

The Role of von Willebrand Factor in Microvascular Surgery in Severely Injured Patients

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Summary: Microvascular anastomosis has become a standard surgical technique for reconstruction because of increasing possibilities, indications, and clinical success regarding the survival of the flaps. However, the main dreaded complications exist in thrombosis. Leaving surgical complications aside, systemic problems like disorder of the coagulation-fibrinolysis system are a significant cause of graft loss usually being unrecognized. Reports exist describing a hypercoagulable state with clotting activation and inhibition of fibrinolysis after trauma and delayed surgery considering the secondary homeostasis. In this clinical case, a patient had a large soft tissue defect at the temporal side of the head after severe trauma. After some days of primary stabilization, reconstruction using a free microvascular latissimus dorsi flap was performed. Multiple revisions of the arterial and venous branches had to be performed intraoperatively due to insufficient flap perfusion. After 24 hours, definitive flap loss occurred due to multiple thrombosis in the arterial and venous branches. Postoperative comprehensive coagulation analysis revealed a distinct activation of primary hemostasis with massively increased von Willebrand factor parameters and factor VIII activity as well as acetylsalicylic acid resistance contributing to thrombotic occlusion. In severely injured patients, comprehensive preoperative determination of the coagulation status (especially those of the primary hemostasis) is indispensable before performing free flap reconstruction surgeries to reduce the risk of microvascular flap loss. (*Plast Reconstr Surg Glob Open* 2021;9:e3836; doi: 10.1097/GOX.0000000000003836; Published online 4 October 2021.)

Soft tissue reconstruction of the scalp and forehead are done in different ways. Smaller defects are reconstructed using split skin grafts or local flaps, whereas larger defects often need to be reconstructed using free flaps. Technical advances, increased experience, and robust training programs have improved success rates of free flap reconstructions up to 97%.¹ Nevertheless, flap loss due to thrombosis remains one of the most dreaded complications. Several studies identified markers of the

secondary hemostasis being responsible for a hypercoagulable state, and for thrombosis, only a few have investigated primary hemostasis.²

Severely injured patients seldom suffer from SIRS (systemic inflammatory response system), a state that can result in multiple organ failure. Main patterns of SIRS are endothelial cell damage, accumulation of leukocytes, disseminated intravascular coagulation, and microcirculatory disturbances.³

In the current case, an extreme increase of von Willebrand factor parameters as well as factor VIII-activity was identified as reason for unexpected flap loss in a severely injured patient. This is an important finding for the optimization of future anticoagulation protocols.

CASE REPORT

A 75-year-old severely injured man with no known clotting disorders presented a large temporal defect after an accident. Surgical debridement was performed to remove the soiled soft tissue areas. In the further course, wound dressing and cleaning was performed daily (Fig. 1).

On day 17 after trauma, soft tissue reconstruction using a microvascular latissimus dorsi flap was done.

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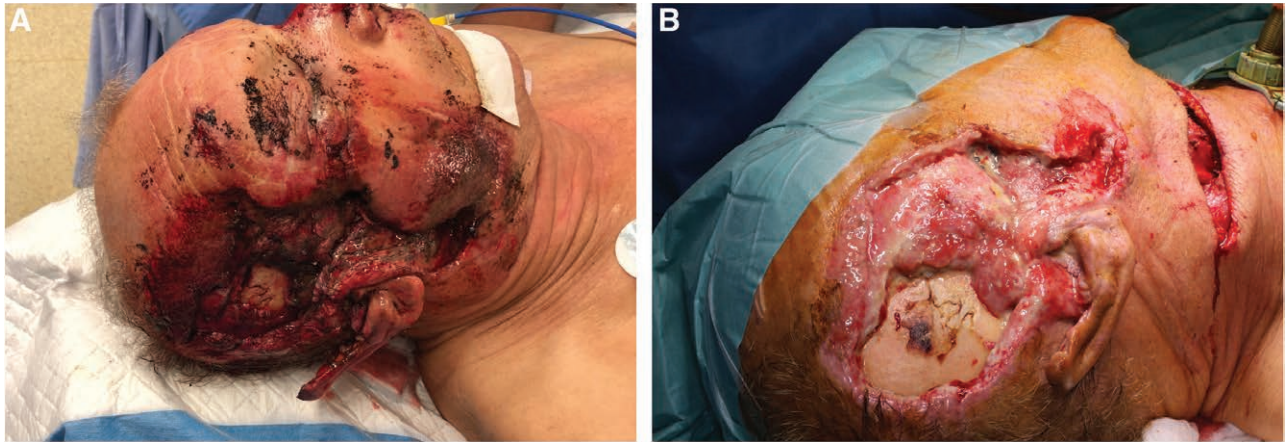


Fig. 1. Clinical images showing the right side face of the patient: (A) directly after trauma; (B) directly before operation on day 17 after trauma.

Vascular anastomoses were done in the neck to the thyroid superior artery and the external jugular vein outside the zone of injury with no surrounding inflammation. Intraoperatively, 300 mg of acetylsalicylic acid (ASA) and a bolus of 1.600IE (20IE/kg) unfractionated heparin (UFH) were injected. A continuous infusion with 500IE/h UFH was started.

After microvascular anastomosis and fixation of a Cook–Swartz probe, the signal disappeared suddenly, during further surgical steps. We reopened the anastomosis and observed multiple thromboses in the arterial vessel.

Despite heparin therapy, reduced bleeding was striking during the entire procedure. Interdisciplinary consensus was to add another 2.500IE UFH bolus. This resulted in an improvement of the blood flow noticeable by the feedback of the Cook–Swartz probe. After surgery, the patient was transferred to the intensive care unit anticoagulated with a continuous infusion of 500IE/h UFH. However, during the night after surgery, signs of microvascular disturbance reoccurred. A second-look operation showed total loss of the transplant due to multiple thromboses in the arterial and venous branches (Figs. 2, 3).

After flap loss, a coagulation analysis was performed (Table 1). It turned out that antithrombin-3 (AT-3) activity (89%) was surprisingly within the normal range (79%–120%). The factors protein C and S with 63% and 45% were slightly decreased, a typical finding in the critically ill patients. In vitro bleeding time was normal despite ASA therapy. Platelet function analysis showed a regular closing time of 96 seconds when stimulated with collagen/epinephrine concomitant with a slightly reduced closing time when stimulated with collagen/adenosine diphosphate. These findings indicate an insufficient effect of ASA. Interestingly, we furthermore found a significant increase in von Willebrand factor activity (vWF:A: 350%, normal range 48%–173%), von Willebrand factor antigen (vWF:Ag: 286%, normal range 50%–170%) as well as factor VIII (fVIII: 337%, normal range 81%–215%). As these findings may occur during COVID-19, fortunately PCR-testing for SARS-CoV2 turned out negative.

Definitive secondary reconstruction was done successfully at an external hospital close to home 3 months after rehabilitation using a radial forearm flap in a noninflammatory condition.

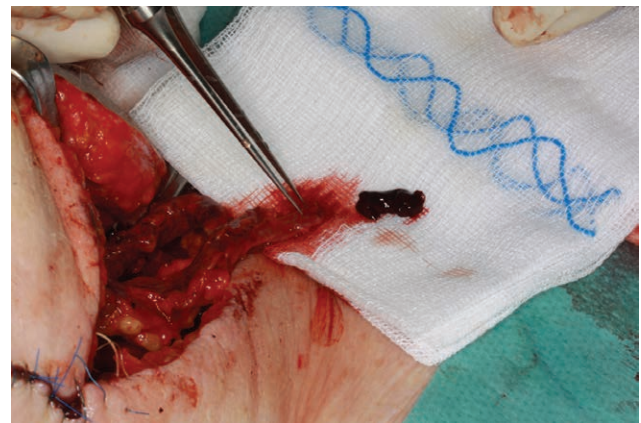


Fig. 2. Image of the latissimus dorsi flap during explantation with visible thrombus.

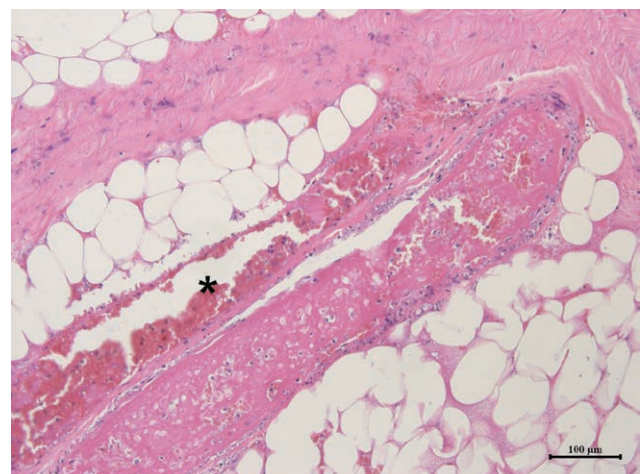


Fig. 3. Histological image of a thrombus within a blood vessel of the removed flap (HE staining; “*” indicates the thrombosis).

Table 1. Overview of the Clotting Parameters Collected after Surgery

Parameter Examined	Normal Range	Value
Antithrombin-3 activity (AT-3)	79%–120%	89%
Bleeding time	Normal	Normal
Factor VIII (clotting)	81%–215%	337%
Platelet function analysis (collagen/adenosine diphosphate)	68–121s	64s
Platelet function analysis (collagen/epinephrin)	84–160s	96s
Protein C (clotting)	70%–130%	63%
Protein S (clotting)	68%–138%	45%
Ratio vWF:A/vWF:Ag	0.73–1.16	1.22
Von Willebrand factor activity (vWF:A)	48%–173%	350%
Von Willebrand factor antigen (vWF:Ag)	50%–170%	286%

DISCUSSION

The hyperactivation of the primary hemostasis with increased von Willebrand factor activity and von Willebrand factor antigen in combination with an increased factor VIII activity combined with excessive complement activation is a possible explanation for the early thrombosis and loss of the latissimus dorsi flap. The findings hint at massive endothelial damage as all these factors are synthesized and stored in endothelial cells. This release into the blood was most likely driven by severe inflammation and loss of membrane integrity caused by the initial trauma. The operation alone and potential vessel injury during vascular anastomosis would not have caused such high values. Increased factor VIII activity levels have furthermore contributed to thrombin activation and consecutive thrombin burst.

Retrospectively seen, the intraoperative treatment with UFH, which was balanced between risk of thrombosis and hemorrhage, was not exhausted. It would have been desirable to measure anti-Xa-activity instead of aPTT.⁴ Alternatively, a perioperative management with low-molecular-weight heparins would probably have been superior compared with UFH, as more reliable anti-Xa-activity is provided by low-molecular-weight heparins.

ASA resistance of platelets is not uncommon, and intraoperative aggregometry probably would have helped better guide platelet inhibiting therapy. Theoretically, short-acting GP-IIb/IIIa-antagonists like eptifibatid would also have been an option.⁵

Only a few studies identifying high levels of von Willebrand factor activity and von Willebrand factor antigen have been published before. Handschel et al could identify significantly higher levels in patients with venous thrombosis.⁶ Du et al observed higher levels after vein ligation in a rabbit model.⁷

To overcome the issue of flap thrombosis, different anticoagulation regimes have been described. They all have in common that mainly ASA (as inhibitor for the primary hemostasis) and substances affecting the secondary hemostasis are administered. Zhou et al, for example, concluded with such a regime that postoperative antithrombotic agents neither provide a significant improvement in the free flap success rate nor decrease the risk of thrombosis.⁸ Khouri et al, who investigated different concentrations of tissue factor pathway inhibitor or heparin, could

also see no differences for intraoperative revision of anastomosis, postoperative thrombosis, or flap failure.⁹ Swartz et al saw, in his retrospective study and analysis including 759 patients, no improvement of free radial forearm flap survival or lower complication rate by anticoagulation drugs.¹⁰

Taken together, this description of flap failure represents a report hinting at an important role of von Willebrand factor regarding flap loss in microvascular surgery. We recommend a detailed preoperative investigation of the coagulation status, including parameters of the primary hemostasis before flap surgery in special cases such as severely injured patients. Anticoagulation regimes should be adapted with interdisciplinary assistance by experts.

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PATIENT CONSENT

The patient provided written consent for the use of his image.

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No ethical approval was needed for this study. The article does not contain any study with human participants performed by any of the authors. The treatment of the patient was not in any way influenced due to this article.

REFERENCES

1. Markey J, Knott PD, Fritz MA, et al. Recent advances in head and neck free tissue transfer. *Curr Opin Otolaryngol Head Neck Surg*. 2015;23:297–301.
2. Pannucci CJ, Kovach SJ, Cuker A. Microsurgery and the hypercoagulable state: a hematologist's perspective. *Plast Reconstr Surg*. 2015;136:545e–552e.
3. Keel M, Trentz O. Pathophysiology of polytrauma. *Injury*. 2005;36:691–709.
4. Vandiver JW, Vondracek TG. Antifactor Xa levels versus activated partial thromboplastin time for monitoring unfractionated heparin. *Pharmacotherapy*. 2012;32:546–558.
5. Cho EH, Ligh C, Hodulik KL, et al. Role of platelet inhibition in microvascular surgery. *J Reconstr Microsurg*. 2014;30:589–598.
6. Handschel J, Burghardt S, Naujoks C, et al. Parameters predicting complications in flap surgery. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2013;115:589–594.
7. Du W, Wu PF, Qing LM, et al. Systemic and flap inflammatory response associates with thrombosis in flap venous crisis. *Inflammation*. 2015;38:298–304.
8. Zhou W, Zhang WB, Yu Y, et al. Are antithrombotic agents necessary for head and neck microvascular surgery? *Int J Oral Maxillofac Surg*. 2019;48:869–874.
9. Khouri RK, Sherman R, Buncke HJ Jr, et al. A phase II trial of intraluminal irrigation with recombinant human tissue factor pathway inhibitor to prevent thrombosis in free flap surgery. *Plast Reconstr Surg*. 2001;107:408–15; discussion 416.
10. Swartz JE, Aarts MC, Swart KM, et al. The value of postoperative anticoagulants to improve flap survival in the free radial forearm flap: a systematic review and retrospective multicentre analysis. *Clin Otolaryngol*. 2015;40:600–609.