Aus dem Institut für Kardiologie, Pneumologie und Angiologie
der Heinrich-Heine-Universität Düsseldorf

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Blood pressure lowering by peripheral arterial angioplasty and relation of patient´s cardiovascular risk factors to localization of the disease

Dissertation

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Widmung/Dedication

To my beloved parents. Without them I would never succeed.

To my siblings for supporting me in good and bad times.

To Alex for being always on my side.

Publikationen / Publications

Angioplasty of Flow-Limiting Stenosis Reduces Aortic and Brachial Blood Pressure in Patients With Peripheral Artery Disease

Busch L, Heinen Y, Stern M, Wolff G, Özaslan G, Tzetou K, Sansone R, Heiss C, Kelm M. Angioplasty of Flow-Limiting Stenosis Reduces Aortic and Brachial Blood Pressure in Patients With Peripheral Artery Disease. J Am Heart Assoc. 2021 Jul 20;10(14):e019724. doi: 10.1161/JAHA.120.019724. Epub 2021 Jul 6. PMID: 34227407; PMCID: PMC8483469.

I. Zusammenfassung (Abstract - Deutsch)

Mit stetig wachsenden Patientenzahlen kommt der peripheren arteriellen Verschlusskrankheit (pAVK) eine zunehmend große Bedeutung zu. Der wichtigste Risikofaktor der pAVK ist die arterielle Hypertonie gefolgt von Rauchen, Diabetes mellitus, Hypercholesterinämie und gestörter Nierenfunktion. Nach Versagen der konservativen Therapiemethoden steht die endovaskuläre Therapie im Vordergrund.

Ziel der Arbeit ist zu untersuchen wie die arterielle Hypertonie, als die wichtigste Komorbidität, von der endovaskulären Therapie beeinflusst wird. Außerdem ist unklar inwiefern die verschiedenen Risikofaktoren die Lokalisation von flusslimitierenden Stenosen der Becken und Beinarterien determinieren aber auch welche von denen mit einer erhöhten Restenoserate assoziiert sind.

Die Studie besteht aus zwei Teilen. Zunächst wurde klinisch bei einem bestimmten Patientenkollektiv im Herzkatheterlabor eine invasive Blutdruckmessung prä- und postinterventionell durchgeführt. Im Anschluss wurden retrospektiv pseudonymisiert die Charakteristika aller im Zeitraum 2011-2016 interventionell behandelten Patienten mit pAVK im Stadium IIb-IV retrospektiv erhoben sowie der periphere arterielle Blutdruck vor und nach der Intervention dokumentiert und statistisch analysiert.
Nach ausführlicher Analyse konnten wir bestätigen, dass der arterielle Blutdruck von der endovaskulären Therapie insbesondere bei weitlumigen Gefäßen beeinflusst wird.

Zusammenfassend ist zu überlegen, ob in der Zukunft eine frühzeitige Optimierung der Blutdruckwerte bei Patienten mit pAVK den Krankheitsverlauf begünstigen würde, aber auch ob eine interventionelle Therapie früher in Betracht gezogen werden sollte, besonders bei Patienten, die neben pAVK unter anderen diversen Komplikationen der arteriellen Hypertonie leiden und sich davon profitieren würden.

II. Zusammenfassung (Abstract - Englisch)

Peripheral artery disease (PAD) is nowadays a major diagnosis found in a rising number of patients. Leaded by arterial hypertension, the most important risk factors that affect the disease are smoking, diabetes, high cholesterol levels and impaired renal function. There are several conservative methods that reduce symptoms and prohibit worsening of PAD. Though in high stage disease or in high symptomatic patients, endovascular therapy is the only method considered.

Aim of our study is to examine the relation between endovascular therapy and arterial hypertension as the major risk factor of the disease. Nevertheless, we were interested to find the correlation of each common risk factor of PAD with the localization of the patient´s lesion and the rate of recurrent disease associated with each comorbidity.

Our study is divided in two parts. First, we invasively measured arterial blood pressure in the catheterization laboratory before and after intervention. The second part was a retrospective study enrolling characteristics of all patients of PAD Fontaine stage IIb-IV that underwent an intervention between 2011 and 2016 but also including measurements of peripheral arterial blood pressure before and after intervention.

After careful statistical analysis we were able to prove that arterial blood pressure is directly related to vessel interventions.

In conclusion it is important to suggest an early initiation of antihypertensive therapy in patients suffering from PAD, as it could positively affect the disease. Moreover, endovascular therapy of PAD may be considered earlier in patients suffering from arterial hypertension as it could help minimize it´s complications.

III. Abkürzungsverzeichnis /Abbreviation

PAD	Peripheral artery disease
SBP	Systolic blood pressure
BP	Blood pressure
DBP	Diastolic blood pressure
LEAD	Lower extremity arterial disease
PWV	Pulse wave velocity
LDL	Low-density lipoproteins
ABI	Ankle-brachial index
DSA	Digital subtraction angiography
CTA	Computed tomography angiography
MRA	Magnetic resonance angiography
PTA	Percutan transluminal angioplasty
Cath-Lab	Catheterisation laboratory
PP	Pulse pressure
AP	Augmentation pressure
AIX	Augmentation index
CASP	Central aortic systolic pressure
cSBP	Central systolic blood pressure
cDBP	Central diastolic blood pressure
CAD	Coronary artery disease
ASS	Acetylsalicylic acid
Fem-orop	Femoropopliteal
ACE	Angiotensin-converting enzyme
ARB	Angiotensin II receptor blockers
CBB	Calcium channel blockers
CFA	Common femoral artery
ECG	Electrocardiogram
BTK	Below the knee
MAP	Mean arterial pressure
CI	Confidence interval

IV. Inhaltsverzeichnis / Contents

1. Introduction

Physiology of our cardiovascular system is a complicated but very important milestone in order to understand and eliminate cardiovascular diseases. Our research interest was raised as a rising number of patients seem to suffer under peripheral artery disease (PAD) and arterial hypertension. It is shown that arterial hypertension itself can highly contribute to the progress of PAD [(1)]. Based on cardiovascular physiology, peripheral obstructions or rigid vessels lead to a higher pressure in our cardiovascular system to maintain this blood flow. This means that eliminating lesions in peripheral vessels could optimize blood flow and significantly contribute to groundly treating arterial hypertension.

1.1: Arterial Hypertension

Hypertension is defined by the European Society of Cardiology as office systolic blood pressure (SBP) values ≥140 mmHg and/or diastolic BP (DBP) values ≥90 mmHg (table 1)

Following classification is established:

Table 1: Classification of office blood pressure [a] and definitions of hypertension grade [b]. [(8)]

Category	**Systolic (mmHg)**	**Diastolic (mmHg)**
Optimal	<120	and <80
Normal	120-129	and/or 80-84
High normal	130-139	and/or 85-89
Grade 1 hypertension	140-159	and/or 90-99
Grade 2 hypertension	160-179	and/or 100-109
Grade 3 hypertension	≥180	and/or ≥110
Isolated systolic hypertension	≥140	and/or <90

It is estimated that in 2015 almost 1.13 billion people were suffering from high blood pressure globally while an increase up to 20% is expected by 2025. Majority of patients were older than 60 years old and lived in central and eastern Europe [(1)].

Hypertension not only remains the leading cause of premature death due to ischaemic heart disease and haemorrhagic/ischaemic stroke but is also related to the incidence of PAD. Due to atherosclerosis peripheral arteries lose their elasticity which leads to generation of higher pressure on the arterial wall and increase of pulse wave velocity (PWV).

1.2: Atherosclerosis

Atherosclerosis is a pathological process that causes disease of the coronary, cerebral and peripheral arteries, and the aorta [(2)]: Damage of the vessels begins in the childhood and advances with aging. Endothelial disfunction is described as the most common pathogenetic factor and includes loss of endothelium-derived natrium oxide due to accumulation of oxidized low-density lipoproteins (LDL) [(3)]. Oxidized LDL cause inflammation, as they adhere macrophages that release various cytokines and inflammatory substances.

Following stages of atherosclerosis are described (Figure 1):

Intima thickening: Intima with adhered smooth muscle cells and extracellular matrix.

Accumulation of fatty streaks: LDL-molecules connected to lipid-laden macrophages (foam cells), extracellular matrix and smooth muscle cells.

Fibrofatty cap / Fibroatheroma: Plaque with a necrotic lipid core covered by a thick fibrous cap, which is a layer of dense collagen and smooth muscle cells.

Vulnerable plaque: Fibroatheroma with a very thin fibrous cap consisting of collagen and very few smooth muscle cells.

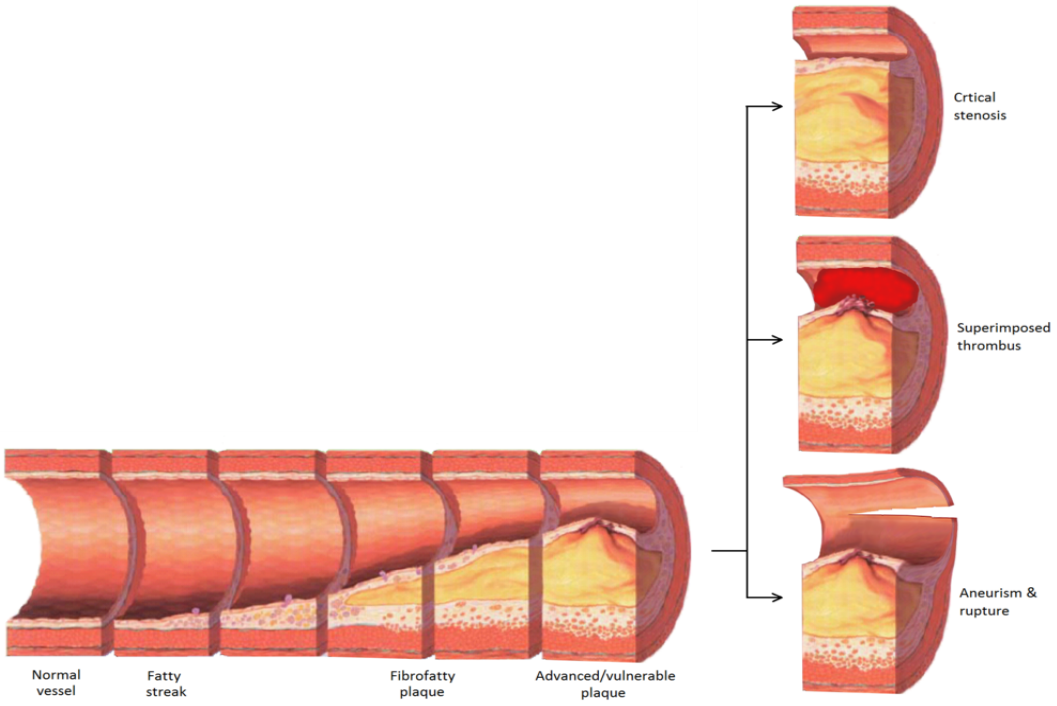


Figure 1: Stages of atherosclerosis (Wikimedia)

1.3: Peripheral artery disease

Peripheral artery disease is defined as a chronic arterial occlusive process of peripheral limb arteries, caused in 95 % of the patients by progressive atherosclerosis [(4)]. Inflammatory, genetic, or traumatic causes of arterial occlusion are only observed in 5% of the patients [(5)].

More than 200 million people worldwide suffer from occlusion of peripheral arteries [(7)]. The prevalence of PAD depends highly on various factors and lies between 3 and 10 percent of the general population [(5)].

PAD is mainly presented in the iliac and femoral arteries, as well as the lower limb arteries (Figure 2). Although rarely, upper extremities and major vessels, such as abdominal aorta or renal arteries can also be diseased.

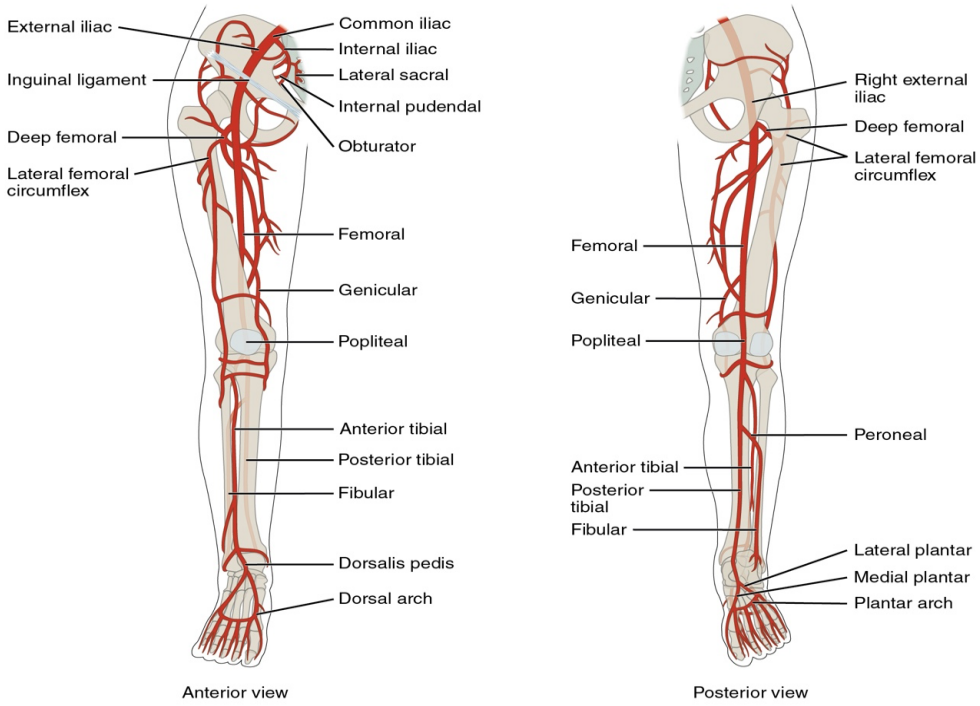


Figure 2: Lower limb arteries (Wikimedia)

Clinical evaluation of the patient is the key to diagnosis and progression-controlling of PAD after obtaining adequate clinical history. Lifestyle, cardiovascular risk factors (diabetes, high blood pressure, smoking) and family history is essential information.

Claudicatio intermittens is the major symptom, defined as ischemic pain of the extremity. As the disease progresses *claudicatio intermittens* is presented more often or even in resting time. Skin lesions occur in severe occlusion or terminal stages of PAD (table 2 and 3).

Table 2: Clinical evaluation of disease progress – Fontaine stages (DGK Guideline 2016)

Fontaine-Stages	**Clinical characteristics**
Stage I	Asymptomatic patient
Stage IIa	Walking distance >200 m
Stage IIb	Walking distance <200 m
Stage III	Ischemic rest pain
Stage IV	Ulceration or gangrene

Table3: Clinical evaluation of disease progress – Rutherford Classification (DGK Guideline 2016)

Rutherford-Classification	**Clinical characteristics**
Stage 0	Asymptomatic patient
Stage 1	Mild intermittent claudication
Stage 2	Moderate intermittent claudication
Stage 3	Severe intermittent claudication
Stage 4	Ischemic rest pain
Stage 5	Minor tissue loss
Stage 6	Major tissue loss (ulceration/gangrene)

Diagnostic methods for PAD:

- Measurement of peripheral blood pressure on both arms:
- Ankle-brachial index (ABI)
- Duplex sonography
- Digital subtraction angiography (DSA)
- Computed tomography angiography (CTA)
- Magnetic resonance angiography (MRA)

Conservative therapy includes smoking cessation, lipid-lowering drugs (LDL<70mg/dl), antithrombotic drugs and antihypertensive drugs (target BP<140/90 mmHg, Patients with diabetes DBP<85 mmHg). Although in a progressive disease only invasive therapy can have a proper result. The major method applied nowadays is called “Percutaneous Transluminal Angioplasty (PTA)” and is performed in the Catheterisation Laboratory (CathLab). In this procedure the vessel is reached by entering the radial or femoral artery. An expanding balloon or stent can be installed to provide adequate perfusion of the vessel.

1.4: Definitions

- Pulse Pressure (PP) = systolic - diastolic blood pressure
- Augmentation Pressure (AP) = central aortic systolic pressure – P2
- Augmentation index (AIX%) = $\frac{\text{Augmentation Pressure (AP)}}{\text{Pulse Pressure (PP)}} \times 100$
- Pulse wave velocity (PWV): velocity that the arterial pulse travels between two vessels.

Important markers of arterial stiffness

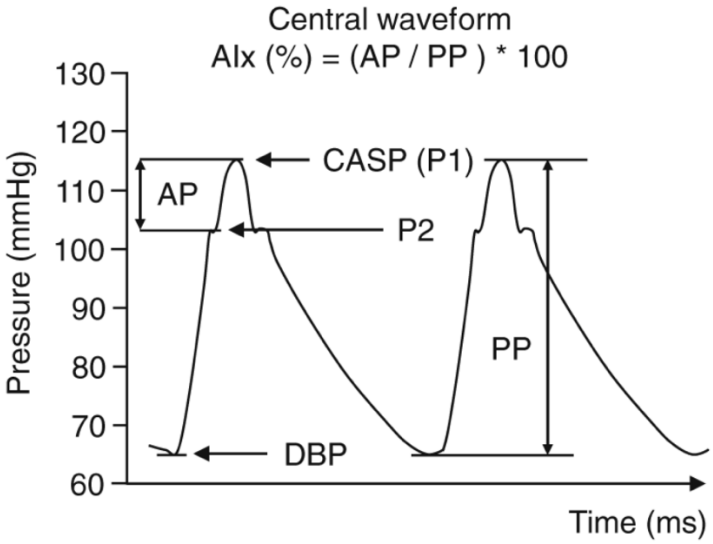


Figure 3: Waveform of central blood pressure (Wikimedia commons)

1.5: Aim of our study

Aim of our retrospective study is to prove that invasive treatment of PAD significantly improves peripheral blood pressure and to relate patient´s characteristics with localisation of their peripheral arterial lesion.

2. Materials and Methods

2.1: Description:

Our study took part in University of Düsseldorf, department of cardiology, angiology and pulmonology and consisted of two parts.
On day of admission identical steps were followed in both groups. At first, patient´s history was obtained carefully from the responsible physician, including age, gender, smoking status, medication and acquired diseases (hypertension, hyperlipidaemia, cardiovascular diseases, diabetes, and renal disfunction). Clinical evaluation regarding PAD defined severity of disease based on Rutherford classification. Clinical examination on day of admission included measurements of peripheral systolic and diastolic blood pressure using Riva-Rocci method and assessment of ABI of the target leg (table 4).

The study was conducted after approval of the local ethics committee and in accordance with the declaration of Helsinki. All patients gave written informed consent prior to procedure.

2.2: Percutan transluminal angioplasty techniques:

The procedure was performed in the catheterisation laboratory under local anaesthesia and the vital signs of each patient were monitored continually by an anaesthesiologist.

Depending on localization of each lesion, various techniques were used:

- Iliac lesions: Angioplasty (Passeo 35, Biotronic®) and implantation of balloon-expandable stents (Dynamic, Biotronic®).

- Femoropopliteal lesions: Angioplasty (Passeo 35, Biotronic®) and treatment with drug coated balloon (Passeo 18, Biotronic®). If necessary, implantation of self-expandable nitinol stents (Innova, Boston Scientific®).

To reach the contralateral lesions we performed a standard “crossover” maneuver (reaching of the contralateral artery by turning the inserted catheter at level of the iliac bifurcation).

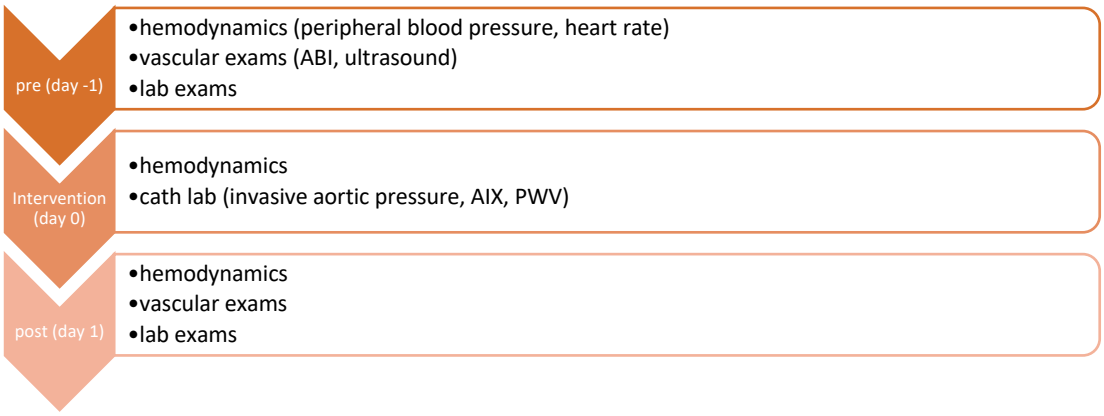
- Below the knee crural vessels: Angioplasty (Passeo 35, Biotronic®). If necessary, implantation of balloon-expandable drug-elunting stents (Xience, Abbott Vascular®).

2.3: Clinical trial: Invasive measurement of central blood pressure and aortic indices

The first group of patients (n=30) underwent an invasive assessment of systolic and diastolic blood pressure (cSBP/cDBP), AIX and aortic PWV before and after angiography and angioplasty of peripheral arteries. Interventions included diagnostic angiography (n=5) and angioplasty of iliac arteries (n=15) or femoropopliteal arteries (n=10).

All patients underwent examinations before and after intervention as shown in table 4.

Table 4: Periinterventional examinations



All patients (n=30) were catheterised via the common femoral artery (CFA) with a standard 6 F sheath (Merit Medical®)[14]. The aorta was divided in four segments: ascending aorta, descending thoracic aorta, suprarenal aorta, and

infrarenal aorta. A calibrated measurement of the pigtail catheter length using the automated Philipps “Xper IM®” cathlab software defined the length of the aorta[14]. The pigtail catheter was placed via the femoral sheath into the artery and then advanced through the aortic valve under X-ray control[14]. At least four cardiac cycles were recorded in each aortic segment and mean aortic pressure (the difference between the systolic and diastolic pressures) was calculated before and after angioplasty[14]. To determine PWV we used the pigtail catheter “pull back” method (movement of the pigtail catheter from the aortic root towards the aortic bifurcation)[14]. The transit time of the pulse wave was measured using ECG gating (acquisition technique that triggers a scan during a specific portion of the cardiac cycle[8]).

Calculation of the values:

- Central pressure: The invasively obtained waveforms were printed using the “HKWin” software (Medizin Technik Komponenten GmbH, HKWin v1.148.2® [14].

- Augmentation index (AIX): The values were calculated by visual measurements based on the following formula:

$$AIX\% = \frac{\text{Augmentation Pressure (AP)}}{\text{Pulse Pressure (PP)}} \times 100$$

- PWV: Two observers calculated the PWV independently and the mean PWV of both measurements was used.

2.4: Retrospective analysis of peripheral blood pressure before and after PTA

The second part of the study primarily enrolled 423 patients who were treated with PTA between 2015 and 2016 in the CathLab of the University hospital of Düsseldorf. Due to inadequate documentation or alteration of vasoactive medication 42 patients were excluded. Therefore, our final cohort included a total of 381 patients. Fifteen patients underwent diagnostic angiography as scheduled.

Angioplasty of the iliac- (n=119), femoropopliteal- (n=208) and BTK-arteries (n=39) was performed, if necessary.

In our study we gained access to the files of all patients using programme “Medico”, after their signed consent. We designed a table with cumulative information grouping patients depending on localisation of their lesions. We collected information about cardiac risk factors such as age, smoking status, underlying cardiovascular-relevant diseases, and medication. Moreover, we included clinical stage of peripheral artery disease based on Rutherford classification.

Each patient´s peripheral systolic and diastolic blood pressure as well as systolic blood pressure of the upper and lower extremities was collected from the hospital Ultrasound records. Ultrasound assessment was performed by a 10MHz transducer (Vivid I, GE) and included common femoral artery (CFA) blood flow measurement as followed:

Volume flow [ml/min] = $\pi * r'$ [cm] $*$ Vmean[cm/sec] $* 60$ [14]

Baseline ABI on site of the lesion such as ABI before discharge was manually calculated by dividing systolic pressure of the leg to systolic pressure of the arm.

Our measurements also included mean arterial pressure (MAP) calculation based on peripheral systolic and diastolic blood pressure as followed [14]:

$$\mathrm{MAP} = \mathrm{DBP} + \frac{1}{3} * (\mathrm{SBP} - \mathrm{DBP})$$

As showed in Table 7 procedural characteristics, such as occlusion percentage, length of the lesion, target vessel diameter, length of stented segment and number of implanted stents were noted in each group of patients.

2.5: Statistical analysis:

For both parts of our study, we statistically analysed the dynamic of central and peripheral blood pressure after the procedure. Following programmes were used for our analysis:

1. GraphPad Prism© version 6.00 (La Jolla, California, USA)
2. IBM SPSS© software 20 version 22.0 (Armonk, NY, USA).

Categorical variables are presented as absolute numbers (n) and percentages (%); statistical comparisons for these were made by the x2 test [14]. Continuous variables are expressed as mean values and standard deviation and compared by the ANOVA F-test [14]. Changes in parameters (Delta) were calculated as post angioplasty values minus baseline (pre angioplasty) values and are expressed as means with 95% confidence intervals (95%CI) [14]. Within-subject changes with single comparisons in hemodynamics were analyzed using a paired Student's T-Test; when deltas were compared between groups, we employed one-way ANOVA with a post-hoc Tukey correction for multiple comparisons [14]. Linear relationships between continuous variables were expressed as Pearson's r. Statistical significance was assumed at $p \leq 0.05$ [14]. To determine predictors of change in peripheral systolic blood pressure (DeltapSBP) in both cohorts, univariate and multivariate logistic regression analysis were performed with comorbidities, hemodynamic characteristics (AIX, PWV, pBP, cBP) and localization of the proximal stenosis (iliac vs. femoropopliteal vs. BTK vs diagnostic angiography) as covariates [14].

2.6: Ethical licence

Our study was proven and accepted by the ethical commission of Heinrich Heine University of Düsseldorf.

Study-Number: 4548 (Day of approval: 23.01.2014)

3. Results

3.1: Impact of angioplasty on central blood pressure and aortic indices

Our cohort involved 30 patients that suffered from symptomatic PAD and were planned for endovascular treatment. In Table 5 we recruited patient´s baseline and procedural characteristics.

Table 5: Baseline and procedural characteristics (n=30) [14].

ABI = ankle-brachial index of the target leg, ACE = angiotensin-converting-enzyme inhibitor, ARB = angiotensin receptor blocker, BTK = below the knee, CAD = coronary artery disease, CBB = calcium channel blocker, Fempop. = femoropopliteal. Categorical variables are presented as absolute numbers (n) and percentages (%); statistical comparisons for these were made by the x2 test. Continuous variables are expressed as mean values and standard deviation and compared by the ANOVA F-test. The values presented in the column "p-value" represent the overall difference between three groups; bold font indicates a significant difference between groups ($p<0.05$)

Baseline characteristics	**Total**	**Iliac**	**Femoropop.**	**Diagnostic angiography**	**p-value**
n (%)	30 (100)	15 (50)	10 (33)	5 (17)	-
Age (yrs)	71 ± 10	69 ± 10	74 ± 8	68 ± 11	0.38
Male (%)	22 (73)	11 (73)	7 (70)	4 (80)	0.92
Smoker (%)	20 (67)	11 (73)	6 (60)	3 (60)	0.74
Hypertension (%)	30 (100)	15 (100)	10 (100)	5 (100)	-
Hyperlipidaemia (%)	23 (77)	12 (80)	7 (70	4 (80)	0.83
CAD (%)	25 (83)	12 (80)	8 (80)	5 (100)	0.55
Diabetes (%)	11 (37)	6 (40)	4 (40)	1 (20)	0.7
Renal railure (%)	13 (43)	6 (40)	5 (50)	2 (40)	0.87
ASS (%)	28 (93)	15 (100)	9 (90)	4 (80)	0.26
Clopidogrel (%)	25 (83)	14 (93)	9 (90)	2 (40)	0.017
Statin (%)	26 (87)	13 (87)	9 (90)	4 (80)	0.87
Antihypertensive treatment (%)	30 (100)	15 (100)	10 (100)	5 (100)	-
ACE (%)	25 (83)	12 (80)	9 (90)	4 (80)	0.78
ARB (%)	4 (13)	3 (20)	1 (10)	0 (0)	0.49
CBB (%)	10 (33)	6 (40)	3 (30)	1 (20)	0.69
ß-blocker (%)	15 (50)	7 (47)	5 (50)	3 (60)	0.88

Clinical stage					
Rutherford 2-3 (%)	24 (80)	13 (87)	6 (60)	5 (100)	0.12
Rutherford 4 (%)	0 (0)	0 (0)	0 (0)	0 (0)	-
Rutherford 5-6 (%)	6 (20)	2 (13)	4 (40)	0 (0)	0.12
Baseline ABI	0.53 ± 0.09	0.52 ± 0.1	0.53 ± 0.12	0.53 ± 0.03	0.97
Procedural characteristics					
0 Stents (%)	6 (20)	0 (0)	1 (10)	5 (100)	< 0.0001
1 Stent (%)	11 (37)	4 (27)	7 (70)	0 (0)	0.02
2 Stents (%)	10 (33)	9 (60)	1 (10)	0 (0)	0.008
>3 Stents (%)	3 (10)	2 (13)	1 (10)	0 (0)	0.7
Length of target lesion (mm)	-	44 ± 7	165 ± 67	180 ± 80	< 0.0001
Length of stented segment (mm)	-	46 ± 9	172 ± 71	0 (0)	< 0.0001
Target vessel diameter (%)	-	8.4 ± 0.7	6 ± 0.9	6.6 ± 1	< 0.0001
Occlusion (%)	16 (53)	6 (40)	7 (70)	3 (60)	0.3
ABI before discharge	0.85 ± 0.16	0.92 + 0.07	0.92 ± 0.07	0.54 ± 0.03	< 0.0001

We invasively obtained central systolic blood pressure (cSBP) and central diastolic blood pressure (cDBP) before and after diagnostic angiography (5 patients) and angioplasty of iliac (15 patients) and femoropopliteal (10 patients) arteries. Stent implantation was performed in all patients that underwent iliac angioplasty and in 90 % of the patients with femoropopliteal angioplasty.

Our results are presented in Table 6. A significantly lower central systolic and diastolic blood pressure occurs after iliac and femoropopliteal angioplasty. Mean arterial pressure also decreased after intervention of iliac and femoropopliteal arteries. Diagnostic angioplasty showed no alterations.

Table 6: Impact on central arterial pressure [14].

Segmental, serial, invasive central blood pressure and mean arterial pressure measurements before and after endovascular treatment. Mean central systolic blood pressure (A, CSBP), mean central diastolic blood pressure (B, CDBP) as measured at baseline before iliac (n=15) or femoropopliteal angioplasty (n=10) or mere diagnostic angiography (n=5). Changes in peripheral arterial pressure (pMAP, C).

A	CSBP baseline		CSBP post		Paired difference (post-baseline)			
	Mean	SE	Mean	SE	Mean	95% CI		p (t-test)
Diagn. angiography	157	4	158	5	1	-1	3	0.22
Iliac angioplasty	173	4	149	4	-24	-27	-21	<0.0001
Femorop. angioplasty	164	5	153	5	-11	-14	-8	<0.0001

B	CDBP baseline		CDBP post		Paired difference (post-baseline)			
	Mean	SE	Mean	SE	Mean	95% CI		p (t-test)
Diagn. angiography	70	2	71	2	1	0	2	0.6
Iliac angioplasty	74	1	66	1	-8	-9	-6	<0-0001
Femorop. angioplasty	76	2	72	2	-4	-6	-3	<0-0001

C	PMAP baseline		PMAP post		Paired difference (post-baseline)			
	Mean	SE	Mean	SE	Mean	95% CI		p (t-test)
Diagn. angiography	98	5	98	5	0	-4	5	0.7
Iliac angioplasty	107	3	96	3	-11	-14	-9	<0-0001
Femorop. angioplasty	105	5	99	4	-6	-9	-3	<0-0001

Central arterial pressure was measured in the following aortic segments: ascending aorta, descending thoracic aorta, suprarenal aorta, and infrarenal aorta (Figure 4).

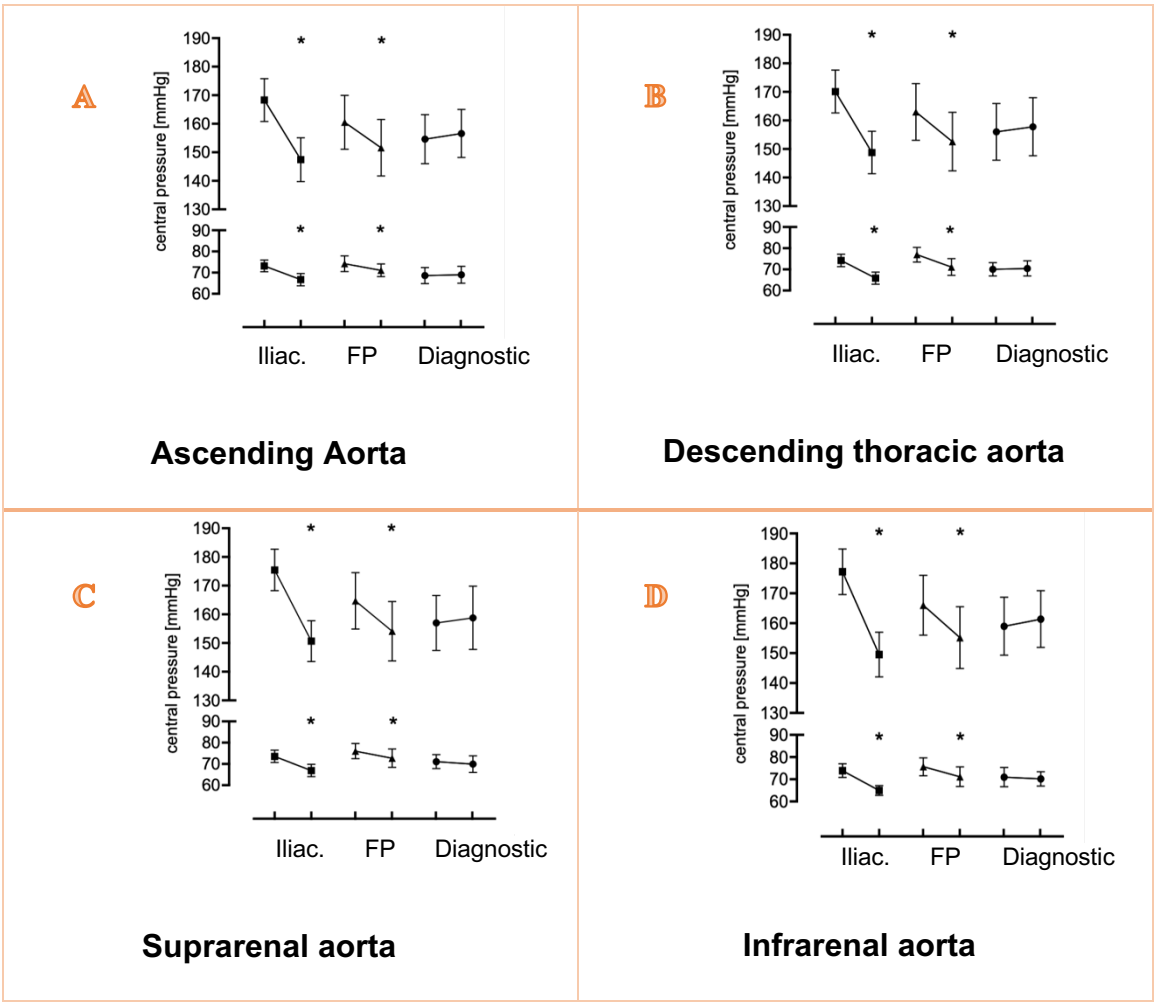


Figure 4: Impact on central arterial pressure measured in aortic sections A, B, C and D [14]

A significant lowering of central systolic blood pressure in proximal and distal sections of the aorta was found after angioplasty of iliac and femoropopliteal arteries. Angioplasty of distal parts of the aorta had a higher lowering effect than proximal sections. A and B showed after iliac angioplasty a decrease of cSBP up to 25 mmHg and of cDBP by up to 5 mmHg while angioplasty of femoropopliteal arteries achieved a lowering of cSBP by up to 10 mmHg. Maximum effect was shown in segments C and D of the aorta as decrease reached up to approximately 30 mmHg after iliac angioplasty and 15 mmHg after intervention on femoropopliteal arteries. Central DBP was almost identical in sections B, C and D and showed a lowering by up to 10 mmHg.

Diagnostic angiography achieved no alterations or showed a minimal increase in all segments of the aorta.

Table 7 depicts the effects of angiography and angioplasty on mechanical indices of the aorta that were obtained invasively during the procedures. Pulse wave velocity (PWV) was minimally or not at all affected by the procedures. On the contrary augmentation index (AIX) showed a significant decrease, especially after iliac angioplasty up to approximately 15 % while femoropopliteal angioplasty lowered AIX by almost 10 %. Angioplasty hat no impact on AIX.

Table 7: Impact on aortic indices [14].

(A) Aortic pulse wave velocity at baseline and after peripheral angioplasty of iliac (n=15) and femoropopliteal (n=10) arteries, as well as mere diagnostic angiography (n=5). (B) change in AIX before and after endovascular treatment or diagnostic angiography.

A	PWV baseline (m/s)		PWV post (m/s)		Paired difference (post-baseline)			
	Mean	SE	Mean	SE	Mean	95% CI		p (t-test)
Diagn. angiography	14.4	1	14.4	0.8	0	-1	1	0.96
Iliac angioplasty	15.4	0.5	15.2	0.5	-0.3	-0.4	0.1	0.07
Femorop. angioplasty	14.3	0.7	14	0.7	-0.3	-0.7	0.3	0.5

B	AIX baseline (%)		AIX post (%)		Paired difference (post-baseline)			
	Mean	SE	Mean	SE	Mean	95% CI		p (t-test)
Diagn. angiography	18	3.4	18	3.2	0	-0.6	1	0.6
Iliac angioplasty	27	2.8	15	2.2	-12	-13.9	-9.6	<0.0001
Femorop. angioplasty	19	2.5	14	2	-5	-7.4	-2.5	0.0013

3.2: Impact of angioplasty on peripheral blood pressure

For our retrospective study we recruited data of 423 patients that were treated for PAD in clinic of Cardiology, Angiology and Pneumology in University of Düsseldorf between 2015 and 2016. As shown in figure 5, 42 patients had to be excluded because of insufficient medical records or alterations in blood pressure medication.

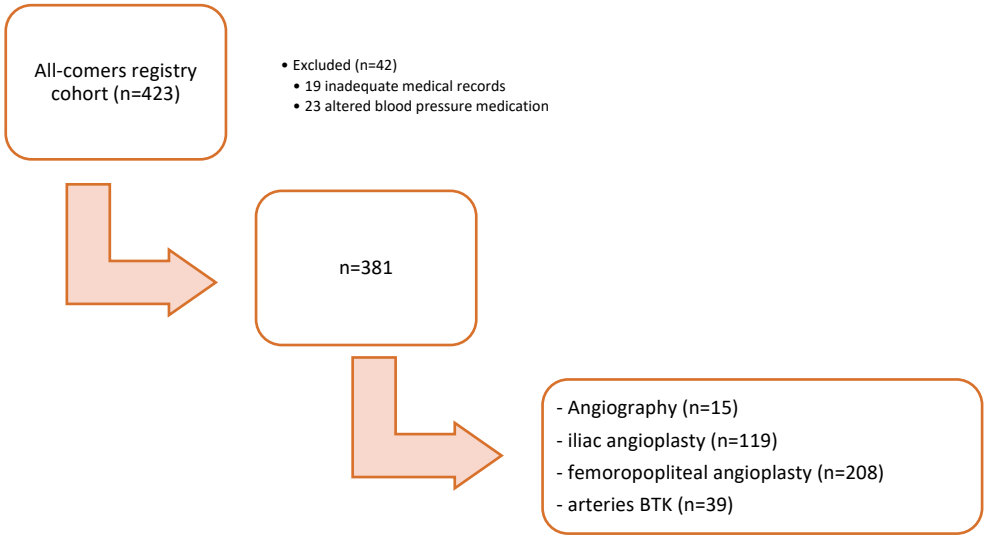


Figure 5: Retrospective study cohort

Following table summarizes all patient´s baseline and procedural characteristics regarding our retrospective study cohort.

Table 8: Baseline and procedural characteristics (n=381) [14].

ABI = ankle-brachial index of the target leg, ACE = angiotensin-converting-enzyme inhibitor, ARB = angiotensin receptor blocker, BTK = below the knee, CAD = coronary artery disease, CBB = calcium channel blocker, Fempop. = femoropopliteal. Categorical variables are presented as absolute numbers (n) and percentages (%); statistical comparisons for these were made by the x2 test. Continuous variables are expressed as mean values and standard deviation and compared by the ANOVA F-test. The values presented in the column "p-value" represent the overall difference between four groups; bold font indicates a significant difference between groups (p<0.05)

Baseline characteristics	**Total**	**Iliac**	**Femoropop.**	**BTK**	**Diagnostic**	**p-value**
n (%)	381 (100)	119 (31)	208 (55)	39 (10)	15 (4)	
Age (yrs)	71 ± 2	70 ± 8	72 ± 8	72 ± 11	68 ± 12	0.09
Male (%)	289 (76)	85 (71)	160 (77)	32 (82)	12 (80)	0.5
Smoker (%)	221 (58)	78 (66)	114 (55)	20 (50)	9 (60)	0.22
Hypertension (%)	337 (88)	106 (89)	187 (90)	32 (82)	12 (80)	0.38
Hyperlipidaemia (%)	290 (76)	100 (84)	149 (71)	29 (75)	12 (80)	0.09
CAD (%)	265 (70)	81 (68)	145 (70)	28 (92)	11 (73)	0.96
Diabetes (%)	170 (45)	40 (34)	98 (47)	26 (68)	6 (40)	0.003

Renal railure (%)	159 (42)	40 (34)	91 (44)	22 (57)	6 (40)	0.07
ASS (%)	351 (92)	115 (97)	190 (91)	33 (85)	13 (87)	0.13
Clopidogrel (%)	305 (80)	102 (86)	169 (81)	28 (71)	6 (40)	<0.0001
Statin (%)	287 (75)	96 (81)	150 (72)	31 (79)	10 (67)	0.27
Antihypertensive treatment (%)	350 (92)	108 (90)	194 (93)	33 (86)	15 (100)	0.19
ACE (%)	210 (56)	70 (59)	110 (53)	22 (57)	8 (53)	0.77
ARB (%)	96 (25)	30 (25)	55 (26)	8 (21)	3 (20)	0.84
CBB (%)	133 (35)	45 (38)	71 (34)	12 (31)	5 (33)	0.85
ß-blocker (%)	207 (54)	75 (63)	132 (64)	23 (59)	7 (47)	0.6
Clinical stage						
Rutherford 2-3 (%)	218 (57)	96 (81)	112 (54)	7 (18)	3 (20)	< 0.0001
Rutherford 4 (%)	34 (9)	10 (8)	18 (9)	3 (7)	3 (20)	0.5
Rutherford 5-6 (%)	129 (34)	13 (11)	78 (37)	29 (75)	9 (60)	< 0.0001
Baseline ABI	0.50 ± 0.11	0.53 ± 0.11	0.50 ± 0.1	0.48 ± 0.15	0.51 ± 0.07	0.036

Procedural characteristics	**Total**	**Iliac**	**Femorop.**	**BTK**	**Diagnostic**	**p-value**
0 Stents (%)	100 (26)	4 (3)	50 (24)	31 (80)	15 (100)	< 0.0001
1 Stent (%)	128 (34)	43 (37)	80 (38)	5 (13)	0 (0)	0.0005
2 Stents (%)	119 (31)	59 (49)	57 (27)	3 (7)	0 (0)	< 0.0001
>3 Stents (%)	34 (9)	13 (11)	21 (10)	0 (0)	0 (0)	0.1
Length of target lesion (mm)	-	42 ± 6	158 ± 51	33 ± 12	210 ± 78	< 0.0001
Length of stented segment (mm)	-	44 ± 5	164 ± 60	12 ± 3	-	< 0.0001
Target vessel diameter (%)	-	8.1 ± 0.6	6.2 ± 0.6	2.9 ± 0.7	6.9 ± 1.2	< 0.0001
Occlusion (%)	250 (66)	62 (52)	142 (68)	33 (86)	13 (87)	0.0001
ABI before discharge	0.9 ± 0.1	0.92 ± 0.1	0.92 ± 0.12	0.84 ± 0.1	0.54 ± 0.11	< 0.0001

In both of our cohorts a remarkable lowering of peripheral pressure was observed. Table 9 shows alterations of peripheral blood pressure in our cohort of 30 patients. Diagnostic angiography had no effect while iliac and femoropopliteral intervention proved to significantly lower peripheral systolic and diastolic blood pressure in our cohort. In detail, iliac angioplasty lowered systolic peripheral blood pressure by 21 mmHg and femoropopliteal angioplasty by 10. Diastolic blood

pressure showed after diagnostic angiography and angioplasty mediocre or no effect.

Table 9: Impact on peripheral arterial pressure (n=30) [14].

Changes in peripheral systolic (pSBP, A) and peripheral diastolic blood pressure (pDBP, B)

A	PSBP baseline		PSBP post		Paired difference (post-baseline)			
	Mean	SE	Mean	SE	Mean	95% CI		p (t-test)
Diagn. angiography	155	8	156	8	1	-2	4	0.5
Iliac angioplasty	177	5	156	5	-21	-25	-17	<0.0001
Femorop. angioplasty	166	8	156	8	-10	-13	-8	<0.0001

B	PDBP baseline		PDBP post		Paired difference (post-baseline)			
	Mean	SE	Mean	SE	Mean	95% CI		p (t-test)
Diagn. angiography	69	4	69	4	0	-5	6	0.8
Iliac angioplasty	72	4	66	3	-6	-9	-3	0.0001
Femorop. angioplasty	74	4	70	3	-4	-7	-1	0.02

An effect was as proven also in our cohort of 381 patients (table 10).

Peripheral systolic as well as diastolic blood pressure showed a significant decrease after therapeutic angioplasty, but not after diagnostic angiography (Table 10). The greatest impact was found in iliac arteries, where postinterventional SBP was 19 mmHg and DBP 5mmHg lower. Similarly, intervention on femoropopliteal arteries altered PSBP by -12 mmHg and PDBP by -4 mmHg. Angioplasty on arteries BTK had a significant effect on PSBP as it improved by -7 mmHg, but a negative effect on PDBP which rose by 1 mmHg. Diagnostic angiography does not seem to improve peripheral blood pressure. PSBP was found 2 mmHg lower and PDBP 5 mmHg higher after intervention.

Table 10: Impact on peripheral arterial pressure (n=381) [14].

Peripheral systolic blood pressure (A, PSBP) and peripheral diastolic blood pressure (B, PDBP) at baseline as measured on the day before and post on the day after mere diagnostic angiography of peripheral arteries (n=15) or elective angioplasty of iliac (n=119), femoropopliteal (n=208), and below-the-knee (BTK, n=39) arteries.

A	PSBP baseline		PSBP post		Paired difference (post-baseline)			
	Mean	SE	Mean	SE	Mean	95% CI		p (t-test)
Diagn. angiography	149	3	147	4	-2	2	-6	0.271
Iliac angioplasty	152	2	133	2	-19	-15	-23	<0.001
Femorop. angioplasty	154	2	143	1	-12	-9	-15	<0.001
BTK angioplasty	143	3	136	3	-7	-1	-14	0.032

B	PDBP baseline		PDBP post		Paired difference (post-baseline)			
	Mean	SE	Mean	SE	Mean	95% CI		p (t-test)
Diagn. angiography	78	2	83	9	5	21	-11	0.460
Iliac angioplasty	77	2	72	2	-5	-2	-9	0.006
Femorop. angioplasty	77	1	73	1	-4	-1	-6	0.002
BTK angioplasty	77	3	77	3	-1	6	-8	0.849

3.3: Adverse effects of both studies

On our both groups minimal side effects occurred (table 11).

Most common complication was postprocedural hematoma (2/30 patients, 13/381 patients) followed by peripheral embolization (0/30 patients, 9/381 patients) and pseudoaneurysm (0/30 patients, 6/381 patients).

Table 11: Adverse effects (A: n=30, B: n=381) [14]

Adverse effects A	All (30)	Iliac (15)	Femorop. (10)	Diagnostic (5)
Peripheral embolization (%)	0 (0)	0 (0)	0 (0)	0 (0)
Hematoma (%)	2 (7)	1 (7)	1 (10)	0 (0)
Pseudoaneurism (%)	0 (0)	0 (0)	0 (0)	0 (0)
Other (%)	0 (0)	0 (0)	0 (0)	0 (0)
Death (%)	0 (0)	0 (0)	0 (0)	0 (0)
Amputation (%)	0 (0)	0 (0)	0 (0)	0 (0)
Lower extremity bypass (%)	0 (0)	0 (0)	0 (0)	0 (0)

Adverse effects B	All (381)	Iliac (119)	Femorop. (208)	BTK (39)	Diagnostic (15)
Peripheral embolization (%)	9 (2)	4 (3)	5 (2)	0 (0)	0 (0)
Hematoma (%)	13 (3)	4 (3)	7 (3)	2 (5)	0 (0)
Pseudoaneurism (%)	6 (2)	0 (0)	5 (2)	1 (4)	0 (0)
Other (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Death (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Amputation (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Lower extremity bypass (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

4. Discussion

4.1 Summary of results:

The first clinical trial (30 patients) showed that angioplasty and stenting of iliac arteries effectively lowered central and peripheral mean arterial pressure, increased blood flow in target leg and leaded to a significant improvement of AIX, PWV and ABI.

The retrospective study with a cohort of 381 patients showed that peripheral blood pressure decreased after iliac (119 patients) and femoropopliteal angioplasty (208 patients). After statistical analysis most of patients were men that aged approximately 70 years old and suffered from disease stage 2-3 (Rutherford). Hypertension was the leading comorbidity (88%) followed by hyperlipidaemia (76%), coronary artery disease (70%), diabetes (45%) and renal failure (42%). More than half of our patients were smokers (58%). All cardiovascular risk factors (smoking, diabetes, hypertension, hyperlipidaemia) leaded to PAD mostly in femoropopliteal arteries. The majority of patients suffered from femoropopliteal disease and needed an implantation of 1 stent. Postprocedural, peripheral systolic and diastolic blood pressure significantly decreased, especially after intervention of iliac and femoropopliteal arteries.

Despite the complicated cardiovascular profile of our patients, adverse effects including postprocedural haematoma, pseudoaneurysm and peripheral embolization were observed in a very small percentage.

4.2: PAD and antihypertensive treatment

Due to sub optimal treatment of hypertension in patients with PAD compared to other cardiovascular diseases[10], many of them have an uncontrolled blood pressure[11] that leads not only to severe progress of PAD but also to major cardiovascular complications. It is shown that lowering peripheral SBP by 10

mmHg or DBP by 5 mmHg can reduce cardiovascular events by approximately 20% and mortality by 15%[1,12,13]. Regarding our results we could reach the effect of antihypertensive medication after our intervention. Therefore, early initiation of antihypertensive drugs and careful consideration of early intervention in several targeted patients should be evaluated. As a method with a high technical success rate and rare complications if performed adequately, PTA could initiate an effective treatment method in patients suffering from hypertension and symptomatic PAD. Aim is to reduce cardiovascular mortality but also prohibit progress of PAD and its limb complications.

4.3 Lowering of central and peripheral blood pressure

PTA in patients with symptomatic PAD achieved a notable lowering effect of central and peripheral blood pressure. The majority of our patients were suffering from arterial hypertension and specifically high systolic pressure while being treated with antihypertensive medication. After angioplasty, systolic pressure could effectively be lowered. The effect on diastolic blood pressure was moderate. We also observed that endovascular treatment affected central and peripheral blood pressure in a different way depending on the localisation of stenosis. PTA of more proximal lesions had a higher effect compared to distal angioplasty. Therefore, we achieved to show that endovascular treatment of PAD and especially in iliac arteries can effectively lower central and peripheral blood pressure.

4.4 Alterations in aortic indices

Physicomechanical indices of the aorta reflect the aortic “stiffness”. Our patients suffered from various comorbidities beside hypertension such as diabetes and chronic kidney failure which consequently leaded to a high baseline PWV and AIX. After endovascular treatment PWV showed no effect while AIX was lower especially after angioplasty of proximal lesions. It is possible that the lowering effect of PTA on blood pressure or the decreased amplitude of pulse reflected wave towards the aorta after angioplasty could be responsible for this result.

4.5 Limitations

Despite our positive and promising results, the current study did now include follow up examinations after discharge. Outside of the present work, a follow-up study was performed with positive results and even showing significant effects on diastolic cardiac function. We hypothesize that limitation of cardiovascular risk factors through lifestyle changes and adequate medication would keep PAD in a stable stage. Therefore, blood pressure should remain in normal levels. Though future research is required to support the hypothesis that blood pressure lowering as a result of angioplasty has a significant effect on patient outcome.

4.6 Conclusion

The current research showed that PTA effectively lowers central and peripheral blood pressure, especially after treatment of proximal lesions. While cardiovascular risk factors such as smoking, hypertension, diabetes can promote PAD and lead to occlusion of peripheral arteries, the the present study indicates that PAD lesions may increase blood pressure. Furthermore, the current study could not specifically prove a relation between localisation of specific lesions and cardiovascular risk factors.

Further studies are required to observe how long the lowering effect of PTA on blood pressure lasts and if endovascular treatment of PAD in patients with arterial hypertension could initiate a new treatment strategy.

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