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Management of postoperative microvascular compromise and ischemia reperfusion injury in breast reconstruction using autologous tissue transfer: Retrospective review of 2103 flaps

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Abstract

Background: Although rates of microvascular thrombosis following free-flap breast reconstruction are low, debate persists about the optimal methods to restore blood flow and prevent ensuing flap shrinkage or fibrosis. Here we evaluate our management of microvascular compromise, including both a review of our approach for restoring blood flow and addressing the ensuing inflammatory changes following ischemia reperfusion.

Methods: We conducted a retrospective review of autologous free tissue transfer breast reconstructions from 1/2010 to 1/2020. Patients who had flaps requiring take-back for salvage were identified. Management of microvascular compromise and ischemia reperfusion injury were recorded.

Results: Of 2103 flaps were used in the breast reconstructions, 47 flaps required take-back for microvascular compromise (2.2%). Most flaps were either completely salvaged ($n = 29$, 61.7%) or partially salvaged ($n = 5$, 10.6%). Thirteen (27.7%) were a total flap loss, for an overall rate of 0.8% (including 3 flaps with no salvage attempt). Management of microvascular compromise most often included revision of the anastomosis ($n = 33$, 70.2%), thrombectomy ($n = 27$, 57.4%), tissue plasminogen activator administration ($n = 26$, 55.3%), and vein grafts ($n = 18$, 38.3%). Management of ischemia reperfusion included intraoperative steroids ($n = 33$, 70.2%), postoperative steroids ($n = 17$, 38.6%), and postoperative therapeutic anticoagulation ($n = 27$, 61.3%). Of 34 salvaged flaps, 5 (14.7%) had partial flap loss and/or fat necrosis on clinical examination at an average follow-up of 2.7 ± 2.8 years.

Conclusions: Salvage of microvascular compromise in autologous breast reconstruction should include restoration of blood flow and management of ischemia reperfusion injury. Attention to both is paramount for successful outcomes.

1 | INTRODUCTION

Recent advancements in breast reconstruction techniques have reduced rates of microvascular thrombosis to as low as 1%–10%

Michelle Coriddi and Paige Myers are co-first authors.

(Bui et al., 2007; Carney et al., 2018; Chen et al., 2007; Hanasono & Butler, 2008; Henderson et al., 2016; Hildago & Jones, 1990; Khansa et al., 2013; Largo et al., 2018; Mirzabeigi et al., 2012; Panchapakesan et al., 2003; Selber et al., 2012). Most flaps can be salvaged when thrombosis occurs in the early postoperative period (Bui et al., 2007; Carney et al., 2018; Chen et al., 2007; Hanasono & Butler, 2008; Henderson et al., 2016; Hildago & Jones, 1990; Khansa et al., 2013; Largo et al., 2018; Mirzabeigi et al., 2012; Panchapakesan et al., 2003; Selber et al., 2012). Multiple flap salvage algorithms, with salvage rates ranging from 50% to 70%, use various approaches, including mechanical thrombectomy, vein grafts, and thrombolytics.

The plastic surgery literature largely focuses on techniques to restore blood flow and not on strategies to limit reperfusion injury—an important cause of tissue damage after long periods of ischemia. The endothelial glycocalyx (EG), a physiologically active barrier that coats all healthy vascular endothelium (Alphonsus & Rodseth, 2014), can be severely injured even after relatively short periods of warm ischemia in shock and sepsis, resulting in capillary leakage, edema, inflammation, platelet aggregation, and hypercoagulability (Chappell et al., 2007). These microvascular changes may be important factors in the no-reflow phenomenon—clinical scenarios in which flap failure occurs despite successful blood flow restoration. Reperfusion injury may also lead to partial flap loss, flap shrinkage, or fat necrosis commonly noted following flap salvage (Alphonsus & Rodseth, 2014; Chappell et al., 2007; Jacob et al., 2009; Lipowsky & Lescanic, 2017). Treatment with steroids, albumin, heparin, and antioxidants may limit EG injury following ischemic injury (Alphonsus & Rodseth, 2014), but these options have not been systematically explored following treatment of microvascular thrombosis.

Herein, we evaluate our management of microvascular compromise following autologous breast reconstruction, including a review of our approach for restoring blood flow and addressing the ensuing inflammatory changes following ischemia reperfusion. The eventual goal is to provide a standardized management plan that not only maximizes the potential for free-flap salvage but also minimizes late tissue injury and flap shrinkage.

2 | METHODS

We conducted an IRB-approved, retrospective review of all patients who underwent breast reconstruction with free tissue transfer from January 2010 to January 2020 at our institution. Patients who underwent surgical treatment of microvascular compromise following their initial surgery were identified. Patients returning to the operating room for reasons other than microvascular compromise (i.e., hematoma) or who were discharged from the hospital with viable flaps but suffered subsequent microvascular compromise with no attempt at salvage ($n = 3$ patients) were excluded from this analysis. These exclusions were done to focus the analysis on the management of both microvascular compromise and ischemia reperfusion injury.

Details of the initial surgery and salvage procedures were noted; microvascular compromise was categorized as arterial, venous, or combined arterial and venous. Surgical techniques used during the salvage procedure were described as pedicle repositioning, mechanical thrombectomy, anastomotic revision, and vein grafting. The use of intraoperative and postoperative pharmacological treatments (including thrombolytics, anticoagulants, and anti-inflammatory therapies) were noted. Using the electronic medical record, complications (including fat necrosis and/or partial flap loss) and revision surgeries were recorded.

Standard microsurgical principles were employed in all cases. All patients were placed on heparin or enoxaparin postoperatively for deep vein thrombosis prophylaxis. Depending on surgeon preference, pharmacologic therapy included 3000 units of intravenous heparin administered 10 min before flap division and/or 325 mg aspirin administered postoperatively for 5 days.

Postoperative flap monitoring consisted of clinical observation, Doppler ultrasonography, pin-prick testing, or a combination of these. Hourly readings were taken for the first 48 h, then every 2 h up to 96 h, then every 4 h until discharge. If microvascular compromise suspected, patients returned to the operating room emergently.

2.1 | Management of microvascular compromise

Re-exploration began with evaluation of the anastomosis using an Acland strip test, Doppler ultrasonography, palpation, SPY fluorescence indocyanine green imaging system (NOVADAQ Technologies, Inc, Mississauga, Canada), or a combination of these. If the anastomosis was deemed patent, it was not revised, but pedicle position and geometry were adjusted. If venous insufficiency was suspected but the primary venous anastomosis was deemed patent, a second venous anastomosis was performed. If anastomoses patency was uncertain, the anastomosis was opened.

If thrombosis was identified and clot was noted in the vessel lumen, systemic heparin (5000 units) was intravenously administered, and thrombectomy and thrombolysis were performed. Mechanical thrombectomy was performed using microvascular forceps or a Fogarty catheter (2–3 French); otherwise, the vessel was simply milked to remove clot followed by a flush of heparinized saline.

Tissue plasminogen activator (tPA) was used for thrombolysis in cases of established clot within the artery or vein, with graded dosing between 5 and 10.5 mg of tPA (diluted as 1 mg/ml). Injection to the artery is done either prior to re-anastomosis or after anastomosis revision is completed by injecting the artery with a 30-gauge needle, bent at a 45° angle. Arterial injection of tPA allows for circulation through the entire flap, maximizing the microthrombolytic effect at the capillary level. When possible, a vein or a side branch were opened as to not allow systemic infusion of the thrombolytic, permitting its frequent and generous administration. However, if no side branch was available and the venous anastomosis was patent, the tPA was allowed to circulate systemically. The half-life of tPA is 2.4 min (Chandler et al., 1997), which is generally shorter than the time needed to revise an anastomosis. Even if administered after the anastomosis is revised, the dose of tPA used during salvage procedures is

relatively small (considering the dose of tPA for treatment of stroke is 0.9 mg/kg up to 90 mg total) and should be well tolerated by the patient.

Revision of the anastomosis to the same recipient vessels without vein graft was performed if no vascular injury was identified. If recipient vessels were unsatisfactory, alternative vessels were used, assisted by an interposition vein graft was needed. If vascular injury was noted in the flap vessel(s) or recipient vessel(s), it was cut back to a healthy, undamaged area. If either the arterial or venous anastomosis required revision and this resulted in a length mismatch between the artery and vein, a vein graft was used to establish a better match instead of revising the patent anastomosis. Because it has a good caliber match to the flap and recipient vessels, the lesser saphenous vein was typically used for vein grafting. The superficial inferior epigastric vein can also be used as a vein graft if this was dissected during flap harvest and is not needed for an additional venous anastomosis.

2.2 | Management of ischemia reperfusion injury

To decrease ischemia reperfusion injury, interventions to protect and repair the EG were employed. If no systemic contraindications to steroids identified, patients were given steroids intraoperatively and placed on a taper postoperatively to decrease ischemia injury. Patients were also placed on therapeutic anticoagulation if anastomotic revision was performed or clot was identified in the vessels. Surgeon preference determined dose of steroids and the type and duration of therapeutic anticoagulation.

2.3 | Outcome

The medical record was examined to determine the length of follow-up and the status of the flap. Flaps were categorized as lost, completely salvaged (soft, supple breast without fat necrosis or substantial shrinkage at most recent follow-up), or partially salvaged (definite areas of palpable fat necrosis or substantial shrinkage of the flap). Complications such as cellulitis, major wound healing issues (requiring operative intervention), and hematomas were noted.

2.4 | Statistical analysis

Descriptive and summary statistics were used to evaluate patient demographics, management of both microvascular compromise and ischemia reperfusion injury, and outcomes. For flaps returning to the operating room more than once for salvage, all maneuvers used for management of microvascular compromise were counted cumulatively and per flap. For management of ischemia reperfusion, methods used were counted per patient. Fisher's exact test was used to evaluate differences in categorical variables, and analysis of variance for two independent samples, 2-sided, was used to evaluate differences in continuous variables between the group of flaps that were lost, flaps that were completely salvaged, and flaps that were partially salvaged. Fisher's exact test was also used to evaluate differences in wound healing complications and cellulitis in patients given postoperative steroids compared with those who were not. A p-value of <.05 was considered significant. IBM SPSS Statistics, version 26, was used for all statistical analysis.

3 | RESULTS

A total of 1452 patients underwent autologous breast reconstructions with 2103 flaps; 47 flaps (2.2%) in 44 patients had microvascular compromise, and the patients returned to the operating room for salvage. Two of these flaps required two salvage attempts; no flaps had more than two salvage attempts. Following surgery, most flaps were either completely salvaged ($n = 29$, 61.7%) or partially salvaged ($n = 5$, 10.6%). The remaining flaps that required surgical treatment of microvascular compromise ($n = 13$, 27.7%) were completely non-viable and were removed either in the initial or subsequent re-operation procedures. Both flaps that required two salvage attempts were lost. Therefore, the total flap loss rate for the study period was 0.8% (including 3 flaps that were excluded from detailed analysis as they presented to clinic with flap loss and there was no attempt at salvage). Patient

TABLE 1 Patient demographics

Characteristic	$n = 44$ patients
Age (years, mean ± SD)	49.4 ± 8.0
Body mass index (mean ± SD)	29.0 ± 5.1
Chemotherapy $n = 35$ (79.5%)	
Preoperative	22 (50.0%)
Postoperative	13 (29.5%)
Radiation therapy $n = 24$ (54.5%)	
Preoperative	20 (45.5%)
Postoperative	4 (9.1%)
Hormone therapy $n = 31$ (70.5%)	
Preoperative	8 (18.2%)
Postoperative	23 (52.3%)
Comorbidities $n = 24$ (54.5%)	
Hypertension	5 (11.4%)
Hyperlipidemia	6 (13.6%)
Diabetes mellitus	1 (2.3%)
Current smoker	2 (4.5%)
Former smoker	10 (22.7%)
Reconstruction timing	
Immediate	27 (61.4%)
Delayed	17 (38.6%)
Reconstruction laterality	
Unilateral	13 (29.5%)
Bilateral	27 (61.4%)
Stacked unilateral	4 (9.1%)

TABLE 2 Description of flaps requiring salvage

Characteristic	$n = 47$ flaps
Flap type	
DIEP	31 (66.0%)
MS-TRAM	12 (25.5%)
DUG	2 (4.3%)
SGAP	1 (2.1%)
PAP	1 (2.1%)
Salvage attempts	
One	45 (95.7%)
Two	2 (4.3%)
Time from end of initial case to start of salvage (hours ±SD)	58.9 ± 51.5
Etiology of compromise	
Arterial	16 (34.0%)
Venous	30 (63.8%)
Both	1 (2.1%)
Outcome	
Completely salvaged	29 (61.7%)
Partially salvaged	5 (10.6%)
Total flap loss	13 (27.7%)

Abbreviations: DIEP, deep inferior epigastric perforator; DUG, diagonal upper gracilis; msMS-TRAM, muscle-sparing transverse rectus abdominis myocutaneous; PAP, profunda artery perforator; SGAP, superior gluteal artery perforator.

characteristics are shown in Table 1. Of note, no patients had a prior history of coagulopathy or were diagnosed with coagulopathy post-operatively. Of the 47 flaps requiring salvage (Table 2), most were either deep inferior epigastric perforator ($n = 31$, 66.0%) or muscle-sparing transverse rectus abdominis myocutaneous ($n = 12$, 25.5%) flaps. The average time to re-exploration was 58.9 hours ±51.5. Etiology of microvascular compromise was most often venous ($n = 30$, 63.8%), followed by arterial ($n = 16$, 34.0%) and combined venous and arterial ($n = 1$, 2.1%).

3.1 | Management of microvascular compromise

During the salvage attempt, mechanical and pharmaceutical techniques were employed to manage the microvascular compromise for flap salvage (Table 3). These included revision of the anastomosis ($n = 33$, 70.2%), thrombectomy ($n = 27$, 57.4%), repositioning the pedicle only ($n = 9$, 19.1%), a second venous anastomosis ($n = 9$, 19.1%), use of Fogarty catheter for manual thrombectomy ($n = 8$, 17.0%), and/or change of recipient vessels ($n = 7$, 14.9%). Eighteen flaps (38.3%) required a vein graft to complete the revision anastomosis. A heparin bolus of 3000 units was given in 32 flaps (68.1%) intraoperatively. tPA was administered to 26 flaps (55.3%) intraoperatively, with an average amount of 4.4 ± 2.5 mg per flap and a maximum dose of 10.5 mg.

TABLE 3 Management of microvascular compromise

Maneuver	$n = 47$ flaps
Revision of anastomosis	33 (70.2%)
Thrombectomy	27 (57.4%)
Pedicle repositioned only	9 (19.1%)
Fogarty catheter used	8 (17.0%)
tPA administered	26 (55.3%)
Amount (mg, mean ± SD)	4.4 ± 2.5
Vein graft	18 (38.3%)
Additional venous anastomosis	9 (19.1%)
Change of recipient vessels	7 (14.9%)
Bolus of heparin	32 (68.1%)

Abbreviation: tPA, tissue plasminogen activator.

TABLE 4 Management of ischemia reperfusion

Method	$n = 44$ patients
Steroids	
Intraoperative	33 (75.0%)
Amount (mg)	6.8 (3.3)
Postoperative	17 (38.6%)
Amount (mg, mean ± SD)[a]	43.0 ± 22.4
Duration (days, mean ± SD)	3.7 ± 1.6
Anticoagulation	
Heparin drip	26 (59.1%)
Therapeutic Lovenox	1 (2.3%)
Aspirin	26 (59.1%)

[a]Amount reported is in dexamethasone equivalents.

3.2 | Management of ischemia reperfusion

Minimizing ischemia reperfusion injury was attempted with use of steroids (Table 4). Intraoperative steroids were administered in 33 patients (75.0%). On average 6.8 ± 3.3 mg of dexamethasone was given during the case. Postoperative steroids were used in 17 patients (38.6%). Postoperative steroids were given for an average of 3.7 ± 1.6 days. On average, a total dose amount of 43.0 ± 22.4 mg of dexamethasone equivalents were given over the postoperative period.

Anticoagulation was used to decrease ischemia reperfusion injury and prevent thrombosis (Table 4). Postoperatively, therapeutic anticoagulation treatment included a heparin drip in 26 patients (59.1%) and therapeutic LMWH (Lovenox) in one patient (2.3%). Dosing of the heparin drip was at a flat rate of 500 units in 18 patients, and was titrated to institutional therapeutic aPTT levels in 8 patients. All remaining patients not on therapeutic anticoagulation were given prophylactic Lovenox. Aspirin was given postoperatively in 26 patients (59.1%).

3.3 | Outcomes

Postoperatively, 3 patients (6.7%) experienced major wound-healing issues requiring a return to the operating room; minor wound-healing issues occurred in 21 patients (47.7%). Cellulitis developed in 10 patients (22.7%). Wound-healing issues and cellulitis were no different in patients who received steroids versus those who did not ($p = .51$ and .37, respectively). No patients suffered a post-take-back hematoma.

Average long-term follow-up for all 44 patients (47 flaps) was 2.7 ± 2.8 years. A minority of flaps ($n = 13$, 27.7%) were lost either at the salvage operation or shortly after (Table 5). Most flaps were either completely salvaged ($n = 29$, 61.7%), with a soft and supple flap at most recent follow-up, or partially salvaged ($n = 5$, 10.6%), with some areas of palpable fat necrosis or visible flap shrinkage. Among these three groups, we found flaps that were lost were more likely to have an arterial cause of flap compromise compared with those that were completely salvaged or partially salvaged ($p = .03$). Those that were partially or completely salvaged were more likely to have a venous etiology compared with those that were lost ($p = .03$).

An additional venous anastomois was significantly more common in the partially salvaged group, followed by the completely salvaged group, and was less often used in flaps that were lost ($p = .05$). While not significant, a few maneuvers to manage the microvascular compromise deserve mention. Revision of the anastomosis,

TABLE 5 Comparison of lost versus completely salvaged versus partially salvaged flaps

Characteristic	Lost flaps ($n = 13$ flaps, 11 patients)	Completely salvaged flaps ($n = 29$ flaps, 28 patients)	Partially salvaged flaps ($n = 5$ flaps, 5 patients)	*p* value
Age (years, mean ± SD)	50.5 ± 7.8	48.5 ± 7.3	52.4 ± 9.8	.53
Body mass index (mean ± SD)	29.9 ± 4.1	28.5 ± 5.6	29.4 ± 3.1	.74
Preoperative radiation	6 (54.5%)	11 (39.3%)	3 (60.0%)	.60
Preoperative chemotherapy	5 (45.5%)	13 (46.4%)	4 (80.0%)	.45
Current or former smoker	1 (9.1%)	9 (32.1%)	2 (40.0%)	.32
Flap type				.48
DIEP	7 (53.8%)	19 (65.5%)	5 (100.0%)	
MS-TRAM	5 (38.5%)	7 (24.1%)	0	
DUG	0	2 (6.9%)	0	
SGAP	1 (7.7%)	0	0	
PAP	0	1 (3.4%)	0	
Time from end of initial case to start of salvage (hours, mean)	76.08	51.84	55.92	.37
Etiology of compromise				.03*
Arterial	9 (69.2%)[a]	7 (24.1%)	1 (20.0%)	
Venous	5 (38.5%)[a]	22 (75.9%)	4 (80.0%)	
Revision of anastomosis	11 (84.6%)	20 (69.0%)	2 (40.0%)	.17
Thrombectomy	10 (76.9%)	16 (55.2%)	1 (20.0%)	.10
Pedicle repositioned only	3 (23.1%)	5 (17.2%)	1 (20.0%)	.86
Fogarty catheter used	2 (15.4%)	6 (20.7%)	0	.85
tPA administered	9 (69.2%)	16 (55.2%)	1 (20.0%)	.21
Vein graft	4 (30.8%)	13 (44.8%)	1 (20.0%)	.50
Additional venous anastomosis	1 (7.7%)	5 (17.2%)	3 (60.0%)	.05*
Change recipient vessels	2 (15.4%)	4 (13.8%)	1 (20.0%)	1.00
Bolus of heparin	11 (84.6%)	19 (65.5%)	2 (40.0%)	.17
Intraoperative steroids	9 (81.8%)	19 (67.9%)	5 (100.0%)	.45
Postoperative steroids	4 (36.4%)	13 (46.4%)	0	.20
Postoperative therapeutic AC	9 (81.8%)	15 (53.6%)	3 (60.0%)	.29
Postoperative aspirin	8 (72.7%)	14 (50.0%)	4 (80.0%)	.33

Note: * denote values that are significant as $p < 0.05$.

Abbreviations: AC, anticoagulation; DIEP, deep inferior epigastric perforator; DUG, diagonal upper gracilis; MS-TRAM, muscle-sparing transverse rectus abdominis myocutaneous; PAP, profunda artery perforator; SD, standard deviation; SGAP, superior gluteal artery perforator; tPA, tissue plasminogen activator.

[a]One flap in this group had both an arterial and venous etiology of flap compromise and therefore was counted in both the arterial and venous categories.

thrombectomy, tPA administration, and a bolus of heparin were more often performed in flaps that were lost, followed by those that were completely salvaged or partially salvaged ($p = .17, .10, .21, .17$, respectively). Administration of postoperative steroids to combat ischemia reperfusion injury was done more often in completely salvaged flaps, followed by flaps that were completely lost. No partially salvaged flaps were given postoperative steroids ($p = .20$).

4 | DISCUSSION

This study supports the evidence in the literature of low acute return to the operating room for salvage following free tissue transfer and a high salvage rate after microvascular thrombosis. Selber et al. (2012) found a 3.3% take-back rate for microvascular compromise with a salvage rate of 58% after reviewing all free flaps performed at a single institution over a 10-year period. Carney et al. (2018) reported a similarly low take-back rate for microvascular compromise of 1.53% and a flap loss rate of 0.55% in 5000 free flaps. Khansa et al. (2013) performed a retrospective review of 612 microsurgical breast reconstructions and found a take-back rate for microvascular compromise of 5.9% and a salvage rate of 77.8%. Our study has take-back and salvage rates consistent with the aforementioned literature. Of 2103 flaps for autologous breast reconstructions, we found a 2.2% take-back rate for microvascular compromise, a 72.3% salvage rate, and an overall flap loss rate of 0.8%. Further, in their series of 1142 free tissue transfers, Chen et al. (2007) report 72 flaps (63.7%) were completely salvaged and 23 (20.4%) were partially salvaged, with 18 flaps (15.9%) failing completely. Aside from the aforementioned study, there is a paucity of research delineating partial versus complete flap salvage. We report a lower partial salvage rate (10.6%), meaning that most salvaged flaps were completely salvaged.

There was more often total flap loss in flaps that experienced arterial compromise, and partial or complete salvage in flaps that experienced venous compromise ($p = .03$). This is likely due to the fact that arterial compromise results in an inadequate oxygen supply and simultaneous deficit in clearance of toxic metabolites to the flap (Nguyen et al., 2013). As a result, reactive oxygen species (ROS) and inflammatory cells accumulate while cytokines release, inducing inflammation. Irreversible microcirculatory damage occurs as a result of ROS. While salvage methods are aimed at re-establishing blood flow and limiting ischemia reperfusion injury, flap injury in some cases may be irreversible. In venous compromise, the in-flow to the flap remains, causing increased intravascular pressure (Nguyen et al., 2013). Subsequently, hemorrhage into the extravascular space causes compression and collapse of the vessels. Further, edema forms in the interstitial tissue and does not allow diffusion of oxygen, propagating tissue damage. However, to some degree, the flap can accommodate an increase of blood by dilating choke vessels (Chang et al., 2004). Research has shown arterial inflow may be more important than venous drainage (Chang et al., 2004; Nakayama et al., 1982; Yamamoto et al., 2009).

Successful microvascular salvage requires management of the initial microvascular compromise and minimization of the subsequent ischemia reperfusion injury. We found that additional venous anastomois was most often performed in the partially salvaged group, followed by the completely salvaged group, and was less often used in flaps that were lost ($p = .05$). This is to be expected given more flaps in the salvaged groups suffered venous compromise. Additionally, in flaps that were lost, either an additional vein was perhaps not indicated or an additional venous anastomosis may have been beneficial but was unable to be performed due to a lack of suitable flap or recipient veins. While not significant in our study, a change to new recipient vessels and vein grafting as part of anastomotic revision deserve mention. Despite literature associating vein grafts with higher complication rates (Maricevich et al., 2018; Nelson et al., 2015), we recommend a low threshold for using vein grafts to provide tension-free pedicle geometry and clean anastomoses between uninjured vessels (Bui et al., 2007).

In our series, the overall rate of tPA use is high at 55.3%, although no significant differences between groups were found. Prior reports of flap salvage use tPA in 13%–30% cases (Khansa et al., 2013; Selber et al., 2012). Use of thrombolytics have shown improvements in fat necrosis, likely due to the lysis of distal clots within the flap (Chang et al., 2011). The use of tPA may allow for restoration of blood flow at the capillary level, thus resulting in a flap that is soft and supple in the long term. Therefore, we advocate for liberal doses and a low threshold for use of thrombolytic in salvage free-flap cases. There is little in the literature regarding dosing of tPA. When looking specifically at the doses of tPA infused, Rinker et al. (2007) reported a 67% free-flap salvage rate after intra-arterial infusions of 2.5–5 mg tPA. Our average was 4.4 mg (range 1–10.5 mg). Importantly, no patients developed a hematoma after tPA administration.

Despite a significant number of studies on the effects of reperfusion injury – and at the pathophysiological level, damage to the EG - in pathologic conditions such as shock and sepsis, as well as preclinical studies in the plastic surgery literature, clinical management of this issue following breast free flap salvage has not been widely discussed. Evidence shows that administration of steroids and prophylactic anticoagulation, can diminish the unfavorable sequelae of reperfusion injury (Chappell et al., 2007; Jacob et al., 2009; Lipowsky & Lescanic, 2017; Spiess, 2017). This focus is novel to the field of microvascular surgery.

Chappell et al. (2007) showed administration of hydrocortisone reduced shedding of the EG of cardiovascular endothelium that is protective against post-ischemic inflammatory leukocytes and interstitial edema. A secondary benefit of steroid administration is stabilization of mast cells, which release stores of damaging proteases responsible for further tissue injury (Chappell et al., 2007). In our study, postoperative steroids were administered more often in flaps that were completely salvaged than in flaps that were lost (46.4% vs. 36.4%). Importantly, we found no increase wound complications in patients treated with steroids, compared with those who were not; this finding is consistent with other previously published studies (Wang et al., 2013). Anticoagulation has also been shown to preserve the EG (Alphonsus & Rodseth, 2014; Chappell et al., 2007; Jacob et al., 2009). Although this study did not find a significant difference between

heparin use in lost flaps, partially salvaged flaps, or completely salvaged flaps, other research has shown a trend to significance with the administration of intraoperative heparin (Mirzabeigi et al., 2012).

Lastly, the time to take-back was, on average, 1 day earlier for flaps that were salvaged (partial and complete salvage) compared to those that were lost, although this was not significant. Perhaps the flaps that were lost experienced microvascular compromise earlier, but this was not detected until a later time, causing more ischemic stress, and potentially more irreversible injury. If a delay to detection of vascular compromise was the cause of a later return to the operating room, it can be theorized that greater oxidative injury resulting in a greater inflammatory response could be to blame.

The retrospective nature of this study is a major limitation. Further, some important interventions (ex: steroid use, post-operative anticoagulation) may not have reached significance levels in this study due to the low number of flaps requiring salvage. Perhaps more definite conclusions can be drawn with a larger sample. Differing surgeon preferences with varying dosages of pharmacologic agents is an additional limitation. Although the importance of the EG has been explored in the context of cardiovascular surgery (Bruegger et al., 2009), solid organ transplantation (Schiefer et al., 2015), and sepsis physiology (Martin et al., 2016), future research regarding its role in microsurgical reconstruction will likely prove beneficial.

5 | CONCLUSIONS

Microvascular breast reconstruction is safe and effective. Flap salvage is accomplished not only by restoration of blood flow but also by minimizing the subsequent ischemia reperfusion injury. This paper outlines key maneuvers and methods for flap salvage with particular focus on the EG as a potential site of intervention to mitigate ischemia reperfusion injury.

DISCLOSURE

Joseph H. Dayan, MD, is a paid consultant for the Stryker Corporation.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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