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Effect of tibial cortex transverse transport in patients with recalcitrant diabetic foot ulcers: A prospective multicenter cohort study

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A R T I C L E I N F O

Keywords:
Diabetic foot ulcer
Tibial cortex transverse transport
Distraction angiogenesis
Limb salvage
Health-related quality of life
Perfusion

A B S T R A C T

Background: Management of recalcitrant diabetic foot ulcer (DFU) remains difficult. Distraction osteogenesis mediates new bone formation and angiogenesis in the bone itself and the surrounding tissues. Recently it was reported that tibial cortex transverse transport (TTT) was associated with neovascularization and increased perfusion at the foot in patients with recalcitrant DFUs and facilitated healing and limb salvage. However, the findings were from several single-center studies with relatively small populations, which need to be confirmed in multicenter cohort studies with relatively large populations. Furthermore, the effect of this technique on patient's health-related quality of life is still unclear.
Methods: We treated patients with recalcitrant (University of Texas wound grading system 2-C to 3-D and not responding to prior routine conservative and surgical treatments for at least 8 weeks) DFUs from seven centers using TTT (a 5 cm × 1.5 cm corticotomy followed by 4 weeks of medial and lateral distraction) between July 2016 and June 2019. We analyzed ulcer healing, major amputation, recurrence, health-related quality of life (physical and mental component summary scores), and complications in the 2-year follow-up. Foot arterial and perfusion changes were evaluated using computed tomography angiography and perfusion imaging 12 weeks postoperatively.
Results: A total of 1175 patients were enrolled. Patients who died (85, 7.2%) or lost to follow-up (18, 1.7%) were excluded, leaving 1072 patients for evaluation. Most of the patients were male (752, 70.1%) and with a mean age of 60.4 ± 9.1 years. The mean ulcer size was 41.0 ± 8.5 cm^2 and 187 (16.6%) ulcers extended above the ankle. During the follow-up, 1019 (94.9%) patients healed in a mean time of 12.4 ± 5.6 weeks, 53 (4.9%) had major amputations, and 33 (3.1%) experienced recurrences. Compared to preoperatively, the patients had higher physical (26.2 ± 8.3 versus 41.3 ± 10.6, p = 0.008) and mental (33.6 ± 10.7 versus 45.4 ± 11.3, p = 0.031) component summary scores at the 2-year follow-up. Closed tibial fracture at the corticotomy site was found in 8 (0.7%) patients and was treated using external fixation and healed uneventfully. There were 23 (2.1%) patients who had pin site infections and were treated successfully with dressing changes. Compared to preoperatively, the patients had more small arteries and higher foot blood flow (8.1 ± 2.2 versus 28.3 ± 3.9 ml/100 g/min, p = 0.003) and volume (1.5 ± 0.3 versus 2.7 ± 0.4 ml/100 g, p = 0.037) 12 weeks postoperatively.
Conclusion: TTT promotes healing, limb salvage, and health-related quality of life in patients with recalcitrant DFUs as demonstrated in this multicenter cohort study. The surgical procedure was simple and straightforward

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and the complications were few and minor. The effect of this technique was associated with neovascularization and improved perfusion at the foot mediated by the cortex distraction. The findings are required to confirm in randomized controlled trials.

The Translational Potential of this Article: TTT can be used as an effective treatment in patients with recalcitrant DFUs. The mechanism is associated with neovascularization and consequently increased perfusion in the foot after operation.

1. Introduction

Diabetes mellitus currently affects 425 million people worldwide [1]. It is estimated that up to one-third of these people will develop a diabetic foot ulcer (DFU) in their lifetime and more than 15% of DFUs result in lower extremity amputation, making this the most common cause of lower extremity amputation [2]. DFU results from multifactors, of which peripheral artery disease and microvascular dysfunction play an important role [3–5]. The vasculopathy not only leads to the development of foot ulceration but also subsequent healing failure and amputation.

Current treatments of DFU includes nonoperative therapies [6,7] and surgeries (debridement, revascularization [8], bone procedures [6, 9–11], tendon-balancing interventions [6,12,13], and microsurgical reconstruction using flaps) [14–16]. These therapies are more effective for localized and mild-to-moderate ulcers while with less effects on diffuse, severe, and recalcitrant ulcers, and are linked with high complication and failure rates [17,18]. Recently, a novel surgical technique, tibial cortex transverse transport (TTT), in which partial corticotomy is created followed by medial and lateral distraction, was developed for the treatment of recalcitrant DFUs [19–24]. This technique is based on distraction osteogenesis in which gradual distraction of osteotomized bone segments results in new bone formation and angiogenesis in the bone itself and the surrounding tissues [25,26]. It has been reported that this technique facilitates healing and limb salvage in patients with recalcitrant DFUs compared to routine surgical treatments and the complications are few and minor [19–21]. Furthermore, neovascularization and increased perfusion were found at the foot after the operation [19]. However, the results were from several single-center studies with relatively small populations that were heterogenous (with multiple comorbidities) [19,21] and need to be confirmed in a large cohort of patients. Additionally, a previous study found that patients undergoing TTT could ambulate after ulcer healing, but functional outcomes regarding health-related quality of life were not assessed [19]. Thus, there is a concern over if this treatment, which includes a lengthy recovery duration, could be superior to major amputation.

Thus, we aimed to investigate the effect of TTT on the proportions of healing, recurrence, and major amputation, health-related quality of life, and complications in patients with recalcitrant DFUs in a prospective multicenter cohort study. We also explored the role of neovascularization and improved perfusion at the foot in the mechanism of this technique.

2. Material and methods

2.1. Patients and study design

We conducted a prospective cohort study of consecutive patients with DFUs treated using TTT in any of 7 tertiary orthopaedic clinics between July 2016 and June 2019. Data of patients' demographic, limb and ulcer-related factors, and combined treatments were collected according to a guideline set by International Working Group on the Diabetic Foot (IWGDF) [27]. Recalcitrant DFUs were defined as those who were at 2-C to 3-D according to University of Texas wound classification system [28] and had failed to respond to previous nonoperative (e.g., footwear and wound care) [6,7] and surgical (serial debridement, revascularization [8], bone procedures [6,9–11], tendon-balancing interventions [6,12, 13], and microsurgical reconstruction using flaps or skin graft [14–16]) management for at least 8 weeks. The study protocol was approved by the institutional review board of each participating center and conducted according to the principles of the Declaration of Helsinki. Written informed consent was obtained from each patient prior to the inclusion of the study.

Patient inclusion criteria comprised diagnosis of diabetes by the American Diabetes Association criteria [29], at least 18 years of age, and recalcitrant foot ulcers of 2-C to 3-D as classified by University of Texas wound classification system [28], and those with a 2-year follow-up. Patients were excluded if they had a malignant disease in the ulcers, ulcers extending above the ankle but too near the surgical area (the distance between the ulcer margin and the surgical area was less than 5 cm), ulcers with the absence of diabetes, or active Charcot arthropathy [30]; infection in the surgical area of the calf; acute critical limb ischemia [31]; autoimmune diseases, present use of corticosteroids, immunosuppressive drugs, and/or chemotherapy; end-stage renal disease [32], history of myocardial infarction or/and stroke within 3 months of the study, or with a life expectancy of less than 2 years. Patients who had end-stage renal disease but were clinically stable with the treatment of dialysis and/or kidney transplantation were included.

2.2. Clinical and imaging evaluation

Ulcer position and duration were registered. Ulcer severity was assessed using University of Texas wound classification system [28] and the wound size was measured after debridement, and ulcer infection was diagnosed according to the International Working Group on the Diabetic Foot/Infectious Diseases Society of America classification system [33, 34]. If diabetic foot osteomyelitis was suspected, a combination of a probe-to-bone test and plain radiograph of the foot was applied to confirm the diagnosis [33,34].

Peripheral arterial disease was defined as the absence of palpable dorsalis pedis and posterior tibial arteries and/or an ankle-brachial index (ABI) < 0.9 [35,36]. Color duplex ultrasound and computed tomographic angiography (CTA) were applied to assess vascular status of the lower limb and to determine whether revascularization was indicated. CT perfusion imaging was performed to evaluate perfusion in the patient's ulcerated feet, as previously described [19,37]. Briefly, the patient's feet and ankles were scanned using a 256 Slice Revolution CT Scanner (General Electric Medical Systems, USA). Images were obtained after injection of 80 ml of a non-ionic contrast agent (iopromide 370 mg/ml) at a flow rate of 4.5 ml/s. A cine mode technique was carried out with the following parameters: reconstruction slice thickness 5 mm, tube voltage 80 kV, fixed tube current 100 mA, 1-s gantry rotation, acquisition time 78 s, with a fixed start delay of 17 s. The images were then transferred to a dedicated workstation (Advantage Windows 4.4, General Electric Medical Systems) and analyzed using a software (CT Soft Tissue Perfusion, General Electric Medical Systems) by a radiologist. The region of interest (ROI) with an area of 74.2 mm^2 was manually drawn to include the most abductor hallucis muscle on the sagittal, coronal, and transaxial images. Blood flow and volume were obtained in four to eight consecutive sections (5 mm).

The presence of peripheral neuropathy was confirmed using 10-g Semmes-Weinstein monofilament [38]. End-stage renal disease was defined as a glomerular filtration rate <15 ml/min/1.73 m^2 according to the chronic kidney disease classification [32]. The health-related quality of life was evaluated using the Medical Outcome Study Short Form Survey (SF-36) which includes physical and mental component summary scores [39,40]. Other demographic and disease variables assessed at baseline were age, sex, glycated hemoglobin (HbA1c), etc.

2.3. Management protocol

The management protocol includes two indispensable components, TTT and surgical debridement of the ulcer, which could be generally performed during the same anesthetic episode (Fig. 1). In patients with suspected or proven diabetic foot infection, empiric oral or intravenous antibiotic treatment was applied according to the International Working Group on the Diabetic Foot/Infections Diseases Society of America guidelines [34,41], which was modified to specific antibiotic agents based on the results of post-debridement wound cultures. In case the infection was severe (grade 4 complicated by necrotizing fasciitis, deep abscess, compartment syndrome, or life-threatening organ dysfunction), urgent (within 6–24 h) debridement was performed to prevent the patient from developing life-threatening sepsis. When the patient presented initially with sepsis or septic shock, emergency (within 6 h) debridement was performed first, sometimes at the bedside, followed by a second-stage procedure of TTT and debridement in the operation room when patient safety prevented it in one setting. After debridement, negative-pressure wound therapy [42,43] was applied to promote wound healing and improve wound bed, if necessary. In patients with femoral-popliteal artery severe stenosis (≥80% of the lumen as evaluated by CTA and ultrasound) or occlusion [19], revascularization (percutaneous angioplasty or bypass surgery) [18,44] was performed prior to TTT (usually with an interval of 5 days) to improve blood supply to the feet. If the patient had systemic comorbidities, they were referred to corresponding specialists for further evaluation and treatment. For instance, in patients with end-stage renal disease but not receiving a kidney transplant, dialysis was carried out; and in patients with coronary artery disease, percutaneous coronary intervention was applied.

2.4. Surgical techniques

TTT was performed according to a protocol described previously [19] (Fig. 2 and Supplemental Video 1). Briefly, under spinal anesthesia or a femoral nerve blockage, a rectangular cortex (5 cm × 1.5 cm) was osteotomized from the anteromedial aspect of the proximal tibia using drill jits and attached to a monolateral external fixator. Following TTT, aggressive surgical debridement was performed to remove necrotic and/or infected tissues, drain abscesses, and open fistulas based on international guidelines [45]. Infected bone was removed and minor amputations (resections through or distal to the ankle) [46] were performed when indicated. Deep tissue samples were collected for histopathologic and microbiological examination to identify causative organisms and their antibiotic sensitivities. No flaps or skin equivalents or grafts were used for the promotion of healing [16,47]. Digital photographs (with scale bars) of the wounds were taken using a standardized protocol. The ulcer size was determined from digital photographs by measuring the maximum length and width using Image Pro Plus software (Media Cybernetics, Rockville, MD) if the ulcers were rectangular or square [19]. If the ulcer was irregular in shape, a sterile transparent sheet was placed in contact with the wound and the wound outline was traced as a continuous line using an indelible felt tip pen. Then digital photographs of the sheet were taken and the wound size was determined using Image Pro Plus software [48].

2.5. Aftercare and cortex transport

After a 4-day latency period, the distraction of the osteotomized cortex was initiated at a rate of 1 mm per day, divided into 4 times, as reported previously [19]. The distraction period was 4 weeks, 2 weeks medially followed by 2 weeks laterally. Aftercare included daily dressing changes and pin site care. The patients were allowed to place their partial weight on the operated limbs early using crutches. When the distraction

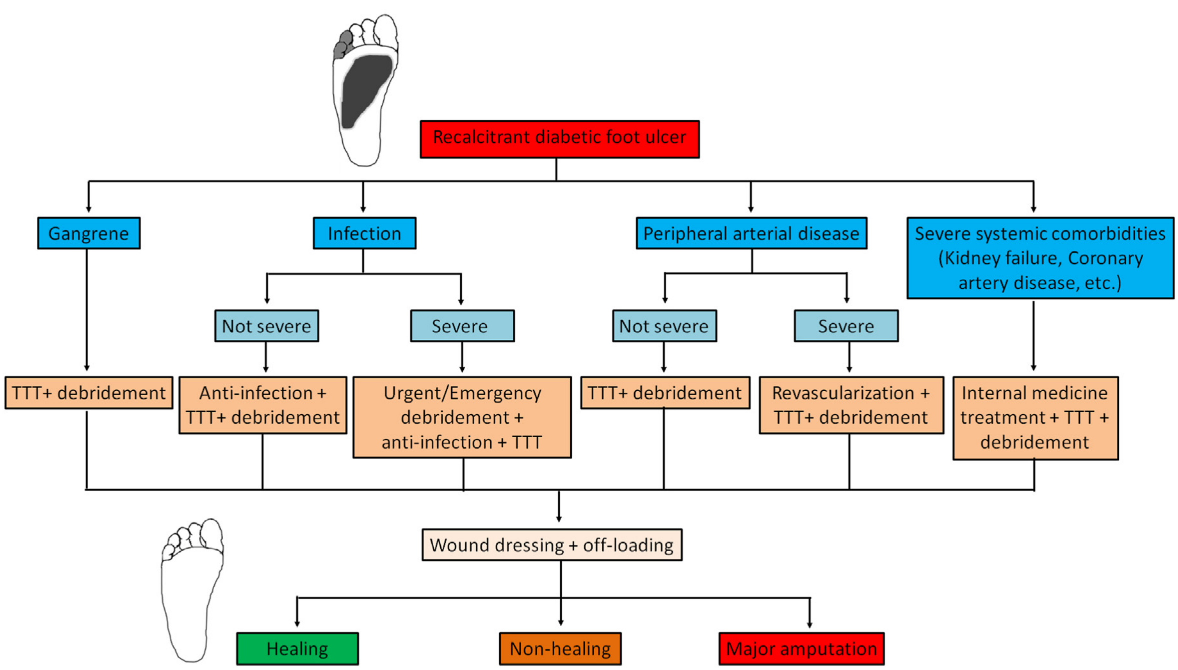

Figure 1. The protocol for the treatment of recalcitrant DFUs using TTT. TTT and surgical debridement were performed on all patients. Antibiotic treatment was applied to patients with suspected or proven diabetic foot infections. Urgent debridement was performed in patients with severe infections. Emergency debridement was performed in patients who presented initially with sepsis or septic shock. Revascularization was performed before TTT in patients with severe peripheral arterial disease. Multidisciplinary team care was applied if the patient had severe systemic comorbidities (kidney failure, coronary artery disease, etc.). Standard wound care and off-loading techniques were applied after the operation.

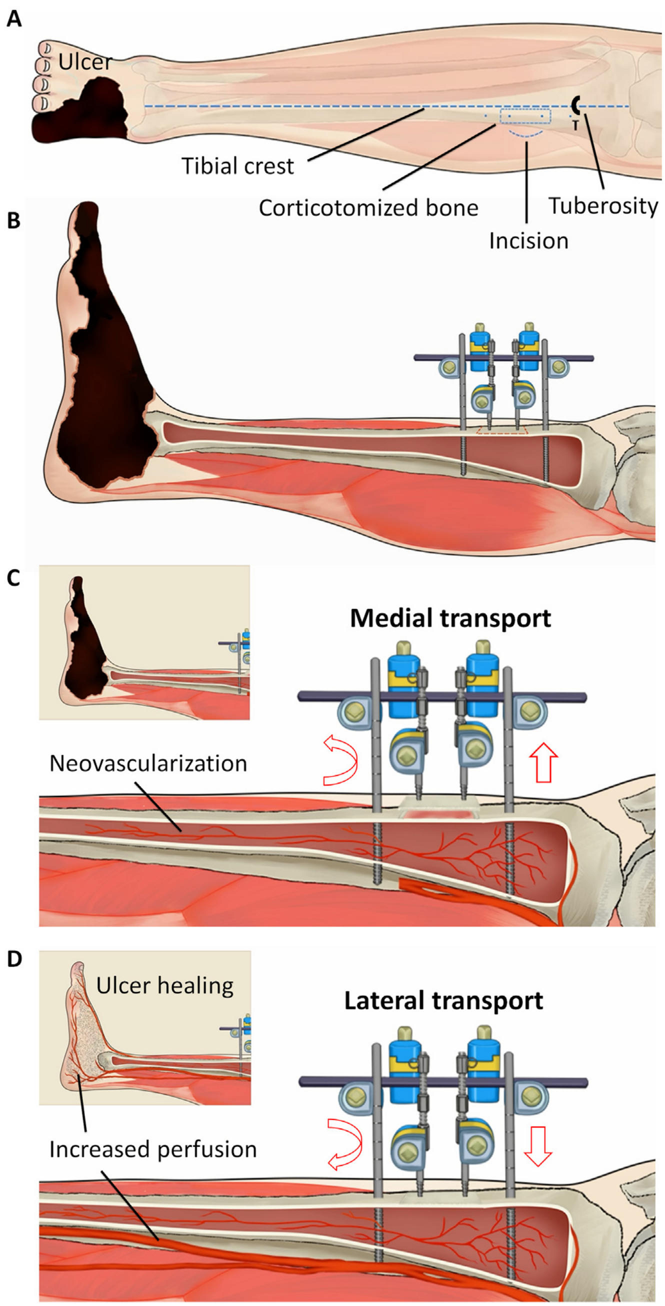

Figure 2. Schematic showing the procedure of TTT (A) A 2-cm curved incision was made, 2 cm medial to the tibial crest and 1.5 cm below the tibial tuberosity (T) of the ulcerated lower limb (Supplemental Video 1). After the exposure of the cortex, corticotomy was performed using multiple unicortical drill holes to attain a rectangle bone segment (B) Two nails were inserted into the corticotomized segment for bone transport and the other two into the tibia for fixation of the external frame. (C–D) Transverse bone transport was performed, two weeks medially (C) followed by two weeks laterally (D). Then the external fixator was removed. The cortex transport results in neovascularization and increased perfusion at the foot occur, eventually the ulcer healing.

was finished, the external fixator was removed. Four weeks later, the patients were allowed to ambulate with full weight-bearing.

2.6. Follow-up

Patients were followed weekly the first 12 weeks postoperatively and further followed every 3 months until the final 2-year evaluation. Digital photographs were taken and ulcer area was evaluated [19]. If major amputation (any resection proximal to the ankle) [46] was indicated, the decision was confirmed by independent investigators blinded to the treatments. After ulcer healing, off-loading shoes and/or soles were used.

2.7. Outcomes

The primary outcomes were the proportion of ulcer healing, recurrence, and patients with limb salvage (without major amputations) at 2-year follow-up. The secondary outcomes included the time to healing, changes in physical and mental component summary scores, and changes in the small-vessels and perfusion at the foot; and the kinds and numbers of complications. A healed ulcer was defined as complete epithelialization with no drainage of a previous ulcer site and maintaining for at least two weeks [46]. Recurrence was considered when a new ulcer occurred, irrespective of location and time, since previous ulcer [46]. These changes were assessed by an independent observer who did not perform the operations or the postoperative wound care.

2.8. Statistical analysis

Data are presented as mean ± standard division (SD) or number (%) as appropriate. Comparison of health-related quality of life and foot perfusion preoperatively and postoperatively were performed using paired t-tests. Statistical significance was set at an alpha level <0.05. SPSS version 20.0 (Chicago, IL, USA) was used for statistical analysis.

3. Results

A total of 1175 patients who underwent TTT within the study period were included. During the 2-year follow-up, 85 (7.2%) patients died from atherosclerotic vascular disease (myocardial infarction and/or stroke). Among the remaining 1090 patients, 18 (1.7%) were lost to follow-up, all after ulcer healing, leaving 1072 patients for evaluation (Table 1 and supplemental Table 1). Most of the patients were male (70.1%) and with a mean age of 60.4 ± 9.1 years.

Of the 1072 patients for final analysis by 2 years, 94.9% had complete ulcer healing (Figs. 3–4, supplemental Fig. 1 and Video 2-4), 4.9% underwent major amputation, and 3.1% experienced recurrences (Table 2). The mean time to healing was 12.4 ± 5.6 weeks. Patients underwent major amputations all before their ulcers were completely healed. Compared to preoperatively, the patients had higher physical (26.2 ± 8.3 versus 41.3 ± 10.6, $p = 0.008$) and mental (33.6 ± 10.7 versus 45.4 ± 11.3, $p = 0.031$) component summary scores at the 2-year follow-up (Fig. 5).

All patients had good union of the osteotomized cortex (Fig. 6). The complications included a few closed tibial fractures at the corticotomy site and pin site infections (Table 2), all occurred in the first quarter of patients recruited. They were treated using external fixators and dressing changes, respectively, and healed successfully. No infections of soft tissue or bone at the corticotomy site were found.

Compared to preoperatively, the patients had more small arteries (Fig. 7) and higher foot blood flow (8.1 ± 2.2 versus 28.3 ± 3.9 ml/100 g/min, $p = 0.003$) and volume (1.5 ± 0.3 versus 2.7 ± 0.4 ml/100 g, $p = 0.037$) 12 weeks postoperatively (Fig. 8).

4. Discussion

The management of recalcitrant DFUs was challenging and several recent single-center studies with relatively small populations reported that TTT facilities healing and limb salvage in patients with recalcitrant DFUs [19,21]. However, this novel technique requires further validation in a multicenter cohort study with relatively large populations. In this prospective multicenter cohort study, we found that TTT promotes healing, limb salvage, and improved health-related quality of life in patients with recalcitrant DFUs, and the complications are few and minor. The treatment effect of this technique is associated with

Table 1
Patient demographic and clinical data.

Variables	Total (n = 1072)
Age (years)	60.4 ± 9.1
Male sex, n (%)	752 (70.1)
BMI (kg/m^2)	22.9 ± 3.2
Type 2 diabetes, n (%)	1052 (98.1)
Diabetes duration (years)	21.7 ± 9.6
HbA1c (%)	9.6 ± 3.6
Coronary artery disease, n (%)	172 (16.0)
Stroke, n (%)	105 (9.8)
End-stage renal disease, n (%)	119 (11.1)
Former or current smoker, n (%)	193 (18.0)
Peripheral arterial disease (PAD), n (%)	871 (81.2)
Severe peripheral arterial disease detected by CTA (stenosis ≥80% or occlusion), n (%)	349 (32.6)
Ankle-brachial index (ABI)	0.46 ± 0.08
Peripheral neuropathy, n (%)	912 (85.1)
Ulcer duration (years)	1.3 ± 0.9
Prior contralateral major amputation, n (%)	104 (9.7)
University of Texas wound classification system, n (%)	
2-C	125 (11.7)
2-D	219 (20.4)
3-B	188 (17.5)
3-C	158 (14.7)
3-D	382 (35.6)
Foot osteomyelitis, n (%)	571 (53.3)
Ulcer area (cm^2)	41.0 ± 8.5
Site of the ulcer, n (%)	
Forefoot	398 (37.1)
Midfoot	309 (28.8)
Hindfoot	178 (16.6)
Extending above the ankle	187 (17.4)
Foot perfusion	
Blood flow (ml/100 g/min)	8.1 ± 2.2
Blood volume (ml/100 g)	1.5 ± 0.3
Quality of life	
Physical component summary score	26.2 ± 8.3
Mental component summary score	33.6 ± 10.7
Current treatment, % (n)	
Debridement	1072 (100)
Revascularization	112 (10.4)
Local or free flap/Skin graft or equivalent	0
Negative-pressure wound therapy	110 (10.3)

Data are presented as the mean ± SD or n (%).
BMI: Body mass index. HbA1c: glycated hemoglobin A1c. CTA: Computed tomography angiography.

neovascularization and increased perfusion at the foot after TTT.

Previous surgical techniques for management of DFUs demonstrated rates of healing ranging from 36% to 83% and rates of limb salvage from 14% to 93% with a follow-up period of 4 months to 2 years [12,47,49]. However, these surgeries were applied to patients with localized ulcers and with relatively few comorbidities [6,12]. Other studies using surgical protocols (early peripheral percutaneous angioplasty, extensive surgical debridement, and broad-spectrum intravenous antibiotic therapy) for more severe DFUs (University of Texas grade 2-C to 3-D) [28] reported healing rates of 60.8% and major amputation rates of 15.7% at a follow-up duration of 20 ± 13 months [50,51]. Chen et al. firstly applied TTT to a single-center cohort of patients (n = 136) with more severe and diffuse DFUs (53% in University of Texas grade 3-D; 10% extending above the ankle; and with a mean ulcer size of 44 ± 10 cm^2) and reported a better outcome (healing rate: 96%; limb salvage rate: 96%) in a 2-year follow-up [19]. In addition, the outcome was better than the comparable control (healing rate 72%; limb salvage rate: 77%; both $p < 0.001$) that received routing surgical treatments including revascularization, free or local flap or skin graft reconstruction [19]. Consistently, another single-center study applying TTT to less severe DFUs (12.9% in University of Texas grade 3-D, with a mean ulcer area of 2 cm^2, and with a popliteal artery patency rate >50%) reported good outcomes (both healing and limb salvage rate were 100%) after a 12-month follow-up [21]. In this study, we performed TTT on patients from multicenters with a relatively large sample size (n = 1072), of whom the risk factors and severity of DFUs were comparable to those treated in a previous study [19]. Our findings are in line with previous single-center data [19,21], and thus confirm the effect of TTT on recalcitrant DFU.

Previous studies on DFU treatment mainly focused on characteristics of ulcers [28,52]. Based on our experience in the treatment of DFUs using TTT [19], we have developed a comprehensive management protocol that takes into account the limb and the patient factors (Fig. 1). And to assure the quality of the current study, this protocol was adopted by surgeons of all the centers. According to this protocol, recalcitrant DFUs can be divided into four types, each of which with the corresponding treatment (Type 1: Gangrene, without infection or severe peripheral arterial disease, treated using TTT and debridement. Type 2: Infection, treated using TTT, debridement, and anti-infection. If the infection is severe, urgent/emergency debridement is necessary. Type 3: Systemic diseases, ulcers accompanied by impaired function or failure of one or more organs (kidney, heart, liver, etc.), treated using TTT, debridement, and multidisciplinary treatment (MDT). Type 4: Arteriopathy, ulcers combined with severe peripheral arterial disease in the major arteries of the lower limb, treated using revascularization, TTT, and debridement). The excellent outcome (healing and limb salvage) we attained following this management protocol suggests that it may serve as a guide for surgeons to apply TTT to recalcitrant DFUs.

According to our management protocol, one important subgroup of DFU patients are those with comorbid infections (ie, with type 2 ulcers). In our previous single-center study on DFUs treated using TTT, we recruited patients with recalcitrant DFUs that were not responsive to previous standard treatment for a relatively long duration (at least 6 months) [19]. This has excluded a portion of patients with shorter ulcer durations but also had recalcitrant DFUs (mainly infective/type 2 ulcers), particularly those initially presented with severe foot infections and/or sepsis or septic shock [34,41]. This portion of patients has a poor prognosis treated using conventional treatments [34,41]. However, with the powerful effect of TTT on promoting wound healing, we could perform aggressive (early and extensive) debridement including drainage of abscesses or infected compartments and resection of deep infected tissues and necrotic or infected bone, although a large wound may be left. Using this approach together with antibiotic therapy, we minimized the diabetic foot infection in this portion of patients and attained excellent outcome (healing and limb salvage). This has been an essential successful application of TTT in DFU treatment which has not been reported in previous studies [19,21]. Thus, to include this portion of patients in the current study, we planned to recruit DFU patients without responsiveness to previous standard treatment for a shorter duration. On the other hand, previous studies focusing on conservative/nonsurgical treatments of DFUs defined non-healing DFUs as those without healing within at least 4 weeks' duration [53,54]. Considering that TTT is a surgical intervention, we have been more cautious in its application and chose a longer duration of unresponsiveness to conventional management (at least 8 weeks).

Limb salvage aims to achieve an ulcer-free foot that is functional. A previous study found that DFU patients undergoing TTT were ambulatory after ulcer healing, but functional outcomes regarding health-related quality of life were not assessed [19]. Thus, there is a concern over whether this treatment, which has a lengthy recovery period, could be superior to major amputation. Thus, we assessed the health-related quality of life of the patients using Short Form 36-item, the most utilized instrument in the evaluation of DFU [40,55], in this study. Our findings of better health-related quality of life (higher physical and mental component summary scores) in patients with healed ulcers and limb salvage than those with persistent ulcers and major amputation (see videos), are consistent with previous studies using other limb salvage surgeries [56–58]. Furthermore, postoperative health-related quality of life was better than preoperatively (see videos), supporting the favorable outcome documented in a previous report using TTT [19]. On the other hand, patients with DFUs usually are older and with multiple

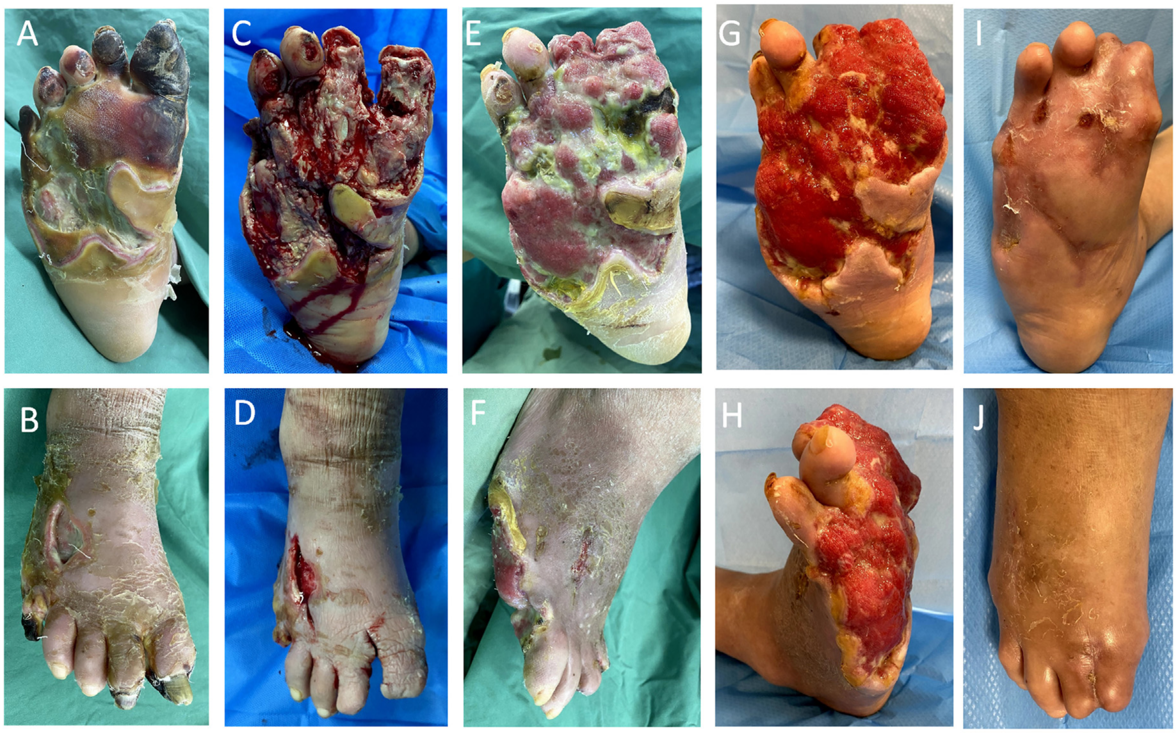

Figure 3. Effect of TTT shown in a typical case of recalcitrant DFU. This was a 61-year-old woman with a DFU at her right foot. (A-B) At admission, the patient had failed to respond to routine treatments for 14 weeks. Before the operation, severe ischemic necrosis involving the forefoot and midfoot was present. The fifth toe was gangrenous and the other toes were partially necrotic. CTA and ultrasound evaluation showed that the popliteal artery had severe stenosis (90% of the lumen) and revascularization (percutaneous angioplasty) was successfully performed. (C-D) Five days after revascularization, TTT and debridement were carried out. The necrotic tissues were removed, the fifth toe was amputated, and the first and the second toes were partially removed. This led to a large wound at the planta. (E-F) Four weeks postoperatively, the wound bed was present with abundant pale pink granulation tissue, part of which was necrotic and infective. (G-H) Eight weeks postoperatively, the granulation tissue was more prominent and redder, without necrosis or infection. Re-epithelialization was evident at the wound edge. (I-J) Twelve weeks postoperatively, the wounds were completely healed. The patient could walk independently (Supplemental Video 2).

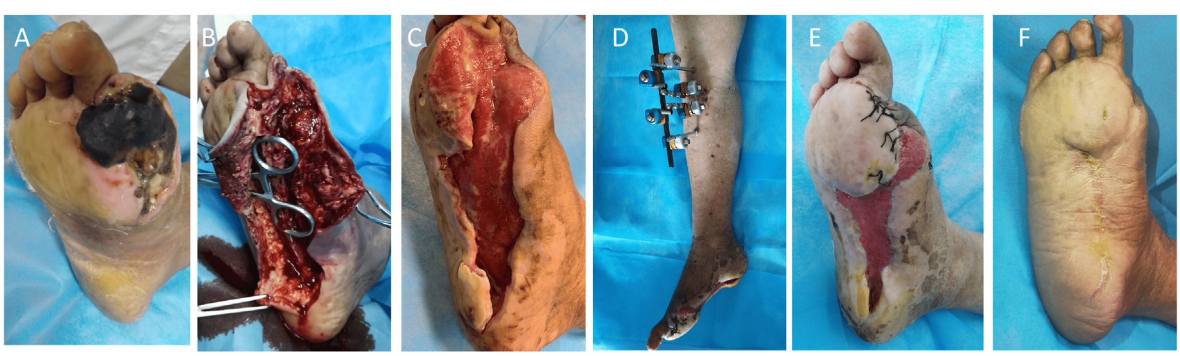

Figure 4. Effect of TTT shown in another typical case of recalcitrant DFU. This was a 61-year-old man with a recalcitrant DFU on his right foot (A) Before debridement, the first toe had been amputated but the wound failed to heal, covered by necrotic tissues and purulent discharge. (B) After debridement, the necrotic tissues were removed and the pus was thoroughly drained by opening the fistulas, leaving a large wound at the planta (C) Two weeks postoperatively, the wound was covered by robust granulation tissue and without infections. (D–E) Four weeks postoperatively, the wound was much narrower with epithelization at the edges, and the external fixator was removed (F) The wound was completely healed 10 weeks postoperatively (Supplemental Video 3).

comorbidities, and thus the rates of re-amputation, contralateral amputation, and premature mortality are relatively high after major amputation [51,57,59]. Thus, limb salvage using TTT may be more suitable than major amputation for patients with recalcitrant DFUs.

A previous study using TTT for recalcitrant DFUs reported few and minor complications [19]. They found 1.5% (two of 136) of closed tibial fractures at the corticotomy site and 2.2% (three of 136) of pin site infections, which were treated successfully using closed reduction and external fixation and dressing changes, respectively [19]. Consistently, using the same surgery protocol in this study, we found only a few closed tibial fractures and pin site infections after TTT that were treated successfully. The complications all occurred in the first quarter of patients recruited, indicating an association with the surgeons' clinical experience. The relatively low complication rates may have been attributable to several reasons. First, the accordion maneuver (2 weeks of medial transport followed immediately by 2 weeks of lateral transport, returning the osteotomized cortex to its original position) was applied during cortex transport, thus avoiding a thicker deformity of the tibia, penetration of the soft tissue, or even osteomyelitis or surgical site infections [60]. Second, the corticotomy site was selected as the anteromedial

Table 2
Outcomes of tibia cortex transverse transport for recalcitrant diabetic foot ulcers.

Items	Values
Healing (n, %)	1017 (94.9)
Time to healing (weeks)	12.4 ± 5.6
Major amputation (n, %)	53 (4.9)
Recurrence (n, %)	33 (3.1)
Closed tibial fracture (n, %)	8 (0.7)
Pin site infections (n, %)	23 (2.1)
Infections at the corticotomy site (n, %)	0

Data are presented as the mean ± SD or n (%).

surface of the proximal tibia which has higher perfusion than the middle and distal thirds; additionally, this site has a larger diaphyseal circumference, reducing the risk of tibial fracture. Third, we excluded patients if they had ulcers that extended above the ankle and were too near the surgical area (the distance between the ulcer margin and the surgical area was less than 5 cm). Because in such a situation, the risk of surgical site infections (soft tissue infections or even osteomyelitis) increases. Another previous study modified the surgery protocol into corticotomies of two bone blocks (2.5 cm × 2.5 cm) instead of one bone block (5.0 cm × 1.5 cm) and reported no fractures at bone transport site or pin site infections [21]. Collectively these results suggest that the procedure of TTT is safe. Considering that two corticotomies is more technically demanding than one corticotomy, a protocol of one corticotomy was adopted in this study.

Small-artery impairments and consequently decreased microperfusion contribute essentially to DFUs [14,15]. Although revascularization may restore the blood flow in the large arteries of the lower extremity, it fails to improve the foot microperfusion completely, leading to non-healing or delayed healing and major amputation [15]. Distraction osteogenesis stimulates angiogenesis in the surrounding soft tissues [25,26]. Furthermore, during the longitudinal distraction of the proximal tibia, the blood flow in the distal tibia increased 7-to-8 folds [61]. Thus, the finding of neovascularization and improved perfusion at the foot after TTT in the current and previous [19] studies are consistent with previous reports [25,26,61]. The neovascularization and improved perfusion at the foot are probably stimulated by TTT and contribute to ulcer healing and limb salvage. Nevertheless, the exact mechanism by which TTT promotes DFU healing needs to be studied in the future.

This study has several limitations. First, this is a multicenter trial which has an inherent problem that the heterogeneity in clinical practice among centers may be a major confounding factor in interpreting the results. For instance, different surgeons of different centers who might have various training levels performed the procedure. To reduce the impact of this factor, six surgeons, one at each center, who were responsible for the study, had been equally and substantially trained by participating in actual operations for three months in the coordinating center (YC's institute) and had independently performed this operation on at least 10 patients before the initiation of this study. In addition, some other surgeons of every center participated independently in data collection and patient evaluation during the follow-up.

Second, there is no control group in this multicenter cohort study and thus comparison of clinical outcome between the TTT and other routine surgical treatments (such as revascularization or flap reconstruction) was not performed. Thus, there may be confounding factors affecting the

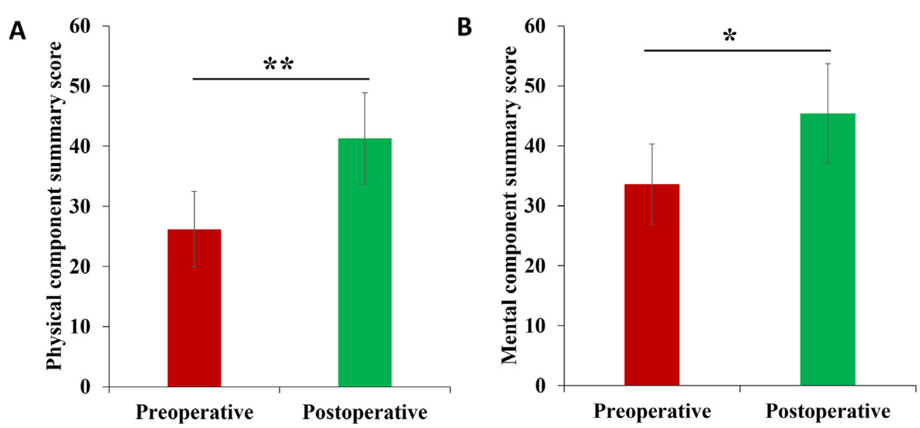

Figure 5. Changes in health-related quality of life in patients with recalcitrant DFUs treated using TTT. The patients had higher physical (A) and mental (B) component summary scores at the 2-year follow-up compared to preoperatively. * <0.05; ** <0.01.

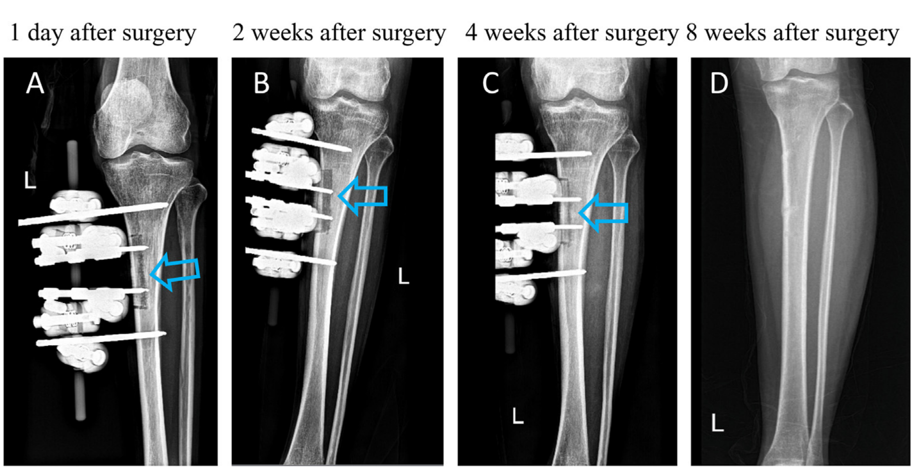

Figure 6. Evaluation of TTT using radiographs (A) The position of corticotomy and external fixator and the size of the cortex fragment were confirmed on radiographs 1 day postoperatively. (B) After a 2-week medial transport, the cortex fragment reached the maximal displacement from the tibial shaft (C) A 2-week lateral transport was performed, returning the cortex fragment to its original position. (D) The cortex fragment was completely united 8 weeks post-operatively (4 weeks after removal of the external fixator).

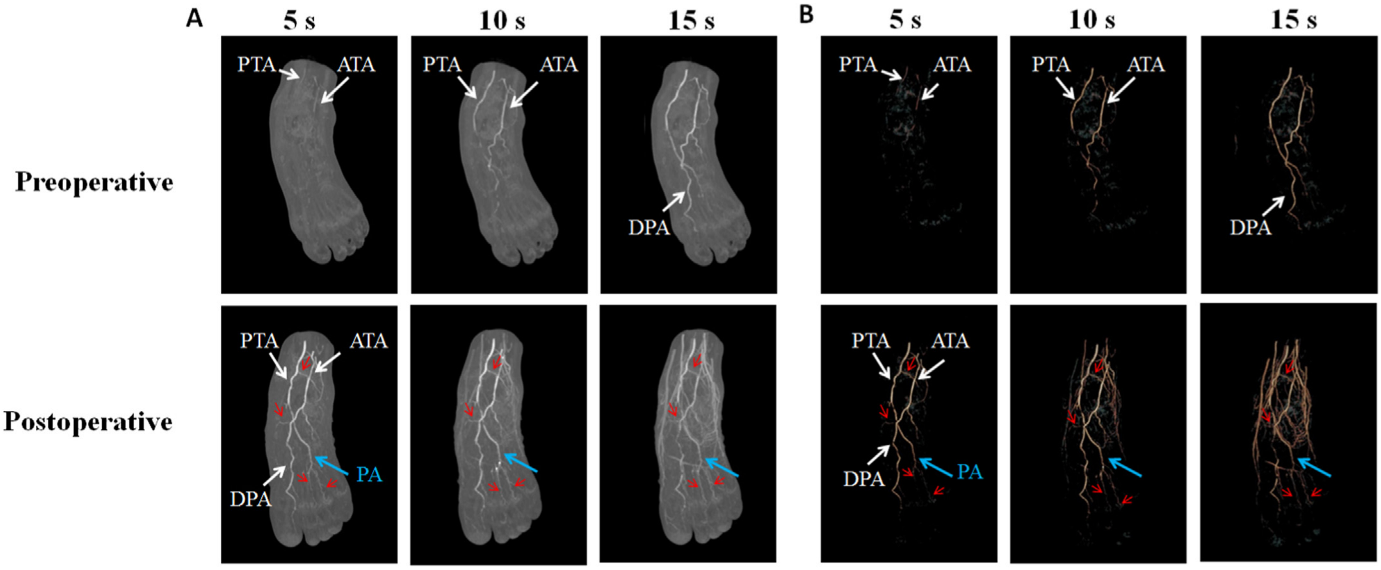

Figure 7. Representative CTA images from a patient with a recalcitrant DFU treated using TTT. The patient had a plantar DFU at the left foot which was completely healed 8 weeks postoperatively (A) The anterior tibial artery (ATA), posterior tibial artery (PTA), and dorsalis pedis artery (DPA) were present earlier and more extensively 12 weeks postoperatively than preoperatively (white arrows). The plantar artery (PA) became visible postoperatively than preoperatively (blue arrows), indicating patency after artery occlusion. Some small arteries were present postoperatively compared with preoperatively (red arrows), suggesting neovascularization. (B) Images showing the corresponding vessels.

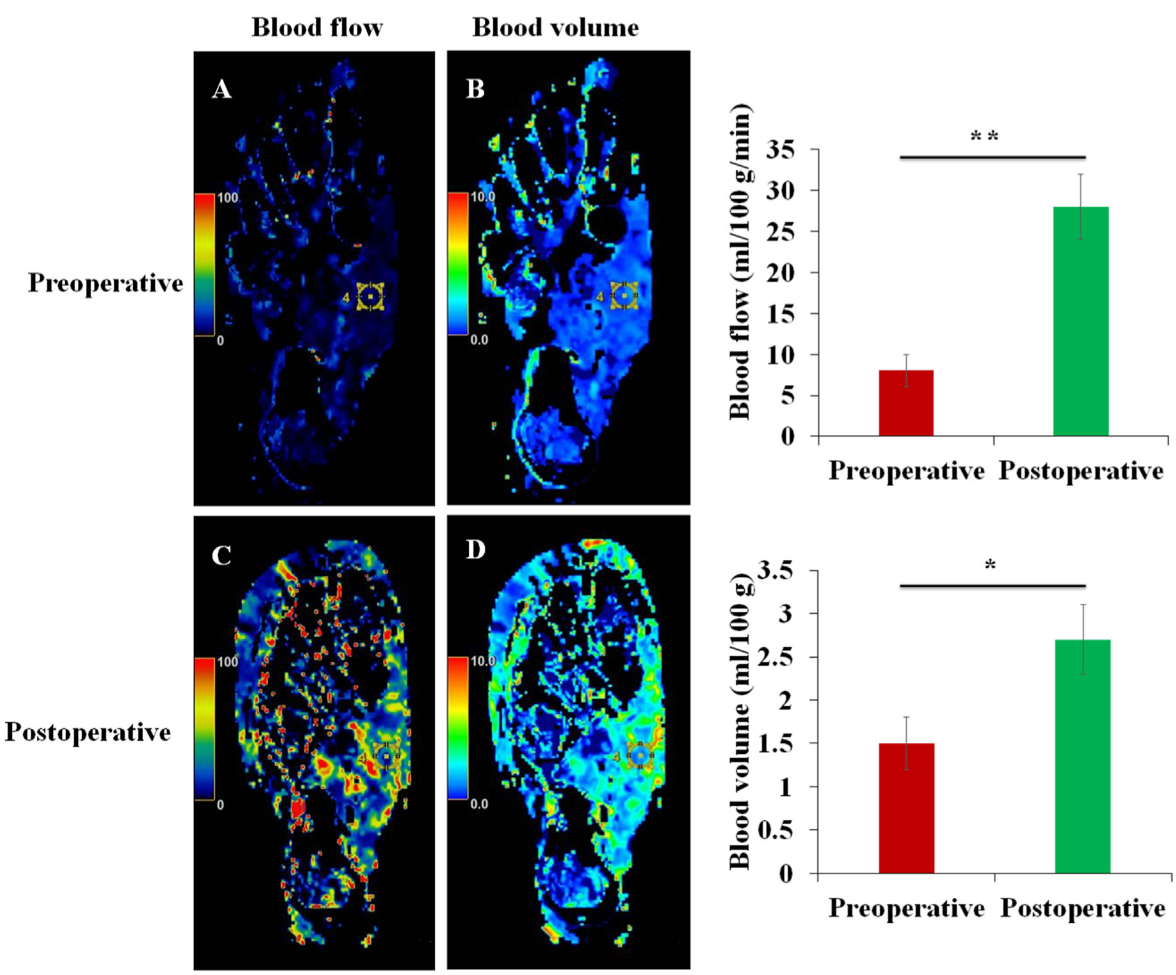

Figure 8. Computed tomography perfusion maps displaying blood flow and volume in feet with DFU treated using TTT. Compared with preoperatively (A-B), the feet tended to have increased blood flow and volume 12 weeks postoperatively when the ulcer had healed (C-D). This observation was confirmed using the statistical analysis. The circles show the region of interest selected at the abductor hallucis muscle. * $p < 0.05$; ** $p < 0.01$.

interpretability of the results. However, a prior single-center study had made such a comparison and found that TTT resulted in markedly higher proportions of ulcer healing and limb salvage and lower recurrences than routine surgical treatments [19]. Moreover, the severity of DFUs and the outcome of this study are comparable to that of the patients undergoing TTT in a previous study [19], which allows the comparison of the results between the two studies. In addition, compared to randomized controlled trials, a cohort study allows for longer observation periods and generally includes a broader spectrum of the population of interest. The results are more likely to represent widespread clinical practice. Therefore, this study may pave way for future comparative studies.

Third, although the relevant data were collected from the involved orthopaedic centers, the ulcers studied may not represent the traits of all patients with DFUs. Particularly, the data were from recalcitrant DFUs, and therefore may not generalize to DFUs of less severity. For instance, previous studies on DFU treatment mostly focused on ulcers distal to the ankle [17]. However, in this study, DFUs extending above the ankle, which is not uncommon in patients with recalcitrant DFUs [19], were also included. These ulcers generally have larger sizes and are more difficult to heal compared to those distal to the ankle. Against this, we attained excellent results (relatively high rates of ulcer healing and limb salvage and low recurrence rates at a mean follow-up period of 2 years), indicating that TTT is an effective procedure to treat recalcitrant DFUs compared with standard surgical therapy. However, because TTT is a surgical intervention, its application to milder DFUs should be cautious. According to our experience in the treatment of milder DFUs using TTT (data not shown), we suggest considering using TTT if the wound is not healing well for more than 8 weeks after other treatments.

Forth, although we evaluated foot perfusion using CT perfusion, a relatively new technique, we did not assess transcutaneous oxygen pressure (TcpO2) which reflects skin oxygenation status and is widely used in foot perfusion evaluation [62,63]. Thus, we had no data on transcutaneous oxygen pressure and could not analyze their correlation with the outcomes. Nevertheless, a previous study has reported increased transcutaneous oxygen pressure12-month postoperatively in DFU patients treated using TTT [21]. Furthermore, previous studies reported that measurement of transcutaneous oxygen pressure is susceptible to temperature variations and poorly repeatable, while CT perfusion is more reproducible and reliable [19,64,65]. The transcutaneous oxygen pressure method is not an imaging modality while CT perfusion can display anatomic structure and provide information on perfusion of soft tissues of the whole foot. Even so, it would be interesting to compare the two techniques in evaluation of perfusion in DFU in the future. In addition, health-related quality of life was evaluated using a generic scale, Short Form-36, but rather a disease-specific one such as the Diabetic foot ulcers Scale (DFS) scale [66]. The Short Form-36 was chosen because it performs well in DFU patients, who generally are eldly and with multiple complications, and is easy to use in a large, multicenter cohort study, yielding results with consistent quality and minimal missing data. Last, our cohort was Asian population, and, thus, our conclusion needs to be confirmed in other populations.

In conclusion, we found that TTT promotes healing, limb salvage, and health-related quality of life in patients with recalcitrant DFUs. The procedure was simple and straightforward and the complications were few and minor. The effect of this technique was associated with neovascularization and improved perfusion at the foot mediated by the cortex distraction. These findings need to be confirmed in randomized controlled trials.

Ethical statement

The study protocol was approved by the institutional review board of each participating center and conducted according to the principles of the Declaration of Helsinki. Written informed consent was obtained from each patient prior to inclusion of the study.

All the authors claim that

1. All authors agree with the submission; 2. The work has not been published or submitted for publication elsewhere, either completely or in part, or in another form or language; 3. No material has been reproduced from another source.

Declaration of competing interest

Each author certifies that he or she has no commercial associations (eg, consultancies, stock ownership, equity interest, patent/licensing arrangements, etc) that might pose a conflict of interest in connection with the submitted article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jot.2022.09.002.

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