with concomitant procedure for another organ (e.g., stomach, colon) or hepatic vascular or biliary tract reconstruction; a procedure without central venous catheter insertion; patients with an American Society of Anesthesiologists physical status classification ≥ 3, patients with cardiac arrhythmias or severe obesity (body mass index ≥ 35 kg/m^2); and patients unable to consent.

Anesthesia for the GDT group

Anesthesia was induced with propofol, fentanyl, remifentanil, and rocuronium, and sustained with sevoflurane or desflurane to maintain bispectral index values within the range of 40–60. Before induction, a thoracic epidural catheter was inserted in patients without contraindications. Intraoperative epidural anesthesia was maintained with a continuous infusion of 0.375% ropivacaine (3–6 ml/hour). Following tracheal intubation, patients were mechanically ventilated at a tidal volume of 8 ml/kg of their ideal body weight (IBW) with a positive end-expiratory pressure of 4 cm H_2O. The IBW was calculated using the following formula: IBW $= 22 \times$ (height [m])^2. Positive end-expiratory pressure was not applied during parenchymal liver resection.

After anesthesia induction, a 22-G radial artery line was inserted and connected to a FloTrac sensor and an EV1000 clinical platform (Edwards Lifesciences, Irvine, CA, USA) for continuous measurement of SVV, cardiac index, and arterial blood pressure. A 12-G double-lumen central venous catheter (SMAC plus; Covidien, Dublin, Ireland) was inserted into the right internal jugular vein for CVP measurement. The midaxillary line at the fourth intercostal space was selected as the pressure measurement reference level. Hemodynamic data were recorded every 20 s using the EV1000 and an external storage device.

The GDT protocol is presented in Fig. 1. We managed three hemodynamic components: SVV, cardiac index, and MAP. We changed the target SVV according to the hepatectomy phase. Before completion of the hepatic parenchymal resection, we restricted fluid infusion to achieve an SVV $\geq 13\%$. After the resection and hemostasis, we administered fluid sufficient to lower the SVV to $\leq 12\%$ to restore the cardiac preload. The cardiac index was maintained at ≥ 2.5 L/min/m^2 to avoid tissue hypoperfusion, and an ephedrine infusion or continuous dobutamine infusion (maximum dose 3 μg/kg/min) was administered as needed to maintain this target value. If the MAP was consistently ≤ 60 mmHg when the cardiac index was ≥ 2.5 L/min/m^2, we started a continuous phenylephrine infusion (maximum dose 0.3 μg/kg/min) to increase the vascular resistance and achieve the target MAP. The patient's hemodynamic status was assessed every 5 min.

Fluids were administered at the discretion of the attending anesthesiologist and included crystalloids (Ringer's bicarbonate or acetate solution) and colloids (6% hydroxyethylstarch 130/0.4 [HES] or 5% albumin solution). We had no specified maintenance or bolus fluid infusion rate, because we did not use infusion pumps in daily practice. The maintenance fluid infusion rate was controlled manually to achieve the target SVV in each phase. Colloid solutions were administered to replace blood loss during parenchymal resection or restore euvolemia after the liver resection. Blood transfusions were performed at the surgeon's discretion.

Conventional L-CVP management during hepatectomy

The only hemodynamic goal of L-CVP management during an open hepatectomy at our institution was to maintain the CVP below 5 mmHg until the parenchymal liver resection was complete. Furthermore, no uniform external reference level for CVP measurements was determined, and the type of infusion fluid and use of vasoactive drugs were at the discretion of the responsible anesthesiologist.

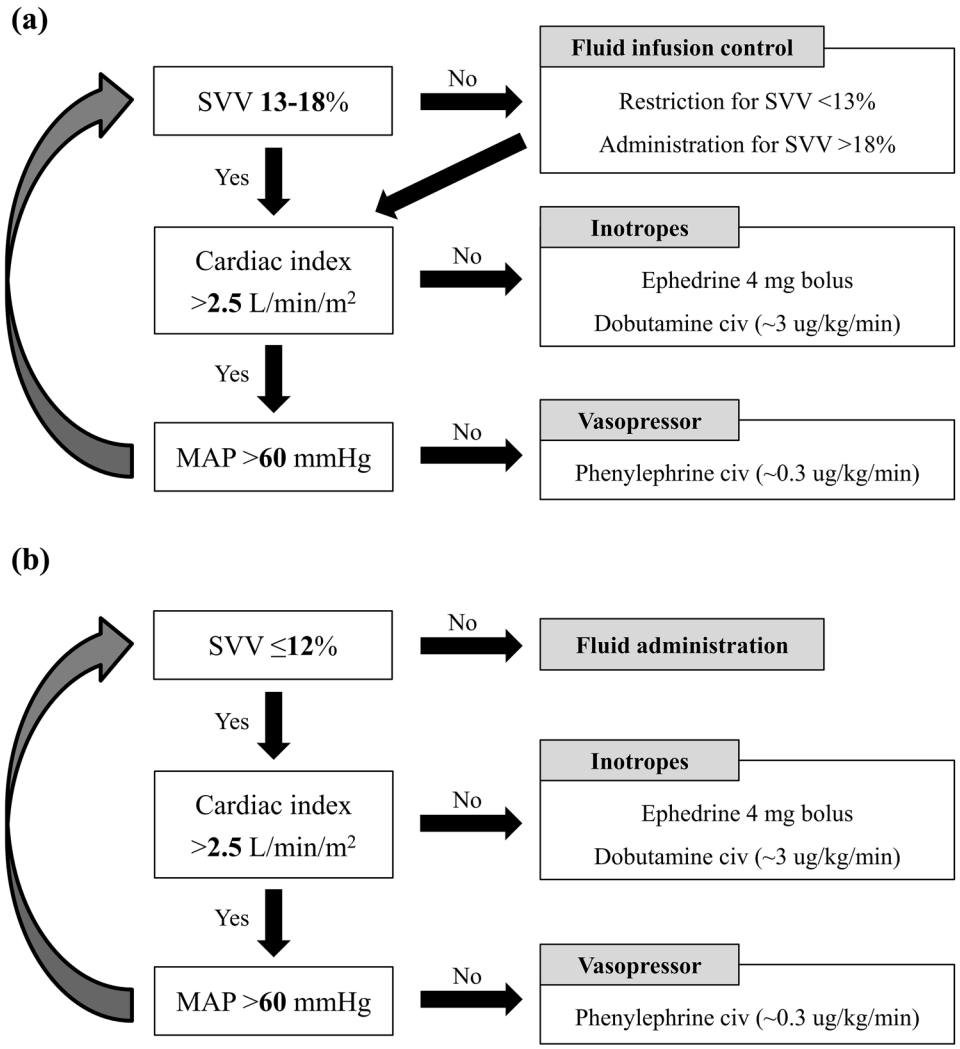

Fig. 1 Goal-directed therapy protcol: **a** liver parenchymal resection algorithm. **b** Post-liver resection algorithm. The hemodynamic status was repeatedly assessed every 5 min. *SVV* stroke volume variation, *MAP* mean arterial pressure, *civ* continuous intravenous infusion

Therefore, within our control group, the between-case differences in hemodynamic management could be considerable.

Surgical techniques

A Mercedes incision was made, followed by a cholecystectomy and pre-resection cholangiography to visualize the bile duct anatomy. We applied the intermittent Pringle maneuver for vascular inflow occlusion during the parenchymal transection in the majority of our cases, while infrahepatic inferior vena cava clamping was rarely used. All liver resections were performed by the same surgical team using a Harmonic Synergy (Ethicon Endo-Surgery Inc., Cincinnati, OH, USA) ultrasonic dissector coagulator and a TissueLink DS3.0 (Medtronic Inc., Minneapolis, MN, USA) saline-coupled radiofrequency ablation device to resect the liver parenchyma, revealing vessels and bile ducts for clipping or ligation.

Outcomes

The standard deviation of blood loss in our hepatectomy cases was too large for us to obtain a sample size sufficient to compare median intraoperative blood loss of two groups directly. Therefore, we investigated whether the GDT change the distribution of the amount of intraoperative blood loss. The proportion of cases in which the intraoperative blood loss was < 400 mL (median blood loss of our hepatectomy cases) was defined as $Prop_{<400}$ and the primary endpoints was to compare the $Prop_{<400}$ to the predetermined 50% threshold that means median. The secondary endpoints included the between-group difference in total intraoperative fluid balance (net value and per kilogram of body weight) and incidence of postoperative acute kidney injury (AKI). The intraoperative total fluid balance was determined by ([infusion volume] + [transfusion volume]) − ([blood loss] + [urine output]). The Kidney Disease Improving Global Outcomes serum creatinine criteria for AKI were used to diagnosis postoperative AKI [11]. We also

performed a multivariate analysis to explore the factors associated with intraoperative blood loss during hepatectomies.

Statistical analysis

In a previous study [8], compared to low SVV management (<10%), high SVV management (10–20%) reduced intraoperative blood loss by 40%. If blood loss was reduced by 40% in each historical control case, the $Prop_{<400}$ was estimated to be 70%. We assumed a type-1 error of 0.05, a power of 0.80, and no continuity correction, and determined that a minimum of 47 patients was required to detect a difference between the $Prop_{<400}$ and 50%. We assumed a 5% dropout rate and found that 50 patients were required for the GDT group.

All data are expressed as medians [interquartile range (IQR)] or numbers (percentage). We compared categorical variables using the chi-squared or Fisher's exact tests and continuous variables with the Mann–Whitney *U* test. A Bonferroni correction was applied for simultaneous comparisons to control the type I error. The primary endpoint was assessed by a one-proportion *Z* test. Multiple linear regression analysis of log-transformed blood loss (to satisfy the normal distribution requirements for linear regression) was performed for all patients. The explanatory variables were selected based on previous reports [12–14].

For statistical analyses, $P < 0.05$ was considered statistically significant. Statistical analyses were performed using EZR version 1.37 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (version 2.4–0; The R Foundation for Statistical Computing, Vienna, Austria) [15].

Results

We included 66 patients in the historical control group. For intervention group, between September 2016 and September 2017, 110 patients were assessed for eligibility. After applying our inclusion and exclusion criteria, 51 patients were scheduled for intraoperative GDT. One patient was excluded due to FloTrac and EV1000 connection issues, and 50 underwent GDT-assisted hepatectomy (Fig. 2). The baseline characteristics of patients are presented in Table 1.

Table 2 shows intraoperative variables in both groups. The $Prop_{<400}$ was 76% (38 of 50) and significantly greater than 50% (95% confidence interval [CI], 62 to 87%; $P < 0.001$). Additionally, GDT group median blood loss

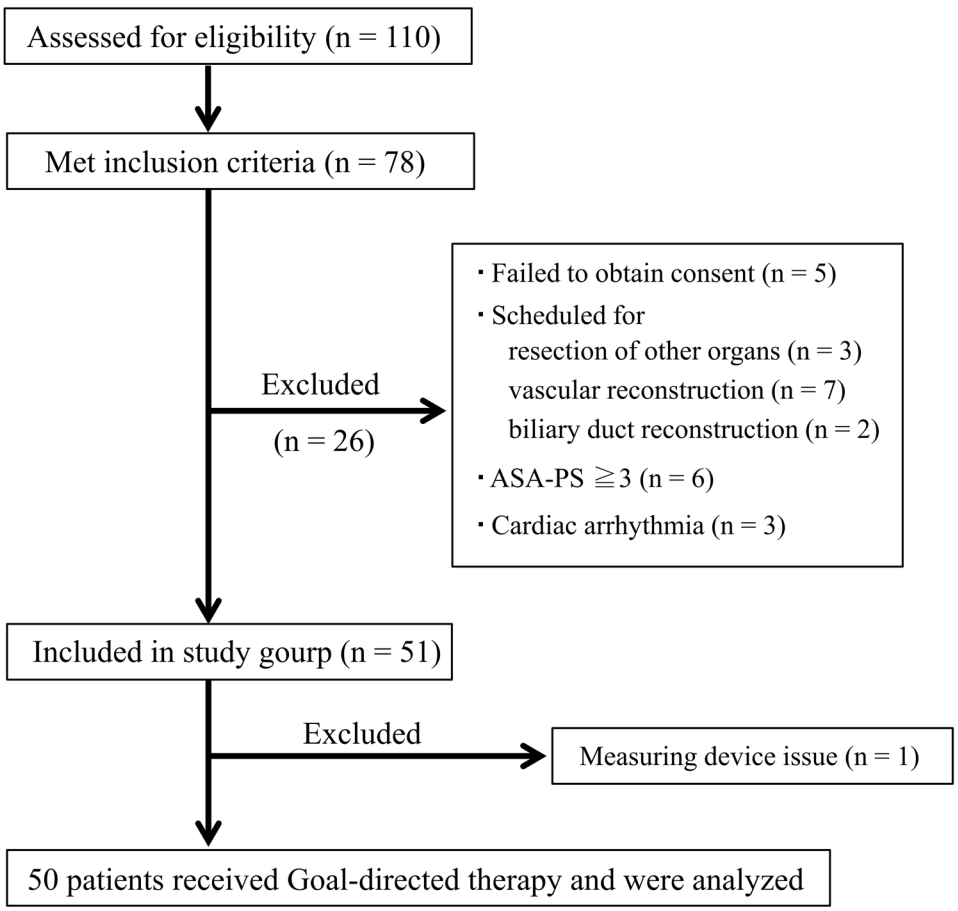

Fig. 2 Study flowchart

Table 1 Preoperative patient characteristics in the study and control groups

	Study group ($n=50$)	Historical control ($n=66$)	P value
Age, years [IQR]	68.5 [57–75]	65.5 [59.3–74]	0.65
Weight, kg [IQR]	62.0 [55.3–67.8]	61.5 [54.3–67.9]	0.69
Height, cm [IQR]	164 [159–169]	163 [156–168]	0.29
Body mass index, kg/m^2 [IQR]	22.8 [21.3–24.7]	23.0 [21.2–25.6]	0.64
Male sex, *n* (%)	43 (86)	47 (71)	0.07
ASA classification, *n* (%)			
I	5 (10)	14 (21)	0.13
II	45 (90)	52 (79)	
Baseline renal function			
eGFR, mL/min/1.73m^2 [IQR]	76.4 [64.8–88.2]	73.0 [62.6–82.0]	0.27
CKD (eGFR < 60), *n* (%)	7 (14)	14 (21)	0.34
Diagnosis			
Hepatocellular carcinoma, *n* (%)	37	36	0.09
Intrahepatic cholangiocarcinoma, *n* (%)	5	4	
Metastatic tumor, *n* (%)	4	9	
Hemangioma, *n* (%)	2	3	
Echinococcus, *n* (%)	2	12	
Other, *n* (%)	0	1	

ASA American Society of Anesthesiologists, *eGFR* estimated glomerular filtration rate, *CKD* chronic kidney disease, *IQR* interquartile range

was 220 mL and it was significantly lower than that of the historical controls (95% CI of difference, 50–255 mL; $P<0.001$). There was a statistically significant between-group difference in the amount of fluid administered intraoperatively (95% CI of difference, 290–855 mL; $P<0.001$). There was no significant difference in the incidence of postoperative AKI between the two groups (OR, 2.05; 95% CI, 0.754–5.54; $P=0.21$). Figure 3 shows four hemodynamic variables (SVV, cardiac index, MAP, and CVP) in the study group and two (MAP and CVP) in the control group. The CVP was significantly higher at the start of the GDT (or surgery), the resection midpoint, and resection completion in the GDT group compared to that in the control group. Some patients could not achieve the hemodynamic goal, particularly the target SVV. However, whether or not the SVV target was reached at the midpoint of the resection, there was no significant difference in the amount of blood loss.

Table 3 shows the association between the natural log-transformed intraoperative blood loss and related variables. Duration of surgery ($P<0.001$) and HES infusion volume ($P=0.035$) were associated with increased blood loss, while epidural anesthesia ($P=0.020$) and GDT ($P=0.031$) were associated with decreased blood loss. The CVP value at the beginning of the parenchymal resection did not significantly affect blood loss. GDT protocol utilization had a raw regression coefficient of -0.37, and its natural exponent (0.69) indicated that GDT decreased the amount of blood loss by 31%.

Discussion

In this study, we demonstrated that high SVV-guided GDT during non-donor hepatectomies could reduce intraoperative blood loss compared to the conventional L-CVP-assisted hepatectomy. Our multiple regression analysis supports this conclusion and revealed that factors such as duration of surgery, HES infusion volume, and epidural anesthesia were also associated with blood loss. Furthermore, compared to conventional fluid therapy, post-resection GDT-guided fluid optimization resulted in a less positive fluid balance without increasing the incidence of postoperative AKI.

Recently, several investigators have reported the benefit of SVV as an alternative to CVP for reducing blood loss during living-donor hepatectomy [8, 9]. We hypothesize that the superiority of SVV is partially due to CVP measurement errors. The between-group difference in initial CVP values likely reflects the imprecision involved in the establishment of the external reference level for measurements which greatly influences CVP measurements [16]. A CVP measurement error could also occur secondary to the intraoperative lateral or longitudinal rotation of the operating table. Owing to the uncertainty involved in CVP measurement, SVV might be a preferable management parameter for hepatectomies.

The optimal SVV threshold for reducing blood loss during liver resection has not been determined. In previous studies of living-donor hepatectomies, the SVV target ranged from 9 to 13%. Dunki-Jacobs et al. [17] reported that an

Table 2 Intraoperative variables in patients undergoing hepatectomy

	Study group ($n=50$)	Historical control ($n=66$)	P value
Epidural anesthesia, *n* (%)	40 (80)	53 (80)	1.00
Duration of surgery, median min [IQR]	313 [288–337]	331 [287–392]	0.13
Duration of resection, median min [IQR]	90 [71–116]	98 [69–124]	0.70
Pringle maneuver, *n* (%)	49 (98)	64 (97)	1.00
Intraoperative blood loss			
Median mL [IQR]	220 [120–376]	385 [200–860]	0.001
Range mL	20–1690	40–4825	
Urine output, median mL [IQR]	234 [141–374]	468 [274–850]	< 0.001
Intraoperative fluids			
Crystalloid, median mL [IQR]	2525 [2100–2850]	2800 [2313–3700]	< 0.001
6% HES 130/0.4 mL [IQR]	0 [0–0]	0 [0–500]	< 0.001
5% Albumin mL [IQR]	0 [0–500]	500 [150–1000]	< 0.001
Intraoperative transfusion			
Received RBC, *n* (%)	3 (6)	14 (21)	0.03
Amount of RBCs			
Median mL [IQR]	0 [0–0]	0 [0–0]	0.02
Range mL	0–560	0–1400	
	Study group ($n=50$)	Historical control ($n=66$)	P value
Received FFP, *n* (%)	8 (16)	20 (30)	0.08
Amount of FFPs			
Median mL [IQR]	0 [0–0]	0 [0–420]	0.06
Range mL	0–720	0–1200	
Intraoperative fluid balance			
Median mL [IQR]	2275 [1951–2669]	2681 [2315–3475]	< 0.001
Median mL/kg [IQR]	37.3 [29.6–44.8]	45.8 [37.3–57.1]	0.02
Surgical procedure[a]			
Minor resection, *n* (%)	13 (26)	28 (42.4)	0.08
Major resection, *n* (%)	37 (74)	38 (57.6)	
Infusion of inotropes and vasopressors			
Phenylephrine, *n* (%)	36 (72)	11 (17)	< 0.001
Dopamine, *n* (%)	0 (0)	19 (29)	
Dobutamine, *n* (%)	17 (34)	1 (1.5)	
Noradrenaline, *n* (%)	0 (0)	1 (1.5)	

HES hydroxyethyl-starch, *RBC* red blood cells, *FFP* fresh frozen plasma, *IQR* interquatile range

[a]Major resection was defined as a resection of at least three Couinaud liver segments

SVV of 13% corresponded to a CVP of 3 mmHg during a hepatectomy, while Lee et al. [9] reported that an SVV of 9%, comparable to a CVP of 5 mmHg, allowed a favorable resection plane as judged by surgeons. In this study, our high SVV target was 13–18% during resection. Therefore, in a significant number of patients, our SVV target was difficult to achieve using fluid restriction alone. However, there was no significant difference in blood loss, whether the SVV target was met at the midpoint of resection or not possibly, because bleeding itself increased the SVV. In previous studies, diuretics such as furosemide and mannitol were also used to reduce the cardiac preload and maintain a high SVV during hepatectomies [8, 18]. Therefore, a lower SVV target, administration of diuretics, or both should be considered in our GDT protocol.

GDT facilitates the optimization of hemodynamic conditions and postoperative recovery and reduces postoperative morbidity in major abdominal surgeries [19]. Unlike other abdominal surgeries, hepatectomies require a complicated hemodynamic management, including fluid restriction in the pre-resection phase and fluid resuscitation in the post-resection phase. During parenchymal liver resection, a high SVV resulted in a favorable resection plane, while maintaining the cardiac output and MAP

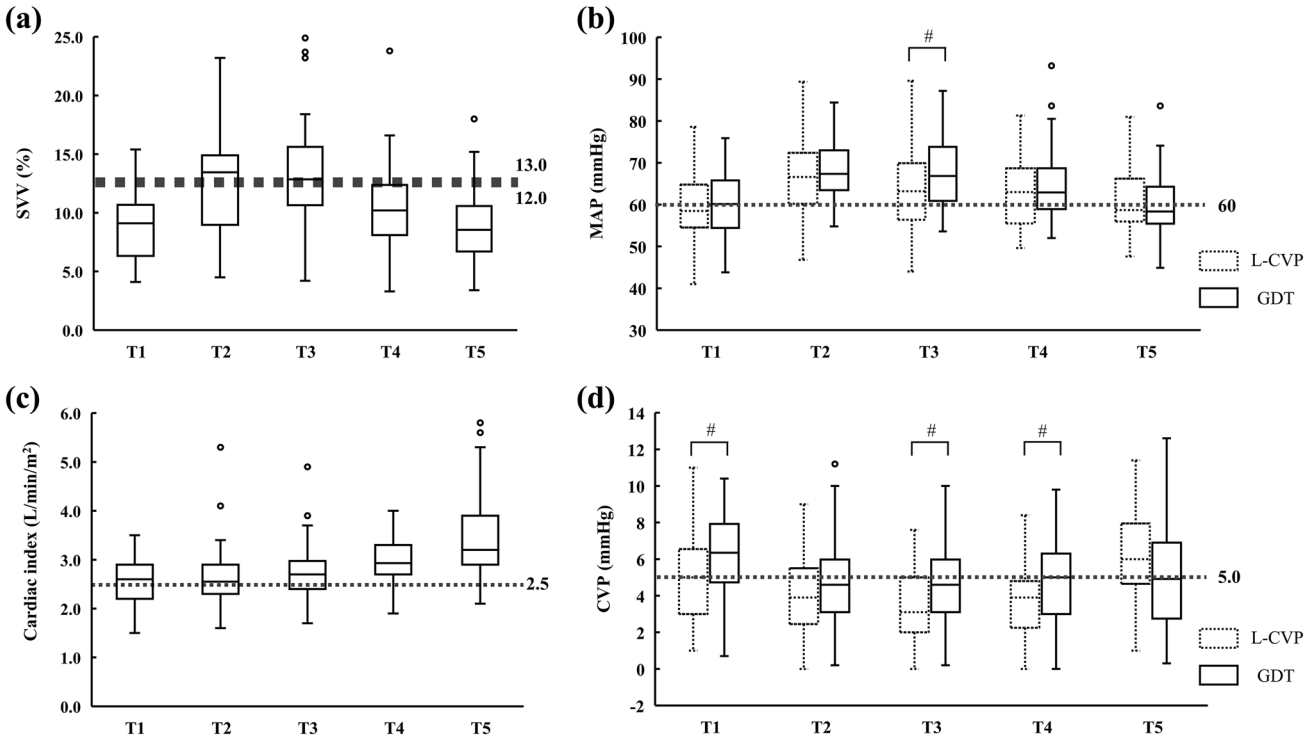

Fig. 3 The hemodynamic variables of 44 study patients and 66 historical controls treated with low-central venous pressure (L-CVP) anesthesia. Hemodynamic data from six study patients were not available because the data storage device failed. Contorol group data included only mean arterial pressure (MAP) and central venous pressure (CVP). **a** Stroke volume variation (SVV). **b** Cardiac index. **c** MAP. **d** CVP. Data were calculated as the mean values aquired 5 min before and after each time point. Data are expressed as the medians and interquartile ranges. Dotted horizontal lines represent the GDT target values of each variable. The SVV goal was not achieved in 36% (16/44) of patients at T3. *T1* the beginning of the interventnion (goal-directed therapy group) or surgery (L-CVP control), *T2* the beginning of the parenchymal resection, *T3* midpoint between T2 and T4, *T4* after completion of the resection, *T5* end of the surgery. #$P < 0.05$ after Bonferroni correction

Table 3 Multiple linear regression analysis of the association of variables with natural log of the amount of intraoperative blood loss

Dependent variables	β	SE	Exp (β)	*P* value
Intercept	3.30	0.67	27.1	< 0.001
Age (year)	0.0074	0.0068	1.0074	0.28
Sex (male)	0.16	0.80	1.18	0.42
Duration of surgery (min)	0.0065	0.0012	1.0066	< 0.001
Major resection[a]	− 0.029	0.17	0.97	0.87
CVP (mmHg)[b]	0.022	0.034	1.022	0.52
HES infusion volume (ml)	0.00045	0.00021	1.00045	0.035
Epidural anesthesia	− 0.48	0.20	0.62	0.020
Application of GDT protocol	− 0.38	0.17	0.68	0.031

β raw regression coefficient, *SE* standard error of raw regression coefficient, *Exp (β)* natural exponent of the raw regression coefficient, *HES* hydroxyethyl starch, *GDT* goal-directed therapy

The R^2 and adjusted R^2 were 0.41 and 0.36, respectively

[a]Major resection (at least three Couinaud liver segments) is compared to minor resection (less than two segments)

[b]The value at the beginning of the parenchymal resection

above the target, ensuring adequate end-organ perfusion. After the resection, SVV-guided fluid administration helped anesthesiologists to optimize the cardiac preload and avoid fluid overload.

Another beneficial effect of using a hemodynamic management protocol is that this policy results in consistent practice regardless of the anesthesiologist's experience or preference. A previous liver-surgery study showed that blood loss varied significantly between anesthesiologists [12], and differences in fluid-management practices between anesthesiologists contributed to this variation.

Although we found that GDT reduced the degree of a positive fluid balance, the median difference was only approximately 400 mL. Lower volumes of colloid solutions (HES and 5% albumin) were used in the GDT group than that used in the control group, which may have contributed to this result. In a previous study comparing GDT and standard therapy in the resuscitation phase of hepatectomies [10], the incidence of postoperative complications was similar in both groups, although the GDT group received less fluid (mean difference, 900 mL). Therefore, the effect of fluid

optimization and avoidance of fluid overload in hepatectomies is unclear.

Our multiple regression analysis suggested that duration of surgery, HES (130/0.4, 6%) infusion volume, epidural anesthesia, and GDT application were associated with the amount of blood loss. Although large molecule HES has negative effects on coagulation [20], third-generation HES (130/0.4, 6%) is considered to have less of an effect on coagulation [21]. Additionally, we cannot conclude that HES had a cause–effect relationship to bleeding, because it may have been used to compensate for blood loss. Although epidural anesthesia has never been reported to reduce blood loss during hepatectomies, it increases the splanchnic vascular capacitance and decreases CVP and portal vein pressure. However, because the pre-resection CVP value was not related to blood loss in this study, the impact of epidural anesthesia on blood loss needs to be further examined.

This study has several limitations. First, this was a before–after design and we did not compare the mean blood loss of two groups due to the aforementioned reason. Thus, it cannot directly prove that our GDT protocol resulted in a decreased blood loss. Additionally, we did not evaluate the effect of the decreased blood loss we observed on mortality and morbidity. Our results indicate that a randomized controlled study comparing clinical outcomes after GDT and L-CVP management should be performed. Second, we did not set a lower SVV limit for post-resection fluid administration. This practice might have contributed to SVV overcorrection. Third, although there are several external reference levels for CVP measurement, we used the midaxillary line at the fourth intercostal space in our study. In the majority of previous studies comparing SVV and CVP during hepatectomies, the reference level for CVP measurement was not indicated. Therefore, the results of studies, comparing the efficacy of SVV and CVP, are not generalizable to cases using various CVP reference levels.

In conclusion, we found that compared to the conventional CVP-assisted hemodynamic management, our GDT protocol of high SVV-assisted liver parenchymal transection followed by SVV-guided fluid resuscitation reduced intraoperative blood loss and positive fluid balance. Further randomized studies are required to confirm the efficacy of GDT during hepatectomies.

Acknowledgements We thank Professor Akinobu Taketomi, Associated Professor Toshiya Kamiyama, and their colleagues of Department of Gastroenterological Surgey I in Hokkkaido University Hospital for their cooperation in perioperative management. We also thank Yoichi Itoh for his advice in setting primary endpoint and statistical analyses.

Author contributions KM contributed to design of study, data analysis, and preparation of the manuscript. He approved the final manuscript. YM helped with design of study and drafting the manuscript and approved the final manuscript. TF, MY, and NT helped with acquisition of original data and approved the final manuscript.

Funding None (Self-funding).

Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest associated with this manuscript.

References

1. Jarnagin WR, Gonen M, Fong Y, DeMatteo RP, Ben-Porat L, Little S, Corvera C, Weber S, Blumgart LH. Improvement in perioperative outcome after hepatic resection: analysis of 1,803 consecutive cases over the past decade. Ann Surg. 2002;236(4):397–406 (discussion -7).
2. Katz SC, Shia J, Liau KH, Gonen M, Ruo L, Jarnagin WR, Fong Y, D'Angelica MI, Blumgart LH, Dematteo RP. Operative blood loss independently predicts recurrence and survival after resection of hepatocellular carcinoma. Ann Surg. 2009;249(4):617–23.
3. Huntington JT, Royall NA, Schmidt CR. Minimizing blood loss during hepatectomy: a literature review. J Surg Oncol. 2014;109(2):81–8.
4. Li Z, Sun YM, Wu FX, Yang LQ, Lu ZJ, Yu WF. Controlled low central venous pressure reduces blood loss and transfusion requirements in hepatectomy. World J Gastroenterol. 2014;20(1):303–9.
5. Hughes MJ, Ventham NT, Harrison EM, Wigmore SJ. Central venous pressure and liver resection: a systematic review and meta-analysis. HPB (Oxford). 2015;17(10):863–71.
6. Zhang XL, Wang WJ, Wang WJ, Cao N. Effectiveness and safety of controlled venous pressure in liver surgery: a systematic review and network meta-analysis. Biomed Res Int. 2015;2015:290234.
7. Kato M, Kubota K, Kita J, Shimoda M, Rokkaku K, Sawada T. Effect of infra-hepatic inferior vena cava clamping on bleeding during hepatic dissection: a prospective, randomized, controlled study. World J Surg. 2008;32(6):1082–7.
8. Choi SS, Jun IG, Cho SS, Kim SK, Hwang GS, Kim YK. Effect of stroke volume variation-directed fluid management on blood loss during living-donor right hepatectomy: a randomised controlled study. Anaesthesia. 2015;70(11):1250–8.
9. Lee J, Kim WH, Ryu H-G, Lee H-C, Chung E-J, Yang S-M, Jung C-W. Stroke volume variation-guided versus central venous pressure-guided low central venous pressure with milrinone during living donor hepatectomy: a randomized double-blinded clinical trial. Anesth Analg. 2017;125(2):423–30.
10. Correa-Gallego C, Tan KS, Arslan-Carlon V, Gonen M, Denis SC, Langdon-Embry L, Grant F, Kingham TP, DeMatteo RP, Allen PJ, D'Angelica MI, Jarnagin WR, Fischer M. Goal-directed fluid therapy using stroke volume variation for resuscitation after low central venous pressure-assisted liver resection: a randomized clinical trial. J Am Coll Surg. 2015;221(2):591–601.
11. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney Int Suppl. 2012;2:1–138.
12. Feltracco P, Brezzi ML, Barbieri S, Serra E, Milevoj M, Ori C. Epidural anesthesia and analgesia in liver resection and living donor hepatectomy. Transpl Proc. 2008;40(4):1165–8.
13. McNally SJ, Revie EJ, Massie LJ, McKeown DW, Parks RW, Garden OJ, Wigmore SJ. Factors in perioperative care that determine blood loss in liver surgery. HPB (Oxford). 2012;14(4):236–41.
14. Chen JS, Huang JQ, Chen XL, Zhan GF, Feng JT. Risk factors associated with intraoperative major blood loss during resection of hepatocellular carcinoma. Hepatogastroenterology. 2015;62(140):790–3.

15. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transpl. 2013;48(3):452–8.
16. Avellan S, Uhr I, McKelvey D, Sondergaard S. Identifying the position of the right atrium to align pressure transducer for CVP: spirit level or 3D electromagnetic positioning? J Clin Monit Comput. 2017;31(5):943–9.
17. Dunki-Jacobs EM, Philips P, Scoggins CR, McMasters KM, Martin RC 2nd. Stroke volume variation in hepatic resection: a replacement for standard central venous pressure monitoring. Ann Surg Oncol. 2014;21(2):473–8.
18. Seo H, Jun I-G, Ha T-Y, Hwang S, Lee S-G, Kim Y-K. High Stroke Volume Variation Method by Mannitol Administration Can Decrease Blood Loss During Donor Hepatectomy. Medicine. 2016;95(2):e2328.
19. Sun Y, Chai F, Pan C, Romeiser JL, Gan TJ. Effect of perioperative goal-directed hemodynamic therapy on postoperative recovery following major abdominal surgery-a systematic review and meta-analysis of randomized controlled trials. Crit Care. 2017;21(1):141.
20. Kozek-Langenecker SA. Effects of hydroxyethyl starch solutions on hemostasis. Anesthesiol J Am Soc Anesthesiol. 2005;103(3):654–60.
21. Oh C-S, Sung T-Y, Kim S-H, Kim D-K, Lim J-A, Woo N-S. Assessment of coagulation with 6% hydroxyethyl starch 130/0.4 in cesarean section. Korean J Anesthesiol. 2012;62(4):337–42.