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Clinical Investigation

JOURNAL OF ENDOVASCULAR THERAPY
A SAGE Publication
An official publication of the ISEVS

Journal of Endovascular Therapy
1–7

DOI: 10.1177/15266028231185506
www.jevt.org
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Intraprocedural, Intra-Arterial CT Foot Perfusion Examination for Assessment of Endovascular Therapy in Patients With Critical Limb Ischemia: A Prospective Pilot Study

Thijs Urlings, MD[1], Apoorva Gogna, MD[2], Mark C. Burgmans, MD, PhD[3], Kiang Hiong Tay, MD[2], Chow Wei Too, MD[2], Ankur Patel, MD[2], Shaun X. Ju Min Chan, MD[2], Leong Sum, MD[2], Nanda Venkatanarasimah, MD[2], Bien Soo Tan, MD[2], Sivanathan Chandramohan, MD[2], Cornelio Gutierrez[2], and Farah Irani, MD[2]

Abstract

Background: Current techniques to evaluate computed tomography (CT) foot perfusion in patients with critical limb ischemia use high contrast doses and cannot be used during endovascular procedures. CT perfusion of the foot with intra-arterial contrast injection during endovascular treatment in a hybrid angiography CT suite might solve these problems. **Purpose:** The main objective of this study was to evaluate whether intra-arterial CT foot perfusion using a hybrid CT angiosystem is feasible during endovascular treatment for critical limb ischemia. **Material and Methods:** This prospective pilot study investigated intraprocedural, intra-arterial CT perfusion of the foot using a hybrid CT angiosystem in 12 patients before and after endovascular treatment for critical limb ischemia. Time to peak (TTP) and arterial blood flow were measured before and after treatment and compared using a paired *t* test. **Results:** All 24 CT perfusion maps could be calculated adequately. The contrast volume used for one perfusion CT scan was 4.8 ml. The mean TTP before treatment was 12.8 seconds (standard deviation [SD] 2.8) and the mean TTP posttreatment was 8.4 seconds (SD 1.7), this difference being statistically significant (p=.001). Tendency toward increased blood flow after treatment, 340 ml/min/100 ml (SD 174) vs 514 ml/min/100 ml (SD 366) was noticed (p=.104). The mean effective radiation dose was 0.145 mSv per scan. **Conclusion:** Computed tomography perfusion of the foot with low contrast dose intra-arterial contrast injection during endovascular treatment in a hybrid angiography CT suite is a feasible technique.

Clinical Impact

Intra-arterial CT foot perfusion using a hybrid CT-angiography system is a feasible new technique during endovascular therapy for critical limb ischemia to assess the results of the treament. Future research is necessary in defining endpoints of endovascular treatment and establishing its role in limb salvage prognostication.

Keywords

CT perfusion, lower limb ischemia, hybrid angiography CT, 3D perfusion map, contrast injection

Introduction

In peripheral arterial disease (PAD) the blood flow to the lower limbs is compromised. Percutaneous transluminal angioplasty (PTA) is the standard treatment for below the knee (BTK) disease in patients with critical limb ischemia (CLI). Technical success rates of PTA are high: 88% to 89%,[1,2] but even after revascularization of all BTK vessels, limb loss occurs in up to 20%.[2] Digital subtraction angiography (DSA) used during endovascular procedures provides only images of the macrovascular system of the foot. As the prognosis for CLI is closely related to functional perfusion (microvasculature), successful wound healing and limb salvage may be better predicted by regional foot perfusion imaging.[3–5] Better defining the endpoint of the endovascular treatment or the need and the extent of possible amputation might impact future clinical decision-making.

While techniques like 2-dimensional (2D) perfusion angiography[6–8] and transcutaneous partial pressure of oxygen allow assessment of the local perfusion of the foot, they do not provide quantitative 3-dimensional (3D) assessment of foot perfusion. This shortcoming was partially solved by computed tomography (CT) perfusion imaging the most frequently used method for ischemia detection in ischemic stroke.[9]

A number of studies have reported the high feasibility and reproducibility of CT foot perfusion at relatively low radiation dose (0.30 mSv) but using high contrast doses (30–100 ml/scan) injected through a peripheral venous cannula.[10–17] The use of high contrast volumes, however, increases the risk of contrast-induced nephropathy, especially in patients with chronic kidney disease (CKD). Furthermore, transferring patients out of the angiography room for CT foot perfusion intraprocedurally increases the procedure time and is logistically challenging. A hybrid angiography CT suite, consisting of a ceiling-mounted C-arm and a dedicated CT scanner which moves on rails using the same integrated fluoroscopy table, (different from cone beam [Dyna] CT where CT-like soft tissue images are generated using a divergent cone beam from the C arm) allows intraprocedural acquisition of perfusion images during endovascular treatment.

In this prospective pilot study, the feasibility of intraprocedural CT perfusion of the foot using a hybrid angiography CT suite was investigated during endovascular treatment.

Figure 1. Simple board-and-strap restraint to reduce patients' motion during the computed tomography (CT) perfusion scan.

Materials and Methods

Study Design and Population

Our research and ethics board approved this study. All patients gave written informed consent. A prospective, single-center pilot study was performed in 12 patients. All patients with CLI referred for endovascular treatment were screened for participation. Duplex ultrasound was performed for all patients prior to intervention. Inclusion criteria: age >45 years, critical limb ischemia (Rutherford category 5 or 6), stenosis/occlusions of the crural vessels (regardless of concomitant femoral and/or iliac lesions), patent dorsalis pedis or plantar artery before treatment, and eGFR >45 ml/min/1.73 m^2 unless on dialysis. Exclusion criteria: acute limb ischemia, subacute limb ischemia requiring thrombolysis as first treatment modality, aortic stenosis/occlusions, previous amputation above the level of the ankle, severe contrast allergy, inability to immobilize foot during perfusion imaging, uncorrectable bleeding diathesis, unsuccessful revascularization. Patients were reviewed in clinic 6 months postprocedure to determine outcome and register potential complications.

Perfusion Imaging (Evaluation)

A board-and-strap restraint was used to reduce patients' limb motion (Figure 1). Antegrade ipsilateral common femoral artery (CFA) access was obtained (6 Fr) using single wall puncture with an 18 G needle under ultrasound guidance. Digital subtraction angiography of the entire limb was performed for all cases followed by CT perfusion scan of

[1]Haaglanden Medical Center, The Hague, The Netherlands
[2]Singapore General Hospital, Singapore
[3]Leiden University Medical Center, Leiden, The Netherlands

Corresponding Author:
Thijs Urlings, Haaglanden Medical Center, Lijnbaan 32, The Hague 2512VA, The Netherlands.
Email: t_urlings@hotmail.com

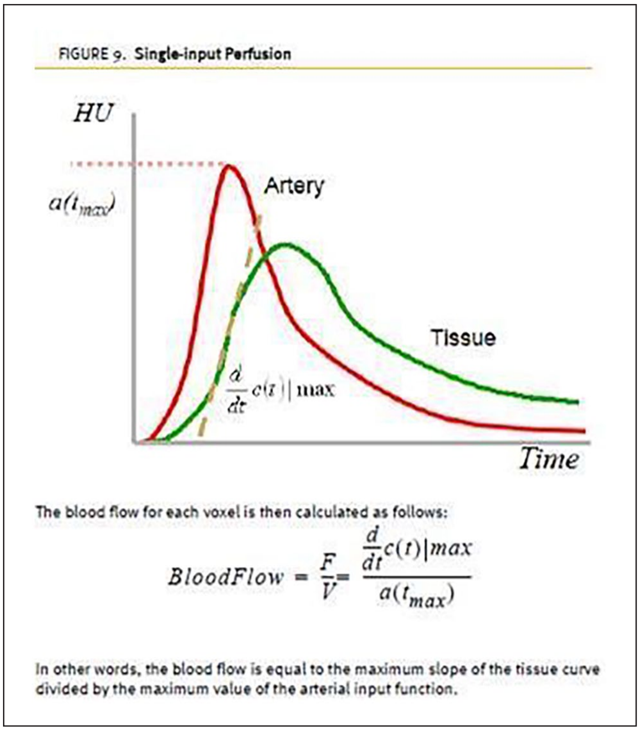

Figure 2. Standard perfusion software with a single arterial input using the upslope method.

the foot and endovascular treatment of the lower limb. After the endovascular treatment, lateral foot DSA and CT perfusion scan of the foot were repeated. All DSA and CT perfusion scans were performed via the antegradely inserted 6 F sheath in the CFA to standardize the injection site. The injection protocol preintervention and postintervention for lateral DSA of the foot and CT foot perfusion were standardized (12 ml, 4 ml/s, 40% diluted Visipaque 270 using a power injector).

All perfusion CT scans were performed in our hybrid angiography CT suite (160-slice CT, Aquilion Prime, Canon Medical Systems, Kanagawa, Japan). The foot was imaged with an 8 cm field of view (repetitive scanning of 4 cm volumes), with scan parameters: 80 kV, 300 mA, rotation time 0.35 s. For CT foot perfusion imaging, 5 seconds of "no contrast" plain imaging is needed to calculate the baseline, so if during lateral DSA of the foot the contrast reached the foot within 5 seconds, a contrast injection delay was introduced using a 2 ml/s saline solution. The image acquisition protocol was as follows: 3.7 s intervals from 0 to 35.5 s after injection, then at 5 second intervals up to 51.9 s.

The dynamic CT volumes were transferred in DICOM format to a 3D workstation (Vitrea, Canon Medical Systems, Kanagawa, Japan). Perfusion software with a single arterial input using the upslope method (Figure 2) was used to calculate the perfusion maps (Figure 3). For their creation, a region of interest was manually drawn for the arterial input function and tissue enhancement curve. From these perfusion maps, the local perfusion could be calculated by placing a region of interest on the different anatomical compartments. The blood flow was calculated as the maximum slope of the tissue enhancement curve divided by the peak enhancement of the arterial input function and expressed as ml/min/100 ml of tissue. The dermal hyperperfusion band was used for calculating the local perfusion at the base and head of the first and fifth metatarsal bones, both on the plantar and dorsal surfaces of the foot, before and after PTA.

Statistical Analysis

The percentage of perfusion scans where the perfusion maps could be drawn was calculated. The relative change in perfusion of the foot and the change in time to peak (TTP) before and after PTA were determined. The changes in TTP and perfusion were tested using a paired *t* test. The mean radiation dose was calculated using for the ankle a conversion factor of 0.0002 mSv/mGycm. A $p<.05$ was considered statistically significant. Statistical analysis was performed using the IBM SPSS software.

Results

The study cohort consists of 12 patients (20 patients were screened, 8 patients were excluded because eGFR <45 ml/min/1.73 m^2 not on dialysis). Demographic data and clinical and treatment characteristics of the participants are summarized in Tables 1 and 2. In all patients, at least one BTK lesion was treated. Below the knee intervention was combined with endovascular treatment of the popliteal artery (n=2; 17%), superficial femoral artery (SFA) (n=2; 17%) or both SFA and popliteal artery (n=5, 42%). A single BTK artery was treated in 2 (17%) patients, two BTK arteries in 7 (58%) patients and three BTK arteries in 3(25%) patients. In all 12 (100%) patients, the perfusion maps could be drawn for the pretreatment and posttreatment perfusion scans. The perfusion and TTP data for the foot before and after treatment are shown in Table 3. The TTP post revascularization was noted to decrease with mean TTP before treatment 12.8 s (SD 2.8) and mean TTP posttreatment 8.4 s (SD 1.7), this difference was statistically significant (p=0.001). There was a tendency toward increased blood flow after revascularization with pretreatment mean perfusion of 340 ml/min/100 ml (SD 174) and posttreatment perfusion of 514 ml/min/100 ml (SD 366) (p=.104). The mean dose length product was 728.4 mGycm (effective dose of 0.145 mSv/CT scan). The contrast dose for both CT perfusion scans together was 9.6 ml.

The data for patient 1 were excluded from the analysis (TTP and perfusion) due to poor procedural outcome. We were only successful in recanalizing the occluded common

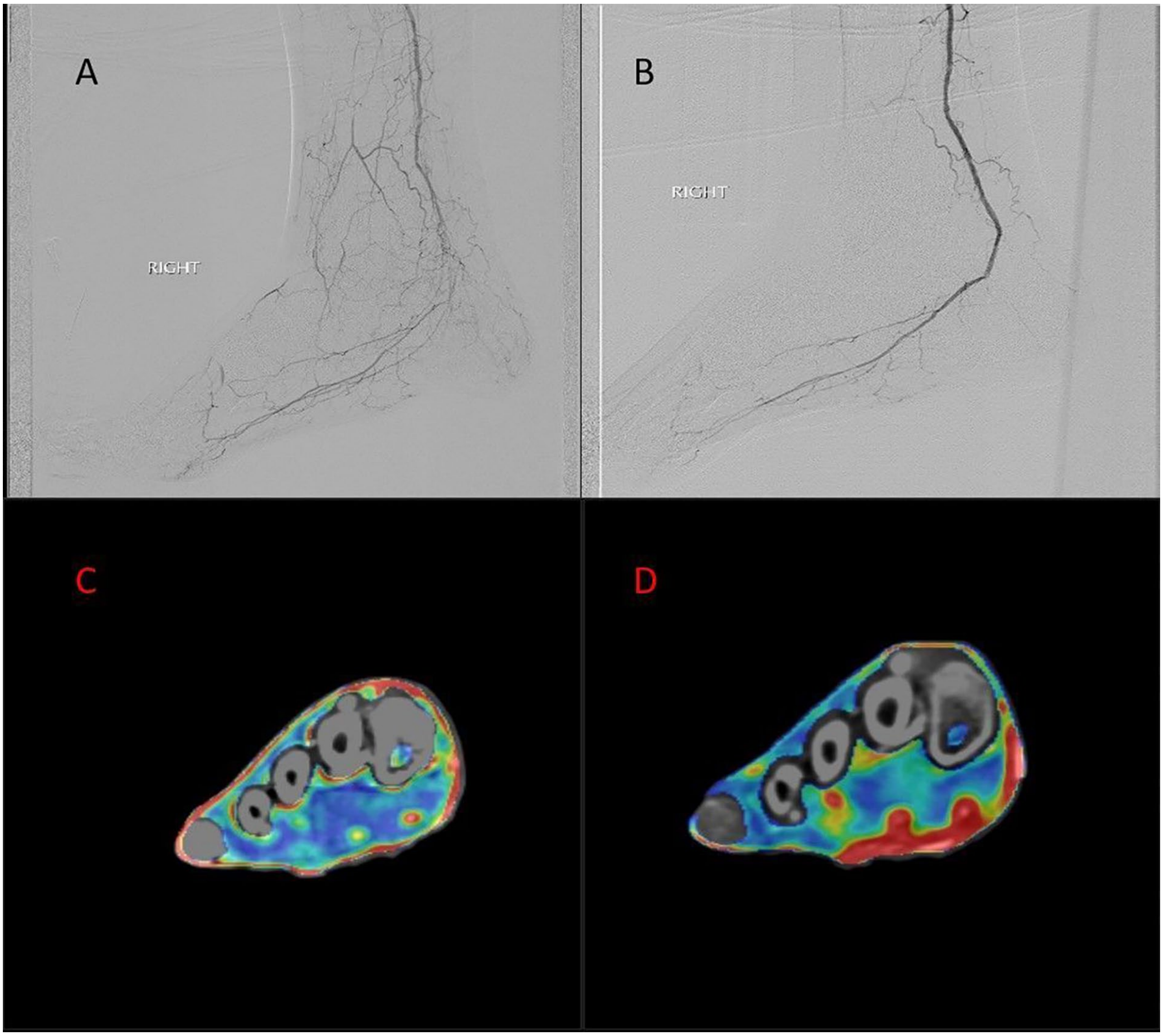

Figure 3. Angiography, from ipsilateral 6 F common femoral artery (CFA) sheath, 12 ml, 4 ml/s, 40% diluted Visipaque, and perfusion maps of the foot in patient one pre- and post endovascular intervention. (A) Lateral digital subtraction angiography (DSA) of the foot before revascularization: Occlusion of the distal posterior tibial artery at the level of the ankle with reconstitution of diminutive medial and lateral plantar branches. Occlusion anterior tibial and peroneal arteries, and the plantar arch. (B) Lateral DSA of the foot after percutaneous transluminal angioplasty (PTA) of the anterior and posterior tibial artery into medial plantar artery with only inflow to medial plantar artery. Dorsalis pedis, arch and lateral plantar artery are occluded. (C) Three-dimensional perfusion map before revascularization. (D) Three-dimensional perfusion map after revascularization with increased perfusion (red) medial part of the foot and decreased (blue) in the lateral part of the foot.

plantar artery into the medial plantar artery and not in the lateral plantar artery and the dorsalis pedis was occluded after the procedure. Post endovascular treatment perfusion CT showed markedly increased perfusion of the medial forefoot with a decrease in the perfusion of the lateral and dorsal aspects of the foot (Figure 3). As the wound was on the lateral side of the foot, the wound did not heal, and forefoot amputation was performed. Major amputations (forefoot or more) or deterioration of the (amputation) wound occurred in the patients (5, 9, 10, 11, 12), in this patient group an average increase of 7% in perfusion was seen, in the other patients (minor amputation and/or wound healing) an increase of 182% was calculated. In the patient group with major amputations or deterioration of the wound, a decrease of 45% was noticed in TTP after the treatment, in the group with only minor amputations or healed wounds, a decrease was seen of 23% in TTP after the treatment. In patients with end-stage renal disease (ESRD; 3, 5, 11, and 12), an average increase of 40% was noticed in perfusion, in patients without ESRD (2, 4, 6, 7, 8, 9, 10) an average increase of 138%. In the patient group with ESRD, a decrease of 35% was noticed in TTP after the treatment, in the group without ESRD, a decrease in TTP was seen of 32% in TTP after the treatment.

Table 1. Patient Characteristics.

Age mean (range)	67.4 (51-76)
Sex	83% male
Ethnicity	Chinese 67%, Malay 17%, Indian 17%
Diabetes	12 (100%)
CVA	(8%)
CAD	9 (75%)
ESRF	5 (42%)
HT	11 (92%)
HLD	11 (92%)
Smoking	2 (17%)

Abbreviations: CAD, coronary artery disease; CVA, cerebrovascular accident; ESRF, end stage renal failure; HLD, hyperlipidemia; HT, hypertension.

Discussion

Computed tomography perfusion assesses the microcirculation of the foot, which might be a more important predictor for wound healing than flow in the macrovascular system. We propose a new technique of CT foot perfusion using intra-arterial contrast injection during endovascular treatment for CLI in a hybrid angiography CT suite. Intraprocedural CT perfusion can potentially assist decision-making in defining sufficiency of revascularization, prediction of wound healing, early amputation (poor perfusion inspite of adequate revascularization) and extent of amputation. In our study, poor clinical outcome (major amputation or deterioration of wound after 6 months) was associated with lower CT foot perfusion values after endovascular treatment. In patients with ESRD, a lesser increase in perfusion was seen in comparison with patients without ESRD in this pilot study. Time to peak seems to be less associated with outcome in this pilot study.

Table 2. Indication for Treatment, Endovascular Treatment, and 6 Months Follow-up.

Pat no	Indication for treatment	Endovascular treatment	6 months follow-up
1	Fourth and fifth toe gangrene	Recanalization and angioplasty anterior tibial, angioplasty posterior tibial, and common plantar artery into medial plantar artery	Forefoot amputation Wound partly healed, improving
2	First toe ulcer	Angioplasty anterior tibial artery, posterior tibial artery, and common plantar artery	Amputation first toe Wound partly healed, stable
3	Fourth toe ulcer	Angioplasty popliteal artery and anterior tibial artery	Amputation fourth toe Wound healed
4	First toe and lateral malleolus ulcer	Angioplasty SFA, popliteal artery and anterior tibial artery and recanalization and angioplasty of the peroneal artery and tibioperoneal trunk	No amputation
5	First toe amputation wound and second toe ulcer	Angioplasty tibioperoneal trunk and peroneal artery and recanalization and angioplasty dorsalis pedis	Forefoot amputation Wound partly healed, improving
6	Second toe gangrene	Angioplasty SFA, popliteal artery and posterior tibial artery and recanalization and angioplasty anterior tibial artery	Amputation second toe Wound healed
7	Fifth toe ulcer	Angioplasty SFA, posterior tibial artery, and peroneal artery	Amputation fifth toe Wound healed
8	Second toe gangrene	Angioplasty SFA and dorsalis pedis and recanalization and angioplasty posterior tibial artery	No amputation
9	First toe amputation wound	Angioplasty SFA, popliteal artery, anterior tibial artery, posterior tibial artery and common plantar artery and recanalization and angioplasty tibioperoneal trunk	Trans-metatarsal amputation first toe Wound not healed, deterioration
10	First toe ulcer	Angioplasty SFA, popliteal artery and tibioperoneal trunk and recanalization and angioplasty peroneal artery	Amputation first toe Wound not healed, deterioration
11	First toe gangrene	Angioplasty SFA, popliteal artery, tibioperoneal trunk and recanalization and angioplasty anterior tibial artery	Below knee amputation Amputation wound healed
12	Fifth toe amputation wound	Angioplasty popliteal artery, anterior tibial artery, posterior tibial artery, and peroneal artery	Forefoot amputation Wound partly healed, improvement

Abbreviation: SFA, superficial femoral artery.

Table 3. Perfusion and TTP Before and After Revascularization.

Patient	Perfusion pre-PTA (ml/min/100 ml tissue)	Perfusion post-PTA ml/min/100 ml tissue	% increase/ decrease	TTP pre-PTA (s)	TTP post-PTA (s)
1	1538	708	−54%	9.7	9.9 (+2%)
2	398	520	+31%	7.7	9.8 (+27%)
3	169	390	+131%	12.8	11.6 (−9%)
4	13	91	+573%	9.8	7.8 (−20%)
5	529	550	+4%	14.9	9.7 (−35%)
6	482	522	+8%	14.9	6.6 (−56%)
7	398	1484	+273%	12.6	8.8 (−30%)
8	408	720	+77%	12.6	6.5 (−48%)
9	608	544	− 10%	13.7	6.6 (−52%)
10	233	266	+14%	17.1	9.6 (−44%)
11	300	277	− 8%	16.6	6.6 (−60%)
12	212	288	+36%	11.7	7.5 (−36%)
Total (excluding patient 1)			+103%		−33%

Abbreviations: PTA, percutaneous transluminal angioplasty; TTP, time to peak.

The first advantage of this technique is direct intra-arterial injection of low dose contrast (4.8 ml per perfusion scan) as compared to up to 100 ml via the peripheral intravenous route.[10–13] Secondly, the ability to use this tool during the endovascular treatment may better help define and predict endpoint of the intervention and outcome in the future. In patient 1, we identified reduced perfusion to the wound area after endovascular treatment, which supported the discussion of further amputation.

On the other hand, our approach requires a hybrid angiography CT suite and the calculation of the perfusion maps and interpretation of the data is time-consuming, adding time to the procedure (on average 10–15 min).

Several other technical issues are important to discuss.[13]

Earlier CT perfusion studies indicate the dermal hyperperfusion band as the most vascularized anatomical area of the foot. However, in our study, the dermal hyperperfusion band was not well identifiable. We attribute this flaw to the loss of spatial resolution. The maximum field of view (FOV) for perfusion on our 160 slice scanner was 4 cm compared to the 16 cm FOV on a 320 slice CT scanner. To obtain an 8 cm FOV to cover the entire foot, repetitive scanning of two 4 cm volumes was performed, increasing the interval between separate acquisitions.[13]

The arterial input signal was placed at the same location in the same artery in the foot before and after revascularization to calculate the perfusion maps of the foot. However, competitive flow from other reperfused BTK vessels could potentially affect the dermal perfusion. As consistency in the calculation of the perfusion maps was necessary for comparing the perfusion before and after revascularization, its relative increase or decrease in perfusion could be used to evaluate the success of the intervention.

Perfusion images are very sensitive to motion artifacts at borders between cortical bone and soft tissue and between soft tissue and air. For patients with critical limb ischemia, it can be difficult to keep the foot stationary for more than 50 seconds. To facilitate the fixation of the foot during the perfusion scan, we used a board-and-strap restraint to reduce patients' motion, however, if the foot is fixed during the perfusion scan, the compression from the restraint might influence the local perfusion.[13]

Other factors like temperature, infection, medication (such as vasodilators), blood pressure, and cardiac function can potentially affect perfusion. In this study, vasodilators were not used/needed during the interventions.

A wide variation in absolute perfusion measurement was noticed among the different patients. Several factors as mentioned above might be of influence. Further larger studies should be performed to assess the impact on outcome of absolute perfusion measurements versus relative increase in individual patients.

The main limitation of the proposed technique is the necessity of a hybrid angiography CT room.

Conclusion

Computed tomography foot perfusion using intra-arterial contrast injection during lower limb endovascular treatment in a hybrid CT angiography suite to generate 3D perfusion maps of the foot is technically feasible. It requires less contrast per perfusion scan, making it more suitable for patients with CKD. Further research is necessary in defining endpoints of endovascular treatment and establishing its role in limb salvage prognostication. Potential future applications of this new approach can be envisioned as objective definition of the endpoint of the revascularization procedure, assessment of the appropriate time and extent of amputation, and therapeutic assessment of new medication, such as stem cell therapy.

Acknowledgments

The authors thank www.enago.com for medical editing of the manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was funded by ACP Singhealth Duke-NUS (pitch for funds).

ORCID iDs

Thijs Urlings https://orcid.org/0000-0003-0329-3227
Mark C. Burgmans https://orcid.org/0000-0001-5258-291X

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