

## Retrospective Study

# Does the advantage of transcutaneous oximetry measurements in diabetic foot ulcer apply equally to free flap reconstruction?

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## Abstract

### BACKGROUND

Transcutaneous oxygen pressure (T<sub>cp</sub>O<sub>2</sub>) is a precise method for determining oxygen perfusion in wounded tissues. The device uses either electrochemical or optical sensors.

### AIM

To evaluate the usefulness of T<sub>cp</sub>O<sub>2</sub> measurements on free flaps (FFs) in diabetic foot ulcers (DFUs).

### METHODS

T<sub>cp</sub>O<sub>2</sub> was measured in 17 patients with DFUs who underwent anterolateral thigh (ALT)-FF surgery and compared with 30 patients with DFU without FF surgery.

### RESULTS

Significant differences were observed in the ankle-brachial index; duration of diabetes; and haemoglobin, creatinine, and C-reactive protein levels between the two groups. T<sub>cp</sub>O<sub>2</sub> values were similar between two groups except on postoperative days 30 and 60 when the values in the ALT-FF group remained < 30 mmHg and did not increase > 50 mmHg.

### CONCLUSION

Even if the flap is clinically stable, sympathectomy due to adventitia stripping during anastomosis and arteriovenous shunt progression due to diabetic polyneuropathy could lead to low T<sub>cp</sub>O<sub>2</sub> values in the ALT-FF owing to its thick fat tissues, which is supported by the slow recovery of the sympathetic tone following FF. Therefore, T<sub>cp</sub>O<sub>2</sub> measurements in patients with DFU who underwent FF reconstruction may be less accurate than in those who did not.

**Key Words:** Arteriovenous shunt; Surgical; Diabetic neuropathies; Free tissue flaps;

Sympathectomy; Blood gas monitoring; Transcutaneous; Diabetic angiopathies

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**Core Tip:** Transcutaneous oxygen pressure (TcPO<sub>2</sub>) is measured low in free flap (FF) reconstruction for the following reasons. The flap itself is thick, making it difficult to accurately measure TcPO<sub>2</sub>, the adventitia stripping that occurs during vessel anastomosis semi-permanently reducing the sympathetic tone of the entire vessel, and the arteriovenous shunt caused by performing FFs and the progression of diabetes, thought to occur. For this reason, long-term periodic TcPO<sub>2</sub> measurement is not useful when FF reconstruction is performed on diabetic foot ulcer.

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## INTRODUCTION

Free flap (FF) is a surgical procedure that involves transplanting a patient's own tissue to the recipient site, similar to free tissue transfer or transplantation. Among the preferred options for soft tissue reconstruction, anterolateral thigh FF (ALT-FF) is a popular surgical technique because of its high reliability and versatility, ease of harvest, and low donor-site morbidity. In addition, the redundancy of the thigh skin allows harvesting of a relatively large flap area to reconstruct the defect site[1].

Several devices are used for FF monitoring; however, no equipment guarantees flap survival[2]. Conventionally, flap monitoring includes skin warmth and color, capillary refill, and hand Doppler monitoring but is subjective and does not objectively guarantee flap survival. Proper blood flow is the most important factor in ensuring flap survival, and measuring tissue oxygen levels is the basis for ensuring proper circulation[3,4]. Oxygen plays an important role in the pathophysiological process of flap survival; therefore, quantifying oxygen concentration *in vivo* is important. In routine clinical settings, oximetry must be noninvasive, reliable, repeatable, and capable of directly measuring partial oxygen pressure. In particular, the instrument must be able to provide repeated measurements in the region of interest to monitor changes in oxygen tension during the observation period.

The measurement of transcutaneous oxygen pressure (TcPO<sub>2</sub>) is a noninvasive and clinically approved method for measuring tissue perfusion. The necessary instrument was originally developed to measure the partial pressure of arterial oxygen and partial pressure of arterial carbon dioxide[5]. These electrodes contain heating coils that increase the temperature, thereby allowing a subsequent increase in integumentary tissue perfusion. The amount of oxygen was calculated from the amount of light absorbed[6]; TcPO<sub>2</sub> was quantitative and free of operator bias[7].

Diabetic foot ulcer (DFU) is one of the most catastrophic complications of diabetes, and peripheral artery disease (PAD) occurs as diabetic neuropathy progresses[8]. As the morbidity period of diabetes increases, sensory nerve function decreases, and wound healing is significantly delayed[9]. In this case, TcPO<sub>2</sub> was initially measured to determine the vascular status of DFU[10]. In patients with diabetes, TcPO<sub>2</sub> values are significantly lower than those in patients who are not, and studies have revealed that low TcPO<sub>2</sub> due to impaired tissue oxygenation may be the cause of DFUs[11,12]; perfusion disorders are indicated by a decrease in skin oxygenation before the appearance of clinical overt microangiopathy. The normal range of TcPO<sub>2</sub> metric value is approximately 60 mmHg regardless of electrode placement[13-15]. Moreover, TcPO<sub>2</sub> must be > 40 mmHg for adequate wound healing, and impaired wound healing occurs between 20 and 40 mmHg[16]. Additionally, wound healing generally fails when TcPO<sub>2</sub> values are < 20 mmHg[17]. In June 2007, the Trans-Atlantic Inter-Society Consensus suggested a standard TcPO<sub>2</sub> value > 30 mmHg for revascularization to prevent lower limb amputation[18,19].

Periodic measurement of TcPO<sub>2</sub> may predict the effects of DFU amputation and diabetic neuropathy treatment based on a decrease in its value[20-22]. Even when FF reconstruction is performed in DFU cases, vessel anastomosis is difficult owing to atherosclerosis, making the operation and surgical prognosis difficult to predict owing to impaired angiogenesis [23]. Therefore, research is required to determine the abovementioned advantages of TcPO<sub>2</sub> measurement when assessed periodically at the FF of the DFU for a longer period of time. In this study, we assumed that the reduced pattern of TcPO<sub>2</sub> would apply equally to FF reconstruction and we decided to conduct a study to determine whether the change in TcPO<sub>2</sub> levels would recover as wound healing occurred. Then, we intended to identify the numerical pattern of change in TcPO<sub>2</sub> and interpret its meaning as the FF was stabilized. Furthermore, we aimed to determine whether periodic TcPO<sub>2</sub> measurements are efficient for FF reconstruction in patients with DFU.

## MATERIALS AND METHODS

### Design

We retrospectively reviewed the records of patients who underwent FF reconstruction between 2021 and 2022 in Soonchunhyang Cheonan Hospital. The wounds of patients requiring FFs were all defective owing to DFU. All FFs were performed using ALT-FFs to minimize selection bias and unify results. ALT-FF was performed by three surgeons at a single institution. In addition to the FF group with DFU patients, a group of DFU patients who did not receive FFs was included to establish a control group.

### Device

TcpO<sub>2</sub> was measured using the TCM400® (Radiometer Medical ApS, Copenhagen, Denmark) (Figure 1). The probes were placed at two locations, and measurements were subsequently performed. One location was the skin perforator of the flap, where the flap pedicle penetrated the skin, and the other was the most distal part of the flap (Figure 2). The contact liquid, supplied by the manufacturer, was applied to the retaining ring to secure the electroprobe. The electrode was measured for 10 min to obtain a stable plateau curve. In this study, the electroprobe setting temperature was adjusted to 41 °C. The room temperature was maintained between 18 °C and 24 °C in the same place before measurement.

### Patients

In total, 22 records of patients with ALT-FF were obtained. Seventeen patients were included in this study after excluding the patients who dropped out and those with incomplete clinical databases. Thirty patients with DFU who did not undergo FF were included.

After the ALT-FF, TcpO<sub>2</sub> was measured on postoperative days (PODs) 1, 5, 10, 15, and 20 for short-term monitoring. Long-term monitoring was performed on PODs 30, 60, 90, and 180. The patients were divided into two groups, *i.e.*, short and long terms based on the measured POD. The changes in time and TcpO<sub>2</sub> value were then investigated. The location of the DFU was classified based on the angiosomes of the anterior tibial artery (ATA) and posterior tibial artery (PTA) in the group that did not receive FF; TcpO<sub>2</sub> was then subsequently measured (Figure 3). Clinical photographs were taken using an ILCE-7M4 (SONY, Tokyo, Japan) camera at a standard distance (40 cm) to assess the wounds and flaps.

### Risk factor designation

Age, sex, glycosylated haemoglobin A, smoking history, preoperative ankle-brachial index (ABI) after hospitalisation, haemoglobin (Hb), creatinine (Cr), nephropathy, angiosome, duration of diabetes mellitus (DM), duration of hypertension (HTN), C-reactive protein (CRP), body mass index, and TcpO<sub>2</sub> values in the FF group and the group without FF were compared. These included variables identified as significant risk factors for DFU amputation in previous studies[24]. The TcpO<sub>2</sub> value of the FF group was based on the perforator when the flap was sufficiently stabilized on POD 30 compared with that of the control group.

### Statistics

This study was performed using SPSS (version 26.0; IBM Corp., Armonk, NY, United States). Categorical variables were compared using Pearson's  $\chi^2$ , Fisher's exact, Student's *t*-, and Mann-Whitney *U* tests. Only variables with *P* < 0.05 were considered statistically significant.

## RESULTS

### Patient demographic characteristics

Based on the medical records, we reviewed 17 patients with DFU who received FFs (FF group) and 30 patients with DFU who did not receive FFs (DFU group). Table 1 presents the demographic characteristics of the FF and DFU groups. Several demographic risk factors were compared between the two groups. ABI, Hb, Cr, duration of DM, and CRP levels were significantly different between the two groups. The ABI group had a higher mean value than the FF group. The TcpO<sub>2</sub> value was 12.01 mmHg at POD 30 in the FF group and 14.50 mmHg in the DFU group, which was significantly low in both groups; no significant difference was noted between the two groups (*P* = 0.812).

In addition, the change in TcpO<sub>2</sub> value based on POD was investigated. A value < 10 mmHg was regarded as a 'very low' TcpO<sub>2</sub> value. On POD 30, ALT FF was successfully performed without complications, despite the very low TcpO<sub>2</sub> values in four patients (23.53%). The change in TcpO<sub>2</sub> value over time showed a significant difference for each POD in the FF group. A comparison of the perforator (branching off from vessels and extending into the skin and fat tissue) and distal portion of the flap based on POD showed no difference according to position (Table 2). However, a significant difference was observed when comparing the short- (until POD 20) and long-term (after POD 30) results through division. The short-term *P* value was 0.006, and the long-term *P* value was 0.002, showing significant changes as POD progressed. Upon short-term follow-up, a gradual increase was observed (Figure 4A), while upon long-term follow-up (POD 30 onwards), a gradual decrease was observed. A similar pattern was observed (Figure 4B). This pattern showed a similar trend in the perforator and distal portions of the flap. However, the TcpO<sub>2</sub> value was low (< 30 mmHg), except for PODs 30 and 60.

**Table 1** Demographic characteristics of patients with diabetic foot ulcer with and without free flap

	Total (n = 47)	Free flap (n = 17)	DFU (n = 30)	P value
Sex				
Male	31 (65.96)	10 (58.82)	21 (70.00)	0.437
Female	16 (34.04)	7 (41.18)	9 (30.00)	
Age	61.36 ± 2.04	54.76 ± 3.62	65.10 ± 2.21	0.013
Smoking history				
Non-smoker	23 (48.94)	11 (64.71)	12 (40.00)	0.104
Smoker	24 (51.06)	6 (35.29)	18 (60.00)	
HbA1c	7.00 (6.00-9.10)	6.20 (5.60-9.00)	7.25 (6.10-9.20)	0.084
HTN				
None	17 (36.17)	9 (52.94)	8 (26.67)	0.072
HTN	30 (63.83)	8 (47.06)	22 (73.33)	
Nephropathy				
None	34 (72.34)	15 (88.24)	19 (63.33)	0.094
Nephropathy	13 (27.66)	2 (11.76)	11 (36.67)	
Angiosome				
ATA	26 (55.32)	7 (41.18)	19 (63.33)	0.138
PTA	21 (44.68)	10 (58.82)	11 (36.67)	
TcpO <sub>2</sub>	13.00 (6.00-22.00)	12.01 (8.01-15.01)	14.50 (6.00-22.00)	0.812
ABI				
Affected side	1.02 ± 0.03	1.14 ± 0.03	0.95 ± 0.05	0.002
Unaffected side	1.06 ± 0.03	1.13 ± 0.02	1.03 ± 0.04	0.024
Creatinine	1.07 (0.72-3.12)	0.74 (0.63-0.86)	1.98 (0.95-6.27)	0.001
Hb	11.10 ± 0.25	11.83 ± 0.31	10.68 ± 0.33	0.024
Duration of DM (yr)	10.00 (5.50-15.00)	3.00 (1.00-10.00)	13.50 (10.00-20.00)	< 0.001
Duration of HTN (yr)	10.50 (10.00-20.00)	11.00 (2.00-20.00)	10.00 (10.00-20.00)	0.666
CRP	11.24 (4.21-35.70)	3.50 (1.70-10.57)	27.78 (8.20-73.71)	< 0.001
BMI	23.96 ± 0.71	23.84 ± 1.28	24.03 ± 0.87	0.896

ABI: Ankle-brachial index; ATA: Anterior tibial artery; BMI: Body mass index; CRP: C-reactive protein; DFU: Diabetic foot ulcer; DM: Diabetes mellitus; Hb: Haemoglobin; HbA1c: Glycosylated haemoglobin A; HTN: Hypertension; TcpO<sub>2</sub>: Transcutaneous oxygen pressure; PTA: Posterior tibial artery.

### Treatments and outcomes

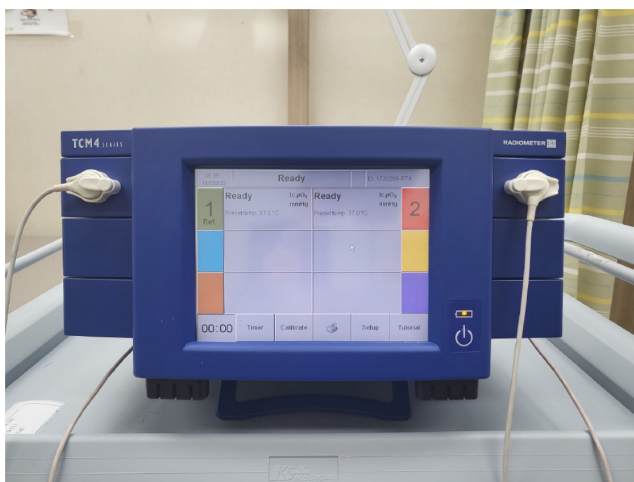
**Case 1:** A 61-year-old man presented with a necrotic DFU, 5 cm × 8 cm in size, on the dorsum of the left foot. The patient had been diagnosed with DM and HTN 20 years prior. The patient underwent reconstruction with an ALT-FF after removing the necrotic tissue and performing several debridements. End-to-end anastomosis was also performed on the dorsalis pedis artery and two vena comitans. Flap failure was not observed, and TcpO<sub>2</sub> was measured according to POD. Limb salvage was successfully performed, and no wound recurrence was noted until POD 360 (Figure 5).

**Case 2:** A 62-year-old man presented with multiple skin defects on the left ankle. The patient had been diagnosed with DM and HTN 3 years prior. The DFU was reconstructed with an ALT-FF after removing the necrotic tissue and performing several debridements. The end-to-side anastomosis was performed on the PTA; end-to-end anastomosis was performed on two vena comitans. Additionally, end-to-end anastomosis was performed in a flow-through manner (conserving vessels through performing end-to-end anastomosis on both sides of the recipient vessel) after identifying one dorsal recipient vein. Flap failure was not observed, and TcpO<sub>2</sub> was measured according to POD. Flap debulking was performed on POD 192 owing to discomfort during ankle joint movement. No wound recurrence was observed until POD 360 (Figure 6).

**Table 2 Comparison of transcutaneous oxygen pressure values based on postoperative day in the group that received free flap**

Value	Perforator	Distal	P value
POD 1	8.64 ± 10.72	8.27 ± 11.62	> 0.099
POD 5	18.64 ± 14.43	19.36 ± 16.11	> 0.99
POD 10	14.00 ± 16.35	16.73 ± 15.51	> 0.99
POD 15	13.82 ± 13.41	16.18 ± 13.40	> 0.99
POD 20	17.82 ± 18.21	31.00 ± 26.81	0.972
POD 30	45.86 ± 33.20	47.14 ± 23.13	> 0.99
POD 60	30.43 ± 21.95	35.57 ± 26.48	> 0.99
POD 90	18.71 ± 5.35	18.71 ± 17.37	> 0.99
POD 180	15.43 ± 11.10	19.57 ± 22.23	> 0.99
POD 360	12.86 ± 7.78	16.43 ± 13.78	> 0.99

POD: Postoperative day.



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**Figure 1 Transcutaneous oxygen pressure measuring instrument (TCM400®).**

## DISCUSSION

In our study, the proportion of TcpO<sub>2</sub> levels in FFs that did not increase by more than 30 mmHg even after POD 30 was 35.3% (6/17). Before discussing, let us firstly mention the relationship between DFU and TcpO<sub>2</sub>. Wound formation in DFU is mostly due to PAD, and there are several ways to examine the peripheral blood flow state[25]. TcpO<sub>2</sub>, skin perfusion pressure, and fluorescence angiography were performed to identify regional tissue perfusion. The advantages and disadvantages of each device are listed in Table 3. The ABI is routinely used to screen for PAD. However, these results are less reliable in patients with diabetes with severe neuropathy and arterial calcification[34]. In such case, TcpO<sub>2</sub> may be helpful in predicting the risk of amputation and disease progression[35-37].

Various factors affect the measurement of TcpO<sub>2</sub>. First, measurement of TcpO<sub>2</sub> is affected by the partial pressure of oxygen in the artery. TcpO<sub>2</sub> decreases in the presence of vascular injury and atherosclerosis[38]. Skin thickness also affects TcpO<sub>2</sub> measurements[39]. Therefore, thick fatty tissues and bones should be avoided. In addition, determining the area of good capillary phenomena remains achievable[40]. Finally, the temperature of the capillary under the measuring electroprobe also has an effect. The electroprobe for TcpO<sub>2</sub> uses heated metal electrodes placed directly on the skin. During the measurement, the skin temperature under the electrode increased by up to 44 °C, thereby dilating the blood vessels of the subdermal plexus and subsequently increasing the oxygen permeability.

Several limitations to TcpO<sub>2</sub> measurement have been noted during wound assessment. First, it requires a considerable amount of time for measurement, which lasts 10-15 min. Second, its sensitivity is low, although it does not cause pain to patients unlike the nerve conduction velocity method. Third, the presence of cellulitis or significant oedema in the tissue interferes with measurement[41]. Fourth, it reflects the state of blood flow only in parts of the skin and not in major blood vessels. Therefore, obtaining accurate values for thick tissues is difficult. Finally, TcpO<sub>2</sub> measurement is heavily

**Table 3 Advantages and disadvantages of devices that determine blood flow status in diabetic foot ulcer**

	Advantages	Limitations
<b>Assessment of disease severity</b>		
ABI (normal range 1.1-1.3)	Widely used, easy to measure	Unreliable in patients with severe PAD, DFU[26]
TBI (normal range 1.0-1.1)	Compensating for ABI limitations, easy to repeat measurement	Decreased accuracy at severe vessel calcification, limitation of diagnostic threshold[27]
Continuous wave Doppler	High accuracy in PAD diagnosis[28]	Decreased accuracy in DFU[28]
Pulse volume recording	Used in PAD diagnosis	Unable to determine exact location, many other variables [29]
<b>Assessment of morphological distribution</b>		
Duplex ultrasound	Noninvasive	Complemented by more detailed image required
Angiography	Detailed images can be provided, fast	Vulnerable to artifacts, risk for contrast nephropathy
<b>Assessment of regional tissue perfusion</b>		
TcpO <sub>2</sub> (normal range 40-70 mmHg)	More sensitive than ABI	DFU, autonomic neuropathy, low accuracy for severe vascular calcification[12]
Skin perfusion pressure	Useful when ABI, TBI are not possible	Requires special equipment and further validation[30]
Fluorescence angiography	Low toxicity compared with angiography, good discriminatory ability[31]	Expensive, requires special equipment
Laser Doppler	Evaluate blood flux rather than blood flow	Vulnerable to motion artifacts and temperature changes, inter-operator variation
Hyperspectral imaging	Useful for determining the effect of DFU treatment	Lack of research on interpretation of results[32]
<b>Molecular imaging</b>		
PET and SPECT	High resolution	Expensive, requires special equipment
Contrast-enhanced ultrasound	Excellent for PAD discrimination[33]	Low accuracy for DFU[33]
Multi-modal MRI	Semi-quantitative evaluations based on relative patient conditions are possible	Take long time, no evidence of effectiveness for DFU

ABI: Ankle-brachial index; DFU: Diabetic foot ulcer; MRI: Magnetic resonance imaging; PAD: Peripheral artery disease; PET: Positron emission tomography; SPECT: Single-photon emission computed tomography; TcpO<sub>2</sub>: Transcutaneous oxygen pressure; TBI: Toe brachial index.

influenced by skin temperature. This measurement is possible only when skin perfusion is measured using a heated metal electrode.

According to our study, the percentage of TcpO<sub>2</sub> levels in FFs that did not increase > 30 mmHg, even after sufficient POD (POD 30), was 35.3% (6/17), which accounted for a fairly large percentage. No increase in the value was noted in these patients even though the flap thickness was significantly decreased. Almost all the TcpO<sub>2</sub> average values were < 30 mmHg except for PODs 30 and 60. In addition, the TcpO<sub>2</sub> value did not increase even though a significant temperature increase was observed when monitored with a thermometer. In addition, low TcpO<sub>2</sub> was measured regardless of which recipient artery (ATA or PTA) was used or whether the anastomosis method was end-to-end or end-to-side. Therefore, the following are reasons for the low TcpO<sub>2</sub> during measurement:

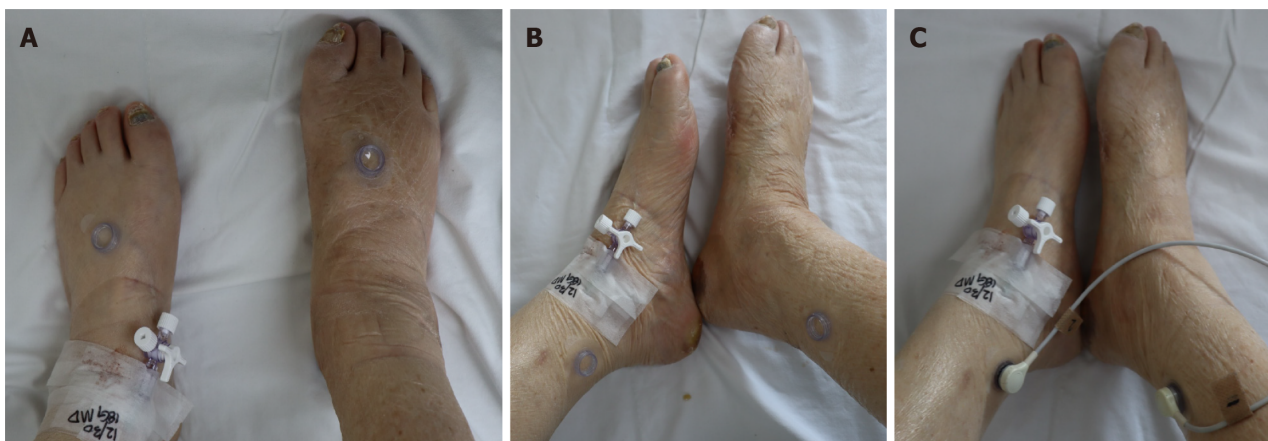
First, mid-thigh tissue was used as the donor site in the case of ALT-FF performed in this study. The ALT-FF is usually at least 1-cm thick during flap elevation. The subcutaneous fat tissue of the thigh is thicker than the other tissues, making it difficult to accurately measure TcpO<sub>2</sub>[42].

Second, since the electroprobe of TcpO<sub>2</sub> consumes oxygen during measurement, it is difficult to measure if the oxygen level that may present on the skin temperature is low. Moreover, the method is prone to calibration errors. In essence, the TcpO<sub>2</sub> value can be measured at 0 mmHg even if the skin flap has significant perfusion[6]. As the temperature of the electroprobe increased, the skin temperature also increased, thereby correcting the value of TcpO<sub>2</sub>. However, in the FF of the DFU, the normal response of the flap skin temperature did not increase even when the electroprobe temperature increased. This may be due to insufficient sympathetic tone[43]. Moreover, this may also be due to the surgical removal of the arterial adventitia by many surgeons during artery anastomosis to prevent vasospasm[44]. Sympathetic innervation of the major vessels of the foot is most evident in the adventitia, which is the outermost layer of the artery (Figure 7)[45]. Nerve regeneration did not occur when a periarterial sympathectomy was performed. Based on these findings, the removal of the adventitia from the FF resulted in semi-permanent sympathetic nerve denervation. A significant TcpO<sub>2</sub> value could not be obtained if the dominance of the sympathetic nerve decreased and the temperature of the flap skin did not increase in response to the temperature of the sensor. Chao and Cheing[46] reported that when the sympathetic nerve



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**Figure 2** A photographic image of transcutaneous oxygen pressure applied to an anterolateral thigh free flap patient. A: On postoperative day 1, free flap operation site surviving well; B: Place two probes on the skin perforator site (site marked 1 in the image) and the most distal part of flap (site marked 2 in the image), respectively.

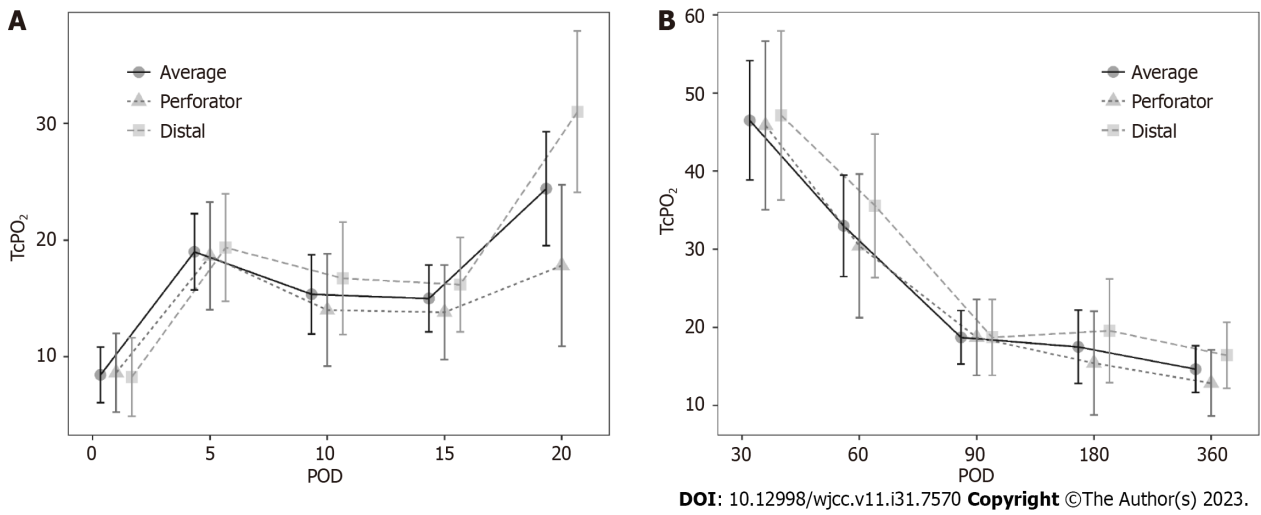


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**Figure 3** A photographic image of transcutaneous oxygen pressure applied to a diabetic foot ulcer patient without free flap reconstruction. A: Probe located in anterior tibial artery; B: Probe located in posterior tibial artery; C: Transcutaneous oxygen pressure measurement.

present in the adventitia is removed, the functions of the smooth muscle and endothelium, which are the vascular structures inside the adventitia, also decrease. Adventitial damage may result in extensive vascular insufficiency. In this study, the ABIs of the FF group were > 0.9, and the average value was higher than that of the DFU group, regardless of whether a wound was present on the left or right side. This indicates that patients in the FF group did not have severe PAD or neuropathy compared with those in the DFU group. Nevertheless, the  $TcpO_2$  value remains low even after a sufficient period of time. Thus, sympathectomy performed during anastomosis may not have been recoverable, and the recovery was insignificant. Furthermore, flap skin reperfusion was not restored. Additionally, if a low  $TcpO_2$  value was observed even with a normal ABI, this finding suggested that diabetic neuropathy was caused by a decrease in sympathetic tone[47].

Third, as diabetic angiopathy progresses, an arteriovenous (AV) shunt develops in the peripheral blood vessels. The skin microcirculation consists of two horizontal plexus structures: The deeper subpapillary plexus and the superficial cutaneous plexus. Among these, the subpapillary plexus is responsible for more than 80% of blood flow[48]. Their actions are regulated by a complex interplay between neurogenic and neurovascular regulation[46]. Arteriovenous vessels have thicker walls and lower resistance than capillaries, allowing blood to flow at a relatively higher rate directly from the arterioles to the venules. In advanced DFU lesions, peripheral capillary resistance increases, and blood flow decreases owing to microvasculopathy caused by advanced diabetic polyneuropathy and vasodilation impairment. Therefore, AV shunting to the subpapillary system, which has a lower resistance than the capillaries, occurs more frequently than in the

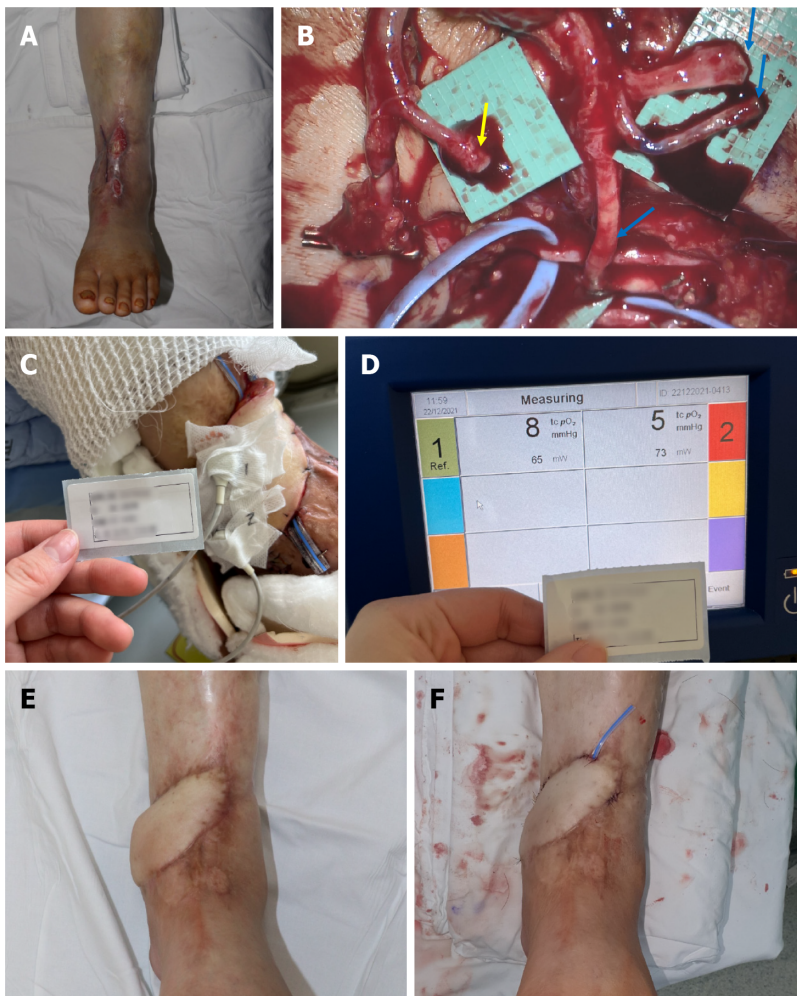


**Figure 4** Change in transcutaneous oxygen pressure during the short-term and long-term period. A: Short-term period. Although the value is low, a gradual increasing pattern is observed; B: Long-term period. Although the value is low, a gradual decreasing trend is observed. POD: Postoperative day.



**Figure 5** Photographic findings of patient 1. A: Diabetic foot ulcer (DFU) on the left foot dorsum with necrotic tissue observed before debridement; B: One artery and two vena comitans successfully undergo end-to-end anastomosis (yellow arrow: Artery, blue arrow: Vein); C: Transcutaneous oxygen pressure measured on postoperative day (POD) 30; D: Successfully reconstructed DFU wound on POD 360.





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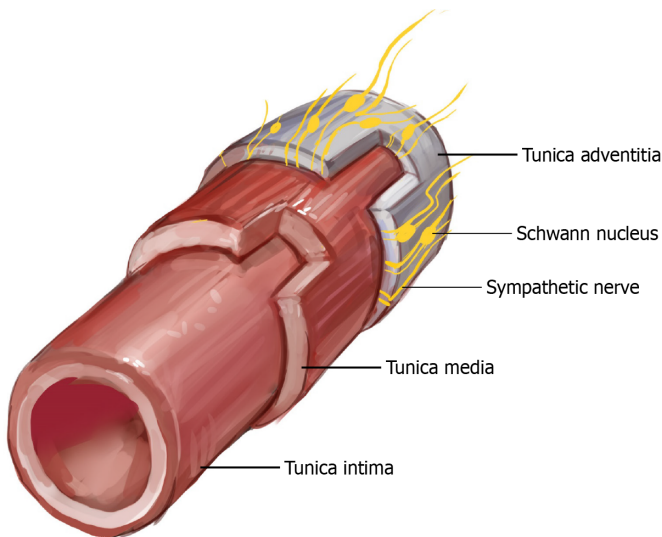
**Figure 6 Photographic findings of patient 2.** A: Preoperative findings, tendon, and periosteum exposed; B: The adventitia is stripped from the artery (yellow arrow), and the three veins are anastomosed (blue arrow); C and D: Transcutaneous oxygen pressure measured at postoperative day (POD) 1. Very low values of 8 and 5 mmHg are shown; E: Before flap debulking on POD 180; F: After flap debulking was performed on POD 192.

normal foot (Figure 8). Early venous enhancement occurs during the early inflammatory reaction of diabetic angiopathy, which supports the maldistribution of blood flow between the nutritional capillaries and subpapillary vessels, and the AV shunt caused by diabetic angiopathy occurs more peripherally[49]. An increased subpapillary AV shunt reduces the exchange of oxygen and metabolites between the capillaries and peripheral tissues, thus leading to ischemia and delayed wound healing. In this study, the FF group had an inadequate oxygen supply to the AV shunt and peripheral tissues. In addition, removal of the adventitia resulted in sympathectomy, whereas regeneration of the removed sympathetic nerve did not occur, resulting in failure to recover from the AV shunt. Even with flap operation, if blood flow was greater to the artery than before or after anastomosis, the theory that the AV shunt increases without the choke vessel opening would have been proven through cadaver and animal studies[50]. Thus, AV shunt can become more severe as diabetic angiopathy progresses. In summary, measuring  $TcpO_2$  appropriately in FFs is difficult because of decreased sympathetic tone, malfunctioning vasculature, and AV shunting.

This study has a statistical limitation; it compared the data of only 17 patients with complete  $TcpO_2$  values, which was insufficient to highlight the complete interpretation of the  $TcpO_2$  numerical pattern. Measuring  $TcpO_2$  at more frequent intervals is also necessary. Thus, a larger multi-institutional study with a larger number of patients is required. In addition, a prospective study may also be required to validate the effectiveness of the risk factors identified in our study for  $TcpO_2$  pattern analysis. In particular, sympathectomy and AV shunt formation, which were suggested as the prime causes of low  $TcpO_2$ , require identification through additional experiments rather than proven only with  $TcpO_2$  or ABI measurements.

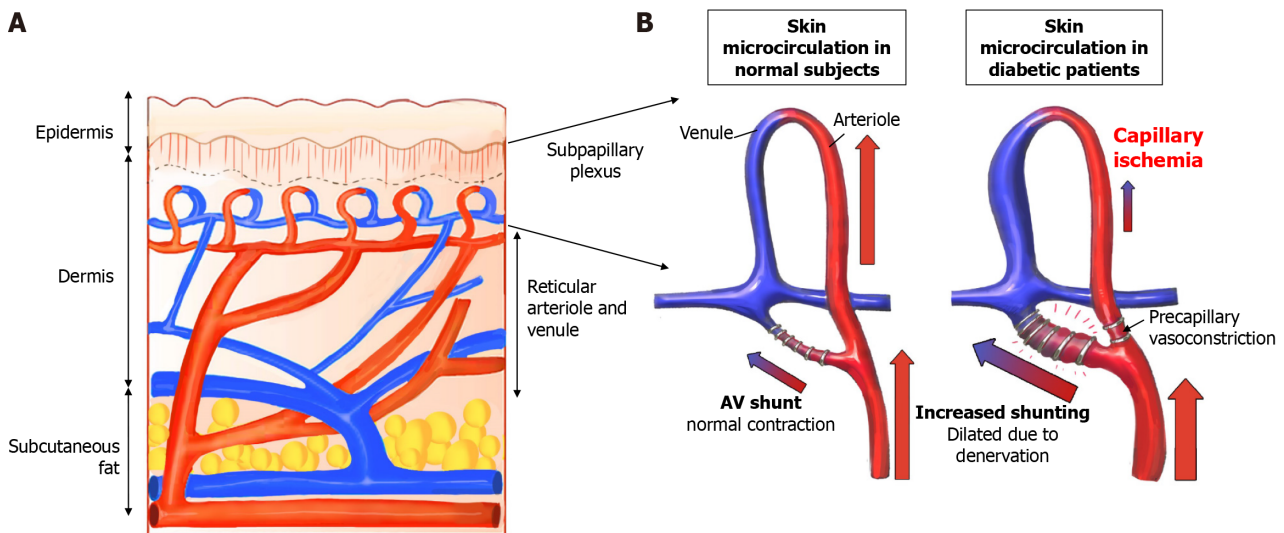
## CONCLUSION

$TcpO_2$  helps assess the therapeutic effect and blood flow in patients with DFU and predicts vascular occlusion in FFs. However, when FF reconstruction was performed in patients with DFU, a successful flap was achieved even with low



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**Figure 7** An illustration depicting intima, media, adventitia, and sympathetic innervation in a cross section of a vessel. Sympathetic nerves are mainly located in the outermost layer, the adventitia.



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**Figure 8** Schematic illustration of the increase in a subpapillary arteriovenous shunt in diabetic patients. A: Cross-sectional structure of the skin; the subpapillary plexus is located in the lower layer of the epidermis; B: In a patient with diabetes, arteriovenous shunt is increased, and periphery blood flow is reduced.

TcpO<sub>2</sub>; no significant increase in TcpO<sub>2</sub> was noted even after a long-term follow-up of > 1 year, which is thought to be owing to the thickness of the ALT-FF, sympathectomy owing to adventitia removal for intraoperative anastomosis, and diabetic AV shunt formation. TcpO<sub>2</sub> becomes low when sympathectomy was performed without regard to the presence of diabetic neuropathy. Therefore, TcpO<sub>2</sub> measurements in FFs after FF reconstruction may not be as useful as those with DFU who did not undergo FF reconstruction owing to the characteristics of FF operation and DFU.

## ARTICLE HIGHLIGHTS

### Research background

Patients with diabetes have lower transcutaneous oxygen pressure (TcpO<sub>2</sub>) levels than those without diabetes, indicating that poor tissue oxygenation may lead to diabetic foot ulcers (DFUs). TcpO<sub>2</sub> measurements can help assess the risk of DFU amputation and the effectiveness of diabetic neuropathy treatment by showing changes in TcpO<sub>2</sub> levels.

### Research motivation

Vessel anastomosis is challenging in free flap (FF) reconstruction for DFU cases because of atherosclerosis and narrowed vessel. Therefore, it is important to study the benefits of periodic TcpO<sub>2</sub> measurement at the FF site of the DFU for a longer period of time.

### Research objectives

Our goal was to find out how TcpO<sub>2</sub> values changed over time and what it meant for the FF stability. We also wanted to see if TcpO<sub>2</sub> measurements were useful for FF reconstruction in DFU patients.

### Research methods

We retrospectively reviewed the records of patients requiring FFs were all defective owing to DFU. In addition to the FF group with DFU patients, a group of DFU patients who did not receive FFs was included as a control group. We then examined how TcpO<sub>2</sub> value changed over time.

### Research results

The FF group had higher levels of ankle-brachial index (ABI), haemoglobin, creatinine, diabetes mellitus duration, and C-reactive protein than the control group. Both groups had low TcpO<sub>2</sub> levels. TcpO<sub>2</sub> levels increased gradually in the short term, but decreased gradually in the long term (after postoperative day 30).

### Research conclusions

There is no significant increase in TcpO<sub>2</sub> was noted even after a long-term follow-up of > 1 year. This may be due to the flap thickness, the sympathectomy from adventitia removal, and the diabetic arteriovenous (AV) shunts. Therefore, TcpO<sub>2</sub> measurements may not be very helpful for FF reconstruction in DFU patients, unlike in DFU patients who did not have FF reconstruction, because of the features of FF surgery and DFU.

### Research perspectives

Future studies should measure TcpO<sub>2</sub> more frequently. A larger and multi-center study with more patients is needed. A prospective study may also confirm the risk factors we found for TcpO<sub>2</sub> pattern analysis. Especially, sympathectomy and AV shunt formation, which may cause low TcpO<sub>2</sub>, need more experiments than just TcpO<sub>2</sub> or ABI measurements.

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## FOOTNOTES

**Author contributions:** Lee DW and Choi HJ contributed to the conceptualization and methodology of this study; Lee DW participated in the formal analysis, visualization, and writing-original draft preparation of this article; Byeon JY and Hwang YS involved in the investigation of this manuscript; Byeon JY and Kim JH contributed to the resources; Lee DW and Hwang YS participated in the data curation; Kim JH and Choi HJ contributed to the supervision; Choi HJ contributed to the project administration and funding acquisition; and all authors have read and agreed to the published version of the manuscript.

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