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# A Comparative Study of Intraoperative Fluid Management Using Stroke Volume Variation in Liver Resection

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**Objective:** The aim of this study is to examine whether intraoperative fluid management with stroke volume variation (SVV) can achieve safe intravenous fluid restriction and contribute to decreasing intraoperative blood loss in liver surgery.

**Background:** In liver surgery, maintaining the central venous pressure (CVP) at a low level is effective in decreasing intraoperative blood loss. Recently, several studies have suggested that SVV obtained using the FloTrac system demonstrated a better fluid responsiveness than CVP.

**Methods:** We enrolled 30 patients undergoing liver resection since May 2015 in this prospective observational study, and we set the SVV target during liver transection at 13%–20% (SVV group). Forty-three cases of liver resection that we performed between January 2014 and March 2015 without using CVP or SVV were used as the Control group. We compared the 2 groups by using intraoperative blood loss as the primary endpoint.

**Results:** There was no significant difference in patient characteristics between the 2 groups. The mean SVV during liver transection in the SVV group was 15.6 ± 4.4%. The infusion

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volume until completion of liver transection in the Control group was 9.4 mL/kg/h, whereas that of the SVV group was 3.3 mL/kg/h, a significantly lower volume ($P < 0.001$). The median intraoperative blood loss was significantly decreased in the SVV group compared with the Control group (391 versus 1068 mL; $P < 0.001$). The intraoperative transfusion rate was also significantly decreased in the SVV group.

**Conclusion:** We demonstrated that intraoperative management with SVV can achieve safe intravenous fluid restriction and is useful for decrease intraoperative blood loss in liver surgery.

*Key words:* Liver resection – Intraoperative monitoring – Stroke volume variation – Surgical blood loss



Maintaining the central venous pressure (CVP) at a low level during parenchymal transection is effective for decreasing intraoperative blood loss in liver surgery. It has been reported that both intraoperative blood loss and blood transfusion were significantly decreased in intraoperative management that maintained the CVP at 5 $cmH_2O$ or lower.[1] Intravenous fluid restriction by low CVP management is still standard in liver surgery. Regarding the relationship between blood loss and postoperative complications, previous reports mentioned that intraoperative blood loss is a risk factor for surgical site infection after liver resections,[2,3] and we believe that decreased blood loss will lead to safer perioperative management. However, to measure CVP, invasive central venous catheterization is necessary. Major complications associated with central venous catheterization include mechanical complications such as arterial puncture, hematoma, pneumothorax, and hemothorax; catheter-related bloodstream infections; and thrombotic complications. The prevalence of mechanical complications, in particular, is reported to be 5%–19%.[4]

The FloTrac system (Edwards Lifesciences, Irvine, California) was developed recently for hemodynamic monitoring during intraoperative circulatory management. This system usually needs cannulation into the radial artery. Although it is not a noninvasive monitor, it is less invasive than central venous catheterization because no large vessels need to be cannulated. It has been confirmed that stroke volume variation (SVV) obtained by the FloTrac system serves as a predictor of fluid responsiveness,[5] and another study has shown that SVV has better responsiveness to decreased circulatory blood volume than CVP dose.[6] In addition, recent reports showed that there was a strong correlation between SVV and CVP in liver surgery, and Dunki-Jacobs *et al* reported that CVP $< 3$ mmHg corresponds with SVV $> 13\%$.[7,8]

We presumed that intraoperative management with SVV as a new indicator alternative to CVP makes it possible to provide safe dry-side management during liver transection. However, there remain few reports indicating that SVV is useful for intraoperative fluid management in conventional liver surgery. Therefore, we conducted a prospective observational dry-side management with the SVV value set to be higher than the cut-off value to verify whether intraoperative management with SVV can achieve safe intravenous fluid restriction and contributes to decreasing intraoperative blood loss in liver surgery.

## Materials and Methods

### *Study design*

This study is a historically controlled prospective observational study to verify whether intraoperative fluid management with SVV can achieve safe intravenous fluid restriction and contributes to decreasing intraoperative blood loss in liver surgery. Forty-three consecutive cases of liver resection that we performed between January 2014 and March 2015 without using CVP or SVV as a predictor for intraoperative management were included as the Control group. Liver resection cases using SVV as a predictor for intraoperative management since May 2015 were accumulated for a prospective observational study (the SVV group). Patients received open liver resections in both groups.

The protocol of this study has been approved by the Institutional Ethical Review Board of the National Cancer Center in Japan. Patient consent was waived owing to anonymization of patient data and the features of this study such as its noninvasiveness and lack of need for material sampling.

*Patients*

Since May 2015, patients scheduled to undergo open liver resection were eligible for this prospective observational study as the SVV group. Operative procedures were intended for anatomic resection for subsegmentectomy or above (≥1 segmentectomy of Couinaud classification), except for left lateral segmentectomy, regardless of biliary reconstruction. Other inclusion criteria were Eastern Cooperative Oncology Group performance status of 0–2 and American Society of Anesthesiologists physical status (ASA–PS) of 1–3. Patients with metastatic liver tumors that required simultaneous resection of the primary lesions and those with severe arrhythmia such as atrial fibrillation were excluded. Forty-three consecutive cases of open-liver resection that we performed between January 2014 and March 2015 without the use of CVP or SVV were selected as the Control group. Their operative procedures were the same as the SVV group. We compared and evaluated the results of both the SVV and Control groups.

*Endpoints and other clinical parameters*

The primary endpoint was intraoperative blood loss. The secondary endpoints included operative duration, intraoperative transfusion rate (red blood cell concentrate), and perioperative complications.

The patient characteristics investigated were sex, age, ASA physical status, with or without viral hepatitis, liver disease (primary liver cancer, perihilar cholangiocarcinoma, metastatic tumor, others), Child–Pugh classification, and indocyanine green retention rate at 15 minutes. The surgical factors included in the analyses were operative procedure, with or without biliary reconstruction, initial/repeat hepatectomy, single/multiple resection, concurrent use/no use of the Pringle maneuver, final in–out balance, infusion volume until completion of liver transection, total dose of vasopressors, mean arterial pressure and heart rate during liver transection, SVV during liver transection, and SVV after liver transection.

*Anesthetic management*

We prescribed the anesthetic management in considering the essential means of getting accurate SVV readings and achieving the target SVV during liver transection in the SVV group. Surgeries were basically performed under general anesthesia combined with epidural anesthesia. Following tracheal intubation, patients' lungs were mechanically ventilated with a constant tidal volume of 8–10 mL/kg. The respiratory rate was set to 10/min as the standard and then adjusted as appropriate based on the results of monitoring the end-tidal $CO_2$ concentration and arterial blood gas analysis. Positive end-expiratory pressure was not used during mechanical ventilation as a rule. Anesthesia was maintained with sevoflurane (1.0%–2.0%), fentanyl, remifentanil, and 0.2% ropivacaine for epidural anesthesia. Systolic blood pressure was maintained at ≥90 mmHg. Vasopressor or additional fluids were administered to maintain systolic blood pressure <80 mmHg. Urine output throughout surgery was maintained at ≥0.5 mL/kg/h to the extent possible. We set a target for SVV during liver transection of 13%–20%. In terms of fluid management, the infusion volume until completion of liver transection was set at ≤5 mL/kg/h and adjusted as appropriate according to SVV. The final in–out balance was set at 5–7 mL/kg/h.

In the Control group, surgery was performed under general anesthesia combined with epidural anesthesia. Circulatory management of blood pressure and urine output in the Control group was similar to that in the SVV group. Intraoperative fluid management, however, was adjusted properly at an anesthesiologist's discretion according to the intraoperative situation.

In both groups, when hemoglobin level is <8 g/dL, we took into consideration the transfusion of red blood cell concentrate.

*Surgical procedure*

Operative procedure was the same in both groups. The surgical team for each operation was composed of 1 consultant and 2 trainees, and there was no change in the members of consultants between the 2 groups. The liver parenchyma was fractured by the clamp-crushing method, and the devices used during liver parenchymal transection included an ultrasonically activated scalpel and an electrocoagulation device.

The Pringle maneuver was applied for intermittent inflow occlusion to reduce blood loss during surgery. It consisted of clamping the hepatic hilum for 15 minutes, followed by release for 5 minutes.

## Statistical Analysis

The intraoperative blood loss in the Control group had a mean logarithmic value of 6.98 (=1069.6 mL)

*Table 1. Patient characteristics*

| Variable | Control group (n = 43) | SVV group (n = 30) | P-value |
|---|---|---|---|
| Age (median) | 70 (26-80) | 67 (50-84) | 0.236 |
| Sex (M/F) | 14/29 | 11/19 | 0.716 |
| HBV (+) | 3 (7.0%) | 1 (3.3%) | 0.501 |
| HCV (+) | 5 (11.6%) | 1 (3.3%) | 0.204 |
| BMI ($kg/m^2$, median) | 21.6 (17.9-30.8) | 21.85 (16.6-28.7) | 0.858 |
| ASA-PS (1/2/3) | 10/32/1 | 4/24/2 | 0.409 |
| Diabetes (+) | 10 (23.3%) | 10 (33.3%) | 0.342 |
| Disease (Primary/Perihilar/Meta/Others) | 18/10/13/2 | 7/10/11/2 | 0.427 |
| Neoadjuvant chemotherapy | 6 (14.0%) | 4 (13.3%) | 0.940 |
| Preoperative Hb level (g/dl, median) | 12.9 (10.2-16.4) | 13.0 (11.2-16.2) | 0.400 |
| Preoperative AST level (U/L, median) | 32 (16-124) | 25 (13-101) | 0.141 |
| Child-Pugh classification (A/B) | 43/0 | 30/0 | – |
| ICG R15 (%, median) | 11.0 (3.2-27.8) | 9.35 (2.7-17.4) | 0.158 |

ASA-PS, American Society of Anesthesiologists physical status; AST, aspartate aminotransferase; BMI, body mass index; Hb, hemoglobin; ICG R15, indocyanine green retention rate at 15min; Meta, metastatic liver tumor; Perihilar, perihilar cholangiocarcinoma; Primary, primary liver cancer; SVV, stroke volume variation.

and a SD value of 0.70. Then, we hypothesized that intraoperative management with SVV reduced the average intraoperative blood loss to 700 mL. To have a 1-sided type 1 error of 5% and a power of 90%, the target accrual was 30 patients in the SVV group.

The data between the 2 groups were statistically analyzed by the $X^2$ test for categoric variables, and by the Mann–Whitney U test for continuous variables. *P* values $<0.05$ were considered statistically significant for all tests. All analyses were performed using PASW (predictive analytics software) version 18.0 (SPSS Inc., Chicago, Illinois).

## Results

### *Patients and characteristics*

We accumulated 30 consecutive cases between May 2015 and February 2016 as the SVV group for a prospective observational study, and compared them with 43 cases in the Control group. Patient characteristics in both groups are shown in Table 1. There were no significant differences in any factors between the Control group and the SVV group.

### *Surgical factors*

Surgical factors are shown in Table 2. For factors such as the operative procedure, with or without

*Table 2 Surgical factors*

| | Control group (n = 43) | SVV group (n = 30) | *P* value |
|---|---|---|---|
| Procedure (SS/S/BS/TS) | 6/7/29/1 | 5/2/21/2 | 0.525 |
| Biliary reconstruction | 15 (34.9%) | 12 (40%) | 0.656 |
| Hepatectomy (initial/repeat) | 41/2 | 26/4 | 0.184 |
| Resection site (single/multiple) | 39/4 | 28/2 | 0.687 |
| Pringle maneuver | 41 (95.3%) | 30 (100%) | 0.231 |
| Final in-out balance (ml/kg/h, median) | 6.1 (1.6–12.0) | 6.15 (4.0–9.3) | 0.690 |
| Infusion volume until completion of transection (mL/kg/h, median) | 9.4 (4.2–19.2) | 3.3 (1.9–8.4) | <0.001 |
| Urine output (mL/kg/h, median) | 1.06 (0.30–5.92) | 0.66 (0.25–2.35) | 0.001 |
| Total dose of ephedrine (mg, median) | 12 (0–40) | 8 (0–30) | 0.036 |
| Total dose of phenylephrine (mg, median) | 0.3 (0–2.8) | 0.3 (0–1.6) | 0.685 |
| MAP during liver transection (mmHg, median) | 69 (52.4–84.8) | 74.75 (58.6–91.9) | 0.027 |
| HR during liver transection (bpm, median) | 74 (51–99) | 77.4 (64–101) | 0.120 |
| SVV during liver transection (%, mean) | – | 15.6 ± 4.4 | – |
| SVV after liver transection (%, mean) | – | 7.5 ± 1.9 | – |

BS, bisegmentectomy; HR, heart rate; MAP, mean arterial pressure; S, segmentectomy; SS, subsegmentectomy; SVV, stroke volume variation; TS, trisegmentectomy.

*Table 3 Primary endpoint*

| | Control-group (n = 43) | SVV group (n = 30) | *P* value |
|---|---|---|---|
| Intraoperative blood loss (mL, median) | 1068 (66–4983) | 391 (97–2498) | <0.001 |

SVV, stroke volume variation.

biliary reconstruction, there was no significant difference between the 2 groups. The average SVV during liver transection in the SVV group was 15.6 ± 4.4%. The infusion volume until completion of liver transection in the Control group was 9.4 mL/kg/h, whereas that in the SVV group was 3.3 mL/kg/h, a significantly lower volume ($P < 0.001$). In all cases, the target SVV (13%–20%) was achieved during liver transection. Urine output throughout surgery was 1.06 mL/kg/h in the Control group and 0.66 mL/kg/h in the SVV group, significantly lower in the SVV group ($P = 0.001$); however, in 25 out of 30 cases, the urine outputs exceeded the targeted 0.5 mL/kg/h. The total dose of vasopressors was higher in the Control group. Average arterial blood pressure during liver transection was 69.0 mmHg in the Control group, and 74.75 mmHg in the SVV group, a significantly higher blood pressure in the SVV group ($P = 0.027$).

### *Endpoints*

The intraoperative blood loss defined as the primary endpoint was a median of 1068 mL in the Control group, and 391 mL in the SVV group, a significant reduction ($P < 0.001$, Table 3).

For secondary endpoints, the operative duration was not significantly different between the 2 groups, but the intraoperative transfusion rate (red blood cell concentrate) was 27.9% in the Control group, and 3.3% in the SVV group, a significantly lower rate ($P = 0.007$). Perioperative complications showed no significant difference between the 2 groups when compared in terms of Grade 3 and higher according to the Clavien–Dindo classification.[9] However, when compared in terms of Grade 2 and higher, perioperative complications showed a significant decrease in the SVV group ($P = 0.029$). We defined acute kidney injury as a serum creatinine value measured on the first postoperative day being increased by ≥0.3 mg/dL above the preoperative value, according to the KDIGO (Kidney Disease Improving Global Outcomes) classification.[10] There was no significant difference in this value between the 2 groups ($P = 0.780$). None of the cases had embolic complications (Table 4).

## Discussion

It has been reported that maintaining CVP at a low level with the aim of reducing intraoperative blood loss during liver surgery is useful. Methods to manage CVP at ≤5 $cmH_2O$, <5 mmHg, or ≤4 mmHg have been reported. These managements lead to intravenous fluid restriction and a reduction in intraoperative blood loss and intraoperative transfusion rates, which in turn shortens hospital stays.[1,11,12] The method, as standard intraoperative management, is also currently applied to laparoscopic liver surgery.[12] As mentioned already, however, CVP measurement needs central venous catheterization, and the complication rate associated with the procedure cannot be disregarded. The frequency of mechanical complications is reported to be 5%–19%.[4] Although another report shows that

*Table 4 Secondary outcomes*

| | Control group (n = 43) | SVV group (n = 30) | *P* value |
|---|---|---|---|
| Operative duration (min., median) | 357 (170–677) | 324 (173–602) | 0.626 |
| Intraoperative transfusion | 12 (27.9%) | 1 (3.3%) | 0.007 |
| Perioperative complication ≧ Grade II[a] | 24 (55.8%) | 9 (30.0%) | 0.029 |
| Perioperative complication ≧ Grade III[b] | 9 (20.9%) | 6 (20.0%) | 0.923 |
| Acute kidney injury[c] | 2 (4.7%) | 1 (3.3%) | 0.780 |
| Embolic complication | 0 | 0 | – |

[a]Complications were defined as situations ≧ Grade II in the criteria of Clavien–Dindo classification.

[b]Complications were defined as situations ≧ Grade III in the criteria of Clavien–Dindo classification.

[c]Acute kidney injury was defined as ≧0.3 mg/dL elevation of serum creatinine level.

SVV, stroke volume variation.

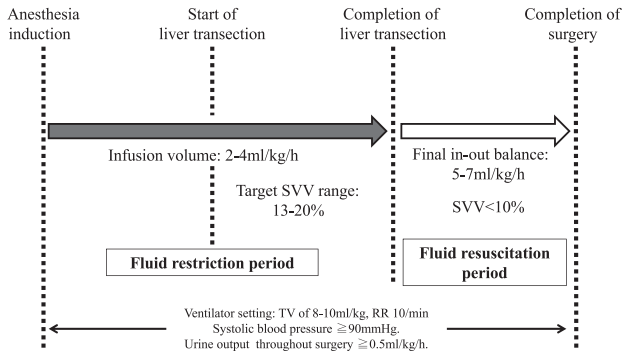


**Fig. 1** Fluid management in liver surgery.

real-time ultrasound-guided central venous catheterization can reduce the frequency of mechanical complications to 0%–1.1%, there is still a high rate of catheter-related bloodstream infections (approximately 10%).[13] In addition, improved and advanced surgical techniques and instruments are providing added patient safety in liver surgery. Under these circumstances, not all patients now need central venous catheterization.

The FloTrac system, used for hemodynamic monitoring during intraoperative circulatory management, is capable of continuously measuring arterial pressure-based cardiac output (CO). With the system installed on an arterial line that is established during surgery, parameters such as CO can easily be determined from analysis of arterial pressure waveforms. Among the parameters obtained from the FloTrac system, SVV indicates the numeric value of respiratory variation in stroke volume (SV) caused mainly by intrathoracic pressure elevation during inspiration on mechanical ventilation. In general, a high SVV value and low values of CO and stroke volume suggest insufficient circulatory blood volume.[14] In recent years, it has been recommended that fluid variables be managed based on the concept of individualized goal-directed fluid management. Dynamic variables such as CO, SV, and SVV, depending on the case, are reported to be useful for fluid management.[15] It has already been confirmed that SVV predicts fluid responsiveness (giving fluids leads to stabilizing the hemodynamic status).[5] SVV is more responsive to decreased circulatory blood volume than CVP, and SVV is also more useful than CVP as an indicator of preload.[6] The frequency of major complications such as permanent ischemic damage, sepsis, and pseudoaneurysm formation associated with peripheral artery catheterization is reported to be <1%.[16] Because of the necessity of arterial line in liver surgery, it can be safely said that using the FloTrac system is less invasive than central venous catheterization. Furthermore, recent reports showed that there was a strong correlation between SVV and CVP in liver surgery.[7,8] It will be important to verify, for added safety, whether intraoperative management with SVV instead of CVP is effective for safe intravenous fluid restriction and decreasing intraoperative blood loss in liver resection.

In the present study, safe intravenous fluid restriction and significant reduction in intraoperative blood loss was achieved with good results by intraoperative management with SVV. We considered that adequate intravenous fluid restriction contributed to bloodless operative field and made it easy to perform liver transection. Regarding the setting of the target SVV, the lower limit value of 13% is generally considered to be the cut-off value of SVV[17] and Dunki–Jacobs *et al* reported that an SVV of 13% corresponds with a CVP of 3 mmHg.[8] To secure safety in dry-side management, we set the upper limit value at 20%. This value was set based on our considerations about SVV fluctuations in laparoscopic liver resection that we previously reported.[18] In actual intraoperative management, infusion volume was generally maintained at 2–4 mL/kg/h from start of anesthetic induction until completion of liver transection (the fluid restriction period). As a result, we achieved the target SVV (13%–20%) in all cases of the SVV group. We defined the fluid resuscitation period as the period from completion of liver transection until completion of surgery, with the target final in–out balance set at 5–7 mL/kg/h. We practiced management with the systolic blood pressure targeted at 90 mmHg or above, and urine output at 0.5 mL/kg/h throughout the surgery (Fig. 1). During the period of this study, 2 reports were presented regarding high SVV management during liver transection in living-donor right hepatectomy set at 10%–20%,[19,20] but there has been no report of management with SVV as an indicator in conventional open-liver resection for liver diseases. In this study, to achieve the target SVV, we mainly addressed fluid restriction only. Seo *et al*, however, reported that administration of mannitol at 0.5 g/kg was effective in high SVV management.[20] Furthermore, some reports show that reverse Trendelenburg position leads to a reduction in CVP,[21] and that low CVP is maintained by vasodilation using isoflurane and sublingual nitroglycerine.[22] It is highly possible that these results will be applied to intraoperative management with SVV in the future.

In this study, there was no case in which the hemodynamic status became remarkably unstable, and the use of vasopressors was required more frequently in the Control group. We speculate that intraoperative blood loss had a stronger influence on hemodynamic status than dry-side management. As for perioperative complications, when compared in terms of Grade 2 and higher according to the Clavien–Dindo classification, the SVV group had a significant reduction. Postoperative infectious complications that required the administration of antibiotics except for prophylactic antibiotics were clearly decreased in the SVV group. It has been reported that intraoperative transfusion is related to immunologic deterioration and perioperative complications.[23] We think that the decrease in both intraoperative blood loss and transfusion rate led to a reduction in complications. As complications associated with dry-side management, there were concerns about kidney injury and embolic complication. However, no significant increase was found as compared with the Control group, and in particular, there was no embolic complication in either of the 2 groups. As for kidney injury, in the SVV group, there was only 1 case in which serum creatinine value measured on the first postoperative day increased by $\geq$0.3 from the preoperative value, but this case was not clinically problematic and did not affect the length of hospital stay. Meanwhile, Correa–Gallego *et al* applied goal-directed fluid therapy using SVV to fluid resuscitation after completion of liver transection, and performed fluid management so that the SVV value can return to a baseline level.[22] The final in–out balance in liver surgery will need further consideration.

There are some limitations in this study. First, operative procedures are considered by covering from subsegmentectomy to operations with biliary reconstruction. The reason why we included subsegmentectomy in the subjects is that we judged hemorrhage risk was high, from the fact that the liver transection area has a relatively large, and that the resection is done in such a manner as to expose the main hepatic vein. Secondly, although intraoperative transfusion rate in the Control group was relatively high, as for the Control group, the cases were selected for the reasons that the operative methods, surgical team, and applicable criteria of blood transfusion are virtually identical to the SVV group. In the 2 groups, there is no significant difference in the rate of hepatocellular carcinoma ($P = 0.649$). Furthermore, as for the cases, including the control group, experienced before we launched this study, we had not routinely practiced intraoperative management aimed at decreasing blood loss such as fluid restriction in liver resection. Given the decreased intraoperative blood loss, we can accept the decrease of intraoperative transfusion rate. Thirdly, this study covers a relatively small number of cases in a single institution. In this connection, we recommend that further validation should be performed through randomized-controlled trials in many institutions. Especially, a future study based on comparisons of the intraoperative fluid management using SVV and the current standard management using CVP will bring about further beneficial information for liver surgery.

Finally, although this study is a historically controlled prospective observational study in a single institution, we suggested that intraoperative management with SVV can achieve safe intravenous fluid restriction and contributes to decreasing intraoperative blood loss in liver surgery.

## Conclusion

In conclusion, by this study we have demonstrated that the intraoperative fluid management with SVV can achieve safe intravenous fluid restriction and contributes to decreasing intraoperative blood loss in liver surgery. It is imperative to accumulate further cases and refine this intraoperative management method. We need to link this study to randomized, controlled trials with larger number of cases in the future, and also hope this study will contribute to further development of this field.

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