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Decrease of peripheral resistance after intraoperative administration of iloprost in patients with and without type 2 diabetes mellitus and with peripheral arterial occlusive disease

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Abstract

Background: In many cases, Ilomedin® infusions are applied as part of a perioperative measure in patients with peripheral arterial occlusive disease because it makes a relevant vasodilatatory effect in patients with type 2 diabetes mellitus and with/without peripheral neuropathy.

Aims: A prospective case–control study was performed to investigate the effect of prostanoids on peripheral resistance in patients with type 2 diabetes mellitus and patients without type 2 diabetes mellitus, as well as the role of peripheral neuropathy in patients undergoing arterial reconstruction.

Methods: Sixty patients undergoing arterial reconstruction were enrolled. Sufficient data were collected on 38 patients. Prior to surgery, peripheral nerve conduction velocity was measured. Blood flow volume at the common femoral artery was assessed intraoperatively using a Doppler flowmeter at four time points: at baseline before arterial reconstruction (T0), after reconstruction (T1), after 5 (T2) and 10 min (T3) after intra-arterial application of 3000 ng of Ilomedin. Peripheral resistance units were calculated as a function of mean arterial pressure and flow volume using the following formula: peripheral resistance unit = mean arterial pressure (mm Hg) / flow volume (mL/min).

Results: Ilomedin produced an immediate and significant drop of peripheral resistance in patients without type 2 diabetes mellitus as well as in patients with type 2 diabetes mellitus. Patients with peripheral neuropathy showed a less pronounced effect to Ilomedin compared to individuals with normal nerve conduction velocity.

Keywords

Peripheral arterial occlusive disease, diabetes, vascular disease, surgery

Introduction

Type 2 diabetes is a typical risk factor in vascular surgery patients. Diabetes predisposes to arterial hypertension, dyslipidemia and advanced atherosclerosis. The large socioeconomic burden of type 2 diabetes in developed countries is undeniable and deserves special consideration in both the assessment and treatment of patients suffering from peripheral arterial occlusive disease (PAOD).[1] Both vascular smooth muscle cell as well as endothelial cell function are affected by diabetes mellitus, which may cause impairment of endothelium-dependent vasodilatation,[2–4] and consequently PAOD.

Iloprost, a synthetic analogue of prostacyclin, is a routinely applied drug considered to promote vasodilation in PAOD patients. However, its molecular mechanism of action as well as its potential limitations when regulatory

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functions of vasodilation are impaired has not been fully elucidated.[5–7] The therapeutic properties of prostanoids in general appear to be primarily due to their vasodilative effects. However, the inhibition of platelet aggregation by limiting platelet function and increasing fibrinolytic activity as well as their antiproliferative effects on vascular smooth muscle cells may also contribute to the improvement of the peripheral circulation.[8] To date, it is still unclear whether there is a relevant vasodilatory effect of prostanoids in patients with type 2 diabetes and whether the presence of peripheral neuropathy modifies the overall effectiveness of iloprost.

The present study was performed to assess the influence of iloprost on peripheral resistance in patients with or without type 2 diabetes mellitus in a clinical setting with special consideration to the presence or absence of peripheral neuropathy.

Materials and methods

Study design and ethics committee approval

A single centre, prospective, nonrandomized interventional study was performed. All patients provided written informed consent. The study was approved by the ethics committee of the city of Vienna in 2012 (EC nr: 11-144-0512) and was extended annually upon written request. Performance of the study complied with the World Medical Association Declaration of Helsinki regarding ethical conduct of research involving human subjects (clinicaltrials.gov identifier NCT 01774058).

Patients

The study was designed to enrol 60 consecutive patients with PAOD undergoing surgical reconstruction of the common femoral arteries and/or above-knee femoropopliteal bypass surgery. As our intention was to assess the hemodynamic effect of iloprost, rather than its clinical merit, we decided to include patients with PAOD Fontaine stage IIb (walking distance less than 200 m), III (rest pain) or IV (tissue loss). Surgical procedures were planned, and the absence of inflow stenosis was verified based on magnetic resonance imaging (MRI) or computed tomography (CT) angiography. Exclusion criteria for participation in the study included contraindications for the application of iloprost, planned spinal anaesthesia and patients with proximal stenoses of the upper arm. Patients were stratified into two groups based on being with type 2 diabetes or without diabetes. Diabetes status was assessed according to American Diabetes Association (ADA) guidelines.[9] Patients with type 1 diabetes were not included. Before surgery, measurement of nerve conduction velocity was performed by a trained nurse at the Department of Physiotherapy using a Keypoint G3 System (Medtronic A/S, Skovlunde, Denmark) to detect a potential presence of neuropathy. Data were analysed by absence/presence of type 2 diabetes and normal/abnormal nerve conduction velocity.

Technique

Surgery was performed under general anaesthesia via a longitudinal skin incision in the groin. After preparation of the common, superficial and deep femoral arteries, baseline measurements (T0) of intraoperative arterial flow was performed using the Sono TT FlowLab instrument (emTec GmbH, Munich, Germany). After systemic administration of 5000 IU of unfractionated heparin, the common femoral and peripheral arterial vessels were clamped. Following a longitudinal arteriotomy, thrombendarterectomy of the common femoral artery was performed in all cases, extending into the deep femoral artery and superficial femoral artery when necessary. In some cases, this was followed by above-knee femoropopliteal bypass surgery. Upon completion of groin reconstruction, Doppler flow measurements were performed at the common femoral artery (T1). The time of arterial clamping was between 30 min and 2 h. Baseline testing was started 5 min after clamp removal and continued until a stable flow volume (VF) measure was achieved for 5 min. Provided a systolic blood pressure equal to or above 100 mm Hg at this point, 3000 ng of iloprost (Bayer Schering Pharma, Zurich, Switzerland), diluted in 15-mL saline solution, was administered into the common femoral artery over 2 min according to a study performed by Smith et al.[10] Distal to the injection site, Doppler flow was then measured at the common femoral artery 5 (T2) and 10 min (T3) after intra-arterial iloprost application. Transmission head size was selected according to vessel diameter individually for each surgical case. During the procedure, systemic arterial blood pressure was continuously documented using a pressure transducer (Datex-Ohmeda Division Instrumentarium Corp. Helsinki, Finland Type F-CU8.05) connected to an intra-arterial cannula placed in the radial artery of the forearm. The result of the arterial reconstruction was routinely checked by intraoperative on-table angiography and the wound was closed. Before discharge from the hospital, the surgical reconstruction was evaluated by duplex ultrasound as well as an assessment of the oscillometric ankle-brachial index.

Statistical methods

Statistical analysis was performed with SPSS 15.0 for Windows (SPSS Inc, Chicago, IL). To allow for comparison of all measurements of intraoperative arterial VF, despite potential differences in blood pressure at the time of Doppler flow measurement, peripheral resistance units (PRUs) were calculated as a function of mean arterial

Table 1. Patient characteristics.

	All patients	Non-DM patients	DM patients	*p* value
Number	38	24	14	
Age (range)	66.26 ± 12.227 (29–91)	66.71 ± 13.691 (29–91)	65.50 ± 9.638 (51–81)	0.773
Gender (male)	31 (81.6)	19 (79.2)	12 (85.7)	0.615
Comorbidities				
Smoking	21 (55.3)	14 (58.3)	7 (50.0)	0.618
Diabetes	14 (63.2)	0 (0)	14 (100)	<0.001
Hypertension	34 (89.5)	21 (87.5)	13 (92.9)	0.604
Hyperlipidaemia	6 (15.8)	5 (20.8)	1 (7.1)	0.264
CHD	31 (81.6)	20 (83.3)	11 (78.6)	0.715
CKD	3 (7.9)	1 (4.2)	2 (14.3)	0.264
COPD	16 (42.1)	12 (50.0)	4 (28.6)	0.197
Peripheral neuropathy	19 (61.3))	9 (47.4)	10 (83.3)	0.045
Premedication				
ASS	32 (84.2)	19 (79.2)	13 (92.9)	0.264
Statins	29 (76.3)	17 (70.8)	12 (85.7)	0.298
B-blocker	16 (42.1)	9 (37.5)	7 (50.0)	0.452
A-blocker	4 (10.5)	2 (8.3)	2 (14.3)	0.564
ACE inhibitor	13 (34.2)	7 (29.2)	6 (42.9)	0.564
Operated leg (left)	16 (42.1)	8 (33.3)	8 (57.1)	0.152
PAD Fontaine stage				
II	32 (84.2)	22 (91.7)	10 (71.4)	0.192
III	1 (2.6)	0 (0)	1 (7.1)	
IV	5 (13.2)	2 (8.3)	3 (21.4)	
ABI before surgery	0.708 ± 0.280 (0.00–1.67)	0.699 ± 0.238 (0.00–1.00)	0.722 ± 0.344 (0.33–1.67)	0.815
ABI after surgery	0.856 ± 0.196 (0.50–1.56)	0.841 ± 0.159 (0.58–1.08)	0.880 ± 0.250 (0.50–1.56)	0.568
Procedure				
Inguinal artery reconstruction	27 (71.1)	18 (75.0)	9 (64.3)	
Femorodistal bypass surgery	11 (28.9)	6 (25.0)	5 (35.7)	
Outflow				
Patent femoral outflow	20 (52.6)	13 (54.2)	7 (50.0)	
PFA collateral outflow	18 (47.4)	11 (45.8)	7 (50.0)	

ACE: angiotensin-converting enzyme; DM: diabetes mellitus; CHD: coronary heart disease; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; ASS: acetylsalicylic acid: representing low-dose aspirin (100 mg); PAD: peripheral arterial disease; ABI: ankle-brachial index; PFA: profunda femoris artery.

pressure (MAP) and VF according to the following formula: PRU = MAP (mm Hg) / VF (mL/min).[10]

The patient population was stratified according to the presence of diabetes and peripheral neuropathy in the operated limb. Kolmogorov–Smirnov testing confirmed normal distribution of all continuous variables. Descriptive statistics (means, standard deviations and ranges) were applied to acquired data, and categorical variables were expressed as frequencies and percentages. Differences between groups were investigated by the Pearson chi-square and Fisher's exact tests. For assessment of changes of peripheral resistance, paired *t* tests were applied with the value gained after surgical reconstruction, but before administration of iloprost (T1) taken as baseline. A *t* test for independent variables was applied to compare PRU changes between groups. A potential impact of gender and age, all determined comorbidities and medications (see Table 1) as well as the PRU before (T0) and after reconstruction (T1) on the effect of iloprost administration was investigated by univariate regression analysis. Variables with a possible influence on iloprost effectiveness were further entered into a multivariate regression model. Patients with missing values were excluded listwise. Values of $p < 0.05$ were considered statistically significant.

Results

From October 2012 to December 2013, 60 consecutive patients were enrolled in the study. During the study period, 22 patients (18 men, 4 women) had to be excluded because of a deviation from protocol: intraoperative

Table 2. Peripheral resistance.

	Patent femoral outflow	PFA collateral outflow	*p* value
Before reconstruction	2.84 ± 6.82	3.38 ± 10.17	0.868
Before iloprost administration	0.31 ± 0.15	0.43 ± 0.29	0.134
5 min after iloprost administration	0.22 ± 0.08	0.25 ± 0.09	0.410
10 min after iloprost administration	0.23 ± 0.11	0.28 ± 0.26	0.457

PFA: profunda femoris artery.
Values are given as peripheral resistance units (PRUs) and were calculated as a function of mean arterial pressure (MAP) and flow volume (VF) according to the following formula: PRU = MAP (mmHg) / VF (mL/min).

hypotension precluding the administration of iloprost ($n=7$), spinal anaesthesia instead of general anaesthesia ($n=5$), inadequate intraoperative Doppler flow measurements ($n=4$) and retraction of consent to participate (n = 1). In five patients, surgery was cancelled due to various reasons: retraction of consent to undergo surgery ($n=2$), cardiac insufficiency ($n=1$), progressive hepatic cirrhosis ($n=1$) and the detection of an infrarenal aortic aneurysm requiring additional treatment ($n=1$).

Thus, data from 38 individuals (31 men, 7 women) were available for the final analysis. Patient characteristics are presented in Table 1. The mean age was 66.3 ± 12.2 years. Fourteen patients had type 2 diabetes and in 21 cases, a diagnosis of peripheral neuropathy was established preoperatively.

In 26 cases, only the femoral bifurcation was reconstructed and in 12 cases above-knee femoropopliteal bypass surgery was performed. Two patients with Fontaine stage IV PAOD had progressive gangrene, despite successful revascularization and subsequently required below-knee amputation. One patient suffered early bypass occlusion after 25 days and was treated successfully by thrombolysis and percutaneous transluminal angioplasty of the distal anastomosis. Three cases of surgical wound infection requiring revision were observed.

There were no serious adverse events applicable to the administration of iloprost: no significant influence on intraoperative MAP was observed. The average decrease of MAP after administration of 3000 ng of iloprost was 6.3 ± 12.0 mm Hg (range: −30 to +17.5 mm Hg) with an MAP decrease of more than 10 mm Hg in 13 cases and more than 20 mm Hg in 4 patients.

Arterial reconstruction resulted in a significant decrease of peripheral resistance in all patients: 3.12 ± 8.57 PRU before reconstruction to 0.36 ± 0.25 PRU before administration of iloprost ($p<0.001$), and there was no significant difference depending on the outflow: PRU decreased from 2.84 ± 6.82 to 0.31 ± 0.15 ($p=0.022$) in patients with outflow to least one patent crural artery and from 3.38 ± 10.17 to 0.43 ± 0.29 PRU ($p=0.022$) in patients with superficial femoral artery (AFS) occlusion who had undergone profundoplasty only. PRU decreased further 5 min after iloprost administration (0.36 ± 0.25 to 0.23 ± 0.09; $p=0.001$), when it reached a stable level.

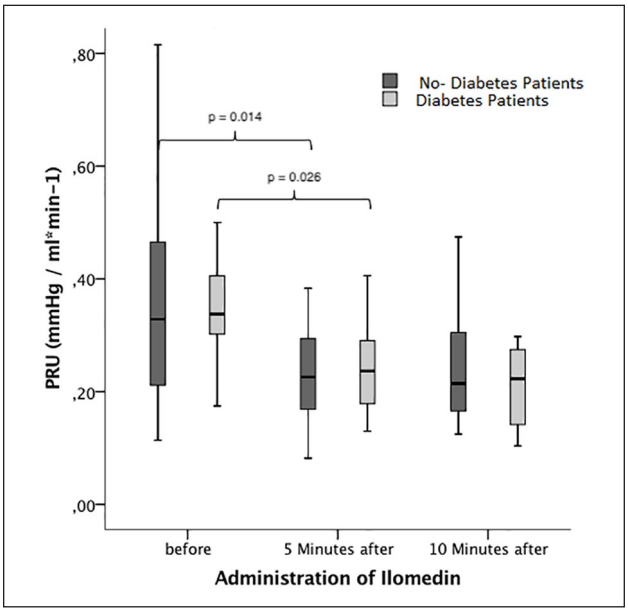

Figure 1. Time course of peripheral resistance units (PRUs) after administration of 3000 ng of iloprost in diabetes and no-diabetes patients. The box plots demonstrate the median, 25th and 75th percentiles with whiskers representing the highest and the lowest values between 1.5 and 3 times the interquartile range (IQR).

This was also independent of the extent of surgical revascularization: 0.31 ± 0.15 to 0.22 ± 0.08 PRU ($p=0.014$) in patients with outflow to least one patent crural artery and 0.43 ± 0.29 to 0.25 ± 0.09 PRU ($p=0.019$) in patients with AFS occlusion who had undergone profundoplasty only. There was no significant difference in peripheral resistance depending on the quality of outflow at any time (see Table 2).

Patients with diabetes versus patients without diabetes

The average decrease of peripheral resistance 5 min after administration of iloprost was significant in patients without diabetes as well as in patients with diabetes: 0.40 ± 0.27 to 0.26 ± 0.20 PRU ($p=0.014$) and 0.36 ± 0.18 to 0.24 ± 0.08 PRU ($p=0.026$; Figure 1), respectively. There

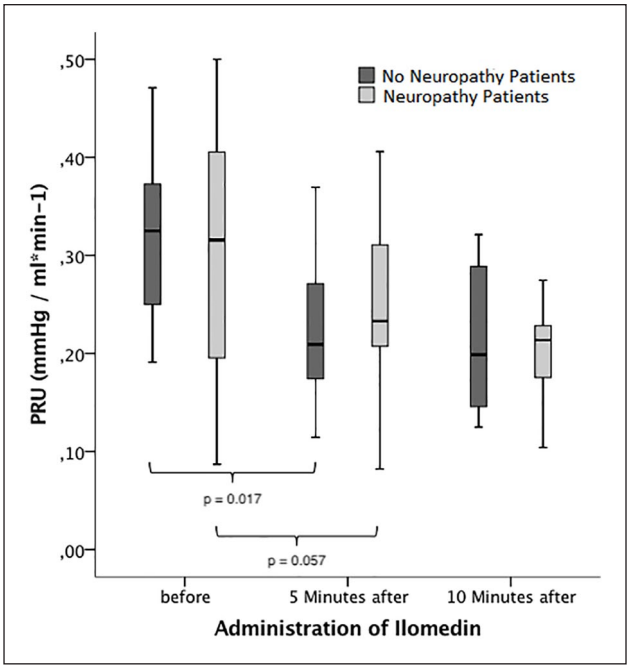

Figure 2. Time course of peripheral resistance units (PRUs) after administration of 3000 ng of iloprost in patients with and without neuropathy. The box plots demonstrate the median, 25th and 75th percentiles with whiskers representing the highest and the lowest values between 1.5 and 3 times the interquartile range (IQR).

was no further decrease of peripheral resistance after 10 min in either group. PRU changes were not significantly different between both patient groups: ($p = 0.84$ after 5 min and $p = 0.27$ after 10 min).

Patients with neuropathy versus patients without neuropathy

Due to a withdrawal of consent for this specific item, preoperative assessment of nerve conduction velocity was available for 31 patients only. A significant decrease of peripheral resistance was observed in patients with normal peripheral nerve function only (0.31 ± 0.09 PRU to 0.22 ± 0.07 PRU; $p = 0.017$ vs 0.37 ± 0.23 PRU to 0.28 ± 0.21 PRU; $p = 0.057$; Figure 2). After 10 min, peripheral resistance had already returned to post-reconstruction levels in patients with normal nerve conduction velocity, while there appeared to be a delayed, although not statistically significant effect of iloprost in neuropathic patients. Again, PRU changes were not significantly different between both patient groups: ($p = 0.90$ after 5 min and $p = 0.16$ after 10 min).

Univariable linear regression analysis suggested that a higher peripheral resistance before administration of iloprost and the presence of chronic obstructive pulmonary disease (COPD) were associated with a more pronounced decrease of peripheral resistance after administration of iloprost. However, the multivariable analysis identified peripheral resistance at baseline as the only independent predictor of the extent of prostanoid effect (Table 3). Accordingly, there was a highly significant correlation between the maximum decrease of PRU after the administration of iloprost and the peripheral resistance after the arterial reconstruction and before iloprost was given ($r = 0.758$; $p = 0.001$; Figure 3). Further analysis showed that COPD patients had a significantly higher peripheral resistance at baseline compared to non-COPD patients (0.29 ± 0.11 PRU vs 0.51 ± 0.31 PRU, respectively; $p = 0.017$) and affected patients had a more pronounced decrease of peripheral resistance after iloprost administration ($51.1\% \pm 25.4\%$ vs $25.1\% \pm 29.6\%$; $p = 0.008$; Figure 4).

Table 3. Univariate and multivariate analyses estimating the association of patient characteristics with the maximum decrease of peripheral resistance (primary endpoint) after administration of iloprost.

	HR	95% CI		*p* value
		Lower	Upper	
Univariate				
PRU after arterial reconstruction [mm Hg/(mL/min)]	78.9	45.6	112.2	<0.001
COPD	25.9	7.3	44.5	0.008
Hyperlipidaemia	27.5	1.2	53.7	0.041
Multivariate				
PRU after arterial reconstruction [mm Hg/(mL/min)]	64.3	26.8	101.8	0.001
COPD	9.8	−8.1	27.7	0.273
Hyperlipidaemia	13.1	−9.3	35.6	0.244

HR: hazard ratio; CI: confidence interval; PRU: peripheral resistance unit; COPD: chronic obstructive pulmonary disease.
The *p* value by the proportional hazard model (Cox regression). Only variables that were significantly associated in the univariate analysis are represented.

Discussion

Iloprost is well known to clinically improve claudication symptoms and further leading to better wound healing; however, the detailed mechanisms of action of this prostanoid are still unresolved. Especially in patients with diabetes, it is not clear whether iloprost also leads to the significant immediate decrease of peripheral resistance that can be regularly observed in patients without diabetes, since mediasclerosis and diabetic peripheral neuropathy could abolish the effectiveness of prostanoids. We could demonstrate that iloprost significantly improved blood flow, both in patients without diabetes and with

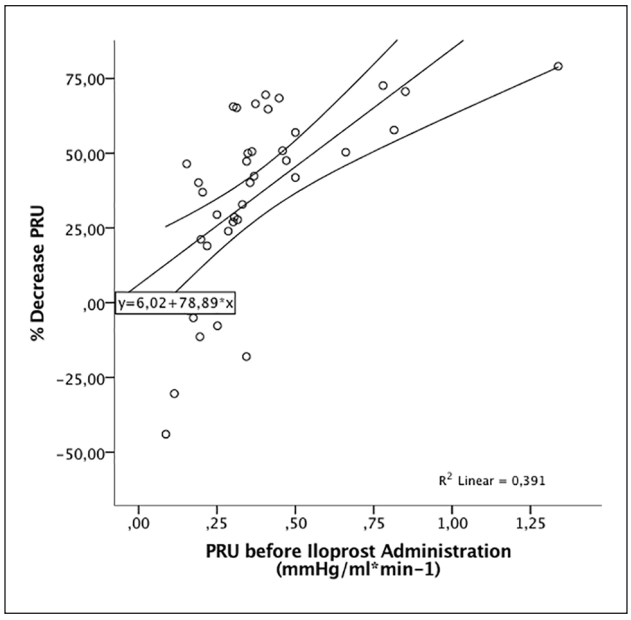

Figure 3. Scatterplot demonstrating the highly significant association of peripheral resistance before the administration of iloprost and the maximum decrease of peripheral resistance after this event.
PRU: peripheral resistance units.

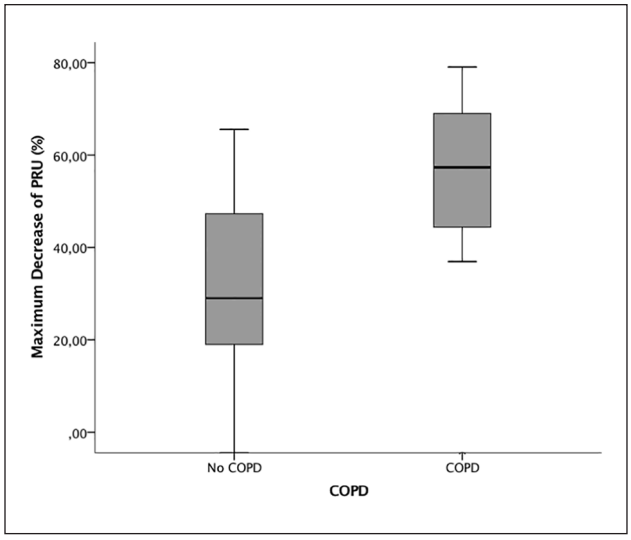

Figure 4. Reduction of peripheral resistance was significantly more pronounced in COPD patients compared to patients with no COPD (51.1% ± 25.4% vs 25.1% ± 29.6%; $p = 0.008$). The box plots demonstrate the median, 25th and 75th percentiles with whiskers representing the highest and the lowest values between 1.5 and 3 times the interquartile range (IQR).
PRU: peripheral resistance units; COPD: chronic obstructive pulmonary disease.

diabetes. Interestingly, the presence of peripheral neuropathy limited the increase of blood flow.

Finally, both increased baseline peripheral resistance and the presence of COPD were associated with a more profound decrease of peripheral resistance after administration of iloprost.

According to a recent meta-analysis, there is moderate-quality evidence indicating small effects of prostanoids on ulcer healing, residual pain relief and the reduction of analgesics consumption when compared with placebo.[10] Even though there was no effect reported on the incidence of total amputations, a subgroup analysis showed a small, non-significant reduction of amputation incidence in patients treated with iloprost.[11]

Spanos and colleagues reported iloprost targeted follow-up and supervised cessation of smoking may lead to improvement in pain-free walking distance, limited use of analgesics, decreased risk of amputation and better self-reported quality of life.[12] Similarly, iloprost showed favourable results in reducing major lower extremity amputations in a recent review.[13]

Another meta-analysis including seven placebo-controlled studies and a total of more than 643 patients with Fontaine stage III or IV PAOD also demonstrated the beneficial effect of parenteral application of prostaglandin E1 in patients with critical limb ischaemia with regard to pain and wound healing.[14] Separately, iloprost showed favourable clinical effects on uremic, severe PAOD patients.[15] Loosemore's meta-analysis reported on a reduction of pain and ulcer size and an improvement of amputation-free survival after a 3- to 4-week application of iloprost.[16] Parenteral prostanoids have been recommended for use in some patients with critical limb ischaemia not suitable for arterial revascularization or after unsuccessful revascularization in national and international guidelines, independent of their diabetic status.[5,17,18] The long-term effects of prostanoids in the treatment of critical limb ischaemia, however, remain unclear.[6] Moreover, it remains unclear which mechanisms of action, including the vasodilatory effect on vessels, the inhibition of platelet aggregation and the inhibition of leucocyte adhesion, are dominant in patients with diabetes versus patients without diabetes.[6,14,16] While previous studies on the effectiveness of prostanoids for the treatment of critical limb ischaemia or PAOD have included patients with diabetes as well as patients without diabetes,[6,11,12,14–16] to the authors' best knowledge, this is the first investigation directly comparing these two populations. While the vasodilatory effect of prostanoids appears to be the predominant factor in most cases, this may not hold true for all patients with diabetes. Chronic hyperglycemia is associated with fibrosis and hyperplasia of the arterial intima and media, changes in the structure of vascular collagen and elastin and endothelial dysfunction, which finally result in increased arterial stiffness in patients with diabetes.[2–4]

Our data indicate that there is a significant vasodilatory effect of iloprost both in patients without diabetes as well as in patients with diabetes: peripheral resistance decreased significantly in both groups after iloprost administration

and the increased vascular stiffness in patients with diabetes did not significantly reduce iloprost effectiveness.

The influence of peripheral neuropathy on the effect of prostanoid administration has not been investigated previously. While there is some evidence that prostanoids may help to ameliorate symptoms of peripheral diabetic neuropathy,[7,19] the matter remains to be fully elucidated. For prostaglandin E1 incorporated into lipid microspheres (Lipo-PGE1), Miyata et al.[20] demonstrated a significantly higher efficacy rate of 83.6% in patients with neuropathic ulcers compared to 68.8% and 65.3% in patients with ischemic or neuroischemic ulcers, respectively. Thus, prostanoids may also be considered effective in patients with neuropathy, which may be due to alternative modes of action including its positive effects on endothelial function as well as exerting anti-oxidative and anti-inflammatory properties.[7,21] The prevalence of peripheral neuropathy in the general population and in persons 70 years or older are known to be 1% and 7%, respectively.[22] Thus, the relatively high rate of peripheral neuropathy in our study population, diabetics and non-diabetics, as detected by nerve conduction velocity was surprising. However, Kim et al.[23] have demonstrated that there was a 82.7% prevalence of diabetic, ischemic or radiculopathic peripheral neuropathy in limbs affected by either critical or non-critical chronic ischaemia if assessed by nerve conduction studies and needle electromyography. Our findings support these data and suggest that the prevalence of subclinical peripheral neuropathy, if properly assessed, may be much higher in PAOD patients than is generally presumed.

Further analysis showed that patients with COPD had a higher peripheral resistance at baseline. The apparently improved effectiveness of iloprost in COPD patients could not be objectified by multivariable analysis. Thus, the more pronounced decrease of peripheral resistance after iloprost administration may be the result of a higher peripheral arterial stiffness in individuals with COPD. In literature, arterial stiffness has been independently associated with the severity of COPD along with inflammation, oxidative stress, and a high sympathetic tone.[24,25] Furthermore, several authors have shown an association of COPD with impaired endothelial function[26,27] and also recent evidence points to substances used for improving pulmonary function in COPD patients also having a beneficial effect on peripheral arterial stiffness.[28,29]

Limitations

The major limitation of this investigation is due to the fact that more than 35% of the patients had to be excluded from the analysis, reducing the final sample size. Our findings should be assessed in a larger patient cohort. According to the instructions for use, iloprost is intended to be administered intravenously. Due to practical reasons, we decided for a local intra-arterial administration and applied iloprost at a dose of 3000 ng, consistent with a previous publication.[10]

Conclusion

While the type 2 diabetes mellitus as a relevant comorbidity to PAOD did not seem to have a relevant impact on iloprost efficacy in the present series, the beneficial effect of peripheral vasodilatation may vary in patients with peripheral neuropathy. Future studies are therefore required to assess the clinical implications of these findings that may range from dosage adaptation when utilizing iloprost in patients suffering from peripheral neuropathy to more aggressive surgical management. Collectively, our findings will contribute to the mounting evidence on the potential of individual iloprost treatment regimens for PAOD patients

Declaration of conflicting interests

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