Injury 50 (2019) 2332–2338

Contents lists available at ScienceDirect

Injury

journal homepage: www.elsevier.com/locate/injury

# Impact of surgical procedures on soft tissue microcirculation in calcaneal fractures: A prospective longitudinal cohort study

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ARTICLE INFO

*Article history:*
Accepted 2 October 2019

*Keywords:*
Calcaneal fracture
Doppler/white light spectroscopy
Extended lateral approach
Microcirculation
Minimalinvasive treatment
O2C®

ABSTRACT

*Purpose:* Wound healing complications are a major concern after open reduction and internal fixation (ORIF) in patients with calcaneal fractures. Microcirculation is known to play a key role in bone and soft tissue healing. The present study aimed to characterize and contrast the dynamics of changes in microcirculation comparing two different surgical procedures: A) ORIF and B) a minimally invasive approach (MIA).

*Methods:* Blood flow (BF[AU]), oxygen saturation ($sO_2$[%]) and relative amount of haemoglobin (rHb[AU]) were measured at two depths (2 mm and 8 mm) non-invasively by spectrophotometry (Micro-Lightguide O2C®, LEA Medizintechnik, Giessen, Germany) before surgery and every 24 h after surgery for a duration of six days. A linear mixed model (LMM) was used to analyse longitudinal data and repeated measurements.

*Results:* Nineteen patients (44 years, range 21.9–71.0 years) were enrolled in the study. Surgical treatment consisted of ORIF ($n = =15$) and MIA ($n = =9$). The postoperative BF and $sO_2$ at the 2 mm and 8 mm depths were higher in the ORIF group (BF: $p < 0.001$, $p = =0.003$; $sO_2$: $p = =0.001$, $p = =0.011$). The BF at the 2 mm and 8 mm depths increased after surgery (2 mm: $p = =0.003$, 8 mm: $p = =0.001$) in both groups. This increase did not correlate with the surgical technique. $sO_2$ and rHb values at the 8 mm depth decreased after surgery ($sO_2$: $p = =0.008$, rHb: $p < 0.001$) in both groups, whereas $sO_2$ at the 2 mm depth increased after surgery ($p = =0.003$). Furthermore, the surgical technique correlated with the postsurgical course of $sO_2$ values at the 2 mm depth ($p = =0.042$).

*Conclusions:* The spectrophotometry results were in line with the generally accepted phases of soft tissue wound healing. Postsurgical changes in microcirculation are predominantly independent of surgical

*Abbreviations:* BF, blood flow [AU]; MIA, minimally invasive approach; rHb, relative amount of haemoglobin [AU]; LMM, linear mixed model; MP, measurement time point; ORIF, open reduction and internal fixation; $sO_2$, Oxygen saturation [%].

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https://doi.org/10.1016/j.injury.2019.10.004

techniques and may be primarily determined by wound and fracture healing. Future studies should focus on the potential of spectrophotometry to monitor wound healing after surgery. Moreover, studies with longer observation periods are needed in order to examine the changes in microcirculation during all wound-healing phases.



## Introduction

Calcaneal fractures are potentially limb-threatening injuries that predominantly result from high-energy mechanisms. This fracture entity constitutes 1–2% of all fractures and represents over 60% of all fractures occurring in the tarsal bones [1–3]. As a consequence of the high-energy mechanism of injury, intra-articular calcaneal fractures often lead to chronic pain and long-term disability due to posttraumatic arthritis [4]. Furthermore, intra-articular fractures make up approximately 75% of calcaneal fractures and are commonly classified in line with Essex-Lopresti and Sanders based on lateral X-ray and CT imaging, respectively [5,6]. Treatment schemes include nonoperative treatment, percutaneous fixation and minimally invasive techniques, as well as open reduction and internal fixation. Despite recent innovations in surgical implants and techniques, the best treatment strategy for displaced calcaneal fractures (Sanders type ≥2) remains controversial [7–10]. Nonetheless, open reduction and internal fixation (ORIF) by application of a low-profile locking plate through an extended lateral approach or the sinus tarsi approach remains the current standard [11–14] (Fig. 1). However, the vulnerable soft tissue coverage over the lateral side of the calcaneus is challenging, resulting in a wound complication rate of up to 30% [10,15–18]. The high complication rates bear the risk of deep infection, osteomyelitis, unsatisfying functional outcomes, revision surgery and eventual amputation [19,20]. Over the past two decades, several risk factors for the occurrence of wound healing complications, such as diabetes mellitus, smoking, open fracture, wound closure technique, fracture severity and an impaired microcirculation have been identified [13,16,17,21–25]. In particular, surgical techniques that have a lower impact on soft tissue microcirculation, such as a minimally invasive approach (MIA) by screw or K-wire fixation, might reduce the rate of soft tissue complications (Fig. 1B) [26–28]. Bentov et al. assumed that minimally invasive techniques minimized soft tissue injury, pain and surgical site infections due to a minor impact on the local function of the immune system and local microcirculation. In addition, subsequent decreases in oxygen supply, hypoxia, acidosis, collection of metabolites and oxidative/nitroxidative stress are factors thought to contribute to higher infection rates [29]. Furthermore, several studies reported that percutaneous minimally invasive techniques lead to an improvement in functional outcomes in patients with calcaneal fractures [27,30]. Carow et al. showed that the blood flow (BF) at the 2 mm depth differed between the regions of different surgical approaches [31]. They assumed that the Palmer approach and the Ollier approach might have advantages compared to other surgical approaches due to higher superficial BF values. In another study, Ganse et al. [34] showed that a minimally invasive approach for the treatment of thoracolumbar fractures led to higher BF values compared to the ORIF group. The study indicated a benefit of minimally invasive techniques regarding soft tissue microcirculation.

In our study, we examined whether MIA at the calcaneus showed postoperatively measured differences in BF, $sO_2$ and rHb values, ideally in the sense of better blood circulation and tissue saturation to optimize wound healing.

## Materials and methods

IRB approval was granted before initiation of the study (EK 346/14) by the Independent Ethics Committee of RWTH Aachen Faculty of Medicine. Written informed consent was obtained from all patients prior to enrolment. The design and procedures of the study were carried out in accordance with the principles of the Declaration of Helsinki.

### *Study population*

Thirty-five patients underwent hospital treatment because of a calcaneal fracture at our level I university hospital between 2014 and 2015. The study was performed on 19 patients; 16 patients were excluded. Inclusion criteria comprised patients aged 18 years or older with intra-articular calcaneal fractures (Sanders type ≥2). Exclusion criteria were uncontrolled medical conditions, such as significant peripheral arterial occlusive disease, polytraumatized patients, open fractures, chronic obstructive pulmonary disease, generalized infections, diabetes mellitus and Raynaud's disease.

### *Treatment algorithm*

In the ORIF group, a low-profile locking plate was applied through an extended lateral approach (Fig. 1A). The MIA was characterized by a short skin incision of 2 cm over the posterior facet

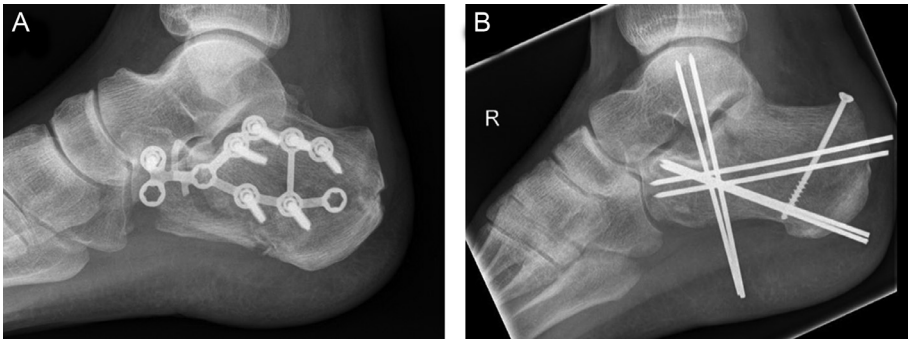


**Fig. 1.** Intraarticular calcaneal fracture. A: ORIF – Low-profile locking plate, B: MIA – Kirschner wire fixation.

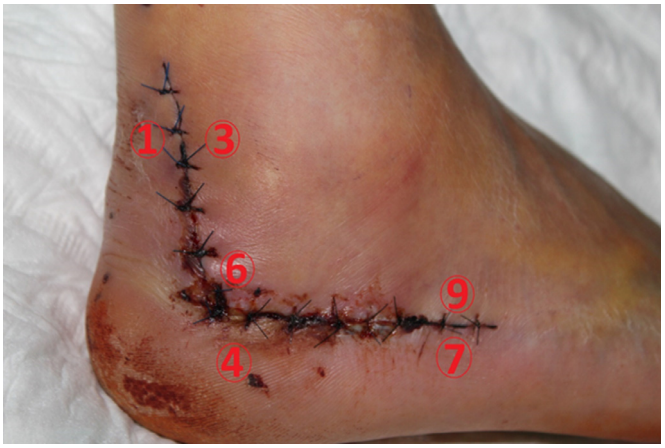


**Fig. 2.** Local measurement points (3, 6, 9) on the lateral calcaneum.

**Table 1**
General characteristics of 19 participants (mean ± standard deviation (range)). Patients with bilateral fractures ($n = =5$) were included.

| Age | 44 ± 13.7 (21.9–71.0) |
|---|---|
| Male/Female | 23/1 |
| Smoker/Nonsmoker | 8/16 |
| Left/Right | 13/11 |
| Height (cm) | 180 ± 7.5 (159–190) |
| Weight (kg) | 85.3 ± 16.2 (54–120) |
| BMI (kg/m$^2$) | 26.3 ± 4.3 (19.4–34.7) |
| ASA 1 | 8 |
| ASA 2 | 15 |
| ASA 3 | 1 |
| ORIF/MIA | 15/9 |
| Sanders classification Type 2 | 4 |
| Sanders classification Type 3 | 18 |
| Sanders classification Type 4 | 2 |
| Essex-Lopresti – Tongue type | 12 |
| Essex-Lopresti – Depression type | 12 |
| Soft-tissue healing complications (ORIF/MIA) | 0/0 |

for reduction and percutaneous K wire fixation (Fig. 1B). The decision of whether surgery was done through an ORIF or MIA was made by clinical criteria. In patients with distinct soft tissue swelling and obesity, MIA was chosen. Follow-up treatment included unloading of the injured extremity for ten weeks in a fracture orthosis boot. From the start of the eleventh week, patients began step-by-step loading in a fracture orthosis boot in the following four weeks until full load.

### *Study protocol*

Basic demographic data (age, smoking history, body mass index) were collected during the hospital stay. A standardized measurement protocol was applied utilizing three predefined local measuring points (LMPs) 3, 6 and 9 (Fig. 2). A mean value over the course of ten seconds was determined for each LMP and parameter. LMP measurements were combined and mean values were calculated. A Micro-Lightguide O2C® spectrophotometer (LEA Medizintechnik, Giessen, Germany) was used for measurements of oxygen saturation ($sO_2$[%]) and blood flow (BF[AU]) at 2 mm and 8 mm depths before surgery and every 24 h until follow-up was completed six days after surgical treatment.

Measurement time points (MTP) were defined as MTP1 = =presurgery, MTP2 = =24 h after surgery, MTP3 = =48 h after surgery, MTP4 = =72 h after surgery, MTP 5 = = 96 h after surgery, MTP6 = =120 and MTP7 = =144 h after surgery. Each evaluation was performed by only one examiner to avoid any inter-observer variation. Furthermore, the surgical procedures were performed by one senior surgeon (MK).

### *Spectrophotometer*

The Micro-Lightguide O2C® spectrophotometer (LEA Medizintechnik, Giessen, Germany) uses Laser Doppler velocimetry and spectrometric techniques to measure rHb in microvessels (up to 100 µm in diameter), the $sO_2$ in capillaries and venules (oxygen extraction) and the BF. Since there is no International System of Units (SI) established, BF and rHb are expressed in arbitrary units (AU).

### *Statistical analysis*

Statistical analysis was performed using SPSS 25.0 software (IBM, Armonk, NY, USA). A linear mixed model (LMM) was used to analyse longitudinal data and repeated measurements. The type of surgical technique and MTP were defined as fixed effects and participants were defined as random effects. A nonparametric Mann-Whitney-Wilcoxon test was applied to abnormally distributed values to compare the groups.

## Results

### *Demographics*

Nineteen patients who met the inclusion criteria were included in the study. Furthermore, five patients presenting with bilateral calcaneal fractures were included. The mean age was 44 years (range 21.9–71.0 years). Fifteen fractures were treated by ORIF and nine fractures were treated by MIA. Eight patients were smokers. No wound-healing complications were observed. Table 1 shows the general characteristics.

### *Blood flow*

Before surgery, BF did not differ between groups at the 2 mm and 8 mm depths (2 mm: $p = =0.57$; 8 mm: $p = =0.66$). The postoperative BF at the 2 mm depth was higher in the ORIF group compared to the MIA group (ORIF 82.9AU ± 38.7 vs. MIA 49.7AU ± 22.2, $p < 0.001$). The BF at the 2 mm depth increased during the postoperative follow-up (48.8AU ± 21.0 to 78.9AU ± 33.5, $p = =0.003$). There was no interdependency between the surgical technique and the postsurgical course regarding the BF at the 2 mm depth ($p = =0.085$; Fig. 3).

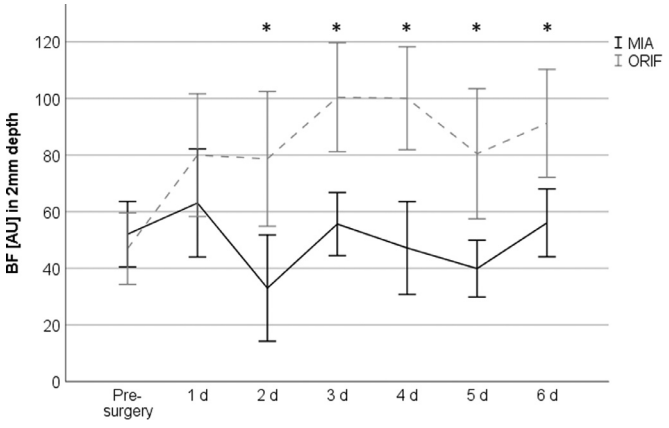


**Fig. 3.** Postsurgical course of BF at the 2 mm depth. Average values. Error bars show SEM. * Significant difference between MIA and ORIF.

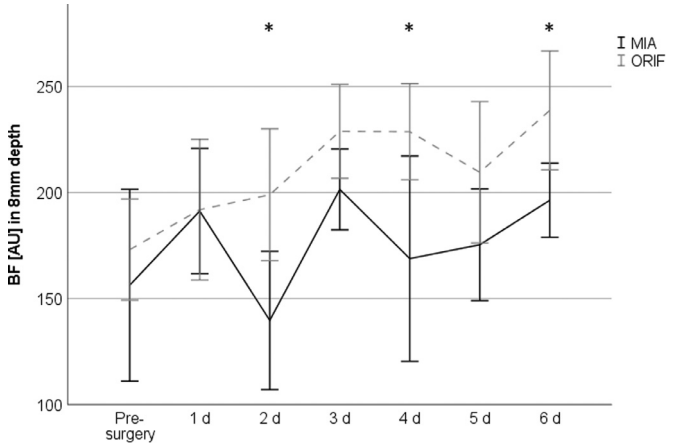


**Fig. 4.** Postsurgical course of BF at the 8 mm depth. Average values. Error bars show SEM. * Significant difference between MIA and ORIF.

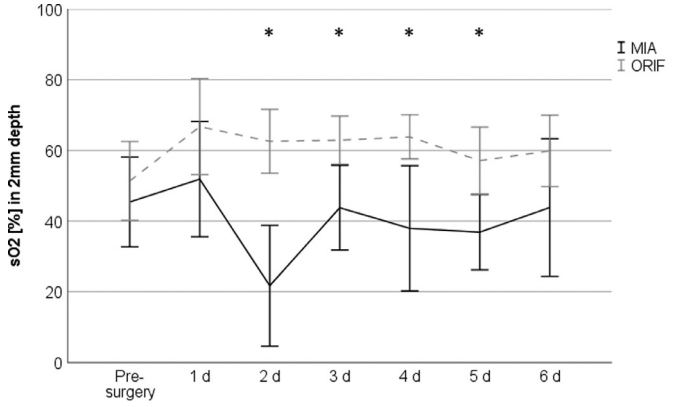


**Fig. 5.** Postsurgical course of $sO_2$ at the 2 mm depth. Average values. Error bars show SEM. * Significant difference between MIA and ORIF.

At the 8 mm depth, BF was higher in the ORIF group than the MIA group (211.0AU ± 53.0 vs. 175.5AU ± 49.4, $p = =0.003$) and BF at the 8 mm depth increased after surgery until the end of the observation period (167.0AU ± 51.6 to 223.9AU ± 47.0, $p = =0.001$). Analogous to BF at the 2 mm depth, there was no correlation between the surgical technique and the postsurgical course regarding BF at the 8 mm depth ($p = =0.273$; Fig. 4).

*Oxygen saturation*

Preoperative $sO_2$ differed between the groups at the 8 mm depth ($p = =0.01$). The postoperative $sO_2$ at both the 2 mm (60.3% ± %17.1 vs. 40.4% ± %22.4, $p = =0.001$) and 8 mm depths (52.8% ± %19.9 vs. 38.1% ± %19.8, $p = =0.011$) demonstrated higher values in the ORIF group than the MIA group. The $sO_2$ increased at the 2 mm depth (49.2% ± %19.6 to 54.3% ± %21.9, $p = =0.003$) and decreased at the 8 mm depth (60.3% ± %20.2 to 38.3% ± %19.0, $p = =0.008$) within the observation period. At the 2 mm depth, an interdependency between the surgical technique and the postsurgical course of $sO_2$ values was found ($p = =0.042$; Fig. 5). This effect was not seen at the 8 mm depth ($p = =0.175$; Fig. 6).

*Haemoglobin*

The rHb values did not differ between groups at the 2 mm and 8 mm depths. Furthermore, there was no change over time in rHb values at the 2 mm depth. However, the total mean rHb decreased within the observation period at the 8 mm depth (70.2AU ± 18.5 to 49.1AU ± 10.5, $p < 0.001$). There was no correlation between surgical technique and the postsurgical course of rHb values at the 2 mm depth ($p = =0.38$). Preoperatively, the rHb did not differ between the groups at the 2 mm and 8 mm depths (2 mm: $p = =0.50$; 8 mm: $p = =1.00$).

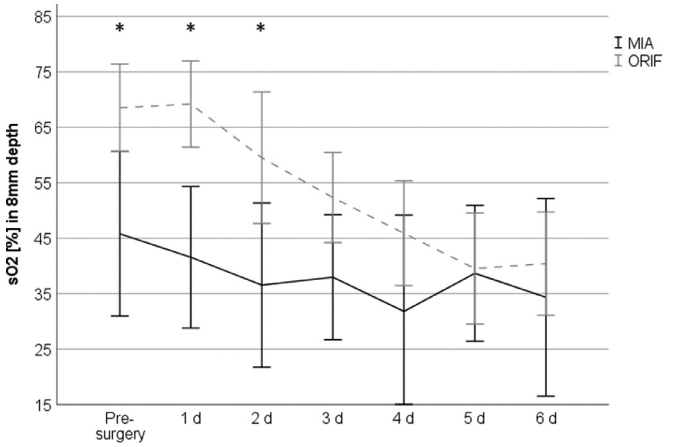


**Fig. 6.** Postsurgical course of $sO_2$ at the 8 mm depth. Average values. Error bars show SEM. * Significant difference between MIA and ORIF.

## Discussion

*Main findings*

The aim of our study was to elucidate postsurgical changes in microcirculation after surgical treatment of calcaneal fractures. Our first hypothesis—that BF, rHb and $sO_2$ values would not differ between the surgical groups—was rejected. The second hypothesis—that BF, rHb and $sO_2$ values would decrease during the postoperative course—was partially rejected. Our third hypothesis—that the postoperative course of BF, rHb and $sO_2$ values would correlate with the surgical technique—was rejected except for $sO_2$ values at the 2 mm depth. To our knowledge, this is the first study to investigate tissue microcirculation after surgical treatment of calcaneal fractures. The main results were:

1 A correlation between the surgical technique and the postsurgical course of $sO_2$ values at the 2 mm depth was found.
2 BF was higher in the ORIF group at the 2 mm and 8 mm depths, and BF increased after surgery in both groups. There was no correlation between the surgical technique and the BF.
3 $sO_2$ at the 2 mm and 8 mm depths was higher in the ORIF group. Furthermore, after surgery, $sO_2$ increased at the 2 mm depth and decreased at the 8 mm depth in both groups. There was no correlation between the surgical technique and the postsurgical course of $sO_2$ values at the 8 mm depth.
4 rHb values did not differ between the ORIF group and the MIA group. rHb values at the 2 mm depth showed no changes after surgery in both groups. rHb values at the 8 mm depth decreased, but there was no interdependency between the surgical technique and the postsurgical course of rHb values.

The great importance of wound healing in calcaneal fracture care is undisputed, as intact microcirculation is among the recently discussed key factors for proper fracture healing and is known to reduce the risk of soft tissue complications [23–25]. We recently provided reference data of healthy hindfeet using the Micro-Lightguide O2C® spectrophotometer. As we described before, the O2C® device enables the transcutaneous measurement of $sO_2$, blood flow and rHb with a high reproducibility [31–35]. Furthermore, oxygen saturation reflects the level of tissue hypoxia,

since an analysis of blood gas and critical tests showed the same results in capillary and venous blood. Moreover, BF can be interpreted as a parameter of microvascular function and angiogenesis [36]. The measurements at the 8 mm depth represent the microcirculation near the fracture site, whereas measurements at the 2 mm depth represent the more superficial transition zone between the dermis and subcutaneous tissue.

Our study revealed higher $sO_2$ and BF values in patients treated by ORIF compared to patients treated by MIA. Furthermore, independently from surgical procedures, $sO_2$ and BF at the 2 mm depth increased after surgery in both groups. $sO_2$ and rHb at the 8 mm depth decreased in both the ORIF and the MIA group after surgery. Interestingly, $sO_2$ values at the 8 mm depth significantly differed preoperatively. Preoperative $sO_2$ values might correlate with the initial soft tissue situation, leading to lower $sO_2$ values in swollen hindfeet. This might explain the lower $sO_2$ values in the MIA group, as the initial soft tissue situation was a criterion for the selection of the MIA procedure. The reason for the lower $sO_2$ values could be greater capillary domains, as oedema increases intercellular spaces. There was a correlation between the surgical techniques and the postsurgical course of $sO_2$ values at the 2 mm depth. MIA was associated with a decrease in postsurgical $sO_2$ values at the 2 mm depth, whereas ORIF was associated with increasing $sO_2$ values at the 2 mm depth.

*Hypoxia and fracture healing*

Literature from the 1970s already described the phenomenon of hypoxia at the fracture site and emphasized the importance of oxygen supply for fracture healing [37,38]. In our study, we observed an increase in $sO_2$ values at the 8 mm depth after MIA and ORIF treatment, indicating the development of a hypoxic environment near the fracture site. This may have been caused by an increase in oxygen consumption and/or an impaired blood supply. Another possible reason is the decreased oxygen binding capacity of haemoglobin under acidic conditions. The current understanding of bone healing phases confirms these findings [39,40]. The role of inflammation in bone healing and the postsurgical course of inflammation as a result of surgical interventions have been well described [41]. Surgical interventions lead to vasodilation and act as a trigger for angiogenesis [41,42]. In order to improve fracture healing, studies have examined the application of a number of techniques, including hyperbaric oxygen therapy to increase the $sO_2$ values on the fracture site [43–45]. However, the therapeutic potential of higher oxygen concentrations and the effect on cell recruitment of macrophages and neutrophils is controversial and might depend on accompanying injuries, such as thoracic trauma [40,46]. Nevertheless, more research is required to investigate the potential of a hyperoxic environment as a therapeutic approach to improve fracture healing in humans [40].

*Microcirculation and soft tissue healing*

To our knowledge, our study is the first to describe changes in soft tissue microcirculation during the early postoperative phase after surgical treatment in patients with calcaneal fractures. We found a correlation between the surgical technique and the postsurgical course of $sO_2$ values at the 2 mm depth, indicating that ORIF treatment led to higher $sO_2$ values at this depth. Furthermore, BF values at the 2 mm depth increased after surgery in both groups. The effect of the surgical technique on superficial $sO_2$ might be a response to more invasive surgical procedures. In the MIA group, a short incision of 2 cm over the posterior facet was performed, and thus the impact on the superficial soft tissue might have been lower. A correlation of the measurement results with the occurrence of postoperative wound complications was not possible in our study, as we did not observe wound healing disorders either in the MIA or in the ORIF group. However, although no reference values for local oxygen saturation have been published to date, we have been able to demonstrate that our results did not differ from those in healthy hindfeet [31]. For this reason, we assume that the values measured by us represent a safe interval for postoperative tissue perfusion according to ORIF and MIA in calcaneal fractures. Furthermore, literature regarding changes in the microcirculation in soft tissue healing is rare. Today we know that VEGF-A, a very effective proangiogenic factor, is produced as a response to hypoxia, mediated by HIF-1. Yousefi et al. showed that microcirculation immediately reorganized after injury in a mouse ear pinna model and collateral vessels supported the damaged tissue. In their study, the tissues underwent the healing phases of inflammation (dilatation of vessels), proliferation and remodelling [47]. Furthermore, Chong et al. reported that neoangenesis of microvessels was promoted from tortuous microvessels in a mouse ear wound-healing model. The proliferation of microvessels was finally terminated 31 days after injury. In our study, we also observed an increase in BF at the 2 mm and 8 mm depths after surgery (soft tissue damage), indicating an increase in microcirculation as a compensatory effect of higher oxygen demand and evacuation of metabolites. Therefore, our results are in line with the generally accepted changes in microcirculation during wound healing phases after surgical intervention due to neovascularisation [48,49]. Furthermore, Demidova-Rice et al. [48] described a model of wound closure in diabetic mice in which the proangiogenic phase lasted for seven days. We observed that BF continuously increased within the first six days after surgery. However, the postsurgical course did not correlate with the surgical technique. It may be assumed that postoperative microcirculation is primarily determined by soft tissue and fracture healing [50]. Interestingly, several studies support the idea that a high level of angiogenesis might be unnecessary in soft tissue healing and might contribute to a scar phenotype [51–56]. This would be a possible explanation as to why rapidly healing wounds (e.g. oral mucosa) do not show increased angiogenesis [57]. However, a distinction is important regarding wound healing under the influence of diseases (e.g. diabetes) and in different age groups (e.g. healing in the elderly), in which angiogenesis is less efficient [29]. In diabetes, immunologic dysfunctions and a deficit of angiogenesis play a major role in impaired soft tissue wound healing [49,58]. Minimally invasive surgical techniques are of great importance to reduce the risk of wound healing complications, especially in the elderly and in patients with an impaired soft tissue envelope [59].

*Clinical impact*

Spectrophotometry is a feasible and non-invasive method to examine changes in microcirculation after calcaneal fractures at the patient's bedside. Our results support the current literature regarding changes in microcirculation in soft tissue healing. However, the question of whether results from spectrophotometry have the potential to be early indicators of impaired wound healing cannot be answered with this study and needs further investigation.

*Limitations*

The study was conducted with a small number of patients. However, the collected information gave enough data for statistical analysis. Also, an observation period of six days was too short to show all phases of microcirculatory change as a response to a surgical intervention. We recommend a longer follow-up for future studies, as wound healing takes several weeks. In addition, preoperative $sO_2$ values showed a difference between the groups at the 8 mm depth. This might be traced back to differences in initial soft

tissue swelling and operation timing. For this reason, future studies should be randomized controlled trials. Finally, spectrophotometry is known to show temporal and intra-individual variation. This is a known weakness of this method [60,61].

## Conclusion

An open surgical technique was associated with more pronounced changes in microcirculation after calcaneal fractures compared to the minimally invasive technique and pre-surgery values. Our results are in line with the generally accepted phases in soft tissue wound healing. Spectrophotometry is a feasible and non-invasive method to examine changes in microcirculation after calcaneal fractures at the patient's bedside. Future studies should try to establish a link between infection and impaired microcirculation in randomized studies of greater collectives and test the impact of possible interventions, such as hyperbaric oxygen therapy. Furthermore, observation periods should be extended to at least 30 days in future studies.

## Declaration of Competing Interest

Ethics approval and consent to participate

Ethics committee of the RWTH Aachen University Hospital, ethics approval EK 346/14.

**Consent for publication**

All authors read and approved the final manuscript and gave permission for publication.

**Availability of data and materials**

Data are available from the corresponding author for researchers.

**Competing interests**

None.

**Funding**

None.

## CRediT authorship contribution statement

**Felix M. Bläsius:** Validation, Visualization, Writing - original draft, Writing - review & editing. **Björn-Christian Link:** Data curation, Formal analysis, Writing - original draft, Writing - review & editing. **Frank J.P. Beeres:** Data curation, Formal analysis, Validation, Visualization, Writing - review & editing. **Lukas D. Iselin:** Data curation, Formal analysis, Writing - original draft. **Benjamin Moritz Leu:** Data curation, Investigation, Formal analysis. **Boyko Gueorguiev:** Validation, Visualization, Writing - review & editing. **Kajetan Klos:** Conceptualization, Methodology, Writing - review & editing. **Bergita Ganse:** Validation, Visualization, Writing - original draft. **Sven Nebelung:** Conceptualization, Methodology, Writing - review & editing. **Ali Modabber:** Writing - review & editing, Conceptualization, Methodology. **Daphne Eschbach:** Validation, Visualization, Writing - review & editing. **Christian David Weber:** Writing - review & editing, Conceptualization, Methodology. **Klemens Horst:** Conceptualization, Methodology, Writing - review & editing. **Matthias Knobe:** Data curation, Formal analysis, Writing - original draft, Project administration, Resources, Supervision.

## Acknowledgments

The manuscript was proofread by Scribendi Inc., 405 Riverview Drive, Suite 304, Chatham ON, Canada.

## Source of Funding

None.

## Conflicts of Interest

The authors report no conflict of interest.

## Ethics

Ethics committee of the RWTH Aachen University Hospital, ethics approval EK 346/14.

## Authors' contributions

BCL, FJPB, LDI, BML and MK had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors meet all three of the requirements for authorship. CDW, KH, SN, AM and KK were highly involved in the planning and execution of this study. BML organized the project by order of the dean's office of study affairs. FMB, BGA, BG, DE and FJPB analysed the data. FMB, BGA, BCL, LDI and MK drafted the manuscript. Furthermore, FJPB, DE, BCL, BG, KK, SN, AM, CDW, KH and FMB were highly involved in the process of data interpretation. They took part in the manuscript review process and revised it critically. In this way they provided important intellectual content in line with the study execution. MK acted as the initiator of the study and was highly involved in the advancement of the conception. All authors read and approved the final manuscript for publication.

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