Ulcer Healing After Peripheral Intervention

– Can We Predict It Before Revascularization? –

Nobuyoshi Azuma, MD, PhD; Atsuhiko Koya, MD; Daiki Uchida, MD;
Yukihiro Saito, MD, PhD; Hisashi Uchida, MD, PhD

Complete ulcer healing is one of the most important goals of treatment for critical limb ischemia; however, it is still difficult to inform patients of the time to ulcer healing before performing revascularization. The time to ulcer healing has a great impact on the cost of treatment and patient's quality of life. To predict it, the factors that influence delayed ulcer healing should be explored. According to a review of the literature investigating ulcer healing after revascularization, the influential factors can be classified into 5 categories: (1) systemic factors; (2) clinical state of tissue defect; (3) infection; (4) wound management strategy; and (5) revascularization strategy (endovascular or open repair, the angiosome concept). It is also important to ensure sufficient blood supply to predict ulcer healing probability in the individual patient. Several new methodologies, such as measuring tissue circulation around the tissue defect and intraoperative imaging techniques, have been reported. Because the status of ischemic tissue loss and wound healing ability can affect the decision-making process in selecting the revascularization strategy, understanding the many factors that influence ulcer healing after revascularization is indispensable for physicians performing revascularization. Accumulating ulcer healing data via well-designed clinical research can help to establish a new paradigm for the revascularization strategy from the viewpoint of ulcer healing. (*Circ J* 2014; **78**: 1791–1800)

Key Words: Angiosome; Critical limb ischemia; Peripheral arterial disease; Revascularization; Ulcers

Advancements in endovascular treatment (EVT) for critical limb ischemia (CLI) have enabled vascular surgeons, cardiologists and radiologists to participate in revascularization procedures. However, the number of experts in post-revascularization ulcer management has not caught up with the increasing number of revascularization procedures. Moreover, both education and knowledge regarding ulcer healing are insufficient for physicians performing revascularization. The treatment guideline for diabetic foot ulcers is well-established,¹ but evidence supporting strategies for the complete healing of ischemic ulcers after revascularization remains scant.

Among the many studies that have reported limb salvage, complete ulcer healing was reported in only 17 studies (0.9%) according to a literature search from 1985 to 2005.² However, ulcer healing after revascularization is a major concern among patients, and the expected healing period is important in terms of health economics and the patient's quality of life (QOL).^{3,4} Furthermore, information clarifying stubborn ulcers is meaningful for preventing the onset of ulcers and to educate the medical personnel who may potentially make an early discovery of such ulcers.

In particular, there has been a tremendous worldwide increase in the number of patients with diabetes mellitus (DM) and the percentage of CLI patients with DM is increasing markedly, currently accounting for 70%.^{5,6} The increase in DM is accom-

panied by an increase in renal diseases, and the incidence of peripheral arterial disease (PAD) among dialysis patients is also increasing. In Japan, 50% of CLI patients have endstage renal disease (ESRD).⁷ Furthermore, populations are aging rapidly in advanced countries; in other words, disease duration is increasing among DM and ESRD patients, in turn, increasing the risk of triggering and advancing arterial diseases. In this patient group, vascular disease is also accompanied by microangiopathy, which causes CLI with tissue loss.

Analysis of the factors that impair the ulcer healing process in highly heterogeneous CLI patient groups is complicated. To establish a revascularization strategy after properly determining the healing vs. impairing factors, it is essential to gather ample data on post-revascularization ulcer healing. However, such reports are few, and even the guidelines do not provide revascularization procedural options from the viewpoint of ulcer healing.

This review organized the reported factors that impair ulcer healing and identified those that clearly have a major effect on revascularization outcome and limb prognosis. We highlight the factors that are useful in planning revascularization strategies from the viewpoint of ulcer healing.

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Department of Vascular Surgery, Asahikawa Medical University, Asahikawa, Japan

Mailing address: Nobuyoshi Azuma, MD, PhD, Department of Vascular Surgery, Asahikawa Medical University, 2-1 Midorigaoka-higashi, Asahikawa 078-8510, Japan. E-mail: nazuma@asahikawa-med.ac.jp

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Table 1. Reports on Ulcer Healing After Revascularization and the Factors Possibly Affecting Ulcer Healing

Author (year)	Type of study	No. of limbs	Patients' background		Revascularization procedure	Factors possibly affecting ulcer healing			
			DM (%)	ESRD (%)		DM	Renal failure	Wound status	Infection
Chung et al ²¹ (2006)	Single Retro	250	66	—	Bypass (infrainguinal)	P=0.23	NS	Extensive TL (P=0.01) [#]	—
Soderstrom et al ¹¹ (2009)	Single Pro	113	50	7	Bypass (infrainguinal)	P=0.05 [#]	P=0.462	UTWCS (NS)	—
Azuma et al ⁹ (2012)	Single Retro	249	81	49	Bypass (infrapopliteal)	P=0.03 [#]	P<0.001 [#]	Heel TL (P<0.001) [#] R6 except heel (P=0.025) [#]	CRP (P=0.822)
Rashid et al ⁵⁵ (2013)	Single Retro	167	76	28	Bypass (infrapopliteal)	—	—	—	—
Varela et al ⁵⁷ (2010)	Single Retro	76	79	4	Bypass/EVT (infrapopliteal)	—	—	—	—
Apelqvist et al ⁸ (2011)	Single Retro	(504) [†]	100	37	Bypass/EVT	—	P=0.005 [#]	Multiple ulcers (P<0.001) [#] Wagner grade (P<0.001) [#]	—
Alexandrescu et al ⁴⁷ (2011)	Single Retro	232	100	18	EVT (infrapopliteal)	—	—	—	—
Kawarada et al ¹⁰ (2012)	Single Retro	106	78	51	EVT (infrapopliteal)	P=0.008 [#]	P=0.133	Rutherford category (P=0.232)	Infected wound [#] (P=0.012) [#]
Soderstrom et al ⁵² (2013)	Single Retro	250	100	16	EVT (infrapopliteal)	—	NS	NS Heel TL (P=0.129)	—
Iida et al ⁷ (2013)	Multi Pro	166	71	52	EVT (infrainguinal)	NS	P=0.15	NS	Infected wound [#] (P=0.04) [#]
Kobayashi et al ⁴¹ (2014)	Single Retro	166	75	49	EVT (infrapopliteal)	NS	P<0.001 [#]	Extensive TL (P=0.002) [#] Heel TL (P=0.002) [#]	Infected wound [#] (P=0.046) [#]

—, not reported. [#]Statistical significance. [†]Revascularized limbs out of 1,146 patients. *Healing time of ulcer on limbs with major amputation was calculated as infinity.

BMI, body mass index; CPA, complete pedal arch; DM, diabetes mellitus; DR, direct revascularization; E, extensive TL; ESRD, endstage renal disease; EVT, endovascular treatment; H, heel ulcer or gangrene; IPA, incomplete pedal arch; IR, indirect revascularization; Multi, multicenter; NPA, no pedal arch; NS, not significant; Pro, prospective; Retro, retrospective; Single, single center; T, toe ulcer or gangrene; TL, tissue loss; UTWCS, University of Texas wound classification system; Y, year.

(Table 1 continued the next page.)

Factors Linked to Delayed Wound Healing After Revascularization

Clinical studies to date that have assessed ulcer healing after revascularization and the factors that impair ulcer healing are summarized in Table 1. Although studies investigating ulcer healing after revascularization are slowly accumulating, most are retrospective single-center studies, and the level of evidence is still low.

As a result of reviewing the literature documenting ulcer

healing, we classified the factors related to delayed ulcer healing into 5 categories: (1) systemic factors (comorbidities); (2) tissue defect factors; (3) infection; (4) inadequate wound management; and (5) inadequate revascularization strategy.

Systemic Factors

Factors affecting ulcer healing that must not be forgotten and are normally raised are systemic diseases and clinical conditions that impair the wound healing process. Among reports to date, many note ESRD and DM as potent factors that impair

Author (year)	Factors possibly affecting ulcer healing				Patients' group	Ulcer healing outcome
	Age	Malnutrition	Target	Other		
Chung et al ²¹ (2006)	P=0.07	Hypoalbumin (P=0.2)	–	Preop. ambulation (P=0.053)	–	76% healed @ 1Y Median healing time: 198 days
Soderstrom et al ¹¹ (2009)	–	–	–	Duration of TL (NS)	–	74% healed @ 1Y Median healing time: 186 days
Azuma et al ⁹ (2012)	NS	Hypoalbumin [#] (P=0.049) [#]	NS		Angiosome DR vs. IR	86.9% healed @ 1Y Median healing time: 82.96 days*
Rashid et al ⁵⁵ (2013)	–	–	NS	Pedal arch quality [#] (P=0.0264) [#]	Pedal arch quality; (CPA, IPA, NPA)	Complete healing 87% (CPA); 85% (IPA); 64% (NPA)
Varela et al ⁵⁷ (2010)	–	–	NS	–	Bypass vs. EVT	Complete ulcer healing @ 1Y 84% (bypass) vs. 87% (EVT), P=0.29 Median healing time 95 days (bypass) vs. 118 days (EVT), P=1
Apelqvist et al ⁸ (2011)	P<0.001	–	–	–	–	52% healed Median healing time 29 weeks
Alexandrescu et al ⁴⁷ (2011)	–	–	Angiosome [#] P=0.018 [#]	–	Angiosome DR vs. IR	71% healed
Kawarada et al ¹⁰ (2012)	NS	–	NS	Pedal arch quality [#] (P=0.02) [#]	Pedal arch classification; (type 1-3)	73.6% healed @ 1Y
Soderstrom et al ⁵² (2013)	–	–	Angiosome [#] P=0.021 [#]	–	Angiosome DR vs. IR	Complete ulcer healing @ 1Y 69% (DR) vs. 47% (IR), P=0.001
Iida et al ⁷ (2013)	NS	Low BMI [#] (P=0.03) [#]	–	–	–	Median healing time 97 days
Kobayashi et al ⁴¹ (2014)	NS	–	Angiosome [#] P=0.012 [#]	–	Location of wounds; group T vs. H vs. E	Median healing time 64 days (T); 168 days (H); 267 days (E)

ulcer healing.^{5,8–12} These disease conditions have been shown to induce decreased skin blood flow because of microcirculatory disorder, and they likely trigger abnormalities even in the molecular biological process involved in the wound healing process, which has not been fully explored.

In addition, several studies report that indices of nutritional state (ie, low BMI⁷ and hypoalbuminemia), also cause reduce the speed of ulcer healing.¹³ We found a clear delay in ulcer healing in dialysis patients with hypoalbuminemia.⁹ In that patient group, improving the albumin level is often challenging, even with nutritional intervention. The reason for this association is not simply that such indices reflect the patient's nutritional state, but the possibility that protein hypercatabolism caused by inflammation may also cause further complications.^{14,15} The serum albumin level is an important indicator that affects wound healing and survival prognosis, but more

sensitive biomarkers that have a faster turnover than albumin are desirable.

Tissue Defect Factors

As guidelines on revascularization, TASC II focus on the nature of vascular lesions, while AHA guideline focuses on patients' prognostic survival.^{16,17} Although guidance is given on the choice of revascularization procedure, none of the guidelines mention anything about the tissue defect status of the ischemic foot in regard to the revascularization strategy. Could it be that foot condition is of no importance when selecting the indications and procedures of revascularization?

To respond to that question, preoperative tissue loss of the foot needs to be examined in detail. Classifications such as that by Wagner and the University of Texas (UT) are commonly used, and all are based on the depth of tissue loss and infection

Table 2. List of Reports Studying Angiosome

Author (year)	Type of study	Revascularization procedure	Bias adjusted	No. of limbs	
				DR	IR
Alexandrescu et al ⁴⁷ (2011)	Single Retro	EVT	No	134	98
Iida et al ⁵¹ (2012)	Single Retro	EVT	Adjusted*	118	118
Kawarada et al ¹⁰ (2012)	Single Retro	EVT	No	–	–
Soderstrom et al ⁵² (2013)	Single Retro	EVT	Adjusted*	84	84
Fossacecca et al ⁴⁹ (2013)	Single Retro	EVT	No	167	34
Varela et al ⁵⁷ (2010)	Single Retro	EVT/bypass (35/41)	No	45	31 [†]
Kabra et al ⁶⁸ (2013)	Single Pro	EVT/bypass (25/39)	No	39	25
Neville et al ⁵³ (2009)	Single Retro	Bypass	No	27	25
Deguchi et al ⁶⁹ (2011)	Single Retro	Bypass	No	30	36
Azuma et al ⁹ (2012)	Single Retro	Bypass	Adjusted*	48	48
Rashid et al ⁵⁵ (2013)	Single Retro	Bypass	No	66	75
Kret et al ⁵⁴ (2014)	Single Retro	Bypass	No	54	52

–, not reported. *Statistical significance. *Background bias adjusted by propensity score method. †IRc group not listed; ††P value for amputation-free survival rate difference between DR and IR.

IRc, IR with collateral. Other abbreviations as in Table 1.

(Table 2 continued the next page.)

status.^{18,19} However, these were originally intended for diabetic foot lesions, not for PAD. On the other hand, the Rutherford classification is for ischemic limbs, and Rutherford category 5 or 6 is based on the extent of tissue loss with an indication of whether the transmetatarsal level is exceeded.²⁰

In a study of ulcer healing after revascularization that was the first detailed study of ulcer healing after bypass surgery, Chung et al reported a cumulative ulcer healing curve by extent of tissue loss, and their results indicated that extensive pedal necrosis at presentation independently predicted delayed wound healing.²¹ Söderström et al investigated the time to complete ulcer healing in relation to the UT classification or the duration of the ischemic tissue defect but reported no statistical significance for either.¹¹ Compared with other sites, mid- and hind-foot tissue loss showed significantly poor ulcer healing. We investigated the clinical results for ulcer healing, focusing on the extent of tissue loss and the location, particularly in terms of heel tissue loss, and reported that both heel and extensive non-heel tissue loss had a significant effect on delayed ulcer healing.⁹ The heel has the most stubborn ulcer healing, and its involvement is directly linked to major amputation.²² Diabetes clinicians, diabetes care nurses, dialysis nurses and other relevant care givers should be informed about this association, and early consultation with a vascular specialist must be recommended. Extensive tissue loss requires sufficient blood flow and usually needs a longer period to cure compared with smaller areas of tissue loss. Thus, extent of tissue loss should matter, and it can be an important factor in determining the revascularization strategy.

Because the preoperative state of tissue loss should have a major influence on the revascularization decision-making process, detailed recordings of the preoperative ulcer state should

have important significance in ongoing or future clinical studies.

Infection

Whether the patient's condition is complicated by infection is also significantly involved in ulcer healing and limb salvage. For some time, the following 3 factors were repeatedly proposed as factors in the formation of diabetic foot lesions: (1) neuropathy; (2) ischemia; and (3) infection.^{1,18} Terashi et al, who proposed the Kobe classification, stress that it is difficult to diagnose infection, particularly in patients with both ischemia and infection.²³ In cases of severe ischemia, the manifestation of clinical infection such as local reddening, swelling, and fever is often masked, because the increase in blood flow with accumulating leukocytes by infection is suppressed. This masked infection worsens rapidly after revascularization and is often missed, likely resulting in major tissue loss. Infections, particularly abscess-forming ones, further aggravate the vascular network of the ischemic limb, inflicting damage; therefore, the tissue loss caused by infection becomes massive. Rogers et al used the expression “stairway to an amputation” for neuropathy and circulatory disturbances complicated by infection that eventually ends in amputation; they asserted the importance of a team approach between those performing the revascularization and those responsible for wound management.¹

Osteomyelitis is difficult to treat, and resection of infected bone will be needed in most cases.²⁴ Furthermore, if osteomyelitis is missed, the infection spreads proximally, and if it reaches the heel bone or another ankle-forming bone, major amputation is unavoidable. If deep infection is suspected, MRI examination is recommended.²⁵

Patients with CLI often have a complicating comorbidity that increases susceptibility to infection, such as DM or ESRD, or

Author (year)	Complete ulcer healing rate				Limb salvage rate			
	DR (%)	IR (%)	P value	Months	DR (%)	IR (%)	P value	Months
Alexandrescu et al ⁴⁷ (2011)	79.1	55.1	<0.018 [#]	12	97.0	84.5	<0.030 [#]	12
Iida et al ⁵¹ (2012)	—	—	—	24	82	68	0.01 [#]	24
Kawarada et al ¹⁰ (2012)	—	—	0.886	—	—	—	0.524	—
Soderstrom et al ⁵² (2013)	69	47	0.021 [#]	12	86	77	0.086	12
Fossacecca et al ⁴⁹ (2013)	57.4	32.3	NM	12	90.4	91.2	NS	12
Varela et al ⁵⁷ (2010)	92	73	0.008 [#]	24	93.0	72.0	0.02 [#]	24
Kabra et al ⁶⁸ (2013)	96.4	83.3	0.21	6	84	75	0.06	6
Neville et al ⁵³ (2009)	91	62	0.03 [#]	—	—	—	—	—
Deguchi et al ⁶⁹ (2011)	73.3	72.2	0.43	—	—	—	—	—
Azuma et al ⁹ (2012)	95.8	91.7	0.185	24	97.8	92.3	0.855	24
Rashid et al ⁵⁵ (2013)	86	79	0.2736	—	—	—	—	—
Kret et al ⁵⁴ (2014)	78	46	0.01 [#]	—	—	—	0.82 ^{††}	—

oral immunosuppressant drugs. Moreover, chronic wound infection is often accompanied by antibiotic-resistant bacteria. Therefore, adequate selection of antibiotics is crucial. For optimal prevention, it is vital to submit a wound culture for testing to clarify antibiotic sensitivity prior to revascularization.

Observation, care, and early response at the onset of an abnormality are indispensable in practicable limb-length preservation.

Wound Management

Even when revascularization is successful, subsequent wound management still carries the possibility of prolonged ulcer healing and major amputation in some cases.

Many wound management guidelines for diabetic foot lesions have been proposed.^{26,27} However, medical personnel in charge of revascularization and wound management should understand the difference between wound treatment post-revascularization and ulcer management in the absence of revascularization; the former is characterized by inflammation and the onset of edema because of the rapid recovery of blood flow. As edema increases the intercellular space, with time it may become a medium or a passageway for infection. Therefore, after revascularization, it is important that necrotic tissue is removed promptly, drainage is performed properly, and the site is observed closely to confirm that no infection has spread proximally.

By properly performing the wound bed preparation, granulation will grow in due course.²⁸ The proliferation of granulation and improvement of the environment are very important. Therefore, if one does not make full use of established evidence regarding wound management, such as selecting an ointment that maintains adequate moisture environment and applying vacuum-assisted closure therapy, wounds in patients with diabetes- and dialysis-related microcirculatory disorders accompanied by increased susceptibility to infection will not heal. It is also imperative to maintain current knowledge about prolif-

eration factors, medications, and new wound dressings.^{26,29–31}

Eventually, complete healing will occur whether one simply waits for secondary healing, or performs a skin grafting, stump closure, or plastic surgery, such as a musculocutaneous flap. Free flap transfer is the ultimate procedure to salvage limbs facing major amputation.^{32,33} Because a vein bypass graft can work as a reliable source of blood supply for the flap, to select bypass surgery as the first line of revascularization may be reasonable in cases of extensive tissue loss that potentially necessitate free flap transfer.

The most important factors in wound management after revascularization are the following: (1) checking whether the revascularized tissue circulation is being maintained or has deteriorated because of restenosis, and (2) checking for signs of infection advancing. If one of these signs is suspected, immediate examination followed by prompt clinical action is essential.

Revascularization Procedure and Target Selection

The choice of an appropriate treatment measure, the revascularization strategy, and the choice of treatment target have a major effect not only on limb salvage but also on the achievement of complete ulcer healing and shortening of the ulcer healing period. By contrast, incorrect revascularization strategy will prolong the ulcer healing period, increasing the opportunity for infection to set in and leading eventually to limb loss.

EVT or Open Repair There is an ongoing debate about the choice of revascularization measure, namely, whether to use EVT or bypass surgery and how to perform it.^{34–37} The AHA guideline based on the results of the BASIL trial^{38,39} emphasizes predicting the survival prognosis and determining the status of available veins.¹⁶ By comparison, the European guideline published the same year recommends EVT as the first-line revascularization procedure.⁴⁰ The opinions of both these guidelines are completely inconsistent. However, no report has discussed whether bypass or EVT should be selected while considering the status of tissue loss before revascularization. For example,

in the case of extensive tissue loss, continuous and ample long-term blood supply is indispensable for complete healing. According to the clinical results of EVT reported by Kobayashi et al, the healing rate of an ulcer in the toe is 75%, whereas in heel tissue loss cases, the healing rate is 52%, and in cases of extensive tissue loss located somewhere other than the heel, the rate is 13%, showing a marked decrease in the ulcer healing rate.⁴¹ This highlights the possibility that EVT has a limited role in extensive tissue loss. To derive parameters conducive to the choice of revascularization method, patient background and wound treatment procedures should be aligned to some extent, and EVT and bypass should be compared. Presently, vascular surgeons and interventional cardiologists are conducting a multicenter prospective study together using the same protocol in Japan. Time to ulcer healing and limb salvage rates are being observed, and such clinical studies are expected to demonstrate the importance of preoperative ulcer status in selecting the revascularization strategy for CLI treatment.⁴²

Restenosis After Revascularization Procedure If the appropriate choice of revascularization procedure is important, then restenosis and obstruction have a major effect on ulcer healing. A clinical study observing patency angiographically after crural artery EVT elucidated that the patency of the revascularized artery segment had a great effect on delayed ulcer healing.⁴³ In that investigation, restenosis or re-occlusion was found in 72% of treated arteries 3 months after balloon angioplasty, and the time to ulcer healing in the restenosis group was significantly delayed compared with the non-restenosis group (127 vs. 66 days). This result demonstrated that it is not easy to maintain adequate blood supply with EVT for the crural artery in patients with extensive tissue loss associated with a lengthy ulcer healing period. Therefore, before initiating treatment in cases of extensive tissue loss, properly predicting the time to ulcer healing will inform the decision about whether to select bypass surgery or to perform repeated EVT.

Is the Angiosome Concept Fact or Fiction? Since Attinger et al advocated the importance of the angiosome concept in lower limb revascularization,⁴⁴ the clinical significance has been widely debated (Table 2).⁴⁵ As reported by Alexandrescu et al in their study titled “Angiosome concept: fact or fiction?”, some reports state that the angiosome concept is very useful clinically, while others state that the angiosome concept, though important as a concept, is not of any particular importance clinically.⁴⁶ Most papers on ulcer healing post-EVT demonstrate the usefulness of the angiosome concept,^{47–52} whereas those on ulcer healing post-bypass are divided on that usefulness. Neville et al reported that the angiosome concept was also relevant to the field of bypass surgery.⁵³ By contrast, we found no difference in propensity-matched pairs even in the limb salvage rate and ulcer healing.⁹ Kret et al found no difference in limb salvage rate but reported that in terms of time to ulcer healing, angiosome-direct treatment (DR) produced significantly better results than angiosome-indirect treatment (IR).⁵⁴

Why do the clinical results regarding the angiosome vary? To answer this question, 3 possible reasons are proposed: (1) a background bias may exist between the DR and IR groups; (2) the significance of the angiosome concept may differ between EVT and bypass surgery; and (3) the arterial-arterial connection between angiosomes may have a greater effect on ulcer healing than does the angiosome concept.

Whether revascularization is DR or IR is only 1 factor among many factors influencing ulcer healing as discussed throughout this review. Background bias regarding the condition of ischemic tissue loss and systemic factors etc is likely. We re-

ported our single-center retrospective clinical results of studying ulcer healing after bypass surgery. In our series, the ulcer healing rate seemed faster if direct revascularization was possible, but after minimizing the background differences with the propensity score method, the positive effect of angiosome-oriented bypass surgery disappeared.⁹ Angiosome-oriented bypass surgery is not always possible, because of infection, extensive tissue loss, and the absence of run-off; therefore, feet that have undergone angiosome-indirect bypass were often subject to more severe conditions before revascularization compared with those that had undergone angiosome-direct bypass.

By contrast, other authors reporting their clinical results after EVT indicate that ulcer healing in the DR group is still significantly superior to that of the IR group, even after minimizing background bias via the propensity score method.^{51,52} EVT can treat arteries running near the ischemic tissue loss and can approach the infectious area, which is a possible explanation for the difference between EVT and bypass surgery. Another important difference between bypass and EVT is the amount of blood supply to the tissue defect. The role of the angiosome concept may be more relevant for EVT, in which a limited blood supply through the treated crural artery can irrigate and focus into tissue loss efficiently if DR can be achieved. The blood pressure loading on the foot artery may also differ between EVT and bypass surgery. Pedal bypass can bring systemic blood pressure directly down the foot arteries: therefore, the possibility that it can cause choked vessels to function more effectively as a network between angiosomes should be examined in the future. The clinical results of IR revascularization may depend on whether the procedure can provide blood supply beyond the angiosome.

Impact of Pedal Arch Quality and the Arterial-Arterial Connection Between Angiosomes Several authors have focused on the role of the arterial-arterial connection between angiosomes. Rashid et al proved the important role of pedal arch quality.⁵⁵ They divided it into 3 groups (complete pedal arch, incomplete pedal arch, and no pedal arch), observing ulcer healing after bypass surgery, and concluded that time to healing was directly influenced by the quality of the pedal arch rather than angiosome-oriented revascularization. Kawarada et al also reported that their pedal arch classification had a great effect on ulcer healing after EVT, and that ulcer healing times were similar between DR and IR.¹⁰ There are also reports stating that IR should be differentiated as IR without collateral and IR with collateral (IRc).^{56,57} However, difficult problems remain regarding how to evaluate the reliability of collateral blood flow on ulcer healing if a stenotic lesion is present in the collateral vessels or the inflow artery of the collateral circulation. There are reports of attempts to evaluate the arterial-arterial connection between angiosomes using local hemodynamic parameters and new imaging methods, as discussed later.^{45,58–61}

Connections between angiosomes and the development of collateral pathways will differ according to the background disease and state of infection. Microcirculatory disorder is often serious in long-term diabetes patients and dialysis patients. Infection also destroys the microcirculatory network of tissues. Iida et al verified this finding using clinical data and concluded that the angiosome concept is important in diabetic and infected patients.⁶² As such, studies examining the type of patients who benefit from revascularization strategies based on the angiosome concept need to be pursued hereafter.

Time to Wound Healing Most patients who undergo revascularization with the hope for limb salvage will ask when the ulcer healing will take place. However, clinical data addressing that question are very limited. Moreover, the ulcer healing

Figure 1. Time to wound healing after bypass surgery.⁹ The time to healing of limbs undergoing major amputation was calculated as infinity. ESRD, dialysis-dependent endstage renal disease; R5, Rutherford category 5; R6, Rutherford category 6; QP, quartile point.

speed differs according to the many factors described before. We classified the time course to ulcer healing post-bypass surgery using the 2 parameters, namely, the presence or absence of dialysis-dependent ESRD and the extent of tissue loss, that had the greatest effect on the ulcer healing period in our series.⁹ As shown by the graph in **Figure 1**, even with the same revascularization method, the time course to healing differs notably according to patient background and ulcer state.

Furthermore, there is no established evidence indicating whether EVT is inferior to bypass in terms of ulcer healing speed. Predicting the time course of healing preoperatively is very important to both the patient and interventionalist, as it facilitates the choice of revascularization procedure and affects the patient's QOL.⁴ We would like to stress that the accumulation of data using standards that integrate most of the ulcer healing factors is linked to an accurate prediction of ulcer healing before intervention.

Prediction of Ulcer Healing Probability in Individual Patients

To predict the probability of ulcer healing in individual patients, several methods are now being studied. The transcutaneous oxygen tension (TcPO₂) measurement method has been used to predict the ulcer healing probability during or immediately after revascularization.⁴⁷ Recently, the usefulness of skin perfusion pressure,⁶⁰ tissue oxygen saturation (StO₂),⁵⁹ and hyperspectral technology⁶³ for assessing the blood supply to each angiosome has been reported.

Moreover, several studies have reported the usefulness of indocyanine green (ICG) imaging as a method for predicting ulcer healing perioperatively.^{58,64,65} After ICG was injected, the contrast effect in the skin in the area of interest is measured, and the degree of ischemia improvement is determined. Furthermore, we have been developing a method called “living

angiosome staining”, which uses multiple detectors to image the foot biplane simultaneously to confirm whether blood flow stained by ICG distributes in the ulcer area without delay (**Figure 2**).⁶⁶ In addition, there is also a report on the use of conventional DSA to predict ulcer healing. Utsunomiya et al focused on densely stained, newly formed capillary blood vessels resulting from ischemia in completion angiography during EVT and called such a finding “wound brush”.⁶¹ The researcher reported that the ulcer healing rate of feet confirmed to have wound brush was significantly superior compared with feet without wound brush.

A reliable assessment method confirming well-improved circulation around ischemic tissue or the ulcer bottom intraoperatively or postoperatively could contribute to decisions about whether to wait for granulation tissue growth or conduct another revascularization.

Future Directions

At the beginning of this year, a new classification system for critical ischemic limbs, the WIFI system, was proposed to systemically assess extent of wound (“W” factor) and severity of ischemia (“I” factor) and status of foot infection (“FI” factor) in the era of vascular disease with diabetes.⁶⁷ The authors recommend the use of this system to collect data in future clinical studies. This recommendation is an epoch-making proposal for filling the gap in current evidence and establishing the viewpoint from ulcer healing in future guidelines regarding revascularization of CLI.

As mentioned earlier, we must not forget that the systemic state and the associated disease state may affect ulcer healing more strongly than the factors defined by the WIFI system. During clinical studies, data should be collected using a fixed rule, and statistical analysis should be performed in consideration of the various factors affecting ulcer healing that have

Figure 2. “Living angiosome staining” as an intraoperative assessment to potentially predict ulcer healing. (A) Referral of a 59-year-old dialysis-dependent patient with ischemic ulcer categorized as Rutherford 6 on the lateral dorsal side of the mid-foot. (B) Preoperative angiogram shows poor run-off of the dorsalis pedis artery, so the terminal posterior tibial artery (so-called common plantar artery) was selected as the distal target of bypass surgery, which was angiosome-indirect revascularization. Because of concern about delayed ulcer healing, intraoperative ICG staining was performed and assessed by 2 near-infrared fluorescence detectors termed a “photodynamic eye” (Hamamatsu Photonics Co. Japan). ICG was injected into the vein graft through a branch, then images from the 2 detectors were recorded simultaneously: (C,D) planar-side detector; (E,F) dorsal-side detector. The numbers listed in these images indicate time after ICG injection. The whitening stain was seen not only in the angiosome-direct side but also the indirect side simultaneously, and the center of the ulcer also started staining in the early phase (red arrow). Intraoperative angiography (G,H) shows good run-off of the lateral planar artery and “wound brush” (white arrow) also can be seen. The ulcer was cured at 6 months after bypass surgery (I). ICG, indocyanine green.

been mentioned here. These considerations are very important for providing guidance on treatment strategies for the heterogeneous CLI patient population.

Conclusions

Revascularization strategies based on ulcer healing prediction and the choice of procedure and target are now important. Fac-

tors that impair ulcer healing are broadly divided into 5 types: (1) systemic condition and comorbidity; (2) extent of tissue loss; (3) infection; (4) inadequate wound management; and (5) inadequate revascularization strategy. The elucidation of these factors and the subsequent collection of data on ulcer healing are urgently important. Moreover, the preoperative tissue loss state and ulcer healing prediction are important when determining the revascularization strategy. These viewpoints regarding ulcer healing must be incorporated into the next CLI treatment guideline to prepare for a coming era of vascular disease related to the global expansion of an aging population with DM.

Disclosures

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