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Assessment of Lower Limb Microcirculation Following Revascularization in Patients with Symptomatic Peripheral Arterial Disease

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Abstract

The occurrence of peripheral arterial disease and the frequency of revascularization surgeries carried out on symptomatic individuals are on a constant upward trajectory. Nonetheless, ambiguity persists around both the hemodynamic surveillance post-revascularization and the ability to anticipate clinical endpoints. The present investigation was designed to probe hemodynamic measures, with particular attention directed at the microvasculature. This single-site, prospective research comprised 29 patients (15 suffering from intermittent claudication [IC] and 14 afflicted by chronic limb-threatening ischemia [CLTI]). Beyond the ankle–brachial index (ABI), we gauged microperfusion metrics—specifically microvascular blood flow, capillary oxygen saturation (SO2), and relative hemoglobin content (rHb)—before and after the revascularization intervention using an oxygen-to-see (O2C) apparatus that combines lightguide spectrophotometry with laser Doppler flowmetry. Recordings were taken with the limb positioned horizontally and elevated. At baseline, the SO2 value obtained with the leg elevated was substantially lower in the CLTI cohort than in the IC cohort (P = 0.0189); in contrast, the remaining microcirculatory measures and the ABI figures did not reach statistical significance. Diabetic subjects displayed a higher flow rate than non-diabetic subjects when the leg was in the horizontal position (P = 0.0162), a disparity that disappeared in the elevated posture. In the wake of successful revascularization, flow increased promptly and significantly, irrespective of leg position, whereas SO2, rHb, and the ABI remained unchanged. Elevated-leg SO2 was markedly lower in CLTI than in clinically compensated peripheral arterial disease, whereas microvascular flow served as a suitable surrogate marker of successful revascularization. In investigations involving surgical or interventional revascularization techniques, noninvasive hemodynamic monitoring of the pedal microcirculation could prove valuable.

Keywords: Peripheral arterial disease, Microcirculation, Lightguide spectrometry, Oxygen to see

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Introduction

Globally, the prevalence of peripheral arterial disease (PAD) and the volume of lower-limb revascularization procedures performed are in continuous growth [1, 2]. The objective of restoring arterial inflow through endovascular or open operative approaches is to ameliorate quality of life and limb salvage prospects while curtailing the morbidity and death rates tied to PAD. For subjects presenting with intermittent claudication (IC), prolonging ambulatory capacity takes precedence; in those reaching the stage of chronic limb-threatening ischemia (CLTI), the priority shifts to averting amputations and their downstream effects [3].

Despite therapeutic gains in the management of PAD, particularly with catheter-based techniques, the degree of clinical success remains suboptimal. One systematic review revealed that one year post-endovascular or surgical revascularization, 40% of lesions in individuals with diabetic foot syndrome and PAD fail to heal, and major amputation is performed on 1 out of every 10 patients [4].

Therefore, the relevance of the microvasculature to the performance and preservation of the lower extremities is receiving growing recognition, partly owing to advances in medical device technology that permit the qualitative and quantitative capture of microcirculatory data. Microcirculatory impairment carries a 4-fold elevation in amputation hazard, and the co-occurrence of PAD alongside microvascular dysfunction is tied to a risk exceeding 20-fold [5]. The role of microcirculation extends beyond CLTI or diabetic foot syndrome, as it also manifests in the clinical presentation of IC in non-diabetic patients [6].

At present, revascularization interventions are chiefly supported by macrovascular diagnostic scrutiny, yet shifts at the microvascular level are seldom tracked around the time of the procedure [7]. This research set out to investigate hemodynamic parameters, focusing on the microcirculation, before and after revascularization attempts.

Materials and Methods

Study design, patient selection, and clinical assessment

Conducted as a single-center prospective pilot study, this work recruited individuals with symptomatic PAD scheduled for lower limb revascularization at the Interdisciplinary Vascular Center of University Medical Center Mannheim, Germany, spanning February 2020 to June 2021. Acceptance into the study required meeting the Rutherford classes 2–5 requirements. The IC patients (Rutherford 2–3) showed either negligible or no discernible gain from a 3–6 month course of conservative care encompassing pharmacotherapy, lifestyle adjustments, and structured exercise. Exclusion criteria included the presence of congestive right heart failure, myocardial infarction, erysipelas, or wounds with extensive tissue destruction (Rutherford 6) situated over the designated measurement zones. Enrollment of consecutive patients was the original intent; however, logistical hurdles and specific pandemic-era precautions interfered with subject accrual. The clinical workup captured demographic details, PAD staging according to the updated Rutherford classification, cardiovascular comorbidities, and predisposing risk factors. Concurrently, the medication regimens were cataloged.

Circulation parameters and data acquisition

Macrocirculation

Visualization of lower limb PAD included invasive angiography at the time of the revascularization intervention, along with ankle–brachial index (ABI) determination before and on the first day after the operation. Measurements were obtained with an 8–10 MHz Doppler probe positioned at the pulse site, held at a 45–60° angle relative to the cutaneous surface. The ABI was computed by dividing the maximal ankle pressure for each leg by the maximal arm pressure. To confirm unimpeded flow through the treated vessel segment or bypass, duplex ultrasound scanning was employed.

Microcirculation

Microcirculatory evaluation was conducted using an oxygen-to-see device (O2C), version III (LEA Medizintechnik GmbH, Giessen, Germany); a detailed account of its physical operating principles has been provided in prior literature [8]. In essence, the microlight-guided O2C unit combines white-light spectrometry (wavelength range, 500–630 nm) with laser Doppler flowmetry (wavelength, 830 nm). Using spectrometry, this combination allows quantification of post-capillary hemoglobin oxygen saturation (SO2, as a percentage) and relative microvascular hemoglobin (rHb, expressed in arbitrary units [AUs]). At the same time, the Doppler shift of the laser light allows estimation of microvascular blood velocity (in AU). The relative microvascular blood flow (in AU) was then computed from the rHb and velocity figures. An LFX-29 probe (LEA Medizintechnik GmbH, Giessen, Germany) was applied over a 10-second acquisition period, and the mean values derived from each recording interval were used in all subsequent analyses.

The recordings were obtained before the revascularization procedure, immediately after its completion, and during the postoperative inpatient period, no sooner than one day following revascularization. All measurements followed a standardized protocol: after a supine rest phase lasting at least 10 minutes, readings were taken at three plantar locations on the foot (medial forefoot, lateral forefoot, and heel) using double-sided adhesive tape (LTDT-001; LEA Medizintechnik GmbH, Giessen, Germany) in two leg configurations—initially horizontal, then in an elevated position achieved with a 30 mmHg positioning aid. The data from the three measurement sites were averaged to produce a single representative value for the entire foot.

Follow-up

The primary emphasis of the study lay on the short-term alterations in hemodynamic variables induced by revascularization. Moreover, an optional follow-up visit was proposed to patients, designed to capture the state of the macro- and microcirculation and to define functional and clinical outcomes at the one- to two-month mark. From a clinical standpoint, wound evolution and the need for reintervention, as well as the incidence of major amputation, were used as secondary endpoints.

Statistics

Sample size estimation was conducted before the analysis. The primary outcome was specified as the difference in microperfusion metrics "pre-OP vs. post-OP." Anticipating a medium effect magnitude (Cohen's D = 0.6), recruitment of 24 individuals was calculated to be necessary for a paired t-test to declare these differences statistically significant (alpha = 0.05, power = 0.8, two-tailed test). Furthermore, with a dropout rate of up to 20%, a cohort of 30 patients was needed to achieve adequate power to detect changes across time points. This sample size estimation utilized the SAS procedure PROC POWER. Various statistical approaches were used to assess the potential effect of the revascularization intervention on lower-limb microperfusion. Paired observations (such as values obtained in the horizontal versus elevated leg postures) were compared using a paired t-test. An independent 2-sample t-test was applied to contrast group averages. A multiway analysis of variance (ANOVA) for repeated measurements was conducted to simultaneously analyze several influencing factors for each distinct microcirculatory variable—namely, SO2, rHb, and flow. This analysis used the SAS PROC MIXED procedure, treating subjects' IDs as a random effect and time, position, and group as fixed effects. The Scheffé test was chosen for post hoc comparisons. All statistical work was performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). Findings from the statistical tests were deemed significant when the resulting P-value was less than 0.05.

Results and Discussion

Clinical characteristics

Altogether, 29 symptomatic PAD sufferers (IC, n = 15; CLTI, n = 14) who received revascularization were entered into the study, after 1 of the 30 initially recruited individuals withdrew their consent without detailing specific reasons. The endovascular regimen comprised prolonged plain old balloon angioplasty, with stent deployment kept as a rescue measure when angiographic findings were suboptimal. No drug-coated balloons, drug-eluting stents, or debulking modalities were utilized. The baseline demographic and clinical attributes are compiled in **Table 1**.

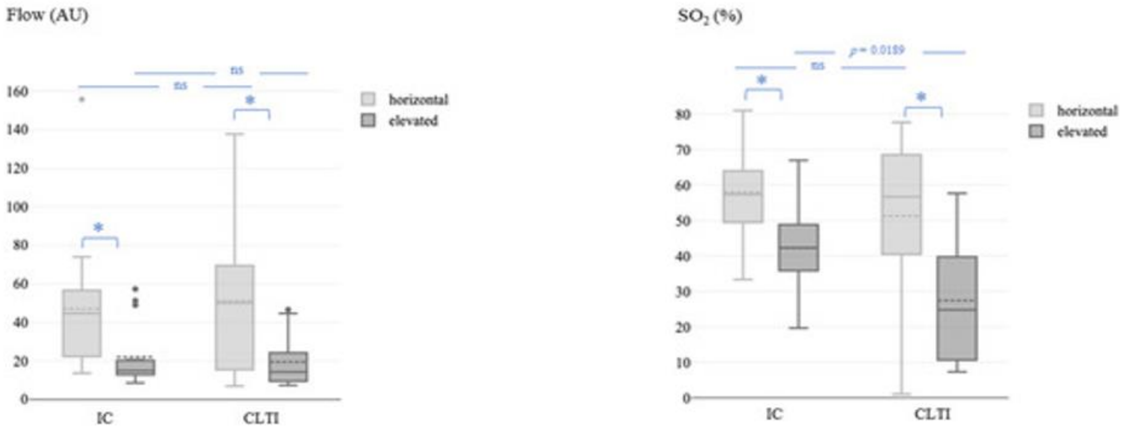
Table 1. Baseline profile of patients presenting with symptomatic peripheral arterial disease (n = 29). Numerical variables are shown as means ± standard deviation. For categorical factors, raw frequencies alongside the respective proportions (in parentheses) are provided.

Age (Years)	**68 ± 9**
Male	21 (72)
Peripheral arterial disease level	
Aortoiliac	7 (24)
Femoro-popliteal	13 (45)
Cruropedal	9 (31)
Crural run-off *	
One-vessel	6 (29)
Two-vessel	6 (29)
Three-vessel	9 (42)
Rutherford clinical category	
2–3 (IC)	15 (52)
4–5 (CLTI)	14 (48)
Prior amputation (ipsilateral + contralateral)	4 (14)
Type of revascularization	
Bypass	19 (66)
Aorto(bi)iliac	6
Aorto(bi)femoral	4
Iliac-popliteal	1
Femoro-popliteal	3
Femoro-crural/pedal	5
Endarteriectomy	5 (17)
Endovascular (PTA/stent)	3 (10)
Endarteriectomy + endovascular	2 (7)
Target limb ankle–brachial index [a]	
ADP	0.53 ± 0.3
ATP	0.52 ± 0.3
Cardiovascular comorbidities and risk factors	
Cerebral vascular disease [b]	8 (28)
Coronary artery disease [c]	19 (66)
Congestive heart failure (stages)	
Preserved	10 (34)
Mid-range	6 (21)
Reduced	3 (10)
Tobacco consumption	
Previous smokers	8 (28)
Current smokers	18 (62)
Diabetes mellitus	10 (35)
Arterial hypertension	25 (86)
Dyslipidemia	25 (86)
Chronic inflammatory disorders [d]	0 (0)
Other comorbidities	
Peripheral neuropathy	5 (17)
Preoperative anemia [e]	14 (48)

All values are expressed as either means ± standard deviation or absolute counts with accompanying percentages (%). * Data were not available for eight individuals receiving aortoiliac/aortofemoral revascularization. [a]: Two patients whose crural arteries were noncompressible and whose ankle–brachial index exceeded 1.3 were excluded, as were two IC patients with an ankle–brachial index reading of 0. [b]: A positive history of transient ischemic attacks or stroke, or a currently documented carotid stenosis (≥ 50% identified sonographically), or a prior carotid revascularization procedure. [c]: Coronary artery disease established through invasive diagnostic workup. [d]: Consisting of rheumatoid arthritis, systemic lupus erythematosus, psoriasis, ankylosing spondylitis, systemic vasculitis, Crohn's disease, and ulcerative colitis. [c]: Defined by a baseline hemoglobin level falling under 13 g/dL in male patients and under 12 g/dL in female patients. Abbreviations: ABI = ankle-brachial index; CLTI = chronic limb-threatening ischemia; IC = intermittent claudication; PTA = percutaneous transluminal angioplasty.

Baseline circulation values

At every recorded time point, microvascular blood flow and SO2 were substantially depressed in the elevated leg configuration relative to the horizontal one across both the IC and CLTI cohorts, whereas rHb displayed no such position-dependent divergence. Before the intervention, SO2 obtained with the leg raised was notably poorer in the CLTI group than in the IC group (27% ± 18% vs. 42% ± 13%; P = 0.0189); this gap was not observed in the horizontal posture, and flow did not discriminate between CLTI and IC in either leg position **(Figure 1)**.



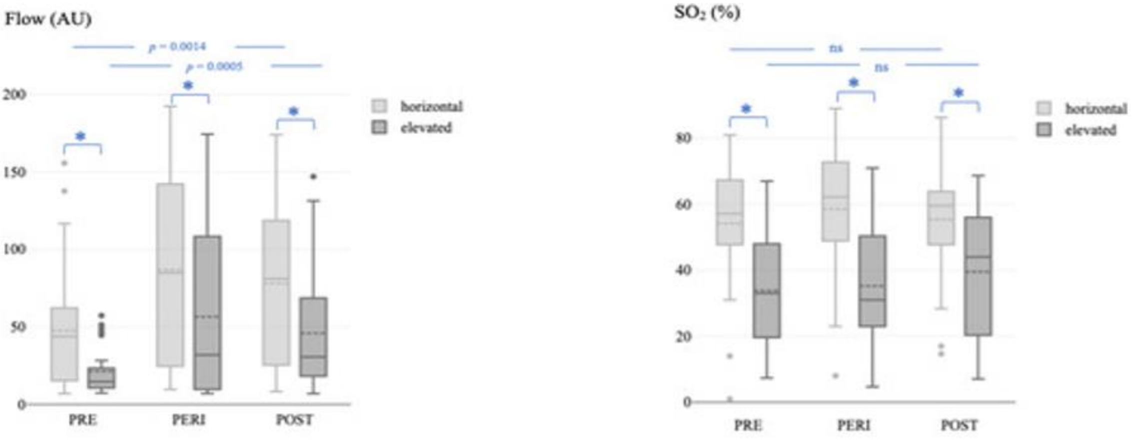
a) b)

Figure 1. Microvascular blood flow (a) and oxygen saturation (b) were recorded at baseline, before revascularization, with the leg positioned horizontally and elevated. Abbreviations: Flow = microvascular blood flow; AU = arbitrary units; SO2 = capillary oxygen saturation; IC = intermittent claudication; CLTI = chronic limb-threatening ischemia. The asterisk (*) denotes a P-value < 0.05.

Worth highlighting, diabetic individuals showed higher microvascular flow outputs than non-diabetic individuals when the leg was in the horizontal position (77.60 ± 46.23 vs. 33.93 ± 21.60 AU; t-test supplemented by Satterthwaite post hoc analysis, P = 0.0162), a disparity that vanished when the leg was placed in the elevated position.

Effect of revascularization

A multiway ANOVA revealed a significant association between the assessment time point and microvascular blood flow, both with the leg horizontal (P = 0.0014) and elevated (P = 0.0005) **(Figure 2a)**. The Scheffé post hoc comparison demonstrated that flow values immediately after the operation and on the first postoperative day surpassed baseline levels in both leg positions (all P < 0.05). By contrast, no significant time-point effect emerged for SO2, whether in the horizontal (P = 0.5375) or the elevated (P = 0.5022) configuration **(Figure 2b)**.



a) b)

Figure 2. Microvascular blood flow (left) and oxygen saturation (right) were assessed pre-procedurally, immediately post-procedurally, and during the postoperative recovery phase, with the limb in both the horizontal and raised positions. Abbreviations: Flow = microvascular blood flow; AU = arbitrary units; SO2 = capillary oxygen saturation; PRE = pre-

revascularization; PERI = directly after revascularization; POST = postoperative course following revascularization. The asterisk (*) marks a P-value < 0.05.

Setting aside ABI values exceeding 1.4 attributable to four subjects with incompressible crural arteries, ABI did not differentiate CLTI from IC either at baseline (0.55 ± 0.24 vs. 0.66 ± 0.20; P = 0.2314) or one day after revascularization (0.74 ± 0.26 vs. 0.93 ± 0.26; P = 0.0947). The ABI rose meaningfully from its pre-procedural level **(Figure 3)** among both IC (P = 0.0415) and CLTI (P = 0.0184) patients.

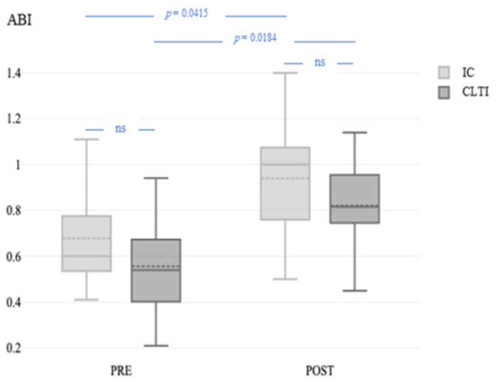


Figure 3. Ankle–brachial index values obtained before the revascularization intervention and at the 1-day postoperative mark among patients with IC and CLTI. Abbreviations: ABI = ankle–brachial index; PRE = before revascularization; POST = one day following revascularization; IC = intermittent claudication; CLTI = chronic limb-threatening ischemia.

Follow-up

Within the follow-up window, 18 of the initial 29 participants (10 IC, 8 CLTI) returned for reevaluation 28 to 59 days after their revascularization. The period saw three surgical reoperations and zero endovascular redo procedures. A single patient underwent bypass thrombectomy for unilateral occlusion of an aortofemoral bifurcation graft. Two CLTI patients progressed to major amputation owing to uncontrollable infection. Beyond these events, the CLTI subset exhibited granulating wound closure.

Repeated-measures ANOVA for SO2 with the leg horizontal yielded no significant time-driven variation (P = 0.698). In the elevated position, however, a significant time effect was present (P = 0.005). Pairwise comparisons identified a statistically significant difference between preoperative and follow-up SO2 levels. Neither microvascular flow nor the ABI departed significantly from previously recorded measures.

Symptomatic PAD goes hand in hand with microvascular derangements. Yet the microcirculation is seldom examined as part of standard PAD care, even as macroperfusion is being directly corrected during revascularization procedures. In the present work, we examined skin perfusion metrics before and after technically successful revascularization in individuals with symptomatic PAD. The core findings of this prospective investigation are as follows:

- At baseline, SO2 measured in the elevated leg position was markedly depressed in CLTI subjects relative to IC subjects (P = 0.019), while ABI readings did not distinguish the two groups.
- Diabetic patients registered higher flow than non-diabetic patients in the horizontal leg position (P = 0.016) but not in the elevated position.
- Upon successful revascularization, flow underwent an immediate and significant upswing in both leg positions, whereas SO2, rHb, and the ABI remained essentially unchanged.

The deficiencies of the ABI as a routine diagnostic instrument for PAD are well recognized, including performance variability, interobserver inconsistency that undermines reproducibility, and a wide range of published sensitivity and specificity figures [9].

Various noninvasive tissue perfusion modalities have been used in PAD research to monitor downstream effects of revascularization. In a systematic review, Wermelink *et al.* [7] judged the diagnostic precision of 10 different techniques to be poor. Present-day guidelines provide threshold values for critically impaired perfusion based on transcutaneous partial pressure of oxygen (TcpO2) readings, supporting the prediction of amputation risk and level. On the other hand, the wide scatter of TcpO2 values hampers its use as a quantitative metric in IC patients, who comprised the bulk of our study sample. For this population, the transcutaneous oxygen exercise profile would constitute a suitable means of interrogating peripheral arterial insufficiency under stress and, paired with O2C, would present a compelling direction for subsequent studies across PAD subgroups. That said, $TcPO_2$ measurement demands considerable time, its outputs hinge on numerous factors, and the underlying evidence base is thin [3]. Employing an O2C system, as in the present study, carries multiple strengths. The technique is noninvasive and painless, data capture is rapid, and it enables the simultaneous recording of several microcirculatory parameters.

Microcirculation during rest and under provocation

In the horizontal leg posture, the median SO2 in our IC subgroup (57%) matched that reported in a prior investigation. Evaluating IC patients, Gyldenløve *et al.* [10] established a median SO2 of 57% (tissue depth, 8 mm) over the symptomatic region at the hallux, whereas our approach averaged recordings from three plantar locations. For CLTI subjects, Rother *et al*. [11] reported a mean baseline SO2 of 46%, which is close to the mean SO2 we documented (51%). As a point of reference, a healthy cohort displayed a mean SO2 of 80%, and leg raising left these readings essentially unaltered [12]. Taken together, SO2—which mainly reflects venous capillary oxygen saturation and may be viewed as a proxy for oxygen extraction—does not appear to provide a reliable indicator for distinguishing among the various clinical stages of PAD. A recent contribution has suggested that oxygen extraction (as evidenced by rising deoxyhemoglobin levels without corresponding shifts in oxyhemoglobin) could intensify with worsening blood flow [13].

Provocative testing often reveals a subclinical deficit in tissue perfusion. Diverse provocation protocols can theoretically be applied, including leg elevation, treadmill challenge (as utilized by Gyldenløve *et al*. [10]), or localized warming [14]; each of these interventions triggered a notable decline in SO2 in the respective studies. In our dataset, the mean elevated-leg SO2 readings were substantially lower in the CLTI subset (27%) than in the IC subset (42%), albeit against a backdrop of wide scatter and considerable between-group overlap. By long-standing convention, SO2 readings above 10% point toward viable tissue at the intended amputation site in critical limb ischemia [15]. This identical cutoff has been employed in coronary bypass surgery to pinpoint myocardial hypoxic territories [16].

Of equal importance, provocation maneuvers also perturb microvascular blood flow. Flow dropped appreciably upon leg elevation in our series and following treadmill exertion in the limbs studied by Gyldenløve *et al*. [10]. In the present work, pre-revascularization mean flow among PAD patients was 47 AU at rest and fell to 22 AU with elevation, a marked divergence from healthy individuals, whose mean flow was 77 AU in the horizontal position and 66 AU when elevated [12]. In contrast to SO2, we know of no validated threshold values for microvascular flow that herald critical ischemia or amputation hazard. Still, a single reading is inadequate to assess perfusion integrity, and a composite of microvascular parameters is necessary to depict tissue perfusion adequacy fully.

Controversy of microcirculation in diabetes mellitus

We detected elevated microvascular blood flow in diabetic patients compared with non-diabetic patients when the leg was resting horizontally, but no meaningful difference emerged when the leg was raised. Without question, the defining difference between PAD and diabetic foot syndrome resides in the superimposition of neuropathy in the latter [17]. That said, the debate over microvascular dysfunction, both in early diabetes mellitus and in mature neuroischemic diabetic foot skin, remains unresolved [18]. Our observation of elevated blood flow in individuals with diabetes aligns with earlier work showing heightened capillary pressure [19] and bolsters the long-standing hemodynamic hypothesis. Hemodynamic stresses trigger vascular adaptations, including capillary remodeling [20]. It must be stressed that a distinction is required between flow channeled through dermal arteriovenous anastomoses and nutritive perfusion; both are presumed to fall under neurohumoral control [21]. Within diabetic foot syndrome, greater microvascular flow is not synonymous with better cutaneous nourishment. Once more, provoked conditions may hold greater interpretive value: the microvascular perfusion reserve, gauged via thallium-201 muscle perfusion imaging, in the lower limbs of individuals with long-standing type 2 diabetes and no PAD was significantly curtailed compared with that of healthy counterparts [22]. Analogously, optical coherence tomography-based flow assessments detected mildly elevated baseline readings in diabetic feet yet a profoundly blunted vasodilatory response to local heating [14].

Microvascular changes following revascularization

Once revascularization was completed, microvascular blood flow increased immediately and significantly. In a systematic review, Normahani *et al*. [23] isolated three studies that captured shifts in microperfusion following percutaneous angioplasty and bypass procedures through laser Doppler techniques, paralleling our methodology. These studies uniformly documented perfusion gains after revascularization. Our findings echo those of Rother *et al*. [11], who tracked microcirculatory dynamics with an O2C device throughout tibial angioplasty in 30 CLTI patients, roughly two-thirds of whom had concomitant diabetes mellitus. We share the authors' view that alterations in tissue perfusion transcend angiosome-defined boundaries. The cited study noted significant discrepancies in ABI improvement and SO2 behavior compared to our results—a difference most plausibly ascribed to cohort heterogeneity involving partially incompressible vessels (excluded from ABI calculations) and an upward trend in microcirculatory indices in most, but not all, participants, as previously observed [24].

While microvascular flow improved immediately upon successful revascularization, SO2 in the elevated position showed significant gains at follow-up compared with preoperative levels. Although the modest sample size and limited set of variables hindered more in-depth correlation analyses, we find it reasonable to postulate that adaptive processes are implicated. Numerous mechanisms may be operative in the aftermath of reperfusion [25], yet these same mechanisms can be subverted by insults such as ischemia–reperfusion damage [26]. This phenomenon, alongside divergent patient populations, revascularization techniques, and measurement tools, may rationalize the heterogeneous findings encountered during longitudinal follow-up. For instance, Ma *et al*. [13] observed no meaningful departure of TcpO2 values from baseline six weeks after endovascular intervention. In contrast, another report [27] involving IC or CLTI patients documented a significant rise over the identical timeframe. Moreover, Kaczmarczyk *et al*. [28] failed to identify a significant effect of PTA on endothelial function metrics—including arterial pulse waveform analysis (aPWA), flow-mediated dilatation (FMD), and the reactive hyperemia index (RHI)—across a one-year observation window.

For patients in whom revascularization is not feasible, the therapeutic armamentarium directed at improving microcirculation and fostering wound closure is considered to have limited efficacy and a weak evidence foundation [29]. Most recently, a pilot study suggested a favorable effect of acupuncture on microcirculatory parameters [30].

Limitations

The inferences that could be drawn were constrained by the modest patient enrollment in this investigation. The follow-up interval in the present work was capped at 4–8 weeks, as the primary interest lay in the acute hemodynamic shifts following revascularization. Future studies incorporating substantially larger cohorts and extended observation periods are warranted to corroborate our findings and enhance overall data quality. Beyond this, the attributes of the diabetic subgroup call for a more granular exploration. Disentangling type 1 from type 2 diabetes, the dependence on insulin therapy, and the burden of additional diabetic complications could shed light on the mechanistic links bridging microcirculation, PAD, and diabetes. Given that O2C spectrometry enables noninvasive capture of four distinct facets of microcirculation, we decided to forgo an invasive reference technique such as TcpO2. Head-to-head comparisons between these modalities ought to be the objective of upcoming trials. We recognize that the toe–brachial index may offer superior sensitivity for PAD detection, particularly in settings of medial calcification where the ABI is artifactually inflated. It should be noted, however, that only 2 individuals in our cohort had ABI readings exceeding 1.3.

Conclusion

While elevated-leg SO2 was substantially lower in CLTI than in clinically compensated PAD, microvascular flow appears to be an appropriate surrogate marker of revascularization success across both disease stages. In investigations employing either surgical or endovascular revascularization strategies, the noninvasive hemodynamic surveillance of pedal microcirculation may prove valuable; nonetheless, larger-scale studies that address potential confounding variables are needed.

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Conflict of interest: None

Financial support: None

Ethics statement: The study protocol was approved by Medical Ethics Commission II of the Faculty of Medicine Mannheim, the University of Heidelberg, Mannheim, Germany (approval code 2019-669N, date 21 May 2019). This study was conducted in accordance with the principles of the 1964 Declaration of Helsinki and all subsequent revisions. The data are protected in accordance with the European Union Data Protection Directive.
Written informed consent was obtained from all patients.

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