Original communication

2D perfusion angiography as quantitative method to evaluate iloprost effect on foot circulation

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Summary: *Background:* Two-dimensional (2D) perfusion angiography is useful for the evaluation of foot perfusion in patients with critical limb-threatening ischemia (CLTI). Iloprost is a synthetic prostacyclin analogue presenting vasodilating properties. Aim of this study was to demonstrate the utility of 2D perfusion angiography as quantitative method to evaluate iloprost effect on foot circulation. *Patients and methods:* Between January 2020 and June 2020 25 patients with CLTI underwent below-the-knee (BTK) endovascular revascularization, intra-arterial administration of iloprost, and assessment of foot perfusion by 2D perfusion angiography. Iloprost was administered as an intra-arterial bolus of 3 μg over 1–3 minutes immediately after BTK revascularization. The 2D perfusion angiography was performed in a standardized manner with a 5-F catheter placed into the popliteal artery. A wide region of interest (ROI) was identified to assess the foot perfusion. Time–density curves were calculated by the perfusion software. Changes of the overall time-density curves before and after the administration of iloprost were evaluated. *Results:* Endovascular revascularization was successful in all cases. The mean reduction of systolic pressure value after iloprost administration was 23.1 mmHg. Eight patients (32%) experienced a minor complication (6 cutaneous rush, 2 symptomatic hypotension >40 mmHg). In 20 patients the time-density curves under ROI increased after the intra-arterial administration of iloprost (+31.6%, range from +4.9% to +78.7%). Five patients had no modification or a slight decrease of foot perfusion after iloprost administration (non-responders patients). *Conclusions:* Patients undergoing intra-arterial administration of iloprost accounted for a not negligible rate of minor complications. 2D perfusion angiography was valuable as quantitative method to evaluate the iloprost effect on foot circulation. This technique could be useful to classify the patients in responders or non-responders to iloprost therapy.

Keywords: perfusion angiography, iloprost, critical limb ischemia, below-the-knee

Introduction

Percutaneous transluminal angioplasty (PTA) of below-the-knee (BTK) arteries in patients with critical limb-threatening ischemia (CLTI) is a common, well-established practice worldwide [1, 2, 3].

Two-dimensional (2D) perfusion angiography is used in the evaluation of foot perfusion after BTK revascularization in patients with CLTI [4, 5, 6].

Medical therapies as adjuvant to lower limb revascularizations are common [7]. Perioperative administration of iloprost improves the early and late rates of patency after peripheral revascularization [8, 9].

Iloprost (Endoprost®, Italfarmaco S.p.A., Milan, Italy) is a synthetic prostacyclin analogue presenting vasodilating, antithrombotic, and anti-inflammatory properties [10]. Intra-arterial administration of iloprost reduces the risk of early elastic recoil after balloon angioplasty of BTK vessels in patients with CLTI [11].

However, some patients are clinically non-responders to medical therapy with iloprost [12].

Aim of this pilot study was to demonstrate the utility of 2D perfusion angiography as quantitative method to evaluate iloprost effect on foot circulation.

Patients and methods

Between January 2020 and June 2020 25 patients with CLTI underwent BTK endovascular revascularization, concomitant intra-arterial administration of iloprost, and assessment of foot perfusion by 2D perfusion angiography.

All data concerning these procedures were prospectively collected in a dedicated database.

CLTI was defined as persistently recurring ischemic rest pain requiring analgesia for 2 weeks or presence of ulceration or gangrene of the foot or the toe associated with an

ankle systolic pressure <50 mmHg and/or a toe systolic pressure of <30 mmHg [13].

All patients had an adequate inflow with femoral pulse and direct multiphasic waveform flow into the femoral bifurcation.

After revascularization patients underwent wound management in a dedicated outpatient foot clinic. All patients underwent double antiplatelet therapy for three months.

Patient evaluations included a clinical examination and Duplex scan at 30 days, 3 months, and 6 months.

Endovascular revascularization

All patients gave their written consent to the procedure approved by the Ethics Committee. All interventions were performed in a hybrid operating room under local anaesthesia. In all patients an echo-guided antegrade 5-F approach was used.

The endovascular procedure was tailored according to the BTK disease. Preoperative diagnostic assessment consisted in Duplex scan. No patient received computed tomography (CT) or magnetic resonance imaging (MRI) before the procedure.

Preoperative angiography was used to classify the patients accordingly to the distribution of the vascular disease (big artery disease, BAD, and small artery disease, SAD) [14].

Technical success was defined as complete restoration of the flow with residual stenosis <30% on the revascularized BTK vessel (one or more for each patient).

Pharmacokinetic properties of iloprost

Iloprost is an analogue of epoprostenol and mimics the pharmacodynamic properties of this compound (inhibition of platelet aggregation, vasodilatation and cytoprotection). Improved metabolic and, in particular, chemical stability enhance the clinical utility of iloprost [15].

Iloprost is usually administered intravenously. Most patients tolerate iloprost infusion rates of up to 2 ng/kg/min. Headache and flushing are extremely common. Higher doses are associated with a significant incidence of gastrointestinal distress, and hypotension.

Iloprost provides a pharmacotherapeutic option for patients with severe peripheral vascular disease. Major contraindications to the intravenous administration of iloprost are unstable angina, recent myocardial infarction, severe cardiac failure, severe arrhythmias, ecent cerebrovascular events.

Administration of iloprost

Iloprost was administered as an intra-arterial bolus of 3 μg over 1–3 minutes immediately after BTK endovascular revascularization and throughout a 5-F catheter placed directly into the mid-part of the popliteal artery.

During administration of iloprost a strict monitoring of blood pressure was made. During the hospital stay all patients received a continuous invasive blood pressure monitoring throughout a transradial access. Any potential complications related to iloprost administration were recorded.

Patients with a systolic blood pressure less than 130mmHg after the BTK endovascular procedure were excluded from the study.

During the hospital stay, responding patients received iloprost intravenously with a low infusion rate, equal to the fixed rate of 2 μg/hour. The minimum duration of infusion was 24 hours.

2D perfusion angiography

All the procedures were performed with an Artis Zee machine (Siemens Medical Solutions, Forchheim, Germany). All images were automatically reconstructed with a postprocessing software on a dedicated workstation (i-Flow software, Siemens Medical Solutions, Forchheim, Germany).

The software is commercially available.

The 2D perfusion angiography was performed in a standardized manner with a 5-F catheter placed at the mid-part of the popliteal artery. Two lateral X-ray foot projections were used for image acquisition. A dedicated footrest for foot fixation was used in order to avoid any movements of the foot or image artifacts.

Images were acquired, before and after endovascular revascularization, with the injection of 12 cc of non-ionic iodinated contrast medium (Iodixanol 320 mg l/ml; Visipaque^{TM} 320, GE Healthcare AS, Oslo, Norway) by a power injector at a flow rate of 3 ml/sec. Three images per seconds were acquired for a total 60 images for each patient (the maximum duration of the registration was 20 sec for each patient).

For each patient two angiographic assessments were performed (before and after the intra-arterial administration of iloprost) (Figures 1 and 2).

To assess the foot perfusion, a wide region of interest (ROI) manually depicted by the same technician in all images on the post-processing workstation directly on the screen using the dedicated software starting from the tibio-talar joint to the mid-metatarsal area.

Statistical analysis

Time–density curves (TDCs) including time on the x axis and number of pixels on y axis were calculated by the perfusion software for each ROI of the angiographic picture.

Changes in percentages of the overall time-density curves before and after the administration of iloprost were evaluated.

Continuous data is expressed as mean±range. Categoric data is expressed as percentages. Statistical significance was defined at the P<.05 level.

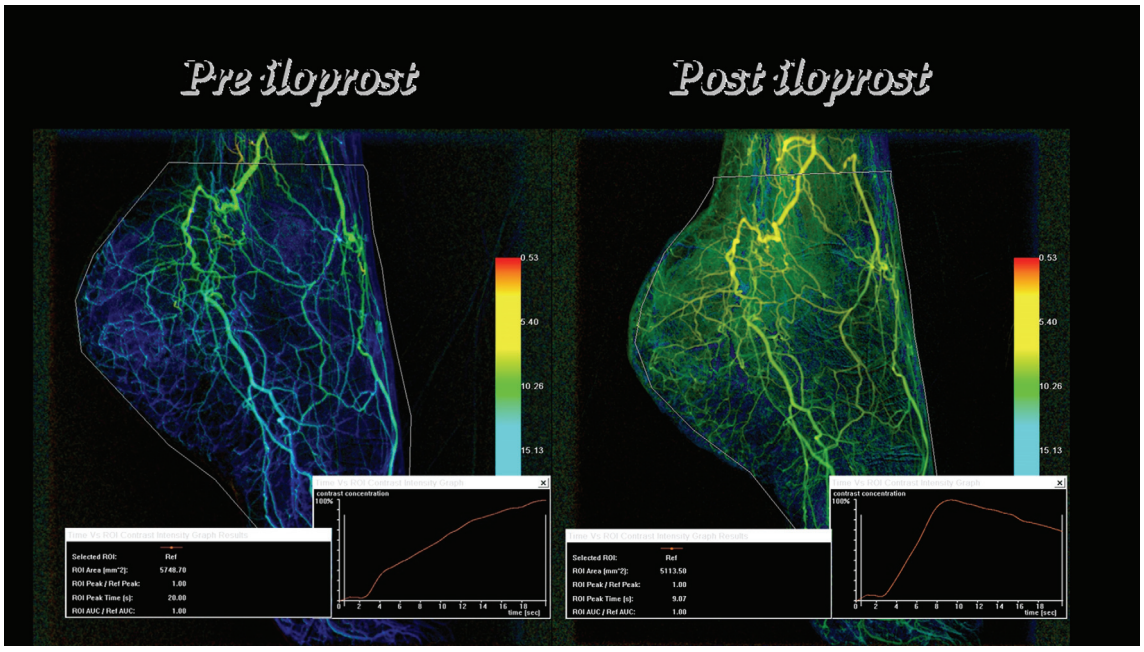

Figure 1. 2D perfusion angiography after BTK revascularization: pre (left) and post (right) administration of iloprost.

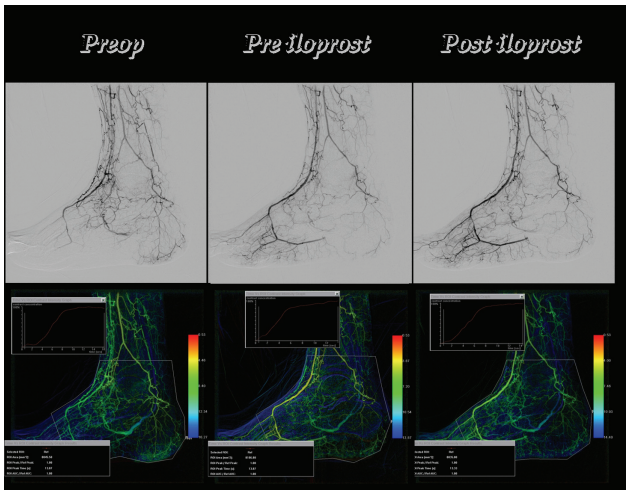

Figure 2. Pedal arch revascularization: operative angiograms (top) and 2D perfusion angiography (bottom).

Table I. Demographic data and preoperative risk factors of all patient's population (N=25)

Male	17 (68%)
Age, y, mean value	67
Patients with age >80 years	3 (12%)
Risk factors	
Smoking	15 (60%)
Hypertension	22 (88%)
Hypercholesterolemia	3 (12%)
Diabetes mellitus	21 (84%)
Insulin treatment	13 (52%)
Coronary artery disease	6 (24%)
Chronic renal failure*	8 (32%)
Dialysis	2 (8%)
Rutherford classification	
5 (minor tissue loss)	20 (80%)
6 (major tissue loss)	5 (20%)

Notes. *Glomerular Filtration Rate <30 mL/min.

Statistical analysis was performed using SPSS software (version 24.0 for Windows; IBM Corporation, Armonk, NY, USA).

Results

Twenty-five patients (male 17, 68%) with a mean age of 67 years (range 55–81 years) were treated.

Demographic data are reported in Table I.

In all cases an occlusion of at least one BTK vessel was present with a mean lesion length of 141.3 mm (range 43–280 mm). All patients had a BAD. In 17 cases (68%) an involvement of small foot arteries was present (SAD).

Endovascular revascularization of the BTK vessels were based on the operator choice by using plain balloon angioplasty in 19 cases (76%), and drug coated balloon angioplasty in 6 cases (24%). No stent was needed for flow-limiting post-angioplasty dissection.

Technical success with successful recanalization of at least one BTK vessel (residual stenosis <30%) was obtained in all patients.

The mean systolic blood pressure before and after the injection of iloprost were 163.7 mmHg (range 130–195) and 140.6 mmHg (range 100–180), respectively. The mean reduction of pressure value was 23.1 mmHg. Eight patients (32%) experienced a minor complication (6 cutaneous rush, 2 symptomatic hypotension >40 mmHg). Patients with symptomatic hypotension were treated with rapid fluid administration and Trendelenburg position.

In 20 patients the time-density curves under ROI increased after the intra-arterial administration of iloprost

(+31.6%, range from +4.9% to +78.7%). Five patients had no modification or a slight decrease of foot perfusion after iloprost administration (non-responders patients).

During the hospital stay iloprost was continuously administered in responders patients. No patient developed any bleeding or systemic complications related to iloprost therapy. All patients received at least 24 hours of treatment. The mean hospital stay was 3.3 days (range 2–9).

After a 6-month follow-up all patients were alive. Overall 6-month primary patency was 76% (19/25). Complete wound healing was obtained in 16/25 (64%) patients. Overall mean time to complete wound healing was 4.1 months. All patients with 6-month complete wound healing had minor tissue loss (Rutherford class 5).

No patient experienced major amputation at 6 months. Two patients with major tissue loss and no wound healing underwent skin graft procedure.

Discussion

Jens et al. [4] firstly described the technique to obtain a high-quality 2D perfusion angiography of the foot in patients with CLTI.

In the present study we applied the same study protocol including the use of iodixanol 320 mg l/ml, the quantity of contrast medium, the injection rate, and the footrest for foot fixation in order to avoid artefacts during the image acquisition.

In a following clinical study Reekers et al. [5] tested the feasibility of 2D perfusion angiography in 89 consecutive CLTI patients undergoing peripheral endovascular procedure. In this clinical series the authors used vasodilation with tolazoline in 12 patients without options for a BTK revascularization procedure. The authors concluded that 2D perfusion angiography allows to quantify the functionality of the foot microcirculation in patients with CLTI by using vasodilatative drugs.

Therefore, 2D perfusion angiography is an established method to determine tissue perfusion in patients with peripheral arterial disease [16]. However, 2D perfusion angiography has not been demonstrated to be a valid method to predict the clinical outcomes. Recently, 2D perfusion angiography was found to be associated with wound healing rate in CLTI patients with ischemic foot wounds and combined femoropopliteal and below-the-knee lesions undergoing isolated femoro-popliteal endovascular revascularization. Anyway, no association between 2D perfusion angiography and transcutaneous oximetry (TcPO2) values was observed [17].

Iloprost has vasodilating, antithrombotic and anti-inflammatory properties [10, 18, 19, 20]. Prolonged infusion of iloprost is a first-line option in the treatment of patients with CLTI unsuitable for revascularization [21], nevertheless several studies have shown a favourable effect also in improving patency and clinical outcomes after revascularization of the lower limbs.

Furthermore, intra-arterial administration is effective in inhibiting the early elastic recoil [11]. In the present study the rate of complications after intra-arterial iloprost administration was not negligible. No patient experienced a major complication but in two patients (8%) a symptomatic hypotension was recorded. During the hospital stay the low-grade intravenous infusion of iloprost in responders patients did not account for bleeding or systemic complications.

Maybe intra-arterial administration of 3 µg over 1–3 minutes is too much higher for the majority of patients. We used this dosage previously reported in other papers [9, 11]. Anyway, further studies are needed to evaluate the appropriate dosage of iloprost for intra-arterial administration.

However, not all patients received benefits from iloprost therapy. Melillo et al. [12] reported the response rate and the predictive criteria in terms of long-term survival in 102 patients with CLTI treated with iloprost; the overall responder rate was 71.2%.

Recently, a new classification of BTK disease has been proposed (BAD and SAD). In addition, the burden of calcium inside the foot vessels has been advocated as potential predictor of poor clinical outcomes [22]. We could just hypothesize the potential benefits of iloprost in SAD disease with low-grade calcifications. Further studies are needed to validate this hypothesis.

Therefore, in our protocol study we decided to evaluate the effectiveness of iloprost in improving the microcirculation of the foot in CLTI patients undergoing BTK procedure [23].

In this pilot study we used the 2D perfusion angiography as quantitative method to distinguish the patients in responders and non-responders to iloprost therapy.

In the present study the rate of responder patients was 80%. Twenty patients had an increase of the area under ROI demonstrating a good but variable response of the foot microcirculation to iloprost treatment. In our center some selected patients with foot wounds and responders to iloprost were followed in an outpatient setting with continuous intravenous administration of iloprost in order to improve the rate of wound healing and the overall rate of patency during the follow-up [24].

The main limitations of this pilot study are the absence of a control group, the small number of patients enrolled, and the absence of a comparative quantitative method alternative to 2D perfusion angiography (for example TcPO2). Therefore, these results should be confirmed in prospective studies with adequate sample sizes.

Conclusions

Patients undergoing intra-arterial administration of iloprost accounted for a not negligible rate of minor complications. 2D perfusion angiography was valuable as quantitative method to evaluate the iloprost effect on foot circulation.

This technique could be useful to classify the patients in responders or non-responders to iloprost therapy.

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