Perioperative Fluid Resuscitation in Free Flap Breast Reconstruction: When Is Enough Enough?

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Background: Perioperative liberal fluid resuscitation (LFR) can result in interstitial edema and venous congestion and may be associated with compromised perfusion of free flaps and higher incidence of wound complications. We hypothesized that restrictive intraoperative fluid resuscitation improves flap perfusion and lowers the wound complication rate in free flap breast reconstruction.

Methods: Patients undergoing free flap reconstruction of the breast from 2010 to 2018 were retrospectively reviewed. The study population was divided into 2 groups, LFR ($\geq 7\,ml/kg/h$) and restrictive fluid resuscitation (RFR) ($<7\,ml/kg/h$). Mean percutaneous oximetry readings of the flap over the first 24 hours were recorded. Primary outcome was development of any wound complication. Secondary outcomes were mean percutaneous oximetry readings within the first 24 hours, length of stay, and development of acute kidney injury.

Results: One hundred twenty-six patients were identified, with 41 patients undergoing LFR. The mean fluid received for the RFR group was 5.5 versus $10.2\,ml/kg/h$ for the LFR group ($P < 0.001$). LFR resulted in a significantly higher incidence of wound complications (76% versus 15%, $P < 0.001$). The mean oximetry readings within 24 hours were significantly lower for the LFR group (41% versus 56%, $P < 0.001$). Urine output intraoperatively and within the first 24 hours was similar between the 2 groups. No patients developed acute kidney injury.

Conclusion: RFR in free flap breast reconstruction is associated with increased flap perfusion and lower incidence of wound-related complications and should be considered whenever possible. (*Plast Reconstr Surg Glob Open 2020;8:e2662; doi: 10.1097/GOX.0000000000002662; Published online 27 March 2020.*)

INTRODUCTION

Free flap breast reconstruction has been gaining popularity among women, especially for those who would prefer not to use implants for their reconstruction.[1–3] Current literature suggests a major complication rate of up to 49%, including wound dehiscence, partial flap necrosis, and deep venous thrombosis, with total flap loss rates of 2.4% in free flap breast reconstruction. Several factors have been associated with the incidence of complications, such as prolonged operative times, prolonged periods of immobilization, and prior history of radiation to the chest wall.[4–6]

Similar to other major surgeries in different surgical specialties, enhanced recovery pathways following breast reconstruction have led to a significant decrease in the use of narcotics and have substantially decreased the length of stay.[7–9] An integral part of enhanced recovery pathways is the use of restrictive fluid resuscitation (RFR) strategies.

Evidence of the utility of RFR is rapidly emerging in the trauma surgery literature, general surgery literature, as well as in the literature discussing free flap reconstruction. A study by Healy et al. concluded that the use of restrictive resuscitation strategies in pancreatectomies is associated with decreased rate of complications[10] Similarly, Kass et al. reviewed 445 patients undergoing free flap reconstruction of defects of the head and neck and concluded that large volume fluid resuscitation (defined as > 5 L of intraoperative fluid administration) was associated with an increased incidence of free flap loss.[11] There is currently no literature to discuss the association between free flap complications and perioperative resuscitation strategies in free flap breast reconstruction.

Liberal fluid resuscitation (LFR), especially in the setting of breast free flap reconstruction, may result in interstitial edema and venous congestion which can impede the

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perfusion of the free flap. Venous congestion in the microvascular level, even when it is not clinically evident immediately, may become apparent with increased incidence of wound complications such as dehiscence or fat necrosis. The goals of the study were (1) to assess if perioperative fluid resuscitation is associated with a higher incidence of wound-related complications, (2) to identify the optimal cutoff for fluid administration, and (3) to evaluate different resuscitation strategies with regard to their impact on wound-related complications in patients following free flap breast reconstruction in an effort to standardize the perioperative care of this patient population.

METHODS

After Institutional Review Board approval, all patients undergoing free flap breast reconstruction at an academic institution from 2010 to 2018 were retrospectively identified and reviewed, using the following CPT codes: 19364 (Breast reconstruction with free flap) and S2068 (Breast reconstruction with deep inferior epigastric perforator flap or superficial inferior epigastric artery flap, including harvesting of the flap, microvascular transfer, closure of donor site and shaping of the flap into a breast). Patients' demographics and clinical characteristics were extracted. Patients with incomplete medical records, those with pedicled autologous reconstruction, and those with implant based reconstruction were excluded from the analysis. Risks factors that are known to be associated with wound healing complications, such as diabetes, smoking history, body mass index, type of flap (deep inferior epigastric perforator, muscle-sparing, or free transverse rectus abdominis muscle flap), immediate versus delayed reconstruction, history of prior abdominal surgery, and use of radiation therapy or chemotherapy before reconstruction were also identified. Intraoperative findings included the amount of fluids given (in milliliters per kilogram per hour), use of blood transfusion, intraoperative patient hemodynamics, estimated blood loss, intraoperative urine output, use of vasopressors, and total anesthesia time.

Patients who underwent immediate or delayed free flap breast reconstruction were included in the analysis. In the operating room, each patient received general anesthesia with the inducing agent that was deemed appropriate by the anesthesia staff and intubated via an endotracheal tube. All patients received an arterial line for hemodynamic monitoring. The decision to proceed with liberal or RFR was based only on the anesthesiologist performing the surgery. All reconstructions were performed by attending plastic surgeons with experience in microsurgical reconstruction. The postoperative protocol for free flap breast reconstruction patients is standardized in our institution. Every patient received rectal aspirin on the table at the end of the surgery. Nil per os status and strict bed rest are maintained for the first 24 hours. Flap monitoring is initiated immediately after the end of the surgery and the patient is transferred to the intensive care unit. Monitoring of the flap perfusion is done every hour by physical exam by the nursing staff, by assessing the Doppler signal and by percutaneous tissue oximetry using the T-stat (Spectros,

Campbell, Calif.). At approximately 5–6 hours after the end of the operation, a physician house staff performs a full assessment of the flap and any issues are discussed with the senior attending. All patients, as part of the standardized protocol followed in the institution, receive an air-warming blanket that is placed around the chest. The percutaneous tissue oximetry monitor is placed on the most medial part of the flap and secured in place to decrease variability.

The present study aimed to identify different fluid resuscitation strategies. To determine the cutoff point between liberal and restrictive resuscitation, a cutoff analysis was performed as described in the Statistics section below. A study by Healy et al. used the Michigan Surgical Quality Database to assess the impact of intraoperative fluid resuscitation strategies following pancreatectomy in Annals of Surgical Oncology. They defined RFR as <10 ml/kg/hour, which is consistent with what the present article's analysis concluded.[10]

The study population was divided into 2 groups based on the intraoperative resuscitation strategy that was deployed (restrictive versus liberal). The patients had a mean follow-up of 6 months with a range of 3 months to 1 year. Primary outcome was the development of any wound complications at any time postoperatively. Both donor site and flap complications were accounted for. Mastectomy flap necrosis or ischemia was not included in the analysis. Fat necrosis was a clinical diagnosis and left to the discretion of the treating plastic surgeon. Those were identified as complete or partial flap loss, wound dehiscence, fat necrosis, and infection of the flap and/or donor site. To avoid any bias from including patients who had a complication due to a technical issue, a subgroup analysis was performed for patients who did not go back to the OR for a revision of their anastomosis. Secondary outcomes included perfusion of the flap at 2, 4, 6, 8, 12, and 24 hours postoperatively as documented by the percutaneous tissue oximetry readings and development of systemic complications. Systemic complications included acute kidney injury, myocardial infarction, deep venous thrombosis, cerebrovascular incidents and systemic infectious complications such as pneumonia and sepsis.

Statistical Analysis

To identify if perioperative resuscitation strategy (PORS) was independently associated with wound complications, the study population was divided into 2 groups based on the development of wound complications. The 2 cohorts were compared for differences between their characteristics using a univariate analysis. Binary variables were compared using Chi-Square or Fisher's exact test as appropriate. For continuous variables, the normality of distribution was first tested. Normally distributed variables were compared using Student's t test, while nonnormally distributed variables were compared using the Mann-Whitney U test. To identify independent predictors of wound complications, a forward stepwise logistic regression was performed using wound complications as the dependent variables and inserting all those variables that differed between the 2 groups at a $P <$ 0.02. Perioperative fluid resuscitation strategy was inserted into the regression as a continuous variable, including the

amount of perioperative fluids given to the patient. Once perioperative fluid resuscitation strategy was found to be independently associated with wound complications, a cutoff analysis was performed to identify the cutoff point to define restrictive versus LFR. PORS was dichotomized using different cutoff points and was inserted into a simple logistic regression with the dependent being the development of complication and the independent variables, all those that were previously identified as independent predictors from the previously performed multivariate analysis. The c statistic of the model, the sensitivity and the specificity were derived from the regression. The process was replicated multiple times using different cutoff points until the optimal cutoff point was identified.

The study population was then divided into 2 groups using the cutoff point (liberal versus restrictive PORS). The 2 cohorts were compared for differences between their characteristics using a univariate analysis as described previously. To assess the impact of PORS on outcomes, multivariate analyses were performed using variables that differed at a $P < 0.05$ between the 2 groups from the previously performed univariate analysis. Adjusted odds ratios and adjusted p values were derived from those multivariate analyses. All analyses were performed using SPSS, version 16 (Chicago, Ill.) (Fig. 1).

RESULTS

A total of 126 patients were identified for analysis. The mean age of the study population was 52 years with a mean body mass index of 33. The vast majority of the patients were white (82%), followed by Hispanics (14%). A total of 64% of the patients received neoadjuvant chemotherapy, while 37% received adjuvant chemotherapy. Adjuvant radiation therapy was received by 13% of the patients. The majority of the patients underwent mastectomy due to breast cancer, while only 28% underwent immediate reconstruction. Bilateral reconstruction was performed in half of the patients.

Independent predictors of developing wound complications were found to be total amount of fluids received in the perioperative period [AOR (95% CI), 1.71 (1.40, 2.10)], followed by total anesthesia time and estimated blood loss. The AUROC (95% CI) for the model was 0.95 (0.91, 0.97, Table 1).

Once the perioperative fluid resuscitation strategy was found to be associated with an increased incidence of complications, a cutoff analysis was performed. Table 2 depicts the different AOR (95% CI), adjusted P, AUROC (95% CI), R^2, sensitivity, and specificity for every different cutoff value. The analysis identified 7 ml/kg/hour as being the optimal cutoff point (Table 2; Fig. 2). The study population was then divided into 2 groups; LFR defined as >7 ml/kg/hour versus RFR defined as ≤7 ml/kg/hour.

A total of 85 patients underwent a restrictive resuscitation strategy, while 41 had a liberal fluid management. The restrictive resuscitation management group had a higher incidence of administering neoadjuvant radiation therapy (38% versus 20%, $P = 0.040$), but otherwise did not differ significantly (Table 3). The mean amount of intraoperative fluids was 7.1 ± 3.1 ml/kg/hour. The liberal group received 10.2 ± 1.9 versus 5.5 ± 2.2 ml/kg/hour for the restrictive group. Anesthesia time and estimated blood loss were similar between the 2 groups (9.3 versus 8.9 hours, $P = 0.318$ and 244 versus 256 ml, $P = 0.640$ for the liberal and restrictive group, respectively). Similarly, the episodes
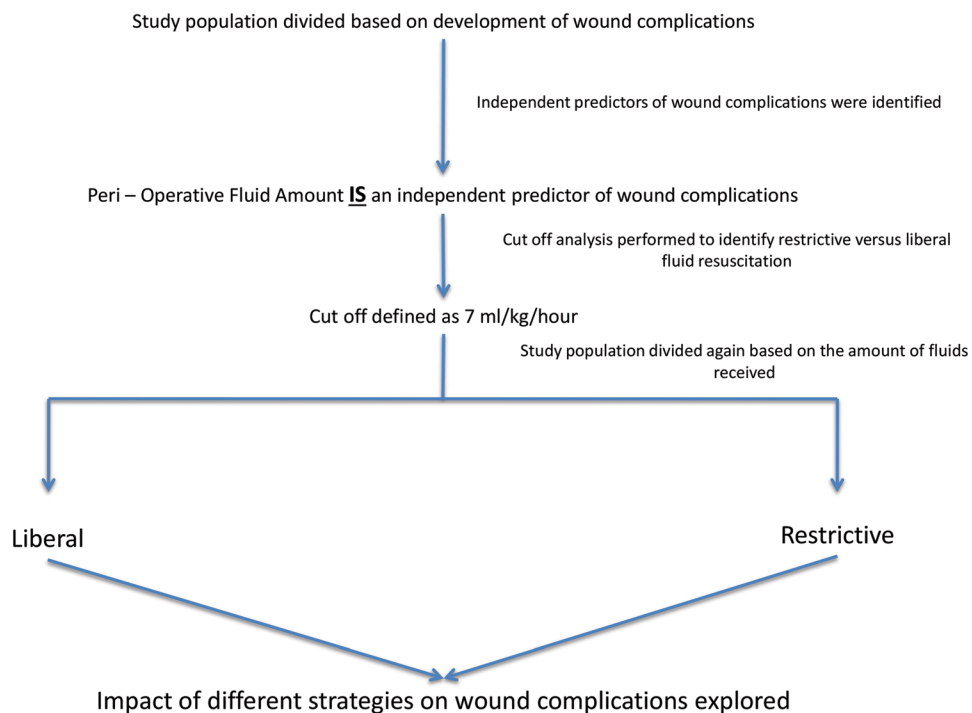

Fig. 1. Study design.

Table 1. Independent Predictors of Complications

Step	Variable	AOR (95% CI)	Adjusted *P*	Cumulative *R²*
1	Perioperative fluid resuscitation*	1.71 (1.40, 2.10)	<0.001	0.399
2	Anesthesia time†	1.73 (1.32, 2.25)	<0.001	0.534
3	Intraoperative blood loss‡	1.06 (1.05, 1.10)	0.049	0.565

Other variables entered in the model: age, diabetes mellitus, history of smoking, neoadjuvant chemotherapy, neoadjuvant radiation, bilateral reconstruction, episodes of intraoperative hypotension, intraoperative use of pressors, total intraoperative urine output, delayed versus immediate reconstruction and type of flap, blood transfusion, use of albumin, and BMI.
* Reported in ml/kg/hour.
† Reported in hours.
‡ Reported in milliliters.
BMI, body mass index.

Table 2. Cutoff Analysis for Intraoperative Fluid Resuscitation

Cutoff	AOR (95% CI)	Adjusted *P*	AUROC (95% CI)	Sensitivity	Specificity
> 3	1.01 (0.45, 1.10)	0.873	0.53 (0.49, 0.55)	0.25	0.80
> 4	1.23 (0.78, 1.65)	0.451	0.71 (0.65, 0.75)	0.54	0.70
> 5	1.45 (0.81, 1.98)	0.201	0.80 (0.78, 0.82)	0.65	0.65
> 6	2.34 (1.45, 3.45)	0.003	0.91 (0.89, 0.95)	0.73	0.60
> 7	2.62 (1.77, 8.94)	< 0.001	0.95 (0.93, 0.98)	0.80	0.55
> 8	2.31 (1.54, 9.21)	0.002	0.92 (0.90, 0.94)	0.80	0.30
> 9	1.54 (0.32, 14.51)	0.349	0.78 (0.75, 0.83)	0.70	0.20

Other variables entered in each of the models include anesthesia time (hours) and intraoperative blood loss (milliliters).

of hypotension (defined as systolic blood pressure <90 mm Hg), use of pressors, and intraoperative urine output were similar between the 2 groups (Table 4). Colloids as part of the fluid resuscitation intraoperatively were utilized in 49% of the patients. The liberal resuscitation group was more likely to receive colloids during surgery (61% versus 42%, *P* = 0.049, Table 4).

Patients who underwent LFR were more likely to have an increased incidence of wound complications overall [76% versus 15%, AOR (95% CI), 2.62 (1.77, 8.94), adj p < 0.001]. While total flap loss was not different between the 2 groups, patients in the liberal resuscitation group were more likely to have a partial flap loss [48% versus 7%, AOR(95% CI), 3.00 (1.70, 12.84), *P* < 0.001], dehiscence [17% versus 4%, AOR (95% CI), 5.17 (1.15, 13.32), adj *P* = 0.033], infection, and fat necrosis [17% versus 7%, AOR(95% CI), 11.92 (2.8, 25.70), adj *P* = 0.001, Table 5]. Systemic complications were not different between the 2 groups (Table 5).

The percutaneous oximetry readings at 2, 4, 6, 8, 12, and 24 hours were examined, stratified by liberal and RFR

strategy. The 2 groups did not have statistically significant different readings in the first 2, 4, or 6 hours. At the 8 hours point, the liberal group had statistically significant lower perfusion as documented by the percutaneous oximetry readings and that difference continued to increase up to 24 hours, with the liberal group demonstrating 41% of tissue oximetry, while the restrictive group demonstrated 56% (Fig. 3).

DISCUSSION

There is an association between the amount of perioperative fluid resuscitation and the development of wound complications in free flap breast reconstruction. It is the first study to our knowledge in the literature to evaluate different strategies of fluid administration in this study population.

While surgeons have always been interested in ways to improve outcomes for patients, public reporting of complications has led to more coordinated efforts across disciplines to reduce the risk of developing adverse outcomes.[12] As part of the above, perioperative fluid resuscitation has been in the spotlight of the literature.[10,13] Fluid resuscitation is mainly aimed at maintaining an acceptable mean arterial pressure to provide adequate perfusion to critical organs, such as the brain, the heart, and the kidneys.[14–16] We hypothesized that aggressive fluid resuscitation results in flap edema due to third spacing, and potential impairment of the perfusion of the distal aspects of the flaps at the level of the capillaries. The above may be clinically evident using tissue oximetry readings or by a higher incidence of wound complications such as wound dehiscence, fat necrosis, and need for debridement. In the present study, patient who underwent a more RFR had better tissue perfusion as documented by the tissue oximetry readings. While this is an interesting finding, it needs to be noted that depending on the skin paddle geometry and perforator anatomy, there is wide variation in initial oximetry readings. To decrease
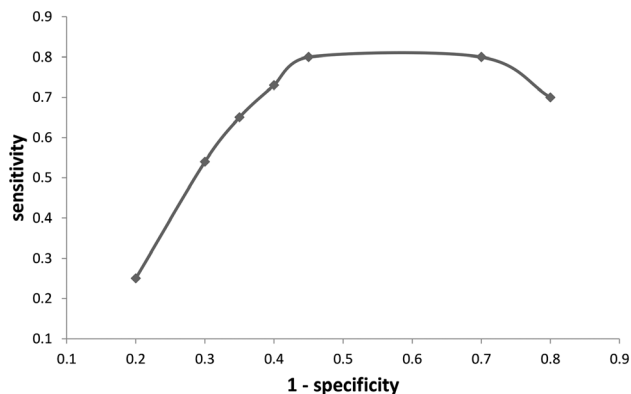

Fig. 2. Cutoff analysis for intraoperative fluid resuscitation.

Table 3. Patient Demographics and Clinical Characteristics

	Overall (n = 126)	Restrictive (n = 85)	Liberal (n = 41)	P
Age (mean, SD)	52 ± 12	52 ± 11	53 ± 13	0.779
BMI (mean, SD)	32.7 ± 5.5	32.5 ± 5.3	33.2 ± 5.9	0.510
Race				
White	103 (81.7)	68 (80.0)	35 (85.4)	
Hispanic	17 (13.5)	11 (12.9)	6 (14.6)	
African American	5 (4.0)	5 (5.9)	0 (0.0)	
Asian	1 (0.8)	1 (1.2)	0 (0.0)	0.384
Prior smoking history	33 (26.2)	25 (29.4)	8 (19.5)	0.236
Diabetes mellitus	32 (25.4)	22 (25.9)	10 (24.4)	0.857
Mastectomy for cancer	119 (94.4)	81 (95.3)	38 (92.7)	0.681
Prophylactic mastectomy	11 (8.7)	6 (7.1)	5 (12.2)	0.335
Type of flap				
DIEP	100 (79.4)	68 (80.0)	32 (78.0)	
Free TRAM	26 (20.6)	17 (20.0)	9 (22.0)	0.592
Neoadjuvant chemotherapy	80 (63.5)	54 (63.5)	26 (63.4)	0.990
Neoadjuvant radiation	40 (31.7)	32 (37.6)	8 (19.5)	0.040
Adjuvant chemotherapy	46 (36.5)	29 (34.1)	17 (41.5)	0.422
Adjuvant radiation	16 (12.8)	11 (13.1)	5 (12.2)	0.888
Immediate reconstruction	35 (27.8)	22 (25.9)	13 (31.7)	0.494
Bilateral reconstruction	65 (51.6)	41 (48.2)	24 (58.5)	0.278
Prior abdominal surgery	17 (13.5)	13 (15.3)	4 (9.6)	0.092

RFR is defined as intraoperative fluid administration of ≤7 ml/kg/hour and liberal as >7 ml/kg/hour. All values are reported in n (%) unless stated otherwise.
BMI, body mass index; DIEP, deep inferior epigastric perforator; TRAM, transverse rectus abdominis muscle.

Table 4. Intraoperative Resuscitation Strategies

	Overall (n = 126)	Restrictive (n = 85)	Liberal (n = 41)	p value
Intraoperative fluids				
Mean, SD	7.1 ± 3.1	5.5 ± 2.2	9.2 ± 1.9	<0.001
Median [Range]	5.9 [2 - 17]	5 [2 - 7]	9 [8 - 17]	<0.001
Anesthesia time	9.1 ± 2.9	8.9 ± 3	9.3 ± 2.8	0.318
Estimated blood loss (mls)	253 ± 135	256 ± 130	244 ± 147	0.640
Estimated blood loss (mls/kg/hr)	0.35 ± .12	0.36 ± 0.11	0.34 ± 0.13	0.640
Episodes of hypertension [n (%)]	99 (78.6)	65 (76.5)	34 (82.9)	0.408
Use of pressors [n (%)]	8 (6.3)	4 (4.7)	4 (9.8)	0.436
Intraoperative urine output	0.6 ± 0.02	0.7 ± 0.02	0.6 ± 0.01	0.332
Blood transfusion [units, n (%)]				
0	114 (90.5)	81 (95.3)	33 (80.5)	
1	4 (3.2)	0 (0.0)	4 (9.8)	
2	8 (6.3)	4 (4.7)	4 (9.8)	0.006
Albumin intraoperative [n (%)]	61 (48.4)	36 (42.4)	25 (61.0)	0.049

Intraoperative fluids reported in mls/kg/hour.
Anesthesia time reported in hours.
Intraoperative urine output Output reported in mls/kg/hour.
All values are reported in mean ± standard deviation unless stated otherwise.

Table 5. Outcomes

	Overall (n = 126)	Restrictive (n = 85)	Liberal (n = 41)	p value	AOR (95% CI)*	adjusted p
Wound complications						
Overall	44 (34.9)	13 (15.3)	31 (75.6)	< 0.001	2.62 (1.77, 8.94)	< 0.001
After excluding anastomosis revisions	38 (30.1)	11 (12.9)	27 (65.9)	< 0.001	1.96 (1.32, 5.43)	< 0.001
Early reoperations	6 (4.8)	2 (2.5)	4 (9.8)	0.085	5.81 (0.94, 15.67)	0.071
Total flap loss	6 (4.8)	2 (2.4)	4 (9.8)	0.087	5.80 (0.90, 13.75)	0.065
Partial flap loss	26 (20.6)	6 (7.1)	20 (48.8)	< 0.001	3.00 (1.70, 12.84)	< 0.001
Dehiscence	10 (7.9)	3 (3.5)	7 (17.1)	0.013	5.17 (1.15, 13.32)	0.033
Infection	13 (10.3)	5 (5.9)	8 (19.5)	0.028	3.81 (1.08, 13.40)	0.037
Fat necrosis	17 (13.5)	4 (4.7)	13 (31.7)	< 0.001	11.92 (2.8, 25.70)	0.001
Donor site	13 (10.3)	6 (7.1)	7 (17.1)	0.117	1.94 (0.51, 7.31)	0.328
Systemic complications	24 (19.0)	13 (15.3)	11 (26.8)	0.148	2.44 (0.90, 6.61)	0.079
					Adjusted Mean Difference	**Adjusted p**
Mean HLOS	5.3 ± 0.5	5.0 ± 0.5	7.2 ± 0.5	0.038	1.7 (0.9, 2.1)	0.015

Values are reported in n (%) unless stated otherwise.
Adjusting for anesthesia time, intra – operative blood loss, neoadjuvant radiation, intra – operative blood transfusion and use of albumin.
Donor site complications include dehiscence, infection and fat necrosis of the donor site. The rest of the outcomes are recipient site associated.
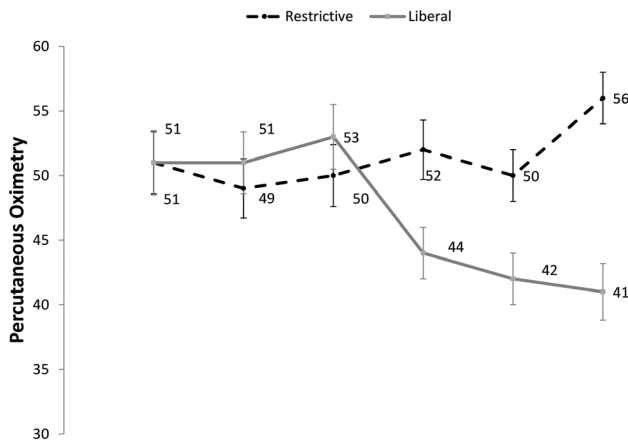HLOS, hospital length of stay.

Fig. 3. Oximetry readings stratified by resuscitation strategy: percutaneous oximetry readings documented at 2, 4, 6, 8, 12, and 24 hours postoperatively. Error bars represent SD. Overlapping error bars suggest no statistically significant difference.

variability, we attach the device at the most medial aspect and we always repeat all measurements at the same spot. However, this does not fully eliminate the variation in the original readings. The higher incidence of fat necrosis that was observed in the present study could also have been a result of flap design (number of perforators, etc.).

Several studies in the general surgery literature have suggested a negative impact of aggressive fluid resuscitation on outcomes following elective surgeries.[17–19] A recent study reviewed 504 patients across the state of Michigan that underwent an elective pancreaticoduodenectomy.[10] The patient population was divided into 3 groups based on the amount of peri operative fluids received (≤10, 10–15, and >15 ml/kg/hour). The authors concluded that the group with the most RFR strategy experienced decreased hospital-level mortality levels, severe complications, and length of stay. The present study similarly found that a RFR strategy resulted in lower length of stay and significantly lower rate of complications. The restrictive group in the present study received a mean of 5.5 ml/kg/hour of crystalloids, while the liberal group received a mean amount of 9.2 ml/kg/hour. As a result, in the restrictive group, a 70-kg woman received about 385 ml of crystalloids per hour while in the liberal group a similar woman received 644 ml per hour. The resuscitative strategy chosen did not reflect a more aggressive crystalloid administration due to intraoperative markers of resuscitation; both groups had similar estimated blood loss, urine output, and anesthesia time. Furthermore, every patient received an arterial line, and there were no differences in their hemodynamic parameters and use of pressors intraoperatively. The decision regarding the resuscitation strategy employed was left to the discretion of the treating anesthesiologist. The data of the present study do not support that the amount of fluids administered was driven by physiologic factors, since the patients in both groups had similar amount of episodes of hypotension and urine output intraoperatively.

The cases reviewed for this study did not use goal-directed resuscitation strategies. Several studies in the

literature have looked at the use of stroke volume variations as a guide to manage the amount of fluids given.[20–23] This resulted in less amount of fluids needed for resuscitation and subsequently lower hospital length of stay. To avoid any bias from including patients who had a complication due to a technical issue, we also looked at patients who did not go back to the OR for a revision of their anastomosis. Similarly, LFR was associated with higher incidence of complications overall. Postoperative care is standardized in the institution and was universal for all the patients, thus providing a homogenous group of patients for comparisons.

One could argue that the benefits of aggressive fluid resuscitation (avoidance of myocardial infarction or acute kidney injury) far outweigh the risks of local wound complications. The present study did not find any difference in the probability of developing systemic complications whether a RFR was used or not.

In conclusion, the present study suggests an association between LFR (defined as >7 ml /kg/hour) and overall incidence of wound complications without a decrease in the incidence of systemic complications in elective free flap breast reconstruction. Future studies include a randomized prospective trial to further delineate if a causation between fluid administration and flap perfusion exists, and if that causation translates clinically in a higher incidence of flap-related complications in the patients undergoing free flap breast reconstruction.

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