ANESTHESIOLOGY

Restrictive *versus* Decision Support Guided Fluid Therapy during Major Hepatic Resection Surgery: A Randomized Controlled Trial

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ANESTHESIOLOGY 2024; 141:881–90

EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Dynamic measures of fluid responsiveness such as derived stroke volume, stroke volume index, stroke volume variation, and systemic vascular resistance index have been used to guide intraoperative fluid administration for many high-risk procedures
- Restrictive fluid administration during specific portions of hepatic resection surgery has become the standard of care to reduce intraoperative bleeding but may be associated with hypoperfusion and hyperlactemia
- It remains unclear whether the use of a proprietary fluid administration decision support system compared to a restrictive fluid strategy using standard dynamic fluid responsiveness measures can improve hyperlactemia after hepatic resection

What This Article Tells Us That Is New

- Ninety patients undergoing major laparoscopic or open hepatic resection were randomized to a decision support or restrictive fluid strategy
- Lactate levels at the end of surgery in the decision support group (median, 2.5 mM; interquartile range, 1.9 to 3.7) were lower than in the restrictive group (median, 4.6; interquartile range, 3.1 to 5.4) for a median difference of 2.1 mM (95% CI, –2.7 to –1.2; $P < 0.001$)
- The exploratory secondary outcome of intraoperative estimated blood loss was not statistically significantly different between the decision support group (median, 450 ml; interquartile range, 300 to 600) compared to the restrictive fluid group (median, 500 ml; interquartile range, 300 to 800 ml; $P = 0.727$)

ABSTRACT

Background: Fluid therapy during major hepatic resection aims at minimizing fluids during the dissection phase to reduce central venous pressure, retrograde liver blood flow, and venous bleeding. This strategy, however, may lead to hyperlactatemia. The Acumen assisted fluid management system uses novel decision support software, the algorithm of which helps clinicians optimize fluid therapy. The study tested the hypothesis that using this decision support system could decrease arterial lactate at the end of major hepatic resection when compared to a more restrictive fluid strategy.

Methods: This two-arm, prospective, randomized controlled, assessor- and patient-blinded superiority study included consecutive patients undergoing major liver surgery equipped with an arterial catheter linked to an uncalibrated stroke volume monitor. In the decision support group, fluid therapy was guided throughout the entire procedure using the assisted fluid management software. In the restrictive fluid group, clinicians were recommended to restrict fluid infusion to 1 to 2 ml · kg^{-1} · h^{-1} until the completion of hepatectomy. They then administered fluids based on advanced hemodynamic variables. Noradrenaline was titrated in all patients to maintain a mean arterial pressure greater than 65 mmHg. The primary outcome was arterial lactate level upon completion of surgery (*i.e.*, skin closure).

Results: A total of 90 patients were enrolled over a 7-month period. The primary outcome was lower in the decision support group than in the restrictive group (median [quartile 1 to quartile 3], 2.5 [1.9 to 3.7] mmol · l^{-1} *vs.* 4.6 [3.1 to 5.4] mmol · l^{-1}; median difference, –2.1; 95% CI, –2.7 to –1.2; $P < 0.001$). Among secondary exploratory outcomes, there was no difference in blood loss (median [quartile 1 to quartile 3], 450 [300 to 600] ml *vs.* 500 [300 to 800] ml; $P = 0.727$), although central venous pressure was higher in the decision support group (mean ± SD of 7.7 ± 2.0 mmHg *vs.* 6.6 ± 1.1 mmHg; $P < 0.002$).

Conclusions: Patients managed using a clinical decision support system to guide fluid administration during major hepatic resection had a lower arterial lactate concentration at the end of surgery when compared to a more restrictive fluid strategy. Future trials are necessary to make conclusive recommendations that will change clinical practice.

(ANESTHESIOLOGY 2024; 141:881–90)

This article is featured in "This Month in ANESTHESIOLOGY," page A1. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org).

Submitted for publication December 9, 2023. Accepted for publication July 16, 2024. Published online first on July 25, 2024.

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 ANESTHESIOLOGY 2024; 141:881–90. DOI: 10.1097/ALN.0000000000005175

<zdoi;10.1097/ALN.0000000000005175>

Fluid therapy is an essential yet controversial component of patient care during major hepatic resection. To decrease venous bleeding and avoid inferior vena cava clamping, a low central venous pressure (CVP) strategy was proposed over two decades ago and has been shown to be effective during hepatectomy.[1,2] This strategy aims to restrict fluid infusion during hepatic resection, which is often followed by liberal fluid infusions to compensate for any deficit that may have occurred before completion of liver resection. It has been implemented into practice in many centers and is considered by experts as standard care during hepatic resection surgery.[3,4] However, fluid restriction strategies are now increasingly called into question because they place patients at risk of poor tissue perfusion, which can result in hyperlactatemia and increased postoperative morbidity.[5,6]

Goal-directed fluid therapy has been proposed as a strategy for volume optimization during hepatic resection,[7,8] but some fear that this approach may push clinicians to administer fluid challenges in excess and potentially increase bleeding. Furthermore, manual goal-directed fluid therapy is not easy to implement, and no robust data exist in the context of hepatic resection surgery. The Acumen assisted fluid management system (Edwards Lifesciences, USA) is a novel decision support system that has been developed to help clinicians manage intraoperative fluid bolus administration.[9–11] This system increases goal-directed fluid therapy protocol compliance and individualizes fluid therapy by adapting hemodynamic thresholds to each patient. Furthermore, this decision support system has been shown to better predict fluid responsiveness than clinicians applying manual goal-directed fluid therapy protocols and may consequently decrease the risk of fluid overload, which is of particular interest during liver surgery.[11] We tested the hypothesis that using this decision support system could decrease arterial lactate at the end of major hepatic resection when compared to a more restrictive fluid strategy.

Materials and Methods

This two-arm, prospective, randomized controlled, assessor- and patient-blinded superiority study was approved by the French Sud Ouest et Outre Mer II institutional review board on October 22, 2022. This approval is available upon request to the corresponding author. The principal investigator (Dr. Joosten) obtained written informed consent from all patients before surgery. The study was first submitted on clinicaltrials.gov (NCT05704387) on July 28, 2022, before enrollment. Its registration was confirmed by clinicaltrials.gov on January 19, 2023. It was carried out at Paul Brousse Hospital, Villejuif, France, from December 12, 2022, to July 17, 2023, and patient follow-up continued until August 14, 2023.

Inclusion and Noninclusion Criteria

Adult patients scheduled for elective major hepatic resection were considered for inclusion. Patients were excluded if they were less than 18 yr, were pregnant, or did not speak French. Patients with significant cardiac arrhythmias were also excluded, because cardiac arrhythmias (*e.g.*, atrial fibrillation) decrease the reliability of pulse contour monitoring measurements.

Randomization and Blinding

Computer-based randomization was carried out by the local affiliated research unit of Paris–Saclay University, Paris, France, where staff placed group allocations into sealed opaque envelops that were stored in the department's research office. Group allocation was disclosed on the morning of the operation. Patients and outcome assessors were blinded to group allocation, but treating clinicians were not because blinding anesthesiologists to a fluid therapy protocol during high-risk surgery is neither feasible nor safe. Neither group assignments nor changes in the clinical protocol occurred during the study.

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Anesthesia Procedure

Patients consulted an anesthesiologist preoperatively for evaluation and premedication recommendations. All patients had a final bedside consultation the day before surgery. When applicable, angiotensin receptor blocker drugs and/or angiotensin-converting enzyme inhibitor drugs were stopped at least 12 h before surgery. The day of surgery, patients entered the operating room after validating a systematic security checklist. All patients were then monitored with a five-lead electrocardiogram, pulse oximetry, noninvasive blood pressure monitoring, rectal temperature, depth of anesthesia monitoring (Bispectral Index, Medtronic, France), train-of-four and post-tetanic count monitor (Train-of-Four scan technology, Imed, France), inspiratory and expiratory gases, and airway pressures. In addition, a radial arterial catheter paired with uncalibrated cardiac output monitoring using the FloTrac sensor linked to the EV1000 clinical platform (Edwards Lifesciences,) was inserted after anesthesia induction. The system measured hemodynamic variables every 20 s. A central venous catheter was also inserted after induction and continuously measured CVP. The EV1000 clinical platform measured and stored stroke volume (SV), SV index, cardiac output, cardiac index, SV variation, CVP, and systemic vascular resistance values. The assisted fluid management software was activated or not, depending on group allocation. After preoxygenation to an end-tidal O_2 concentration of at least 90%, anesthesia was induced with propofol (2 to 3 mg · kg^{-1}) and sufentanil (0.1 to 0.3 μg · kg^{-1}), and muscle relaxation was induced with atracurium (0.5 mg · kg^{-1}). Mechanical ventilation was initiated with a targeted tidal volume of 7 to 8 ml · kg^{-1} of ideal bodyweight and a positive end expiratory pressure of at least 5 cm H_2O. The respiratory rate was adjusted to achieve an end-tidal CO_2 pressure between 34 and 38 mmHg. Prophylactic antibiotics were administered 30 min before incision. Anesthesia was maintained with sevoflurane, whose concentration was adjusted to maintain a Bispectral Index between 40 and 60. Sufentanil (10 to 25 μg · h^{-1}), ketamine (0.1 mg · kg · h^{-1}), and lidocaine (1.6 mg · kg^{-1} · h^{-1}) were used to control nociception, and a continuous atracurium (10 to 20 mg · h^{-1}) infusion maintained deep to moderate neuromuscular blockade (train-of-four ratio less than 2). Postoperative nausea and vomiting prevention consisted of an intravenous bolus of 8 mg of dexamethasone administered before incision, and droperidol and ondansetron was administered before tracheal extubation based on the patient's Apfel score. Postoperative pain was anticipated and treated with paracetamol (unless the patient had signs of liver insufficiency or had hypersensitivity or intolerance), ketoprofen (unless the patient had massive intraoperative bleeding, acute or chronic renal failure, gastric ulcer, hypersensitivity or intolerance), and nefopam (unless the patient had glaucoma, epilepsy, ischemic heart disease, prostate hyperplasia, or hypersensitivity or intolerance). Extubation of the trachea was performed in the operating room or in the postanesthesia care unit (PACU), depending on the postoperative status of the patient. In the PACU, morphine was titrated to maintain a verbal numerical pain score less than 4. Due to the absence of an overnight PACU in our institution, all patients were admitted to the intensive care unit (ICU) for observation the night after surgery. Patients who required reoperation were also observed overnight in the ICU.

Fluid and Hemodynamic Management

In the decision support group, anesthesiologists were instructed to administer a fluid challenge whenever it was proposed by the assisted fluid management software. The software consists of two layers: a population model and a bolus log model, as described previously.[11] Briefly, the software considers the patient's SV and SV variation, and to a lesser extent mean arterial pressure (MAP), heart rate, and systemic vascular resistance, to suggest fluid challenges and then assesses the patient's response to fluids. The population model predominantly considers SV variation. The bolus log model analyses each patient's response to a bolus and predominantly considers SV and changes in SV to modify the threshold proposed by the population model. In essence, it individualizes fluid therapy to the patient's needs. Anesthesiologists set the targeted increase in SV at 10% after a fluid challenge as the default value for this trial and informed the algorithm when surgeons used a laparoscopic approach (because the software can take this into account and make appropriate adjustments). Although anesthesiologists had the option to refuse boluses or to administer boluses outside of recommendations to provide a supplemental level of safety, 100% compliance with decision support suggestions was strongly encouraged as long as it would not result in patient harm. Moreover, the fluid strategy could also be adapted during surgery to have a more restrictive strategy (*e.g.*, 15% targeted increase in SV). Three anesthesiologists (S.C., M.S.-P., and A.J.) highly trained in using the assisted fluid management software handled fluid therapy for all patients included in the decision support group. They acted as the attending anesthesiologists during the surgical cases. Fluid therapy was decision support guided in this group from the placement of the arterial catheter until the end of surgery.

In the restrictive fluid group (control group), anesthesiologists had access to the same advanced hemodynamic device, but the decision support function was not activated. Clinicians were instructed to consider SV and SV variation values, but the fundamental goal was to limit fluid administration to 1 to 2 ml · kg^{-1} · h^{-1} of lactated Ringer's solution before the end of hepatic resection (restrictive prehepatectomy fluid therapy). Blood loss could be compensated during surgical dissection if necessary. There was no compensation for diuresis. Additional fluids could be administered only if the clinicians assessed the patient as having a high risk of complications due to inadequate preload (*e.g.*, if

major bleeding occurred). After completion of the hepatic resection and adequate hemostasis, clinicians were free to administer fluids as they saw fit and continued to have access to the advanced hemodynamic variables obtained from the EV1000 clinical platform. At no time was the decision support software activated in the control group. Consequently, this group had an initially restrictive prehepatectomy fluid approach up to the end of liver resection, which was then followed by a more liberal and clinician-dependent fluid strategy. Clinicians continued to have access to advanced hemodynamic parameters. For consistency, we use the term "restrictive" throughout the article. Patients in the restrictive group were cared for by a team of anesthesiologists specializing in hepatobiliary anesthesia, including the three anesthesiologists that cared for patients randomized into the decision support group.

In both groups, fluid consisted of 250-ml boluses of a balanced crystalloid solution. Albumin 5% solutions could also be used at any time in both groups at the discretion of the anesthesiologist. MAP was kept above 65 mmHg using norepinephrine infusion (standardized dilution at 100 μg · ml^{-1}) during surgery. Transfusions (packed red blood cells) were administered in accordance to the French national guidelines. These recommendations have thresholds but stress the importance of evaluating the patient's tolerance to anemia before deciding to administer blood. The thresholds are as follows: 7 g · dl^{-1} if the patient has no comorbidities, 8 to 9 g · dl^{-1} if the patient has cardiovascular comorbidities, and 10 g · dl^{-1} if the patient is suffering from acute coronary disease or acute heart failure. Transfusions were consequently decided by the attending physician, in accordance with national recommendations, based on each patient's comorbidities and clinical tolerance to anemia. During surgery, patients were cared for by one attending anesthesiologist and one nurse anesthetist.

Outcome Measures

The primary outcome was lactate level at the end of surgery (measured during skin closure). Key secondary exploratory outcomes were intraoperative blood loss, amount of intraoperative vasopressors, fluids, the incidence of acute kidney injury, and postoperative complications using the Clavien–Dindo classification (each complication being graded). An exploratory *post hoc* analysis of other outcomes included net fluid balance (*i.e.*, the sum of all infused fluids and blood products minus the sum of blood loss and diuresis), intraoperative hemodynamic values (all hemodynamic variables were collected at 20-s intervals with the advanced hemodynamic monitor and averaged from the time of arterial catheter placement to the end of surgery), postoperative care unit (h) and hospital lengths of stay (days), other lactate values, lactate thresholds, and clinician behavior regarding decision support results (*e.g.*, bolus refusal). Lactate was sampled through an arterial catheter during distinct intraoperative periods: before surgical incision, during liver resection, at the end of surgery (primary outcome), and upon arrival to the PACU. Postoperative complications were either noted in the medical record by surgical medical staff unaware of patient group allocation or derived from laboratory values. All outcome data were collected by research staff that was blinded to group allocation. The definitions of postoperative complications can be found in supplemental digital content 1 (https://links.lww.com/ALN/D644). There were no changes in the trial outcomes after the trial commenced. The original protocol in French is available upon request from the corresponding author.

Sample Size Calculation

Retrospective data of patients who underwent major hepatic resection in our center revealed that when a restrictive fluid strategy is applied, the lactate level at the end of the surgery is 4.02 ± 1.88 mmol · l^{-1}. We thus calculated that 43 patients per group were required to have 84% power at a two-sided α-level of 0.05 to demonstrate a 30% decrease in lactate level in the decision support group (a decrease from 4.02 to 2.81 mmol · l^{-1}). This 30% decrease in lactate level is clinically meaningful, because Vibert *et al.*[12] showed that a lactate level greater than 3 mmol · l^{-1} after an elective hepatectomy is an early predictor of postoperative complications. Considering potential dropout, we decided to include 45 patients per group (90 patients in total).

Statistical Analysis

Patient characteristics and study variables were summarized using means and SDs, medians [quartiles], or frequencies (percentages), as appropriate. Baseline characteristics were compared between groups using standardized mean differences, which were computed using methods described by Yang and Dalton.[13] The groups were formally compared using *t* test or Mann–Whitney U test depending on the variable, whereas categorical variables were analyzed using a chi-square test. Differences between groups were also presented with estimated differences and 95% CI using the standard *t* interval for most continuous variables, the binomial distribution for binary variables, and the bootstrap percentile method (1,000 replications) for variables known to be skewed (*e.g.*, intraoperative estimated blood loss, length of stay). All analyses were conducted using IBM SPSS (version 28, USA) or R (version 4.1.0, www.r-project.org, Austria), and the data were analyzed using an intention-to-treat approach. No interim analysis of the primary endpoint was performed. For the primary outcome, $P < 0.05$ was considered as statistically significant. For all other outcomes, we did not apply corrections for multiple comparisons or perform an *a priori* power analysis and should be considered as exploratory.

Results

Between December 12, 2022, and July 17, 2023, 90 patients were enrolled, with 45 patients being randomized to each group (fig. 1). Distributions of patient's characteristics between groups were similar at baseline (table 1) because standardized mean differences ranged from 0.00 to 0.32 with an average of around 0.14, which is generally considered a "small" effect size. Duration of surgery and total pedicular clamping were also not different between groups (table 1).

Primary and Secondary Outcomes

Lactate at the end of surgery was lower in the decision support group than in the restrictive group (median [quartile 1 to quartile 3], 2.5 [1.9 to 3.7] mmol · l^{-1} *vs.* 4.6 [3.1 to 5.4] mmol · l^{-1}; median difference, −2.1; 95% CI, −1.2 to −2.7; $P < 0.001$; table 2). Lactate values were normal at the start of surgery, but values began to increase after surgical incision (fig. 2; table 3). There was no difference in blood loss and red blood cell transfusion between the two groups. Total intraoperative fluid volume was not different between groups, but fluid volume administered before the end of hepatic resection was higher and total dose of noradrenaline was lower in the decision support group. There was no difference in the incidence of acute kidney injury and in postoperative complications assessed using the Clavien–Dindo classification (table 2). No patient was readmitted to the ICU after initial ICU admission postsurgery except those who had a redo surgery.

Exploratory *Post Hoc* Analysis

CVP, SV, and cardiac indexes (from placement of the appropriate catheter to the end of surgery) were all significantly higher in the decision support group compared to the control group. The percentage of preload dependence during surgery was lower in the decision support group (table 3). Lactate values remained lower in the decision support group upon admission to the PACU (fig. 2; table 3). In the PACU, 12 patients had a lactate above 3 mmol · l^{-1} in the decision support group compared to 35 patients in the restrictive group ($P < 0.001$). All patients had their trachea extubated before transfer to the ICU for overnight observation. The incidence of major complications was not different between groups, although urinary infections and composite minor complications were less frequent in the decision support group (supplemental digital content 2, https://links.lww.com/ALN/D645). Two patients in the restrictive fluid group had suspected intraoperative gas emboli and developed acute hemodynamic instability associated with a reduction in arterial Po_2 and end-tidal CO_2. These events resolved within minutes of appropriate

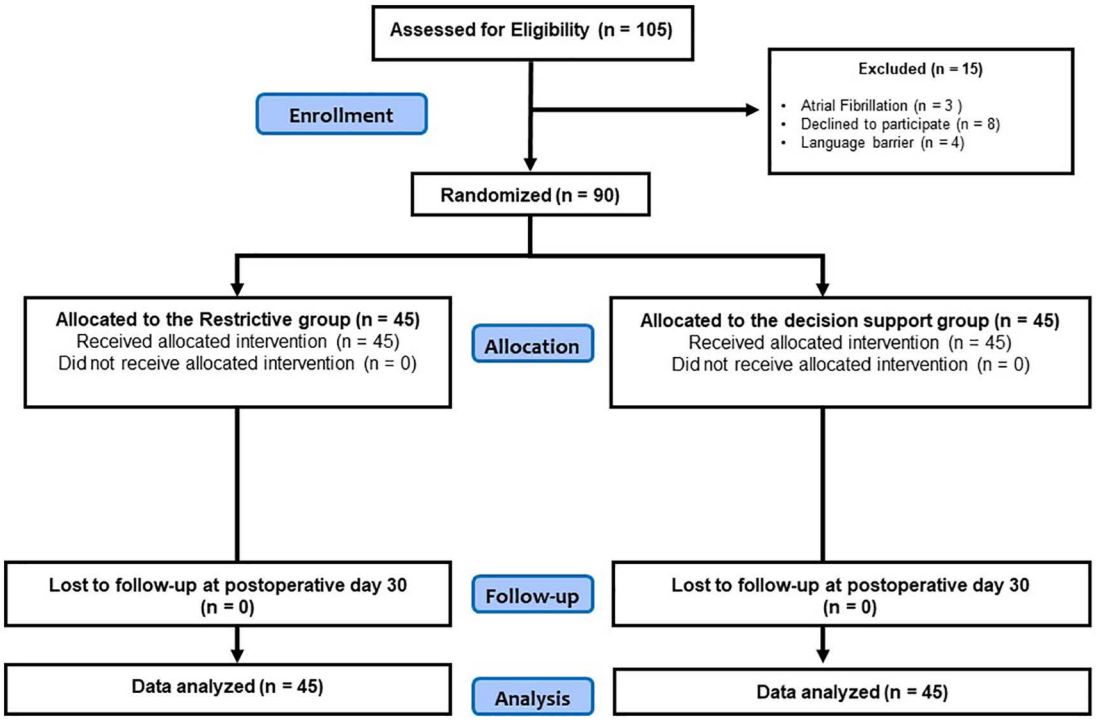

Fig. 1. Inclusion flowchart.

Table 1. Baseline Characteristics

Variables	Restrictive Group (N = 45)	Decision Support Group (N = 45)	Standardized Mean Difference
Age, yr	62 ± 16	59 ± 13	0.21
Sex, male, N (%)	21 (47%)	28 (62%)	0.32
Weight, kg	75 ± 17	76 ± 14	0.02
Height, cm	169 ± 9	170 ± 8	0.18
Body mass index, kg · m^{-2}	27 ± 6	26 ± 5	0.06
Preoperative systolic arterial pressure, mmHg	141 ± 18	139 ± 18	0.09
Preoperative hemoglobin, g · dl^{-1}	12.6 ± 2.0	13.0 ± 1.7	0.21
Preoperative creatinine, mmol · l^{-1}	79 ± 16	77 ± 22	0.32
Medications, N (%)			
Aspirin	7 (16%)	9 (20%)	0.12
β-Blocker	4 (9%)	8 (18%)	0.26
Angiotensin-converting enzyme inhibitor	5 (11%)	7 (16%)	0.13
Angiotensin II receptor blockers	6 (13%)	6 (13%)	0.00
Statin	9 (20%)	9 (20%)	0.00
Calcium blocker	6 (13%)	7 (16%)	0.06
Antidiabetic drugs	9 (20%)	8 (18%)	0.06
Comorbidities, N (%)			
Ischemic heart disease	2 (4%)	6 (13%)	0.32
Coronary artery bypass graft surgery	0 (0.0%)	1 (2%)	0.21
Arterial hypertension	17 (38%)	19 (42%)	0.09
Hyperlipidemia	10 (22%)	9 (20%)	0.05
Stroke	1 (2%)	2 (4%)	0.12
Chronic obstructive pulmonary disease	2 (4%)	3 (7%)	0.10
Diabetes	11 (24%)	11 (24%)	0.00
Type of surgery			0.25
Left hepatectomy, N (%)	16 (36%)	15 (33%)	
Right hepatectomy, N (%)	24 (53%)	21 (47%)	
Other, N (%)*	5 (11%)	9 (20%)	
Laparoscopic surgery, N (%)	5 (11%)	8 (18%)	0.19
Surgery duration, min	341.5 ± 82.9	321.0 ± 103.6	0.21
Patients with more than five pedicular clampings, N (%)	4 (9%)	6 (13%)	0.14
Total pedicular clamping duration, min	45.7 ± 25.8	43.0 ± 26.7	0.10

The data are presented as number (%) or mean ± SD. N indicates the number or frequency (%).

*Includes trisegmentectomy, right lobectomy, and central hepatectomy.

therapeutic intervention, and no long-term complications associated with these events occurred. Hospital length of stay was slightly shorter in the decision support group. In the assisted fluid management group, the targeted SV increase after a fluid challenge was changed to 15% in four patients and to 20% in one patient during a part of the dissection phase (all were done in laparoscopic major hepatic resections). Nine patients in the decision support group had at least one fluid bolus recommendation that was refused by the clinicians (median fluid challenges of these nine patients, 2; range, 1 to 5), mainly because they occurred just after a pedicular clamping. Additionally, in 23 patients, clinicians initiated a fluid challenge outside of the decision support recommendation (median fluid challenges of these 23 patients, 1; range, 1 to 4). No patient required caval exclusion due to uncontrolled venous bleeding.

Discussion

Under our study conditions, patients managed using a decision support system to guide fluid therapy had lower arterial lactate and the end of a major liver surgery than patients managed using a more restrictive fluid strategy. Although patients in the decision support group received more fluids before the end of hepatic resection, no increase in the exploratory outcomes of blood loss or transfusion was observed. A more restrictive approach during hepatic resection in the control group appears to have led to higher norepinephrine requirements to maintain MAP target values, which was associated with increased systemic vascular resistance and decreased cardiac output. Time spent in a preload dependent state was also longer in the restrictive group.

The lower arterial lactate concentrations at the end of surgery in the decision support group, despite similar total intraoperative infused fluid volume, are best explained by targeted optimization with fluid boluses that decreased time in a preload dependent state. This ultimately may have led to improved tissue perfusion reflected by a lower arterial lactate at the end of surgery. Of note, arterial lactate increased in both groups during surgery, likely as a result of the multiple hepatic pedicular clamping maneuvers, and both their duration and number were similar between groups. However, the significantly higher increase

Table 2. Primary and Exploratory Secondary Outcomes

Variables	Restrictive Group (N = 45)	Decision Support Group (N = 45)	Difference (95% CI)	*P* Value
Primary outcome				
Lactate at the end of surgery, mmol · l^{-1}	4.6 [3.1–5.4]	2.5 [1.9–3.7]	2.1 (1.2 to 2.7)	< 0.001
Secondary exploratory outcomes				
Estimated blood loss, ml	450 [300–600]	500 [300–800]	–50 (–150 to 200)	0.727
Total dose of noradrenaline, mg	1.7 [1.2–2.7]	1.0 [0.4–2.2]	0.7 (0.0 to 1.1)	0.011
Total amount of fluid received, ml	3,250 [2,500–4,000]	3,500 [2,800–4,500]	–250 (–250 to 1,000)	0.246
Before end of hepatic resection, ml	1,000 [750–1,750]	1,500 [1,250–2,250]	–500 (–1,000 to –6.35)	0.001
After hepatic resection, ml	2,000 [1,500–2,500]	1,800 [1,250–2,500]	200 (–196 to 500)	0.194
Acute kidney injury, N (%)	12 (26.7%)	8 (17.8%)	8.9% (–8.4% to 25.6%)	0.310
Postoperative complications at 30 days, by Clavien–Dindo grade*				0.114
I	4 (9)	4 (9)		
II	6 (13)	1 (2)		
IIIa	0 (0)	0 (0)		
IIIb	4 (9)	1 (2)		
IVa	9 (20)	13 (29)		
IVb	0 (0)	0 (0)		
V	2 (4)	0 (0)		

The values are reported as medians [quartile 1, quartile 3] or frequencies (%) and compared between groups using *t* test, Mann–Whitney U test, or chi-square test with appropriate CI. For variables known to be skewed (*e.g.*, estimated blood loss, length of stay), we report medians [quartile 1, quartile 3], compare groups with the Mann–Whitney U test, and report a difference in medians (with 95% CI) estimated from 1,000 bootstrapped samples.

*Clavien–Dindo classification: Each postoperative complication was graded.

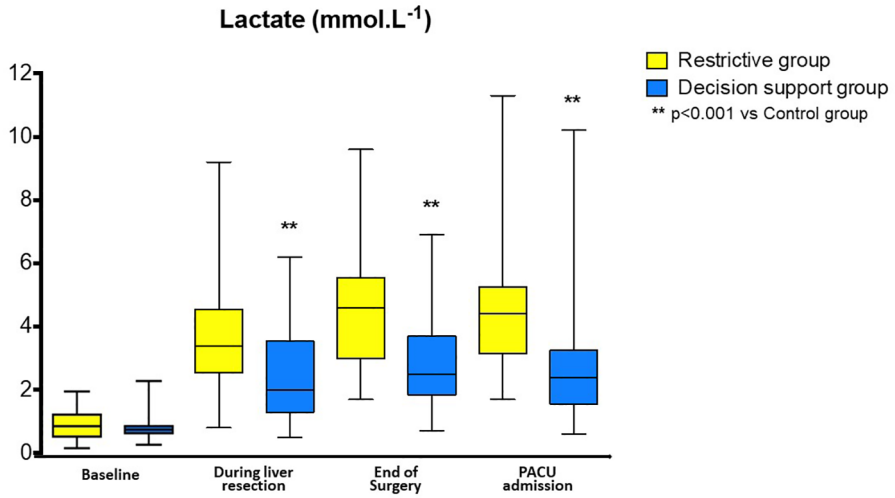

Fig. 2. Evolution of lactate values during major hepatectomy. The lactate values were measured before surgical incision, during liver resection, at the end of surgery (skin closure), and upon arrival to the postanesthesia care unit (PACU).

in lactate in the restrictive group supports the hypothesis that another cause may have contributed to this hyperlactatemia (*e.g.*, tissue hypoxia due to inadequate perfusion; fig. 2). Fewer patients in the decision support group had a lactate greater than 3 mmol · l^{-1} (12 *vs.* 35), indicating that optimizing fluid status with decision support may potentially decrease this risk. Whether a 30 to 40% decrease in arterial lactate concentration at the end of the surgery is clinically meaningful remains an open question. One may argue that this reduction in arterial lactate may ultimately have a limited impact on patient outcome. Nonetheless, it has been shown that a lactate level greater than 3 mmol · l^{-1} in this population is associated with increased morbidity and mortality.[12] Moreover, having a lower lactate level at the end of any surgery remains of interest because it contributes to the decision regarding whether patients can go to a lower dependency care unit after surgery. This significant reduction in lactate concentration may thus be

Table 3. Exploratory Intraoperative Outcome

Variables	Restrictive Group (N = 45)	Decision Support Group (N = 45)	Difference (95% CI)	*P* Value
Intraoperative fluid				
Total crystalloid, ml	2,500 [2,250–3,000]	3,250 [2,300–4,000]	−750 (−1,000 to 0)	0.056
Total albumin, ml	500 [0–1,000]	0 [0–1,000]	500 (−487 to 500)	0.248
Total volume of packed red blood cells, ml*	1,000 [375–1,625]	750 [500–750]	250 (−500 to 1,125)	0.905
Urine output, ml	575 [300–800]	500 [320–775]	75 (−150 to 235)	0.904
Net fluid balance, ml	1,925 [1,470–2,735]	2,250 [1,900–3,310]	−325 (−1,200 to 70)	0.052
Hemodynamic data				
Mean arterial pressure, mmHg	82.7 ± 5.1	84.6 ± 6.9	−1.9 (−4.5 to 0.6)	0.134
Heart rate, beats/min	77 ± 12	76 ± 9	1.0 (−3.5 to 5.5)	0.661
Central venous pressure, mmHg	6.6 ± 1.1	7.7 ± 2.0	−1.1 (−1.8 to −0.4)	0.002
Stroke volume index, ml · m^{-2}	35 ± 7	42 ± 7	−6.7 (−9.6 to −3.9)	< 0.001
Stroke volume variation, %	11 ± 3	8 ± 2	3.1 (2.1 to 4.2)	< 0.001
Cardiac index, l · min^{-1} · m^{-2}	2.6 ± 0.7	3.1 ± 0.5	0.5 (−0.8 to −0.2)	< 0.001
Indexed systemic vascular resistance, dyne · s · cm^{-5} · m^{-2}	2,474 ± 621	1,977 ± 530	497.1 (255.1 to 739.0)	< 0.001
Preload dependence, % of surgery time†	31.6 ± 21.3	9.5 ± 12.2	22.1 (14.8 to 29.4)	< 0.001
Hypotension, % of surgery time‡	5.6 ± 4.2	4.3 ± 4.1	1.3 (−0.5 to 3.0)	0.153
Lactate values, mmol · l^{-1}				
Lactate before skin incision	0.9 [0.7–0.9]	0.8 [0.6–1.2]	0.1 (−0.1 to 0.4)	0.317
Lactate during liver resection	3.4 [2.6–4.6]	2.0 [1.3–3.6]	1.4 (0.3 to 2.4)	< 0.001
Lactate at postanesthesia care unit arrival	4.4 [3.2–5.3]	2.4 [1.6–3.3]	2.0 (1.2 to 2.6)	< 0.001

The values are reported as means ± SD or medians [quartile 1 to quartile Q3] and compared between groups using *t* test or Mann–Whitney U test with appropriate CI. For variables known to be skewed (*e.g.*, crystalloids), we report medians [quartile 1, quartile 3], compare groups with the Mann–Whitney U test, and report a difference in medians (with 95% CI) estimated from 1,000 bootstrapped samples.

*Volume of packed red blood cell transfusions among transfused patients only. †Stroke volume variation above 12%. ‡Mean arterial pressure of less than 65 mmHg.

caused by better tissue perfusion and oxygenation despite only a relatively small increase in infused volume preceding hepatic resection (*i.e.*, a median difference of 500 ml), which did not apparently increase bleeding. This can be explained by the observation that in the decision support group, the software consistently recommended fluid boluses to achieve optimal SV, whereas in the restrictive group, fluids were held until their restriction led to hemodynamic instability and potentially tissue hypoperfusion. Once liver resection was completed in the restrictive group, anesthesiologists then attempted to compensate this restriction by abundantly administering fluids after the completion of hepatic dissection based on the data from the advanced hemodynamic monitoring device. Although the decision support patients had optimized SV and minimal fluid dependence throughout the vast majority of their intraoperative care, patients in the restrictive group potentially suffered not only from poorly timed fluid administration but also from fluid restriction during the periods at highest risk of hemodynamic instability (*i.e.*, preceding and during hepatectomy).

Other studies have applied a goal-directed fluid therapy strategy during the entire intraoperative period in hepatic surgery patients, but none have tested the use of a decision support system to guide fluid therapy in this population. Our study parallels previous results indicating that optimizing preload with fluids is feasible during liver resection and does not increase blood loss when compared to a more restrictive fluid strategy.[7,8] Using the assisted fluid management decision support software offers three theoretical advantages over a classical goal-directed strategy. First, it provides a more personalized approach to fluid therapy thanks to its software's adaptive layer that modifies fluid bolus recommendations based on each patient's response. Second, it may theoretically offer a potential increase in protocol compliance by continuously assessing fluid status and informing clinicians as soon as it considers a patient to be fluid responsive. This is supported by the observed differences in preload dependence, which was more than three times longer in the restrictive group. Third, because the decision support system has been shown to better predict a patient's response to fluids than experienced anesthesiologists, the risk of excessive fluid administration is probably reduced.[11]

It is important to remember, however, that this decision support tool is not capable of situation awareness. Consequently, it is possible to have a fluid recommendation due to conditions that do not truly reflect inadequate fluid status. For example, if the surgeon mobilizes the liver in such a way as to obstruct the inferior vena cava, the software may consider the patient fluid responsive. Administering a fluid bolus at that time, however, would be unsuitable. In this case, releasing the inferior vena cava after inappropriately excessive fluid administration might lead to higher CVP and bleeding. Vigilance and evaluation of recommended boluses is thus mandatory when using such decision support tools. In our study, clinicians refused fluid challenges in nine patients, which attests to the importance of clinical

interpretation and situation awareness.[14] Decision support must be seen as a tool that can help anesthesiologists in their management, but it does not replace their clinical judgment, especially during surgeries that are associated with complex hemodynamic alterations (*e.g.*, compression of the vena cava or aortic cross-clamping).

Despite its strengths, this trial also had limitations. We investigated the impact of a decision support system on tissue perfusion using lactate as a surrogate measure, which can be criticized from two perspectives. On the one hand, perhaps a more direct measurement of tissue perfusion, such as sublingual microcirculation, could have given a clearer picture of systemic alterations in the restrictive group. On the other hand, directly investigating the effect on patient outcome has greater clinical impact and is the ultimate goal of improving fluid management. Furthermore, it is essential to underline that all outcomes other than arterial lactate at the end of surgery were exploratory. Another limitation concerns the generalizability of our results because our study focuses solely on major hepatic resection. The impact of this decision support strategy during other surgeries, such as lower-risk hepatic resection or another specific population (*e.g.*, major vascular surgery), still needs to be determined. Another potential limitation regarding our study conditions is that decision support uses pulse contour analysis and dynamic parameters of fluid responsiveness. Dynamic parameters of fluid responsiveness, such as SV variation and pulse pressure variation, require a mechanically ventilated tidal volume that creates sufficient pressure to induce variations preload and afterload of both the left and right ventricles.[15] Although there is a general consensus that the ideal tidal volume for these indexes is $8\,ml \cdot kg^{-1}$, there is growing evidence that dynamic indicators of fluid responsiveness can still provide information at lower tidal volumes.[16] For example, a recent meta-analysis indicated that a tidal volume less than $8\,ml \cdot kg^{-1}$ did not affect SV variation's capacity to predict fluid responsiveness.[17] Heart rate to respiratory ratio is another factor that, in ideal conditions, should be controlled.[18] It is a limitation of our study that we did not measure this ratio. Nonetheless, our results confirm previous studies that have used assisted fluid management decision support software and indicate that this tool provides information to better optimize SV. An additional limitation to consider is that clinicians were aware that they participated in a study. As such, there is a possible Hawthorne effect, which may have affected the overall performance of the anesthesiologists in both groups. Although this may affect the overall values of the studied outcomes, the differences found between groups should still remain. Finally, the decision support tool was used in our study by three anesthesiologists highly trained in this system. Just like any tool or technique, this decision support tool has a learning curve, and clinicians will have to learn not only how to use it but also its limitations. The potential benefit of this decision support system, when expanding its use to more clinicians, should be further investigated. A large multicenter stepped wedge cluster randomized trial is currently ongoing to assess the impact of this decision support system on patient outcome.

Conclusions

Patients managed using a clinical decision support system to guide fluid administration during major hepatic resection had a lower arterial lactate concentration at the end of surgery when compared to a more restrictive fluid strategy. This may be due to a better maintenance of tissue perfusion during major hepatic resection.

Acknowledgments

The authors thank the anesthesiology and surgical teams of Paul-Brousse Hospital (Villejuif, France) for help with this study.

Research Support

Support was provided solely from institutional and/or departmental sources.

Competing Interests

Dr. Cannesson, Dr. Joosten, and Dr. Rinehart are consultants for Edwards Lifesciences (Irvine, California). Dr. Coeckelenbergh began giving scientific presentations that were sponsored by Edwards Lifesciences and consulting for this company in 2024 after the initial submission of this manuscript. Dr. Cannesson and Dr. Rinehart have ownership interest in Sironis (Irvine, California), and Sironis has developed a closed-loop fluid system, the software of which is used in the assisted fluid management system (Edwards Lifesciences). Dr. Cannesson is also a consultant for Masimo (Irvine, California) and has shares in Perceptive Medical (Newport Beach, California). The other authors declare no competing interests.

Reproducible Science

Full protocol available at: ajoosten@mednet.ucla.edu. Raw data available at: ajoosten@mednet.ucla.edu.

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Supplemental Digital Content

Supplemental Material 1. Definitions of complications, https://links.lww.com/ALN/D644

Supplemental Material 2. Exploratory *post hoc* analysis of mortality and morbidity, https://links.lww.com/ALN/D645

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