

# Remote Ischemic Preconditioning in Microsurgical Head and Neck Reconstruction: A Randomized Controlled Trial

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**Background:** The free flap failure rate is 5% in head and neck microsurgical reconstruction, and ischemia–reperfusion injury is an important mechanism behind this failure rate. Remote ischemic preconditioning (RIPC) is a recent intervention targeting ischemia–reperfusion injury. The aim of the present study was to investigate if RIPC improved clinical outcomes in microsurgical reconstruction.

**Methods:** Head and neck cancer patients undergoing tumor resection and microsurgical reconstruction were included in a randomized controlled trial. Patients were randomized (1:1) to RIPC or sham intervention administered intraoperatively just before transfer of the free flap. RIPC was administered by four 5-minute periods of upper extremity occlusion and reperfusion. Clinical data were prospectively collected in the perioperative period and at follow-up on postoperative days 30 and 90. Intention-to-treat analysis was performed.

**Results:** Sixty patients were randomized to RIPC (n = 30) or sham intervention (n = 30). All patients received allocated intervention. No patients were lost to follow up. At 30-day follow-up, flap failure occurred in 7% of RIPC patients (n = 2) and 3% of sham patients (n = 1) with the relative risk and 95% confidence interval 2.0 [0.2;20.9], *P* = 1.0. The rate of pedicle thrombosis was 10% (n = 3) in both groups with relative risk 1.0 [0.2;4.6], *P* = 1.0. The flap failure rate did not change at 90-day follow-up.

**Conclusions:** RIPC is safe and feasible but does not affect clinical outcomes in head and neck cancer patients undergoing microsurgical reconstruction. (*Plast Reconstr Surg Glob Open* 2020;8:e2591; doi: [10.1097/GOX.0000000000002591](https://doi.org/10.1097/GOX.0000000000002591); Published online 21 January 2020.)

## INTRODUCTION

Microsurgical reconstruction has improved oncologic and functional outcomes for head and neck cancer patients undergoing resection of large tumors.<sup>1</sup> However, the free flap failure rate is estimated to 5% in meta-analyses of head and neck reconstruction,<sup>2,3</sup> and vascular pedicle occlusion

inducing flap ischemia–reperfusion injury is the most common cause of free flap failure.<sup>4</sup> Ischemia–reperfusion injury includes the cell damage sustained during free flap ischemia and the paradoxical aggravation of tissue injury by flap reperfusion.<sup>5</sup> Endothelial leukocyte and platelet adhesion during reperfusion induce inflammation and microcirculatory thrombosis and hence reduced capillary flow or ultimately the no-reflow phenomenon.<sup>6–8</sup> Thus, interventions targeting flap ischemia–reperfusion injury should be explored.

In 1992, Mounsey et al demonstrated that ischemic preconditioning by preclamping of the vascular pedicle reduced infarct size in porcine latissimus dorsi flaps

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following ischemia–reperfusion.<sup>9</sup> Ten years later, it was proven that brief periods of tourniquet-induced limb ischemia and reperfusion were as effective as pedicle preclamping in reducing infarct size of the rat epigastric adipocutaneous flap.<sup>10</sup> This treatment is termed remote ischemic preconditioning (RIPC).<sup>11</sup>

Remote ischemic conditioning may improve the outcome of microsurgical reconstruction through the following mechanisms: first, attenuation of flap ischemia–reperfusion injury and infarct size as reported in experimental studies;<sup>12,13</sup> second, augmentation of flap blood flow and oxygen saturation after transfer as reported in a human study;<sup>14</sup> and third, inhibition of thrombus formation on a thrombogenic microvascular anastomosis as shown in a rat model.<sup>15</sup> Accordingly, RIPC may reduce the risk of free flap failure, partial flap necrosis, and vascular pedicle thrombosis. Previous clinical studies reporting ischemic conditioning of pedicled and free flaps have not included a control group with sham intervention making the treatment effect inconclusive.<sup>14,16</sup>

The objective of this study was to analyze clinical outcomes in a randomized controlled trial designed to investigate the effects of RIPC on hemostasis and fibrinolysis in head and neck cancer patients undergoing microsurgical reconstruction.<sup>17</sup>

## PATIENTS AND METHODS

### Trial Design

This is a substudy utilizing clinical data that were prospectively collected during a single-center, single-blinded, randomized controlled trial investigating the effects of RIPC compared with sham intervention on hemostasis and fibrinolysis in head and neck cancer patients undergoing microsurgical reconstruction.<sup>17</sup> The trial was conducted at the tertiary referral center for microsurgical reconstruction at the Department of Plastic and Breast Surgery at Aarhus University Hospital, Aarhus, Denmark. Inclusion criteria were: (1) patients aged  $\geq 18$  years, with (2) a histologically verified or clinically suspected malignant tumor in the oral cavity, maxillae, mandible, pharynx, larynx, and/or esophagus, scheduled for (3) tumor resection and immediate microsurgical reconstruction with a single free flap. Exclusion criteria were: (1) arterial and/or venous thromboembolism within the past 3 months and (2) microsurgical reconstruction planned with more than 1 free flap. Study approval was obtained from the Central Denmark Region Committees on Health Research Ethics (journal no. 1-10-72-140-15) and the Danish Data Protection Agency (journal no. 1-16-02-358-15). The trial was registered at ClinicalTrials.gov (NCT02548377) on September 14, 2015. Written informed consent was obtained from all patients, and the study was performed in compliance with the Declaration of Helsinki.

### Interventions

Patients were operated on using a 2-team approach with head and neck surgeons performing tumor resection and plastic surgeons preparing the free flap simultaneously. General anesthesia was induced with propofol and

remifentanyl intravenously and maintained using sevoflurane after the patient was tracheostomized, if needed. Propofol was only used for maintenance of general anesthesia if sevoflurane was contraindicated. Tumor resection was classified as mandibulectomy (segmental or marginal, with or without floor of mouth resection), maxillectomy, oral cavity resection, laryngopharyngectomy, partial glossectomy, or orbital exenteration. Tumor resection was defined as composite resection if it included more than one of these categories. The free flap was ischemic at room temperature during transfer, and both the arterial and venous microvascular anastomoses were sutured with 9-0 nylon under the operating microscope.

An autoRIC Device (CellAegis Devices Inc., Toronto, Canada), which is an automated, single-button start, inflatable tourniquet for remote ischemic conditioning, was attached to the patient's unilateral upper arm before surgery (Fig. 1). The autoRIC Device is approved for investigational use in the United States of America. Upon activation, the autoRIC Device automatically administers 4 cycles of 5-minute upper extremity occlusion and 5-minute reperfusion. The device inflates to 200 mm Hg during occlusion periods. The patient's upper extremity was covered with a transparent, sterile drape, designed for C-arm x-ray cover, to monitor safety and efficacy of RIPC intervention. A study investigator observed for pallor of the upper extremity during occlusion.

Randomization and administration of allocated study intervention was performed 35 minutes before expected free flap ischemia and transfer. RIPC was administered by activating the autoRIC Device. In sham intervention, the autoRIC Device was attached to the patient but never inflated.

Antibiotic prophylaxis was administered with metronidazole (B. Braun Melsungen AG, Melsungen, Germany)



**Fig. 1.** Administration of study intervention. The autoRIC Device was attached to the upper arm in all patients. Randomization and administration of allocated study intervention were performed 35 minutes before expected transfer of the free flap. In patients randomized to RIPC, the autoRIC Device was activated and the device automatically administered 5-minute upper extremity occlusion followed by 5-minute reperfusion repeated for a total of 4 cycles. In patients randomized to sham, the autoRIC Device was not activated. Transparent sterile drapes over the upper extremity provided easy activation of the autoRIC Device and monitoring of safety and efficacy of the study intervention.

and cefuroxime (B. Braun Melsungen AG) intravenously during surgery and postoperatively until the third postoperative day. Thromboprophylaxis was administered by dalteparin (Fragmin, Pfizer Inc., New York, NY, USA) or tinzaparin (Innohep, LEO Pharma A/S, Ballerup, Denmark) subcutaneously just before surgery, 6 hours after surgery, and once daily from the 1st to 28th postoperative day. Postoperative free flap perfusion was monitored by clinical observation and handheld Doppler flow measurement hourly for the first 24 hours, every second hour 24–48 hours postoperatively, and every third hour 48–72 hours postoperatively. Buried flaps were monitored using the Cook-Schwartz Doppler Probe (Cook Group Inc., Bloomington, IN, United States) for 72 hours postoperatively.

### Outcomes

The primary endpoint was the effect of RIPC on platelet aggregation on the first postoperative day, which previously has been published.<sup>17</sup> The following flap-related endpoints were measured at 30-day follow-up: (1) free flap failure defined as circulatory failure, (2) vascular pedicle thrombosis inducing secondary flap ischemia, (3) type and timing of vascular pedicle thrombosis, (4) reoperation for flap site dehiscence, (5) reoperation for flap site wound infection, and (6) antibiotics for flap site wound infection. Free flap failure was also measured at 90-day follow-up. The following clinical endpoints were also measured at 30-day follow-up: reoperation for hematoma, reoperation for donor site dehiscence, reoperation for donor site wound infection, antibiotics for donor site wound infection, admission to intensive care unit after the first postoperative day, days with feeding tube dependency until oral feeding was allowed by the attending plastic surgeon, days with temporary tracheostomy until decannulation by the attending anesthesiologist, length of hospital stay, and mortality. The following clinical endpoints were measured at 90-day follow-up: days until postoperative radiotherapy was initiated and mortality.

For patients receiving 2 free flaps during the primary operation, only data on the originally planned flap are presented. For patients receiving a new free flap during follow-up because of free flap failure, this new flap and following related reoperations are not included in the data analyses.

### Randomization

Patients were randomized intraoperatively (1:1) to RIPC or sham intervention in a computer-generated randomization sequence with varying block sizes of 2, 4, 6, and 8. The allocation cards were packed in numbered, opaque, and sealed envelopes by a scientist not affiliated with the present trial. Patients and care providers were blinded to the study intervention. Investigators and operating surgeons were not blinded.

### Statistics

The sample size calculation has previously been published with the biomarker platelet aggregation as primary endpoint.<sup>17</sup> Data distribution was assessed by

quantile–quantile plots of continuous variables grouped after study intervention. Variables that followed normal distribution are presented as mean  $\pm$  SD or mean with 95% confidence interval (CI). For variables that did not follow normal distribution, normality could be obtained by logarithmic transformation before analysis. These variables are presented as median with interquartile range. Continuous variables were tested with the unpaired *t* test, and Welch's approximation was used for variables with unequal variances. Categorical variables were tested with Fisher's exact test grouped after study intervention, and the relative risk (RR) with 95% CI was calculated for outcome variables. All analyses were performed as intention-to-treat.  $P < 0.05$  was considered statistically significant. Statistical analyses were performed in Stata/IC 13.1 (StataCorp LP, College Station, TX, USA).

## RESULTS

### Study Population

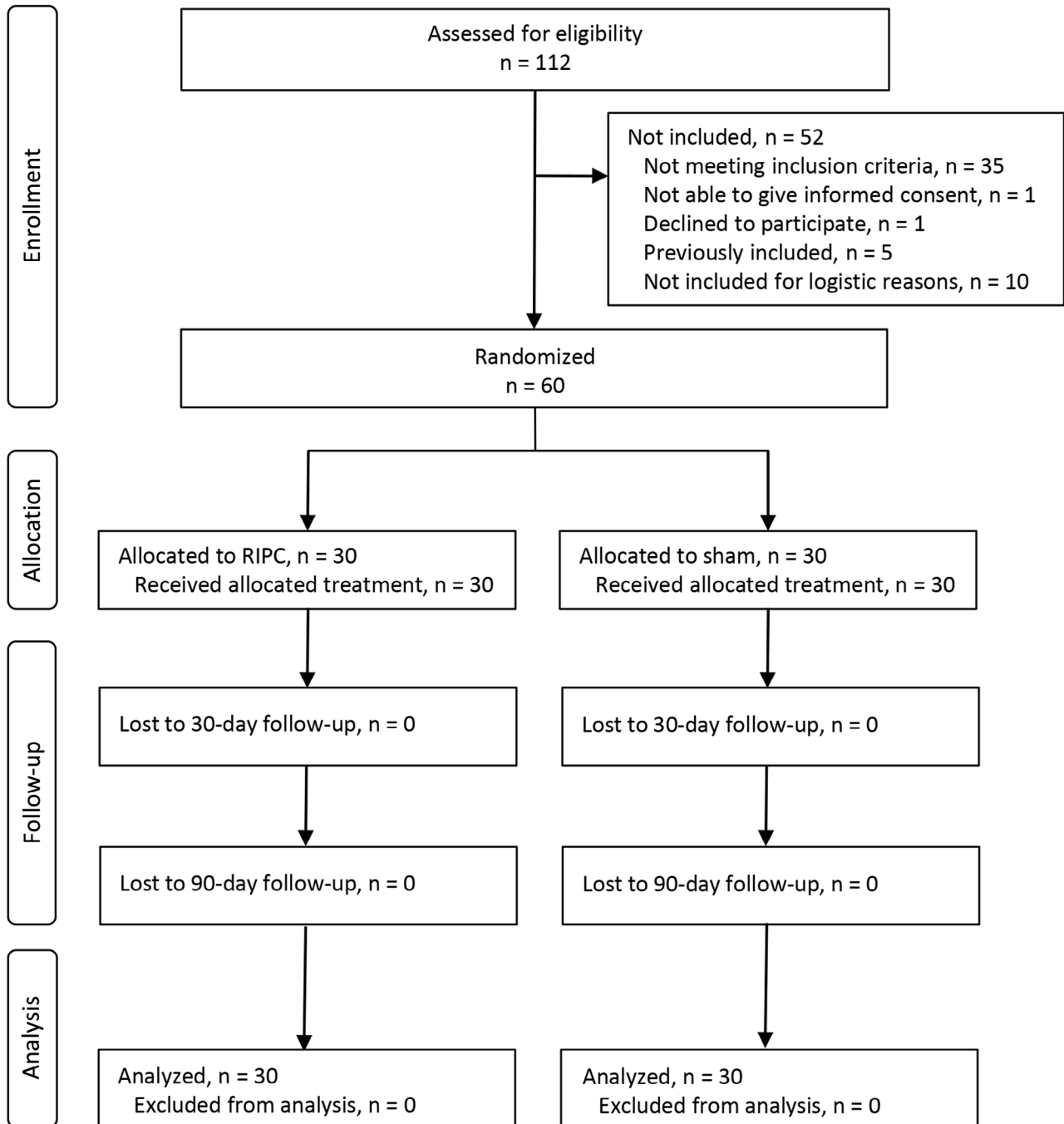
Sixty patients were included in the trial; 30 patients were randomized to RIPC, and 30 patients were randomized to sham intervention. All patients received their allocated study intervention. Patients were included between August 2015 and November 2017, and follow-up was completed in February 2018. No patients were lost to follow up (Fig. 2).

These protocol deviations occurred after allocation of study intervention: 3 patients underwent reconstruction with 2 free flaps because of tumor resection larger than expected or unreliable perforators to the skin paddle of the osteocutaneous fibula flap (2 RIPC, 1 sham); the pathology report described no residual malignant cells in 1 patient who had received preoperative radiotherapy (sham) and another patient who had undergone recent nonradical tumor resection (RIPC); and 1 patient had a benign ameloblastoma with no malignant transformation (sham). All patients were included in the intention-to-treat analysis in their original allocated groups.

The 2 groups were similar in preoperative demographics, comorbidities, and cancer status (Table 1). Surgery time, anesthesia, tumor resection, free flap reconstruction, and free flap ischemia time did not differ between the 2 groups (Table 2).

### Flap Complications

Three RIPC patients (10%) suffered vascular pedicle thrombosis postoperatively and underwent acute reexploration of the vascular pedicle (Table 3). Correspondingly, vascular pedicle thrombosis induced secondary flap ischemia in 3 sham patients (10%) of which 2 thrombi occurred during the primary operation and 1 thrombus occurred during the first 24 hours postoperatively leading to acute reexploration of the vascular pedicle. Both groups had 1 case of arterial pedicle thrombosis and 2 cases of venous pedicle thrombosis. Hence, the RR of vascular pedicle thrombosis was 1.0 [0.2;4.6] and did not differ between groups ( $P = 1.0$ ). Flap pedicle thrombosis induced free flap failure in 2 RIPC patients (7%) and 1 sham patient (3%), all within 30-day follow-up,



**Fig. 2.** CONSORT flow diagram of the trial. Sixty patients were included and randomized 1:1 to RIPC (n = 30) or sham intervention (n = 30). All patients received their allocated study intervention. Follow-up was performed on the 30th and 90th postoperative day, and no patients were lost to follow up. Analyses were performed as intention-to-treat.

resulting in an RR of 2.0 [0.2;20.9] which was not significantly different between groups ( $P = 1.0$ ). Furthermore, the 2 groups did not differ in flap site dehiscence (RR 1.0 [0.2; 6.6],  $P = 1.0$ ) or flap site infection (RR 1.0 [0.3; 3.6],  $P = 1.0$ ).

**Other Clinical Outcomes**

There were no significant differences between the 2 groups in donor site or systemic complications (Table 3).

The 2 groups did not differ in intensive care treatment, tracheostomy dependency, feeding tube dependency, or length of hospital stay (all  $P \geq 0.28$ ). At 90-day follow-up, the RIPC group and sham group did not differ in time until adjuvant radiotherapy was initiated with the mean [95% CI] time 52 [45;58] versus 52 [45;59] days ( $P = 0.89$ ) (Table 4). At 30-day follow-up, 1 RIPC patient was deceased after having been diagnosed with pulmonary embolism, and at 90-day follow-up, another RIPC patient



**Table 1. Preoperative Characteristics**

Variable	RIPC (n = 30)	Sham (n = 30)	P
Sex (man/woman)	18/12	19/11	1.0
Age (y)	67 ± 10	64 ± 12	0.22
Body mass index (kg/m <sup>2</sup> )	25 ± 4	23 ± 4	0.18
<b>Comorbidities</b>			
Smoking			
Active	12 (40%)	16 (53%)	0.45
Former	15 (50%)	10 (33%)	
Never	3 (10%)	4 (13%)	
Alcohol consumption (1 unit = 12 g)			0.77
<21 units/wk	21 (70%)	23 (77%)	
≥21 units/wk	9 (30%)	7 (23%)	
American Society of Anesthesiologist classification			
I	1 (3%)	0	0.20
II	13 (43%)	19 (63%)	
III	16 (53%)	11 (37%)	
Charlson's comorbidity score	5 (4–6)	5 (4–6)	0.98
Peripheral artery disease	4 (13%)	2 (7%)	0.67
Diabetes mellitus	3 (10%)	3 (10%)	1.0
<b>Cancer status</b>			
Head and neck cancer type			
Oral cancer	23 (77%)	21 (70%)	0.49
Sino-nasal cancer	2 (7%)	5 (17%)	
Laryngeal cancer	1 (3%)	0	
Hypopharyngeal cancer	1 (3%)	3 (10%)	
Skin cancer	1 (3%)	0	
Other	2 (7%)	1 (3%)	
Tumor histology			
Squamous cell carcinoma	25 (83%)	24 (80%)	
Carcinoma, other	3 (10%)	3 (10%)	
Osteosarcoma	1 (3%)	1 (3%)	
Ameloblastoma	0	1 (3%)	
No residual tumor	1 (3%)	1 (3%)	
Secondary malignancy	4 (13%)	3 (10%)	1.0
Prior head and neck cancer treatment			
Surgery	12 (40%)	9 (30%)	0.59
Radiotherapy	13 (43%)	9 (30%)	0.42

Continuous variables are presented as mean ± SD with *P*-value from unpaired *t* test. Categorical variables are presented as number of patients and frequencies or median and interquartile range with *P*-value from Fisher's exact test.

**Table 2. Operative Characteristics**

Variable	RIPC (n = 30)	Sham (n = 30)	P
Surgery time (min), mean ± SD	398 ± 78	417 ± 95	0.41
General anesthesia time (min), mean ± SD	515 ± 66	518 ± 106	0.90
Anesthetic used for maintenance			
Sevoflurane	26 (87%)	29 (97%)	0.35
Propofol	4 (13%)	1 (3%)	
Temporary tracheostomy	23 (77%)	23 (77%)	1.0
Permanent stoma	2 (7%)	4 (13%)	0.67
Tumor resection			
Composite resection	14 (47%)	12 (40%)	0.29
Mandibulectomy	7 (23%)	11 (37%)	
Maxillectomy	3 (10%)	3 (10%)	
Oral cavity	4 (13%)	0	
Laryngopharyngectomy	2 (7%)	3 (10%)	
Partial glossectomy	0	1 (3%)	
Neck dissection			
Not performed	9 (30%)	8 (27%)	
Ipsilateral	15 (50%)	16 (53%)	
Bilateral	6 (20%)	6 (20%)	
Free flap reconstruction			
Fasciocutaneous	16 (53%)	10 (33%)	0.39
Osteocutaneous	9 (30%)	8 (27%)	
Bone	1 (3%)	2 (7%)	
Musculocutaneous	0	3 (10%)	
Muscle	2 (7%)	4 (13%)	
Jejunum	2 (7%)	3 (10%)	
Free flap ischemia time (min), median (IQR)	58 (49–94)	58 (41–70)	
Converted to 2 free flaps	2 (7%)	1 (3%)	1.0

Continuous variables are presented as mean ± SD or median and IQR with *P*-value from unpaired *t* test. Categorical variables are presented as number of patients and frequencies with *P*-value from Fisher's exact test. IQR, interquartile range.

**Table 3. Clinical Outcomes at 30-d Follow-up**

Variable	RIPC (n = 30)	Sham (n = 30)	RR [95% CI]	P
<b>Vascular flap complications</b>				
Free flap failure	2 (7%)	1 (3%)	2.0 [0.2;20.9]	1.0
Flap pedicle thrombosis	3 (10%)	3 (10%)	1.0 [0.2;4.6]	1.0
Vessel occluded				
Arterial thrombosis	1	1		1.0
Venous thrombosis	2	2		
Time of pedicle thrombosis				
Intraoperatively	0	2		0.40
≤24 h postoperatively	2	1		
24–48 h postoperatively	1	0		
<b>Other flap complications</b>				
Flap site dehiscence, reoperation	2 (6%)	2 (6%)	1.0 [0.2;6.6]	1.0
Flap site infection, reoperation	4 (13%)	4 (13%)	1.0 [0.3;3.6]	1.0
Antibiotics flap site infection	8 (27%)	6 (20%)	1.3 [0.5;3.4]	0.76
<b>Other clinical outcomes</b>				
Hematoma, reoperation	3 (10%)	6 (20%)	0.5 [0.1;1.8]	0.47
Donor site dehiscence, reoperation	1 (3%)	0	n/a	1.0
Antibiotics donor site infection	2 (7%)	1 (3%)	2 [0.2;20.9]	1.0
ICU admission	5 (17%) (n = 29)	5 (17%) (n = 30)	1.0 [0.3;3.2]	1.0
Days with feeding tube dependency, mean [95% CI]	17 [14;20] (n = 27)	16 [13;19] (n = 28)		0.68
Days with temporary tracheostomy, median (IQR)	5 (2–7) (n = 22)	6 (3–12) (n = 23)		0.28
Hospital stay (d), median (IQR)	9 (7–13) (n = 29)	9 (7–13) (n = 30)		0.75
Mortality	1 (3%)	0	n/a	1.0

Continuous variables are presented as mean with 95% CI or median and IQR with *P*-value from unpaired *t* test. Categorical variables are presented as number of patients and frequencies with RR and 95% CI and *P*-value from Fisher's exact test. Number of patients analyzed in the RIPC group is 29 when indicated, because 1 patient expired before 30-d follow-up.

ICU, intensive care unit; IQR, interquartile range; n/a, not applicable

**Table 4. Clinical Outcomes at 90-d Follow-up**

	RIPC (n = 30)	Sham (n = 30)	RR [95% CI]	P
Free flap failure	2 (7%)	1 (3%)	2.0 [0.2;20.9]	1.0
Planned postoperative radiotherapy	10 (34%) (n = 29)	14 (47%) (n = 30)		0.43
Days until radiotherapy, mean [95% CI]	52 [45;58] (n = 10)	52 [45;59] (n = 14)		0.89
Postoperative visits to outpatient clinic, mean [95% CI]	2.5 [1.7;3.3] (n = 29)	2.3 [1.7;2.9] (n = 30)		0.72
Mortality	2 (7%)	0	n/a	0.49

Continuous variables are presented as mean with 95% CI with *P*-value from unpaired *t* test. Categorical variables are presented as number of patients and frequencies with RR and 95% CI and *P*-value from Fisher's exact test.

had expired from complications to a hip fracture sustained after hospital discharge. Hence, the mortality rate was 7% in the RIPC group and 0% in the sham group at 90-day follow-up (*P* = 0.49).

No adverse events were detected related to administration of RIPC on the upper extremity, specifically, no pain, skin changes, or neurovascular complications.

### DISCUSSION

RIPC did not affect clinical outcomes in head and neck cancer patients undergoing microsurgical reconstruction. However, the present randomized controlled trial demonstrates no adverse events or prolongation of surgery time related to RIPC, meaning that RIPC is safe and feasible in microsurgical reconstruction.

Previous experimental studies showed that RIPC attenuated flap ischemia–reperfusion injury and reduced final infarct size.<sup>10,12,13</sup> Furthermore, we have previously shown that remote ischemic “per”conditioning, which is the brief period of limb ischemia and reperfusion administered

after the onset of flap ischemia but before flap reperfusion, also attenuated flap ischemia–reperfusion injury in a porcine model.<sup>18</sup> The present study is the first randomized controlled trial investigating RIPC in microsurgical reconstruction, whereas remote ischemic conditioning has been studied extensively in related fields of tissue ischemia–reperfusion injury. Two randomized controlled trials on living donor kidney transplant recipients demonstrated that remote ischemic conditioning improved early graft function but did not affect long-term graft function measured by postoperative serum creatinine changes.<sup>19,20</sup> Further, 2 multicenter, randomized controlled trials showed no benefit of RIPC in reducing postoperative myocardial infarction, stroke, or mortality after open-heart surgery.<sup>21,22</sup> Contrary to this, acute ST-elevation myocardial infarction patients randomized to remote ischemic preconditioning had improved myocardial salvage and reduced mortality at 3.8-year follow-up compared with patients randomized to sham intervention after primary percutaneous coronary intervention.<sup>23,24</sup> Hence, based

on these previous high-quality studies, remote ischemic conditioning attenuated ischemia–reperfusion injury in transplanted kidneys and acute ischemic myocardium post percutaneous coronary intervention, whereas any protection offered to the myocardium during open-heart surgery requiring cardiopulmonary bypass was insufficient to reduce postoperative myocardial infarctions.

The tissue-protective mechanisms behind remote ischemic conditioning are not fully understood, but experimental studies on tissue flaps have shown inhibition of pro-inflammatory cytokine release,<sup>18</sup> possible changes in the local coagulation environment,<sup>25</sup> stimulation of nitric oxide release,<sup>26</sup> opioid-receptor-mediated effects,<sup>13</sup> and mitochondrial  $K_{ATP}$  channel effects.<sup>27</sup> The present study did not directly measure flap ischemia–reperfusion injury, but RPC failed to reduce the rate of flap failure, which is the ultimate result of ischemia–reperfusion injury.

Kolbenschlager et al demonstrated that remote ischemic conditioning augmented blood flow and oxygen saturation in free flaps when it was administered postoperatively, but the study did not include clinical outcomes.<sup>14</sup> Augmented cutaneous microcirculation was also measured on the thigh of healthy subjects after remote ischemic conditioning in 2 studies.<sup>28,29</sup> Furthermore, ischemic preconditioning by preclamping of the vascular pedicle improved survival area of the transverse rectus abdominis musculocutaneous flap to the same extent as surgical delay in a rat model.<sup>30</sup> The mechanism behind improved cutaneous microcirculation likely involves vasodilation potentially mediated by nitric oxide.<sup>26</sup> Hence, these previous human and animal studies indicate that remote and local ischemic conditioning may reduce the risk of partial flap necrosis. In the present study, no patients developed partial flap necrosis, which could be explained by the small size of flaps used for head and neck reconstruction not including several vascular territories. Furthermore, the rate of flap site dehiscence, which can be caused by restricted peripheral flap blood supply, did not differ between groups. Hence, the data of the present study do not show reduced risk of partial flap necrosis by RPC.

RPC reduced thrombus formation and downstream embolization in a rat model of an arterial microvascular anastomosis with intraluminal exposure of full vessel thickness.<sup>15</sup> In addition, previous randomized controlled trials with patients undergoing invasive heart procedures showed reduced platelet activity after RPC.<sup>31,32</sup> Also, remote ischemic conditioning when administered daily as a long-term intervention increased fibrinolysis in 2 studies including patients with cerebrovascular or chronic ischemic heart failure, respectively.<sup>33,34</sup> As reported in our previous article, we hypothesized attenuated platelet aggregation and increased fibrinolysis after RPC, thus creating a favorable coagulation profile with reduced risk of flap vascular pedicle thrombosis.<sup>17</sup> However, RPC did not affect platelet aggregation and fibrinolysis in head and neck cancer patients undergoing microsurgical reconstruction, corresponding to the clinical data in the present study showing no protection from RPC against vascular pedicle thrombosis. However, it should be noted that

factors other than hypercoagulation contribute to pedicle thrombosis such as hematomas and vessel kink.<sup>35</sup>

The strength of the present study is the randomized controlled trial design with prospective data collection. All patients received the allocated study intervention, and we monitored safety and efficacy of tourniquet occlusion in the RPC group with transparent surgical drapes (Fig. 1). We administered the study intervention immediately before free flap transfer, because tissue protection from RPC occurred in a 2-phased response lasting from 0 to 4 hours and 24 to 72 hours after the intervention in an experimental study of muscle flaps.<sup>36</sup> The advantages of RPC over local ischemic preconditioning, the latter performed by preclamping of the vascular pedicle, is that RPC does not prolong surgery time, and there is no risk of damage to the vascular pedicle.

The main limitation of the present study is the small sample size making the trial underpowered for detecting statistically significant differences in clinical outcomes. Furthermore, the study population of head and neck cancer patients is heterogenous in terms of age, sex, and comorbidities. However, we chose this population because it experiences a high rate of postoperative complications, and hence, there is potential for improvement. The optimal RPC protocol is unresolved: 10-minute ischemic periods were superior to 5-minute periods in increasing cutaneous blood flow and oxygen saturation at the thigh of healthy subjects.<sup>37</sup> Furthermore, 10-minute extremity ischemia–reperfusion cycles were used in experimental studies with attenuation of flap ischemia–reperfusion injury.<sup>10,13,18</sup> However, we administered four 5-minute periods of upper extremity ischemia and 5-minute reperfusion in the present study, because 5-minute extremity ischemia and reperfusion periods were used in the majority of clinical trials on surgery and cardiac procedures and in the human flap study by Kolbenschlager et al.<sup>14,21–23,38</sup> Finally, we did not include direct measures of flap ischemia–reperfusion injury with, eg, microdialysis or histologic examination,<sup>39</sup> for which reason we might miss a protective effect by RPC that did not translate into reduced clinical complications.

Future randomized controlled trials should investigate the effects of RPC on partial flap necrosis in microsurgical breast reconstruction with abdominal perforator flaps including more than 1 vascular territory. Furthermore, remote ischemic preconditioning should be investigated as a tissue-protective intervention in replantation of amputated body parts exposed to prolonged ischemia, and an adjunct to reexploration of the vascular pedicle in free flap pedicle thrombosis.

## CONCLUSIONS

RPC is safe and feasible in patients undergoing microsurgical reconstruction, but our data failed to demonstrate improved clinical outcomes in patients randomized to RPC compared with sham intervention. Given that RPC is a safe and low-cost intervention, even small improvements in outcomes should be considered important, which warrants further studies.

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