

Bigdeli Amir (Orcid ID: 0000-0001-8852-5132)

Kotsougiani Dimitra (Orcid ID: 0000-0003-2685-1105)

a) Title

„Evaluation of perfusion by near-infrared fluorescence imaging in late pedicle obstruction of a parascapular flap to the lower extremity: A case report“

b) Authors

Felix F. Strübing¹; Amir K. Bigdeli, MD¹; Volker J. Schmidt, MD¹; Spyridoula Maraka, MD²; Ulrich Kneser, MD¹; Dimitra Kotsougiani, MD¹

c) Affiliations

¹Department of Hand-, Plastic- and Reconstructive Surgery, -Burn Center-, BG Trauma Center Ludwigshafen, Hand and Plastic Surgery, University of Heidelberg, Germany

²Division of Endocrinology and Metabolism, Center for Osteoporosis and Metabolic Bone Diseases, University of Arkansas for Medical Sciences and the Central Arkansas Veterans Health Care System, Little Rock, Arkansas, United States

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as doi: [10.1002/micr.30366](https://doi.org/10.1002/micr.30366)

d) Funding/Grants

No funding was received.

e) Correspondence to:

Dimitra Kotsougiani, MD

Department of Hand, Plastic, and Reconstructive Surgery,

BG Trauma Center Ludwigshafen, Hand and Plastic Surgery, University of
Heidelberg, Germany

Ludwig Guttmann Str. 13 67071 Ludwigshafen, Germany

Phone: +49 621-6810-8924

Fax: +49 621-6810-211

E-Mail: dkotsougiani@googlemail.com

f) Running head:

„Near-infrared fluorescence imaging in late free flap pedicle obstruction“

g) Level of evidence:

Case report

h) Ethical approval statement:

This is a report of a clinical case with all investigations and treatment carried out to a high ethical standard. The case report includes routine, retrospective and anonymized patient's data, procedural parameters and outcomes and thus is in accordance with the Declaration of Helsinki without need for further ethical consultation.

Abstract

Late free flap failures due to pedicle obstruction are rare adverse events. **The purpose of this report is to present a case in which the near-infrared indocyanine green video angiography (ICG-NIR-VA) was used to evaluate the perfusion in a compromised fasciocutaneous flap in the late postoperative period.** A 55-year-old male patient, who initially suffered from an open tibial fracture, developed concurrent osteomyelitis with fistulae of the proximal tibia requiring excision. Reconstruction was achieved using a parascapular flap of 25x8cm, anastomosed to an arterio-venous (AV) Loop in the adductor canal. On the 2nd postoperative day the patient developed a thrombosis of the AV-Loop. After thrombectomy, the postoperative course was uneventful. Seven weeks postoperatively the patient presented with a mottled, partially bluish and cold flap. Anticoagulation prophylaxis was stopped two days earlier. Angiography confirmed a thrombus in the arterial pedicle leading to flap ischemia. Near infrared guided fluorescence imaging revealed a delayed recapillarization of the proximal part of the flap closest to the vascular pedicle, albeit flap overall perfusion remained intact. Thus, no surgical intervention was undertaken. However, anticoagulation and prostaglandin therapy was initiated and the flap was salvaged. Genetic analysis uncovered a polymorphism in the prothrombin genes. The flap remained viable and without further complications until the last follow-up visit at 36 weeks after microsurgical reconstruction. **The patient was fully mobilized with complete return to function.** Near-infrared guided fluorescence imaging may be a viable tool for the assessment of late fasciocutaneous free flap complications and

guide the decision-making process.

Introduction

Free tissue transfer has become a routine procedure for reconstruction of complex lower extremity soft-tissue defects with failure rates below 5%¹. It is believed that fasciocutaneous flap autonomization of the vascular pedicle is completed approximately four weeks after surgery and that secondary refinement procedures can be performed safely in the third month postoperatively².

Late free flap failure, occurring after the 7th postoperative day, is a rare event. Only about 1-2% of free flap compromises occur in the late postoperative period^{3,4}. Many reasons have been reported, including thrombosis, infection and compression of the pedicle⁴.

Frequently, the patients have been discharged before the onset of the first symptoms of late pedicle obstruction, impeding diagnostic measures. Furthermore, free flap salvage might be technically challenging in the late postoperative period, in particular in patients presenting belatedly. Therefore, some centers advise the patients to stay close to the area of the hospital for a certain period of time after microvascular free flap reconstruction⁵. Conventional methods of diagnosing late free flap failure include clinical examination, computed tomographic angiography, conventional angiography and Doppler sonography^{6,7}. Lately near-infrared indocyanine green video angiography (ICG-NIR-VA) has been used to evaluate free-flap perfusion⁸. Intraoperatively it may detect arterial spasms, venous congestion or regional hypoperfusion of free flaps⁸.

The purpose of this report is to present a case in which the near-infrared indocyanine green video angiography (ICG-NIR-VA) was used to evaluate the perfusion in a compromised fasciocutaneous flap in the late postoperative period.

Case Report

A 55-year-old male patient with a history of smoking fell from a ladder and sustained a tibia fracture 15 years ago. Concurrent wound infections and chronic tibial osteomyelitis resulted in a tissue defect in the area of the knee and proximal third of the right tibia (Figure 1A). Microbiological analysis of bone samples showed *Staphylococcus aureus* susceptible to, among others, flucloxacillin. Therefore, the patient was put on flucloxacillin therapy for six weeks after radical debridement and insertion of Gentamicin-PMMA-chains. To achieve wound coverage, a free fasciocutaneous parascapular (PSC) flap of 25x8cm was microsurgically transplanted (Figure 1C). Arterial and venous anastomoses were performed end-to-end to an arterio-venous (AV) loop (Figure 1B). For creation of the AV-loop, the great saphenous vein of the contralateral leg was harvested and anastomosed to the superficial femoral artery and the accompanying vein in the adductor canal. A bolus dose of 3000 units of unfractionated heparin was administered intraoperatively for thrombosis prophylaxis. Since Rotational Thromboelastometry (ROTEM) analysis was normal, low-molecular-weight heparin (LMWH) was used for postoperative deep vein thrombosis prophylaxis.

On the first postoperative day, the flap exhibited clinical signs of arterial insufficiency. Immediate reoperation verified a ten-centimeter-long thrombus within the arterial part of the AV-loop, requiring subsequent thrombectomy. No technical problems, such as kinking of the pedicle, leakage or compression of the arterial anastomosis were evident. The salvage procedure was successful and the further postoperative course

was uneventful. Anticoagulation was consecutively continued using continuous intravenous unfractionated heparin infusions, aiming for a partial thromboplastin time (PTT) of 40-45 seconds. Five days after revision, prophylactic anticoagulation was continued with LMWH (0.4ml once daily). The patient was discharged from the hospital on the 15th postoperative day.

On the 49th postoperative day, the patient noted that the flap had become partially bluish and cold. In the next morning, the patient presented at our outpatient clinic. No trauma was reported and the patient was in a healthy and good condition. The patient was wearing his custom-made compression garments for the lower extremity. According to the patient, LMWH prophylaxis was stopped two days earlier, corresponding to the sixth postoperative week. The clinical examination showed a partially bluish, cold, mottled flap in the proximal part of the parascapular flap, corresponding to the area of the medial knee, and raising the suspicion of a vascular flap pedicle thrombosis (Figure 2A). Computed tomographic angiography confirmed the suspected diagnosis, revealing a large thrombus with almost complete occlusion of the arterial side of the AV-Loop starting three centimeters beyond the origin of the saphenous vein graft from the arteria femoralis superficialis. To assess the flap perfusion an ICG-NIR-VA system (Fluobeam 800, Fluoptics, France) was used that features a unique fusion image with the ability to overlay infrared images onto white light images with a colour-coded perfusion scale⁹. This allows the surgeon to analyze free flap perfusion on real-time and to assess hypoperfused flap areas⁹. Therefore, an area with known good perfusion, such as the untouched skin around the flap, was

compared to the fluorescence signal strength of the flap. A relative fluorescence intensity of less than 33% was correlated to poor flap perfusion¹⁰. Interestingly, all flap zones were sufficiently perfused, whereby the zone with the closest proximity to the flap pedicle -in the area of the medial knee- showed a delayed, albeit sufficient perfusion (Figure 3A). In consideration of the ICG-NIR-VA result we decided against surgical revision. Instead the patient was admitted to our hospital and put on therapeutic anticoagulation therapy for seven days with LMWH (0.6ml twice daily). In addition, Prostaglandin E1 (PGE1) was administered intravenously twice daily in a dose of 40ug. To determine the reason of the recurring thrombotic events laboratory tests and genetic analysis for coagulopathies were performed. Elevated levels of factor VII, fibrinogen and anti-phospholipid antibodies were found. Furthermore, it was revealed that the patient suffers from polymorphisms in the genes coding for prothrombin (Prothrombin G20210A wild type, Prothrombin A19911G heterozygous, Factor V A6755G heterozygous). **The patient was discharged in the 9th week after microsurgical reconstruction, when the bluish color had disappeared with only remaining signs of epitheliolysis (Figure 2B).**

Despite abrupt occlusion of the arterial axis of the AV loop, one month later, corresponding to eleven weeks after the microsurgical procedure, the entire flap was successfully integrated to the recipient site and showed an adequate perfusion pattern. The follow-up ICG-NIR-VA at this time point verified a homogenous perfusion of the complete parascapular flap (Figure 2C and 3B). In the latest follow-up visit in the 36th week after the transplantation the PSC flap perfusion was intact.

The patient was fully mobilized without the need for crutches and showed complete return to function. The patient had come back to his previous occupation as a forklift operator and was satisfied with the reconstructive outcome.

Discussion

Late free flap ischemia, occurring later than one week after the microsurgical reconstructive procedure, is a rare event⁴. Reported causes are thrombosis of the anastomotic site, compression or injury of the pedicle, infection and locoregional tumor recurrence.

The critical interval for free flap autonomization of the vascular pedicle differs between fasciocutaneous and muscle flaps. Experimental research in rats has shown a reliable fasciocutaneous autonomization as early as five to ten days following reconstruction, whereby muscle flaps autonomy is reliable at twenty-one days^{11,12}. Accordingly, Yoon and Jones demonstrated in a systemic analysis an earlier flap survival of fasciocutaneous flaps when compared to muscle flaps after free flap pedicle obstruction¹³. However, four weeks following surgery, autonomization of fasciocutaneous free flaps seems to be completed due to neovascularization and angiogenesis allowing secondary refinement procedures¹³. In our case, on the contrary, ischemia of the parascapular flap was seen at over seven weeks post-surgery. In particular, the flap area around the knee with the closest proximity to the vascular pedicle, exhibited clinical signs of hypoperfusion. A possible explanation might represent the ischemic gradient model, which describes an enhanced neovascularization in the area furthest from the pedicle¹⁴. Another hypothesis is that the traumatic and infectious background of recipient site might impair the process of neoangiogenesis, since the quality of the wound bed and flap randomization are associated³.

Salvage procedures of free flaps with a comprised perfusion pattern remain a great challenge with success rates ranging from 30% to 60%¹⁵. The main therapeutic alternatives are take-back surgery with thrombectomy and conventional thrombolytic measures or minimal-invasive thrombolysis. In the latter, catheter-directed endovascular urokinase infusion is used to dissolve the thrombus¹⁶. In addition, flap salvage might be achieved by conservative treatment as in our case¹³. Since the patient presented in our outpatient clinic almost twelve hours after the first signs of flap ischemia, flap recovery from this situation is usually unlikely¹⁷. However, catheter directed thrombolysis using urokinase has shown to be successful in the late salvage of head and neck, breast and extremity reconstruction and may have been considered as an therapeutic option in our case, if we would have not been satisfied with the ICG-NIR-VA result^{16,18}. Instead, we used a combination therapy, consisting of LMWH and PGE1 for flap salvage. Prostaglandin E has multiple effects on microcirculation with relevant antiischemic, fibrinolytic and antiinflammatory properties. Experimental work in rats has demonstrated the value of PGE1 for improvement of microcirculation in random pattern flaps¹⁹. Furthermore, Hong et. al analyzed the effect of PGE1 on ischemia-reperfusion injury in musculocutaneous flaps in rats. Histological and immunohistochemical studies showed PGE1 to reduce leukocyte adhesion and to decrease expression of ICAM-1 on the surface of the endothelium after reperfusion, demonstrating a tissue protective effect of PGE1²⁰. Furthermore, in a clinical study Rodriguez Vegas et al. presented their antithrombotic pharmacologic treatment in free flap surgery which includes the intra- and

postoperative administration of PGE₁²¹. Faced with two consecutive thrombotic events in the postoperative course, we performed extensive laboratory and genetic analysis to reveal a coagulopathy disorder. The laboratory tests performed are similar to that of other institutions²². However, early coagulation diagnostics may have prevented the second thrombotic event and should be therefore reconsidered after early AV-loop thrombosis. Long-term anticoagulation therapy could be in these cases indicated. Since late pedicle obstruction can lead to free flap ischemia even months after surgery, patients should be informed about the clinical signs of late free flap ischemia during the discharge interview and counselled to present immediately in the case of such symptoms.

As early as 2002, Holm and colleagues published a prospective, clinical study of the use of near-infrared fluorescence imaging for intraoperative free flap evaluation⁸. They were able to detect arterial spasms, venous congestion or regional flap hypoperfusion. Recently, indocyanine green-based angiography has been introduced for skin-flap perfusion evaluation after mastectomy²³. Furthermore, Mücke et al. presented the additional value of indocyanine green assisted videography in the early postoperative monitoring of transplanted epigastric flaps in an experimental study with rats with a positive predictive value of flap necrosis of 97%²⁴. However, infusion of indocyanine green dye is not without risks and has some limitations. Possible adverse side effects are rare, but include headache, urticaria, hypotension and cardiac arrest²⁵. Since many indocyanine green dyes contain sodium iodide, preoperative screening for hyperthyroidism is advised.

ICG-NIR-VA may represent a viable tool to guide the decision-making process in late fasciocutaneous free flap complications and needs further investigation to prove its reliability.

Figures

Figure 1: Pre- and intraoperative aspect of the lower extremity defect, AV-Loop and parascapular (PSC) flap: **A** Preoperative aspect of the wound on the proximal lower right leg, Gentamicin-PMMA-chains **were** clearly visible in the opened tibia shaft; **B** Intraoperative aspect of the AV-Loop in the adductor canal, the loop **was** well perfused; **C** The parascapular flap immediately after transfer and inlay of multiple drains

Figure 2: Clinical aspect of the parascapular (PSC) flap on the right lower leg of the patient: **A** On hospital admission in the 7th week postoperative after PSC flap reconstruction, the flap was bluish and mottled in the proximal part; **B** On the day of hospital discharge (9th week postoperative) the bluish color had disappeared with remaining signs of epitheliolysis; **C** In the follow up examination 11 weeks after the reconstructive procedure, the soft tissue had recovered completely and all zones of the flap were viable.

Figure 3: Near-infrared imaging of the parascapular (PSC) flap immediately following indocyanin green injection: **A** On the day of hospital admission, 7 weeks after the reconstructive procedure the proximal part of the PSC flap showed signs of hypoperfusion (white arrow); **B** In the follow up examination 4 weeks after the

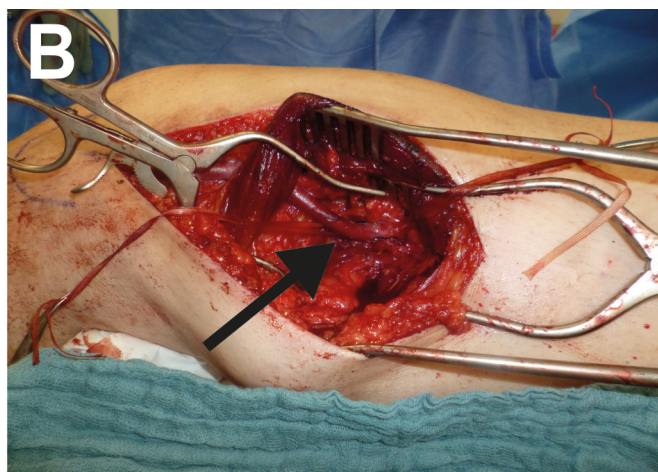
intervention (11 weeks after the microsurgical procedure) the flap was well perfused in all zones.

References

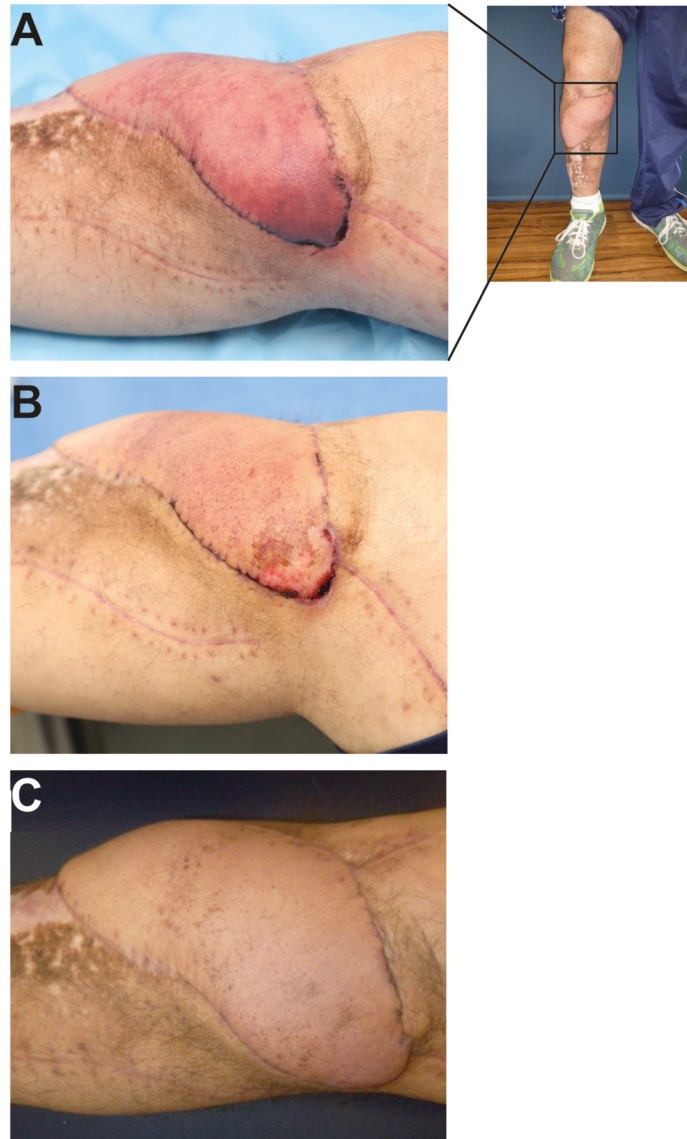
1. Xiong L, Gazyakan E, Kremer T, et al. Free flaps for reconstruction of soft tissue defects in lower extremity: A meta-analysis on microsurgical outcome and safety. *Microsurgery*. 2016;36(6):511-524. doi:10.1002/micr.30020.
2. Kotsougiani D, Platte J, Bigdeli AK, et al. Evaluation of 389 patients following free-flap lower extremity reconstruction with respect to secondary refinement procedures. *Microsurgery*. 2017;79(Suppl 3):371. doi:10.1002/micr.30219.
3. Salgado CJ, Smith A, Kim S, et al. Effects of late loss of arterial inflow on free flap survival. *J Reconstr Microsurg*. 2002;18(7):579-584. doi:10.1055/s-2002-35095.
4. Wax MK, Rosenthal E. Etiology of late free flap failures occurring after hospital discharge. *Laryngoscope*. 2007;117(11):1961-1963. doi:10.1097/MLG.0b013e31812e017a.
5. Largo RD, Selber JC, Garvey PB, et al. Outcome Analysis of Free Flap Salvage in Outpatients Presenting with Microvascular Compromise. *Plastic and Reconstructive Surgery*. 2018;141(1):20e–27e. doi:10.1097/PRS.0000000000003917.
6. Granzow J, Li AI, Caton A, Boyd JB. Free Flap Survival Following Failure of the Vascular Pedicle. *Ann Plast Surg*. 2015;75(1):44-48. doi:10.1097/SAP.0000000000000136.
7. Salgado CJ, Moran SL, Mardini S. Flap monitoring and patient management. *Plastic and Reconstructive Surgery*. 2009;124(6 Suppl):e295-e302. doi:10.1097/PRS.0b013e3181bcf07b.
8. Holm C, Tegeler J, Mayr M, Becker A, Pfeiffer UJ, Mühlbauer W. Monitoring free flaps using laser-induced fluorescence of indocyanine green: a preliminary experience. *Microsurgery*. 2002;22(7):278-287. doi:10.1002/micr.10052.
9. Bigdeli AK, Gazyakan E, Schmidt VJ, et al. Indocyanine Green Fluorescence for Free-Flap Perfusion Imaging Revisited: Advanced Decision Making by Virtual Perfusion Reality in Visionsense Fusion Imaging Angiography. *Surg Innov*. 2015;23(3):249-260. doi:10.1177/1553350615610651.
10. Moyer HR, Losken A. Predicting Mastectomy Skin Flap Necrosis with Indocyanine Green Angiography: The Gray Area Defined. *Plastic and Reconstructive Surgery*. 2012;129(5):1043-1048. doi:10.1097/PRS.0b013e31824a2b02.

11. Mücke T, Borgmann A, Wagenpfeil S, et al. Autonomization of epigastric flaps in rats. *Microsurgery*. 2011;31(6):472-478. doi:10.1002/micr.20892.
12. Bradshaw K, Wagels M. Perfusion of muscle flaps independent of the anatomical vascular pedicle: Pedicle autonomy. *J Plast Reconstr Aesthet Surg*. 2017;70(11):1547-1555. doi:10.1016/j.bjps.2017.05.049.
13. Yoon AP, Jones NF. Critical Time for Neovascularization/Angiogenesis to Allow Free Flap Survival After Anastomotic Thrombosis without Surgical Intervention. *Plastic and Reconstructive Surgery*. 2015;136(4 Suppl):19. doi:10.1097/01.prs.0000472296.47202.d8.
14. Murohara T. Angiogenesis and vasculogenesis for therapeutic neovascularization. *Nagoya J Med Sci*. 2003;66(1-2):1-7.
15. Bui DT, Cordeiro PG, Hu Q-Y, Disa JJ, Pusic A, Mehrara BJ. Free Flap Reexploration: Indications, Treatment, and Outcomes in 1193 Free Flaps. *Plastic and Reconstructive Surgery*. 2007;119(7):2092-2100. doi:10.1097/01.prs.0000260598.24376.e1.
16. Trussler AP, Watson JP, Crisera CA. Late free-flap salvage with catheter-directed thrombolysis. *Microsurgery*. 2008;28(4):217-222. doi:10.1002/micr.20480.
17. Hanasono MM, Butler CE. Prevention and Treatment of Thrombosis in Microvascular Surgery. *J Reconstr Microsurg*. 2008;24(05):305-314. doi:10.1055/s-2008-1080530.
18. Parry D, Byrne P, Scott DJA, et al. Pharmacological salvage of a combined distal bypass and free flap with catheter-directed thrombolysis. *British Journal of Plastic Surgery*. 2002;55(2):140-144. doi:10.1054/bjps.2002.3744.
19. Tønseth KA, Sneistrup C, Berg TM. Prostaglandin E1 Increases Microcirculation in Random Pattern Flaps on Rats Measured with Laser Doppler Perfusion Imaging. *Plast Reconstr Surg Glob Open*. 2017;5(1):e1202. doi:10.1097/GOX.0000000000001202.
20. Hong JP, Chung YK, Chung S-H. The Effect of Prostaglandin E1 Versus Ischemia-Reperfusion Injury of Musculocutaneous Flaps. *Ann Plast Surg*. 2001;47(3):316.
21. Vegas JMR, Alonso MER, Saavedra PPT. PGE-1 in replantation and free tissue transfer: Early preliminary experience. *Microsurgery*. 2007;27(5):395-397. doi:10.1002/micr.20377.

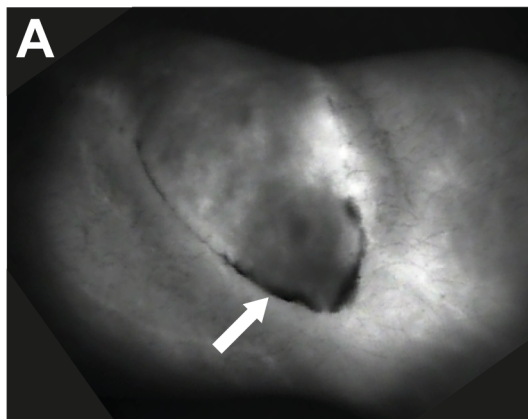
22. Herrera FA, Lee CK, Kryger G, et al. Microsurgery in the Hypercoagulable Patient: Review of the Literature. *J Reconstr Microsurg.* 2012;28(05):305-312. doi:10.1055/s-0032-1311687.
23. Griffiths M, Chae MP, Rozen WM. Indocyanine green-based fluorescent angiography in breast reconstruction. *Gland Surg.* 2016;5(2):133-149. doi:10.3978/j.issn.2227-684X.2016.02.01.
24. Mücke T, Fichter AM, Schmidt LH, Mitchell DA, Wolff K-D, Ritschl LM. Indocyanine green videoangiography-assisted prediction of flap necrosis in the rat epigastric flap using the flow @800 tool. *Microsurgery.* 2016;37(3):235-242. doi:10.1002/micr.30072.
25. Benya R, Quintana J, Brundage B. Adverse reactions to indocyanine green: a case report and a review of the literature. *Cathet Cardiovasc Diagn.* 1989;17(4):231-233.



micr-18-0042-File002.tif



micr-18-0042-File003.tif



micr-18-0042-File004.tif