RESEARCH LETTER

Assessing the Microcirculation of the Foot with Laser Speckle Contrast Imaging During Endovascular and Hybrid Revascularisation Procedures in Patients with Chronic Limb Threatening Ischaemia

Bryan Wermelink [a,b,*,‡], Onno A. Mennes [c,d,‡], Jeff G. Van Baal [d,e], Wiendelt Steenbergen [c], Robert H. Geelkerken [a,b], on behalf of the study group [†]

[a] University of Twente, Multi-Modality Medical Imaging group, TechMed Centre, Enschede, The Netherlands
[b] Medisch Spectrum Twente, Department of Vascular Surgery, Enschede, The Netherlands
[c] University of Twente, Biomedical Photonic Imaging group, TechMed Centre, Enschede, The Netherlands
[d] Ziekenhuisgroep Twente, ZGT Academy, Almelo, The Netherlands
[e] Cardiff University, School of Medicine, Wales, UK

In peripheral arterial disease the tissue microcirculation becomes impaired, ultimately resulting in chronic limb threatening ischaemia (CLTI) in 5% of cases.[1] CLTI prognosis is poor unless successful revascularisation is performed.[2] Endovascular and hybrid revascularisation procedures are performed under fluoroscopic and angiographic guidance to visualise the per-operative impact on the macrocirculation. Unfortunately, both lack the ability to visualise the impact on microcirculation, while restoring the microcirculation plays a pivotal role in CLTI.[3] By introducing additional per-operative assessment of the microcirculation, the impact of revascularisation on the microcirculation can be assessed in real time. This allows the surgical team to extend or adjust the revascularisation procedure in a timely manner, improving (prediction of) the clinical outcome.

Laser speckle contrast imaging (LSCI)[4] is a contactless, non-invasive, optical imaging technique able to image the microcirculation down to a tissue depth of 0.6 mm. Laser light scatters from the illuminated tissue surface, creating an interference pattern, a so called speckle pattern, that is recorded with a digital camera. Higher velocity or a higher concentration of moving erythrocytes creates blurring in the recorded speckle pattern. By analysing the speckle contrast of the recorded images, blood flow maps are generated instantaneously and expressed in instrument specific arbitrary perfusion units (PU).

Although LSCI is stable and reproducible,[5] per-operative applicability is new. Furthermore, a relationship between per-operative LSCI parameters and clinical outcome parameters has not been investigated yet. The present study aimed to determine the interobserver variation of per-operative LSCI scans and explore the potential relationship between per-operative LSCI parameters and clinical outcome parameters in patients with CLTI.

Thirty consecutive patients with CLTI were included between February and September 2019 in Medisch Spectrum Twente (Enschede, The Netherlands). Approval of the medical research ethics committee was acquired (NL66041.044.18) and all patients provided written informed consent. Patients older than 18 years with a Rutherford classification ≥ 4 undergoing a first revascularisation procedure under general anaesthesia (GA) in the hybrid operating theatre were included. Patients with a previous revascularisation or amputation in the ipsilateral lower limb were excluded.

LSCI measurements were started before instigation of GA, after proper positioning and temperature (20°C) acclimatisation of the patient. Following the revascularisation LSCI measurements were continued for 10 minutes under GA. Each procedural event such as incision, sheath insertion, percutaneous transluminal angioplasty, stent placement, clamping or re-opening of vessels, and administered medication was annotated. The surgeon was blinded for LSCI data during the procedure.

LSCI data of each patient were analysed post-operatively by a single investigator (BW). A random sample of 20% of the LSCI data was analysed independently by a second investigator (OAM) to measure the interobserver variation (ICC). For each measurement 13 different regions of interest (ROI) were drawn manually, based on pre-determined anatomical landmarks, to determine the mean perfusion in different areas of the foot. Furthermore, three time periods of interest (TOIs) were selected for analysis during different stages of revascularisation. TOI 1 was from the start of the measurement until GA was administered, TOI 2 was from GA administration until incision or sheath insertion, and TOI 3 included the final 10 minutes of measurement. Analysis of the LSCI data showed no statistically significant difference between the two observers and the ICC was good to excellent (ICC $= 0.825 - 1.000$).

To determine the potential relationship between per-operative LSCI parameters and clinical outcome, parameters including technical success of the procedure, Rutherford classification, global anatomic staging system classification (GLASS), (time to) wound healing, wound ischemia and foot infection classification (WIFI), ankle brachial index (ABI), and walking distance were collected before and after

* Corresponding author. University of Twente, Multi-Modality Medical Imaging group, TechMed Centre, Enschede, the Netherlands.
E-mail address: b.wermelink@utwente.nl (Bryan Wermelink).
[†] Saskia H. Aarnink, Roland Beuk, Marjolein Brusse-Keiser, Marieke Haalboom, Rombout R. Kruse, Srirang Manohar, Robbert Meerwaldt, Theo Menting, Boudewijn L. Reichman, Riemer H.J.A. Slart and Edith M. Willigendael
[‡] B. Wermelink and O.A. Mennes share first authorship.

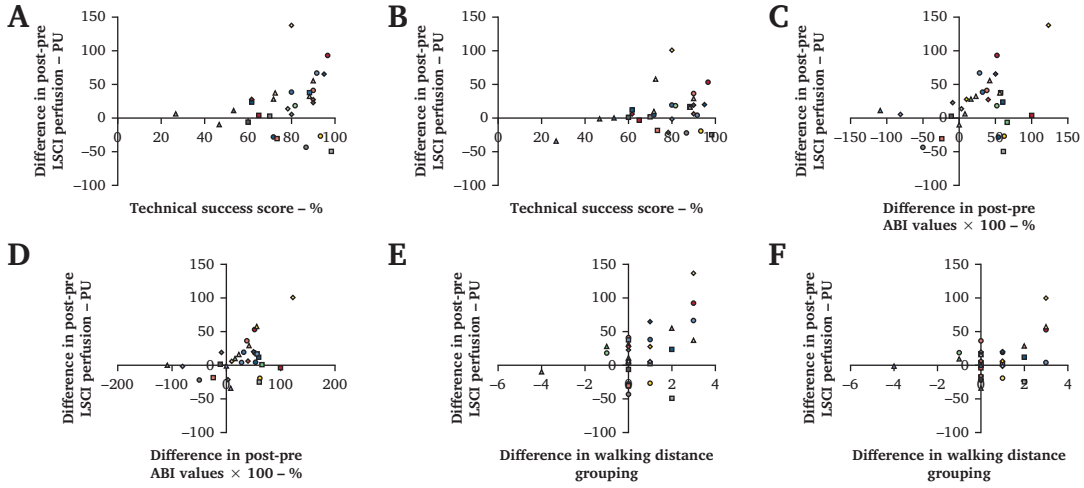

Figure 1. Visualisation of the difference in pre- and post-revascularisation clinical parameters *vs.* the difference in laser speckle contrast imaging (LSCI) perfusion values between three time periods of interest (TOI) in 30 patients with chronic limb threatening ischaemia: (A) technical success *vs.* LSCI TOI 3 − TOI 1, (B) technical success *vs.* LSCI TOI 3 − TOI 2, (C) ankle brachial index (ABI) × 100% *vs.* LSCI TOI 3 − TOI 1, (D) AP *vs.* LSCI TOI 3 − TOI 2, (E) walking distance *vs.* LSCI TOI 3 − TOI 1, (F) walking distance *vs.* LSCI TOI 3 − TOI 2. Walking distance was grouped as: 1 = 0 − 100 m, 2 = 101 − 500 m, 3 = 500 − 1000 m, 4 ≥ 1000 m. Each colored shape represents an individual patient.

revascularisation, up to six months after the revascularisation procedure. For the LSCI outcome aspect, the difference between TOI 1 and TOI 2 was determined to determine the influence of GA on LSCI measurements. The difference TOI 3 - TOI 1 showed the change between baseline perfusion without GA and the post-operative perfusion under GA. The difference TOI 3 − TOI 2 was used to determine pre and post revascularisation LSCI differences during GA. Finally, the changes in perfusion, between TOI 3 − TOI 1 and TOI 3 − TOI 2, were related to changes in clinical parameters to determine the relationship between LSCI parameters and clinical parameters. When LSCI perfusion values increased, the clinical outcome parameters improved and when LSCI perfusion values decreased, the clinical outcome parameters also decreased in the majority of patients (Fig. 1). However, using the Pearson's correlation coefficient no statistical correlations were found between LSCI parameters and clinical outcome parameters. The absence of statistical correlations could be a result of the heterogeneity of the patient population, with different Rutherford classifications, presence/absence of diabetes mellitus, per-operative medication with vasoconstriction (e.g., norepinephrine) or vasodilation (e.g., GA) effects or the clinical endpoints.

In conclusion, this study showed that analysis of LSCI data is highly reproducible, next to the already proven stability and reproducibility of the measurements itself, with a good to excellent ICC. Confirmation of a positive correlation between LSCI parameters and clinical outcomes must be the subject of prospective clinical trials with larger patient populations.

CONFLICT OF INTEREST AND FUNDING

No conflicts of interest. This study was supported financially by an unrestricted research grant from the Pioneers in Health Care Innovation Fund, established by the University of Twente, Saxion University of Applied Sciences, Medisch Spectrum Twente, ZiekenhuisGroep Twente and Deventer Hospital. This project was funded by the TKI High Tech Systems and Materials (HTSM) via the Dutch Ministry of Economic Affairs and Climate Policy's PPS bonus scheme for Research and Innovation. OAM: NWO domain Applied and Engineering Sciences, project 14538, and Diavasc Foundation.

REFERENCES

1 Becker F, Robert-Ebadi H, Ricco JB, Setacci C, Cao P, De Donato G, et al. Chapter I: Definitions, epidemiology, clinical presentation and prognosis. *Eur J Vasc Endovasc Surg* 2011;**42**:4–12.
2 Hirsch AT, Haskal ZJ, Hertzer NR, Bakal CW, Creager MA, Halperin JL, et al. ACC/AHA 2005 practice guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): Executive summary. *Circulation* 2006;**113**:1474–547.
3 Wermelink B, Ma KF, Haalboom M, El Moumni M, de Vries JPPM, Geelkerken RH. A systematic review and critical appraisal of peri-procedural tissue perfusion techniques and their clinical value in patients with peripheral arterial disease. *Eur J Vasc Endovasc Surg* 2021;**62**:896–908.
4 Heeman W, Steenbergen W, van Dam GM, Boerma EC. Clinical applications of laser speckle contrast imaging: a review. *J Biomed Opt* 2019;**24**:1.
5 Mennes OA, Van Netten JJ, Van Baal JG, Steenbergen W. Assessment of microcirculation in the diabetic foot with laser speckle contrast imaging. *Physiol Meas* 2019;**40**:ab2058.

Keywords:
Chronic limb threatening ischaemia, Endovascular revascularisation, Laser speckle contrast imaging, Microcirculation, Peripheral arterial occlusive disease

Available online 8 April 2022

https://doi.org/10.1016/j.ejvs.2022.03.036