Effects of Remote Ischaemic Preconditioning on Arterial Stiffness in Patients Undergoing Lower Limb Angiographic Procedures: A Randomised Clinical Trial

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WHAT THIS PAPER ADDS

This study evaluates for the first time the effects of remote ischaemic preconditioning (RIPC) on arterial stiffness parameters in patients with symptomatic peripheral arterial disease (PAD) undergoing digital subtraction angiography (DSA). The study shows that RIPC may modulate arterial stiffness and this effect is more pronounced in patients after stenting. As DSA is an additional risk factor in PAD patients with concomitant high cardiovascular risk, RIPC as adjunctive treatment may improve vascular function in these patients and have some clinical impact.

Objectives: Remote ischaemic preconditioning (RIPC) is a phenomenon that promotes protection of tissues and organs against ischaemia reperfusion injury. RIPC has been shown to reduce myocardial and renal injury but its effect on arterial stiffness in patients undergoing lower limb digital subtraction angiography (DSA) is unknown. The aim of this study was to evaluate the effect of RIPC on arterial stiffness in patients with peripheral arterial disease (PAD) undergoing lower limb DSA.

Methods: In the RIPC intervention, the blood pressure cuff on the arm was inflated to 200 mmHg or to 20 mmHg above systolic pressure, and in the sham intervention to 20 mmHg. For both, the procedure was repeated for four five minute cycles at five minute intervals between the cycles. Changes in heart rate corrected augmentation index (AIx@75), augmentation index (AIx), carotid femoral pulse wave velocity (PWV), and haemodynamic parameters were measured before and 24 h after DSA.

Results: 111 (RIPC 54, sham 57) patients with symptomatic lower limb PAD scheduled for DSA were randomised. 102 patients (RIPC 47, sham 55) were included in final analysis. RIPC significantly improved AIx (-5.46% in RIPC and -1.45% in sham group; $p = .05$), but not AIx@75 (-4.88% in RIPC and -1.38% in sham group; $p = .07$) or PWV (-0.41 m/s in RIPC and -0.27 m/s in sham group; $p = .74$). In the RIPC group a significant reduction in AIx ($p = .002$) and AIx@75 ($p = .003$) was noted after stenting when compared with the sham intervention. AIx ($p = .001$), AIx@75 ($p = .002$), mean arterial ($p = .01$), peripheral ($p = .02$), and central systolic blood pressure ($p = .006$) were significantly reduced only in the RIPC group 24 h after DSA.

Conclusion: This study evaluates for the first time the effects of RIPC on arterial stiffness parameters in patients with symptomatic PAD following DSA. RIPC may modulate arterial stiffness following a DSA procedure and is more pronounced in patients after stent placement.

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INTRODUCTION

Peripheral arterial disease (PAD) is a common condition caused by a steno-occlusive lesion of one or more arteries in the upper or lower extremity. Because of structural and functional changes in the arterial wall, it is accompanied by

increased arterial stiffness. PAD is an independent risk factor for morbidity and mortality caused by coronary and cerebrovascular diseases.[1,2] As the incidence of PAD is increasing with the ageing of the world population,[2] the number of diagnostic lower extremity angiography procedures and endovascular interventions for diagnosing and treating PAD has also grown exponentially.[3] Recent studies have shown an association between endovascular procedures and long term loss of kidney function, cardiovascular events, and mortality.[4,5] Therefore, novel methods should be introduced to improve treatment and to lower the additional risk caused by medical care.

Remote ischaemic preconditioning (RIPC) is a phenomenon in which repeated short ischaemic episodes at a distant site, followed by reperfusion, promote protection of tissues and organs against ischaemia reperfusion injury. RIPC has been shown to reduce the peri-operative incidence of myocardial infarction, if performed before percutaneous coronary intervention,[6] and to significantly lower the incidence of contrast induced acute kidney injury after contrast media administration.[6,7]

A recent study demonstrated no significant effect of RIPC on arterial stiffness parameters in PAD patients undergoing vascular surgery,[8] but in another study RIPC was found to reduce pulse pressure and augmentation pressure in patients with angina pectoris compared with a sham procedure.[9] One possible explanation of the haemodynamic change could be that RIPC improves endothelial function.[10] Because it has been shown that patients with PAD have increased arterial stiffness and endothelial dysfunction in the macro- and microcirculation,[11,12] it was hypothesised that RIPC may have an effect on arterial stiffness and haemodynamic parameters in patients with PAD. In the current study the effect of RIPC on arterial stiffness and haemodynamic parameters was compared with the effect of sham procedure in PAD patients undergoing a lower limb angiography procedure.

METHODS

Trial design

PAD patients scheduled for lower limb DSA were included in a double blind randomised controlled trial to compare the effect of RIPC on arterial stiffness and the haemodynamic profile with the effect of a sham procedure. The trial was approved by the Research Ethics Committee of the University of Tartu. The study was registered at the US National Institutes of Health and US National Library of Medicine clinical trials register (ClinicalTrials.gov) (identifier: NCT02700958).

Study population

All participants were recruited from the Department of Vascular Surgery, Tartu University Hospital, Estonia. The inclusion and exclusion criteria are described in Table 1.

Study interventions

Interventions were performed by the study director by inflating a standard blood pressure cuff on the participant's

Table 1. Inclusion and exclusion criteria of the study on remote ischaemic preconditioning on arterial stiffness parameters in patients with symptomatic peripheral arterial disease undergoing digital subtraction angiography

Inclusion criteria
Age ≥18 years
Symptomatic atherosclerosis of the lower extremity arterial disease (Stages II—IV by Fontaine)
Hospitalised for angiography
Written informed consent
Exclusion criteria
Age <18 years
Estimated glomerular filtration rate measured on admission to hospital <30 mL/min/1.73m^2
Simultaneous participation in any other clinical trial
Coexisting upper limb pathology limiting the use of the cuff
Active malignant tumour (in remission for <5 years or ongoing treatment)
Documented allergic reaction to iodinated contrast agent
Acute infection (body temperature ≥38 °C, C reactive protein ≥50 mg/L)
Cardiac rhythm abnormalities (atrial fibrillation, frequent supraventricular and ventricular complexes)
Home based oxygen treatment
Inability to lie supine for 40 min
Vascular surgery in the axillary region
Documented upper limb deep vein thrombosis

upper arm. The RIPC intervention was performed by inflating the cuff to 200 mmHg for five minutes. If the participant's systolic blood pressure exceeded 180 mmHg prior to randomisation, the cuff was inflated to 20 mmHg above systolic pressure. The sham intervention was accomplished by inflating the cuff to 20 mmHg for five minutes. Both in the RIPC and sham intervention, the cycle was repeated four times with a five minute deflation period between. The schedule of the patients undergoing angiography was known beforehand. Because of the unpredictable duration of the first angiographic procedure and possible additional emergency procedures that might have shifted the time schedule, the study intervention was performed as close as possible before the subsequent angiographic procedure. The angiographic procedure was performed under local anaesthesia with lidocaine.

Study outcomes

The primary study outcomes were registered as a change in augmentation indices (augmentation index [AIx], augmentation index corrected to a heart rate of 75 beats per minute [AIx@75]) and carotid femoral pulse wave velocity (PWV). AIx@75 was selected as the primary outcome following a power analysis based on the measurements of the first 30 study participants considered as a pilot study. The haemodynamic profile (central and peripheral diastolic and systolic blood pressure, heart rate, mean arterial pressure, peripheral and central pulse pressure) and the augmentation indices were obtained from the brachial artery, and PWV was obtained from the carotid and femoral arteries non-invasively in the fasting state with a

Sphygmocor XCEL PWA & PWV device (software version 1.2, AtCor Medical, West Ride, Australia) as described earlier by Hwang et al.[13]

The secondary outcomes were a change in AIx, PWV, haemodynamic profile, and elasticity indices of the large (C1) and small (C2) arteries. C1 and C2 were obtained using the HDI/PulseWave CR-2000 research CardioVascular Profiling System (Hypertension Diagnostics, Inc., Eagan, MN, USA).

Baseline measurements were made by the study director on the eve of the day before angiography. Second measurements were made by a member of the study group, who was unaware of the assigned intervention, on the morning of the day following DSA.

Sample size

No previous study has measured the effect of RIPC on pulse wave velocity or augmentation indices before the onset of a trial. The required sample size was calculated after recruitment of 15 patients in the RIPC group and 15 patients in the sham group. The desired difference in the magnitude of the effect in AIx@75 was considered to be 5%. Using a one-tailed Welch's t test, it was established that 47 patients had to be included in each group to reach a statistical power of 80% and an α of .05.

Randomisation and blinding

By applying the stratified permuted block randomisation technique, six strata were formed combining age ($\geq$75 or $<$ 75) and estimated glomerular filtration rate ($\geq$90, 60–89 or 30–59, mL/min/1.73 m^2). Block size was set to randomly permutate between 2 and 4. The randomisation sequence was conducted prior to the beginning of the study by the study group's randomiser using the WINPEPI computer program.[14] The results were manually sealed into non-transparent envelopes tagged by the number of strata and order of randomisation. Participants were recruited by the study director and were assigned in the order of enrolment in the strata based on age and estimated glomerular filtration rate. The envelope of assigned intervention was opened immediately before the initiation of the intervention.

The participants were blinded by concealing the cuff's pressure gauge. The medical personnel in charge of the treatment of the participants were informed about their patient's consent to participate in the trial, but they were kept blinded to the applied intervention. Statistical models were developed and analysis was made without knowledge of the assigned intervention.
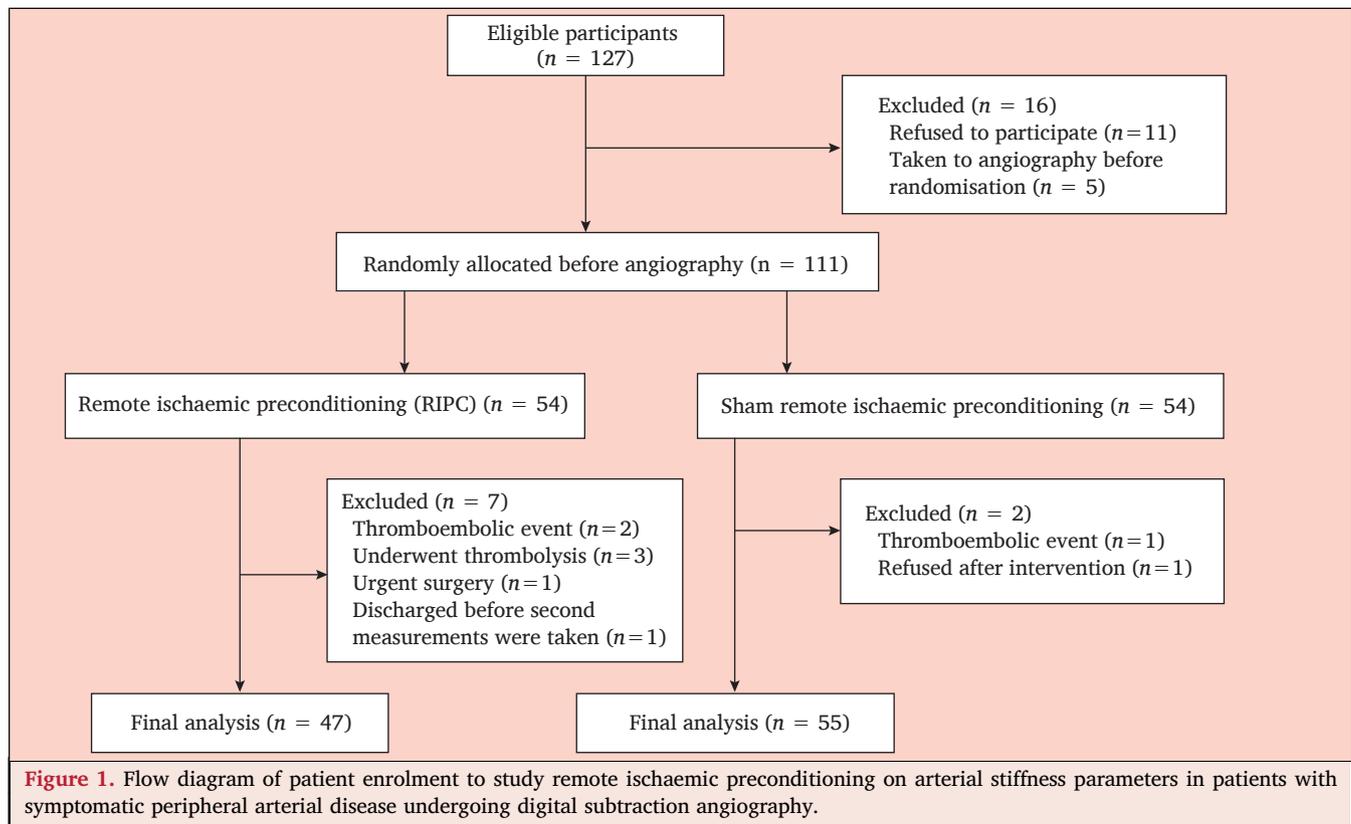
Statistical analysis

Continuous variables were compared using Student's t test or the Wilcoxon rank sum test as appropriate. Categorical variables were compared with the chi-square test. The ANOVA test was used to adjust for potential confounding factors. A p value of $<$ .05 was considered significant in all tests.

RESULTS

Between February 2016 and March 2018, 127 non-consecutive patients with PAD scheduled for peripheral DSA were invited to participate in the trial. Of these patients, 116 agreed and 11 refused (Fig. 1). Because of changes in the angiography schedule, five patients were referred for the angiography procedure before being randomised for intervention. Fifty-four participants were allocated to the RIPC group and 57 to the sham group. Seven patients in the RIPC group did not complete the study protocol: two patients were excluded after a thrombo-embolic complication with consequent surgical thrombectomy, three patients were excluded because of thrombosis observed on angiography with consequent thrombolysis, one was excluded because of surgery performed on the same day after angiography, and one was discharged from hospital before the second measurements were taken. Two patients did not complete the study protocol in the sham group: one revoked agreement after intervention and one was excluded after a thrombo-embolic complication was observed on angiography with consequent surgical thrombectomy. Altogether, 47 patients from the RIPC group and 55 from the sham group were included in final analysis.

The baseline demographic and haemodynamic parameters are presented in Table 2. The median time from the beginning of intervention to the beginning of angiography was 80 min (IQR 60–118) in the RIPC group and 79 min (IQR 64–112) in the sham group (p = .38). There was no significant difference between RIPC and sham intervention regarding the time spent for angiography (32 min and 35 min; p = .11, respectively) or the time from the beginning of intervention to the time when second haemodynamic measurements were taken (23 h 49 min and 24 h 13 min; p = .18, respectively). During angiography, stents were placed in 23 patients in the RIPC group and in 30 patients in the sham group (p = .57). Two or more stents were placed in eight patients in the RIPC group and 15 in the sham group (p = .32).

RIPC significantly improved AIx compared with the sham control (−5.46% and −1.45%; p = .05, respectively) (Fig. 2) and this improvement remained significant after adjusting for diabetes (p = .05). Compared with the sham control, RIPC did not significantly reduce AIx@75 (−4.88% in RIPC and −1.38% in sham group; p = .07) or carotid femoral PWV (−0.41 m/s in RIPC and −0.27 m/s in sham group; p = .74) (Table 3). After adjusting AIx for mean arterial pressure, sex, age, heart rate, and height, no significant difference was noted between the RIPC group and the sham group (p = .11). In the RIPC group a significant decrease of AIx and AIx@75 occurred after stenting compared with the sham group intervention (p = .002; p = .003, respectively) (Fig. 3). There was no significant change in AIx or AIx@75 between the RIPC and sham intervention in patients who had not received stents during DSA (p = .60; p = .46, respectively). Only in the RIPC group were AIx (p = .001), AIx@75 (p = .002), mean arterial pressure (p = .01),

Figure 1. Flow diagram of patient enrolment to study remote ischaemic preconditioning on arterial stiffness parameters in patients with symptomatic peripheral arterial disease undergoing digital subtraction angiography.

peripheral ($p = .02$) and central systolic blood pressure ($p = .006$) significantly reduced 24 h after DSA compared with the baseline measurements. Both in the RIPC and sham groups a significant change in carotid femoral PWV ($p = .02$; $p = .03$, respectively), central blood pressure ($p = .006$; $p = .01$, respectively), and peripheral pulse pressure ($p = .01$; $p = .04$, respectively) was observed 24 h after DSA.

DISCUSSION

This study has evaluated for the first time the effect of the RIPC procedure on arterial stiffness and haemodynamic parameters in patients with PAD undergoing DSA. RIPC significantly decreased AIx after a lower limb angiographic procedure, but does not significantly reduce AIx@75 or carotid femoral PWV. Only in the RIPC group were AIx, AIx@75, mean arterial pressure, peripheral and central systolic blood pressure significantly reduced 24 h after DSA. In the RIPC group a significant decrease of AIx and AIx@75 occurred after stenting compared with the sham group intervention.

Even though PWV, defined as the speed of travel of the pulse wave along an arterial segment, has been considered a gold standard for measuring arterial stiffness, occlusive lesions potentially present in PAD patients might cause false measurements.[15] Instead surrogate markers for arterial stiffness, for example central systolic blood pressure, pulse pressure, and AIx, which provides additional information about pulse wave reflection,[15] can be used to describe the possible effect RIPC may impose on arterial stiffness and haemodynamic profile. AIx, defined as the ratio of augmentation pressure (the difference between the first and second systolic peaks of the arterial waveform) to pulse pressure as a percentage, has been independently associated with PAD,[16] severity of lower limb perfusion impairment,[17] and shorter walking distance.[18] Considering that patients with PAD often have concomitant atherosclerotic lesions, including coronary artery disease, they are at great risk of cardiovascular events.[19] It has been shown that higher AIx is accompanied by an increase in central systolic blood pressure and a decrease in diastolic pressure. This is because the pulse wave, reflected from stiff arteries and atherosclerotic lesions, which arrives in systole leads to higher myocardial oxygen demand, reduced coronary blood flow, myocardial ischaemia, and heart failure through increased afterload.[15,20] Hence it is reasonable to assume that the reduction in AIx as well as in peripheral and central systolic pressure and mean arterial blood pressure found in this trial, should be beneficial to patients with PAD undergoing DSA.

It has been reported that exposure to contrast media during lower limb DSA reduces renal function and increases the risk of long term cardiovascular events and mortality.[4,21] RIPC has been shown to protect against contrast induced acute kidney injury through increased generation of nitric oxide (NO).[22] Moreover, increased inflammatory response and oxidative stress as a result of ischaemia reperfusion injury following revascularisation

Table 2. Baseline characteristics of patients with symptomatic peripheral arterial disease (PAD) undergoing remote ischaemic preconditioning (RIPC) or sham remote ischaemic preconditioning before digital subtraction angiography

Characteristics	RIPC (n = 47)	Sham (n = 55)	p
Demographic			
Male − n (%)	33 (70.2)	48 (87.3)	.06
Mean age ± SD − y	66.1 ± 10.2	65.1 ± 11.4	.67
Weight ± SD − kg	75.7 ± 17.5	78.4 ± 16.8	.44
Body mass index (IQR) − kg/m^2*	25.6 (22.8−30.3)	25.7 (23.5−29.4)	.69
Concomitant diseases			
History of smoking − n (%)[†]	36 (76.7)	41 (74.5)	.99
Stage of PAD III or more[‡]	24 (51.1)	26 (47.3)	.86
Stage of PAD III − n (%)[‡]	9 (19.1)	10 (18.2)	
Stage of PAD IV − n (%)[‡]	15 (31.9)	16 (29.1)	
Diabetes − n (%)	11 (23.4)	14 (25.5)	.75
eGFR			
<90 − n (%)[§]	28 (59.6)	31 (56.4)	.90
60−89 − n (%)[§]	19 (40.4)	20 (36.4)	
30−59 − n (%)[§]	9 (19.1)	11 (20.0)	
Hypertension − n (%) [‖]	33 (74.5)	29 (56.4)	.11
Statin use − n (%)	19 (42.6)	16 (29.1)	.32
Haemodynamic parameters			
PSBP ± SD − mmHg	144.0 ± 22.0	138.7 ± 17.1	.19
PDBP ± SD − mmHg	77.1 ± 12.0	75.7 ± 9.7	.54
CSBP ± SD − mmHg	132.2 ± 19.2	126.3 ± 13.8	.08
CDBP ± SD − mmHg	78.1 ± 11.9	76.8 ± 9.8	.54
MAP ± SD − mmHg	97.9 ± 13.3	94.7 ± 10.7	.19
PPP (IQR) − mmHg*	65 (53.5−79.0)	62 (54.5−69.0)	.20
CPP (IQR) − mmHg*	53 (42.5−65.7)	47 (42.2−54.2)	.09
CPP/PPP ± SD	0.81 ± 0.05	0.79 ± 0.06	.08
AIx ± SD − %	36.6 ± 11.8	33.9 ± 11.8	.25
AIx@75% ± SD − %	31.8 ± 11.8	30.0 ± 11.8	.45
Heart rate ± SD − 1/min	65.2 ± 9.8	67.3 ± 10.4	.29
C1 (IQR) − mL/mmHg × 10*	11.7 (9−13.72)	12.2 (8.75−14.75)	.33
C2 (IQR) − mL/mmHg × 100*	2.7 (1.45−4.08)	3.2 (2.35−4.08)	.50
SVR (IQR) − dyne × s × cm^{-5}*	1564 (1326−1945)	1588 (1404−1831)	.87
PWV (IQR) − m/s*	8.8 (8−10.2)	8.9 (7.7−10.0)	.67

Data are given as n (%), mean ± standard deviation (SD), or median (interquartile range [IQR]) unless otherwise indicated.

AIx = augmentation index; AIx@75% = heart rate corrected augmentation index; C1 = large artery elasticity index; C2 = small artery elasticity index; CDBP = central diastolic blood pressure; CPP = central pulse pressure; CSBP = central systolic blood pressure; eGFR = estimated glomerular filtration rate; MAP = mean arterial pressure; PAD = peripheral arterial disease; PDBP = peripheral diastolic blood pressure; PPP = peripheral pulse pressure; PSBP = peripheral systolic blood pressure; PWV = pulse wave velocity; SVR = systemic vascular resistance; y = years of age.

* Non-normal distribution (median and IQR are presented instead of mean ± SD).
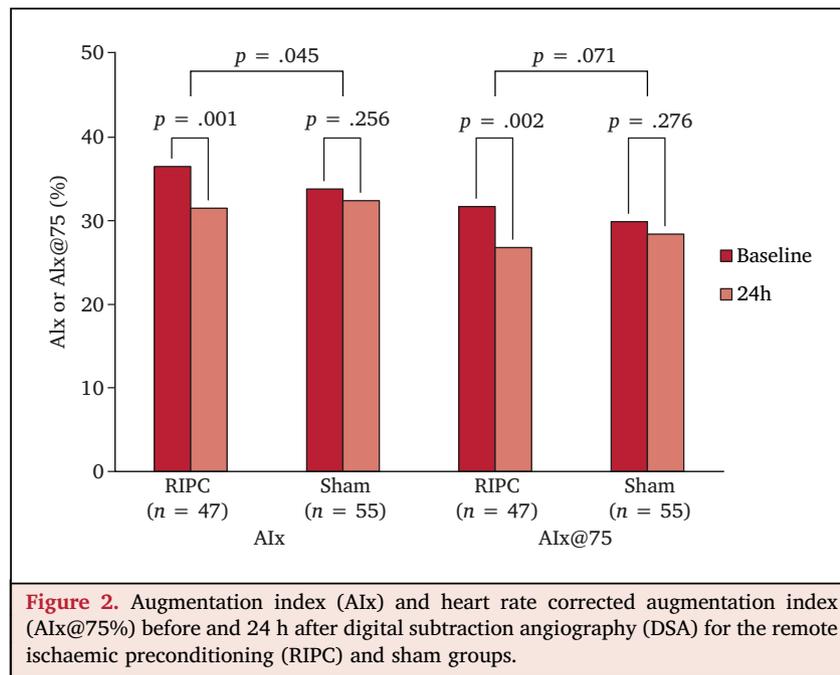
† Current and ex-smokers.

‡ Stage of peripheral arterial disease by Fontaine's classification.

§ mL/min/1.73 m^2.

‖ On medication.

has been shown to cause vascular dysfunction.[23] RIPC imposes a biphasic pattern against ischaemia reperfusion injury induced endothelial dysfunction,[24] with the first wave of protection lasting up to two hours and the second window of protection covering 24−48 h after the onset of the stimulus.[10] Previously, the effect of the acute phase of RIPC on arterial stiffness and the haemodynamic profile was shown by Zagidullin et al., where a significant reduction in peripheral and central systolic pressure, as well as in augmentation pressure was noted in coronary heart disease patients, with a possible explanation for the improvement in endothelial function.[9] As similar haemodynamic changes were observed in the present study 24 h after applying the preconditioning stimulus (AIx, AIx@75, mean arterial pressure, and peripheral and central systolic blood pressure were significantly reduced in the RIPC group), it is suggested that RIPC also provides improvement in the haemodynamic profile in the delayed phase of protection. As most of the patients leave hospital one day after successful endovascular therapy, the high rate of readmissions because of procedural complications[25] might be avoided by reversing the pathophysiological responses to lower limb angiographic procedures beyond hospital stay. Measurement of arterial stiffness and haemodynamic profile after the endovascular procedure may provide a better insight into overall vascular function, thereby enhancing risk prediction and possibly providing earlier treatment.

Figure 2. Augmentation index (AIx) and heart rate corrected augmentation index (AIx@75%) before and 24 h after digital subtraction angiography (DSA) for the remote ischaemic preconditioning (RIPC) and sham groups.

The exact mechanisms of RIPC and how it affects the vasculature are complex and beyond the scope of this paper. However, RIPC reduces platelet activation, which is present during limb ischaemia[26] and has been proposed to be one of the contributors to ischaemia reperfusion injury.[27] In addition, RIPC downregulates pro-inflammatory genes[28] and has been shown to improve endothelial function when measured with flow mediated dilatation.[10] By modifying smooth muscle tone of the vascular wall with different mediators such as NO produced by the functional endothelium, RIPC has vasodilating effects on the peripheral vasculature. This may reduce reflection and augmentation of the pulse from peripheral sites as seen in the RIPC group in the present study.

A significant difference was noted between the RIPC group and the sham group in AIx and AIx@75 after stenting. Even though a definite causal link cannot be established based on this study, one of the possible explanations why the observed changes occurred in this group, might be improved endothelial function as described previously, because augmentation indices decreased only in the group subjected to RIPC and stenting, but not in the same settings in the sham group
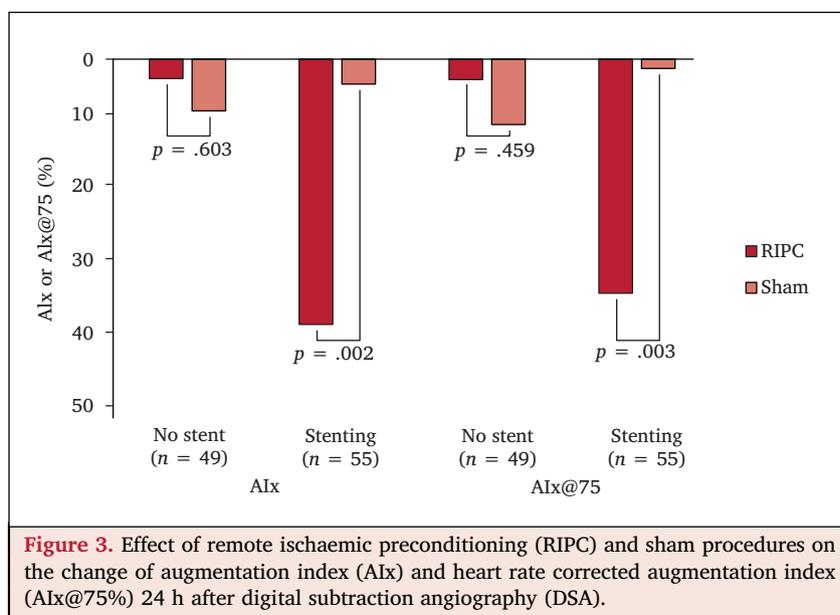
Table 3. Change in haemodynamic parameters in patients with symptomatic peripheral arterial disease (PAD) undergoing remote ischaemic preconditioning (RIPC) or sham remote ischaemic preconditioning before digital subtraction angiography

Haemodynamic parameter	RIPC (n = 47)		Sham (n = 55)		p
	Mean ± SD or Median (IQR)	p	Mean ± SD or Median (IQR)	p	
ΔPSBP ± SD − mmHg	−6.23 ± 18.21	.02	−3.02 ± 13.78	.11	.32
ΔPDBP ± SD − mmHg	−1.81 ± 7.16	.09	−0.69 ± 7.89	.52	.46
ΔCSBP ± SD − mmHg	−6.92 ± 16.42	.006	−2.72 ± 11.72	.09	.15
ΔCDBP ± SD − mmHg	−1.81 ± 7.07	.09	−0.55 ± 7.88	.60	.40
ΔMAP ± SD − mmHg	−3.70 ± 9.95	.01	−1.04 ± 9.81	.44	.18
ΔPPP ± SD − mmHg	−4.43 ± 12.62	.03	−2.33 ± 8.35	.04	.36
ΔCPP ± SD − mmHg	−5.11 ± 13.69	.006	−2.17 ± 6.35	.01	.14
ΔCPP/PPP ± SD	0.04 ± 0.10	.008	0.02 ± 0.09	.21	.22
ΔHeart rate ± SD − bpm	1.15 ± 8.41	.35	−0.28 ± 9.93	.84	.44
ΔC1 (IQR) - mL/mmHg x 10*	0.3 (−1.5 − 2.3)	.18	0.03 (−2.09 − 1.5)	1.0	.32
ΔC2 (IQR) - mL/mmHg x 100*	−0.1 (−0.8 − 0.43)	.34	−0.45 (−1.1 − 0.55)	.05	.37
ΔSVR (IQR) - dyne x s x cm^{-5}*	103.5 (−186.5 − 312.0)	.28	−9.25 (−143.0 − 139.5)	.94	.29
ΔPWV (IQR) - m/s*	−0.3 (−0.85 − 0.1)	.02	−0.35 (−0.95 − 0.4)	.04	.74

Data are presented as mean ± standard deviation (SD) or median (interquartile range [IQR]).
C1 = large artery elasticity index; C2 = small artery elasticity index; CDBP = central diastolic blood pressure; CPP = central pulse pressure; CSBP = central systolic blood pressure; MAP = mean arterial pressure; PDBP = peripheral diastolic blood pressure; PPP = peripheral pulse pressure; PSBP = peripheral systolic blood pressure; PWV = pulse wave velocity; SVR = systemic vascular resistance.
* Non-normal distribution.

Figure 3. Effect of remote ischaemic preconditioning (RIPC) and sham procedures on the change of augmentation index (AIx) and heart rate corrected augmentation index (AIx@75%) 24 h after digital subtraction angiography (DSA).

or in patients who had received only RIPC without stenting. It can be speculated that in the preconditioned vessel vasodilatation in peripheral muscular arteries reduced pulse wave reflection that subsequently translated into a reduction in augmentation indices 24 h after angiography. As RIPC has been shown not to evoke an immediate consequence on the structural composition of the arterial wall, it is obvious why no reduction was seen in PWV.

Even though in animal models RIPC has been shown to have clear beneficial effects, clinical trials have failed to establish a reduction in major adverse cardiac and cerebral events, often because of the possible heterogeneity of the study population.[29] No previous studies were found evaluating the effect of RIPC on lower limb endovascular procedures. Most relevant studies have focused on coronary interventions or surgical procedures by measuring renal and cardiac parameters. Different comorbidities may also affect the effect of RIPC. Reduction in the incidence of acute kidney injury after RIPC was recently shown in non-diabetic patients with moderate renal failure following percutaneous coronary intervention.[8] Diabetes has been a major confounding factor in many clinical studies as it may induce both autonomic and peripheral neuropathy. The effect of RIPC on these patients might be reduced as both the first and second RIPC windows are dependent on the presence of intact neural pathways.[30]

Limitations

There are several limitations to this study. As power analysis was performed and group sizes were calculated for AIx@75, larger sample sizes may be needed to prove the association between RIPC and AIx and other haemodynamic parameters. As a significant decrease of peripheral and central pulse pressure occurred as well as PWV both in the control and RIPC groups, physiological circadian changes, difference in the time of the day when the baseline and second measurements were performed

might have influenced arterial stiffness and haemodynamic parameters. Furthermore, as endovascular treatment has been shown to have a net positive effect on arterial stiffness,[31] it also might have influenced the outcomes of this trial. In addition, as the analyses were made on all symptomatic lower limb PAD patients as a whole group, the effect of RIPC may have varied between the different stages of the disease, and sites of atherosclerotic lesions, as well as the specific treatments during angiography, including the type and location of the stents. Furthermore, as the presence of neuropathy in diabetics was not measured, possible unequal distribution between the RIPC group and sham group might have affected the results.

Conclusion

As patients with PAD are at high risk of major adverse cardiovascular events and as DSA is an additional risk for PAD patients, RIPC may offer an effective adjunctive treatment modality. This study evaluated for the first time the effects of RIPC on arterial stiffness parameters in patients with symptomatic PAD following DSA. The results of this study indicate that RIPC may positively modulate the indices of arterial stiffness following the DSA procedure and this effect is more pronounced in patients after stenting. Further research focusing on whether the observed changes in the haemodynamic profile translate into changes in survival, organ damage, and overall impact on PAD treatment, is needed.

CONFLICTS OF INTEREST

None.

REFERENCES

1 Aboyans V, Ricco J-B, Bartelink M-LEL, Björck M, Brodmann M, Cohnert T, et al. 2017 ESC guidelines on the diagnosis and treatment of peripheral arterial diseases, in collaboration with the european society for vascular surgery (ESVS). *Eur J Vasc Endovasc Surg* 2018;**55**:305−68.

2 Fowkes FGR, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. *Lancet* 2013;**382**:1329−40.

3 Goodney PP, Tarulli M, Faerber AE, Schanzer A, Zwolak RM. Fifteen-year trends in lower limb amputation, revascularization, and preventive measures among Medicare patients. *JAMA Surg* 2015;**150**:84−6.

4 Sigterman TA, Krasznai AG, Snoeijs MG, Heijboer R, Schurink GWH, Bouwman LH. Contrast induced nephropathy and long-term renal decline after percutaneous transluminal angioplasty for symptomatic peripheral arterial disease. *Eur J Vasc Endovasc Surg* 2016;**51**:386−93.

5 Prasad A, Ortiz-Lopez C, Khan A, Levin D, Kaye DM. Acute kidney injury following peripheral angiography and endovascular therapy: a systematic review of the literature. *Catheter Cardiovasc Interv Off J Soc Card Angiogr Interv* 2016;**88**:264−73.

6 Pei H, Wu Y, Wei Y, Yang Y, Teng S, Zhang H. Remote ischemic preconditioning reduces perioperative cardiac and renal events in patients undergoing elective coronary intervention: a meta-analysis of 11 randomized trials. *PLoS One* 2014;**9**:e115500.

7 Moretti C, Cerrato E, Cavallero E, Lin S, Rossi ML, Picchi A, et al. The EUROpean and Chinese cardiac and renal Remote Ischemic Preconditioning Study (EURO-CRIPS CardioGroup I): a randomized controlled trial. *Int J Cardiol* 2018;**257**:1−6.

8 Kepler T, Kuusik K, Lepner U, Starkopf J, Eha J, Lieberg J, et al. The effect of remote ischaemic preconditioning on arterial stiffness in patients undergoing vascular surgery: a randomised clinical trial. *Eur J Vasc Endovasc Surg* 2019;**57**:868−75.

9 Zagidullin N, Scherbakova E, Safina Y, Zulkarneev R, Zagidullin S. The impact of remote ischemic preconditioning on arterial stiffness and heart rate variability in patients with angina pectoris. *J Clin Med* 2016;**5**.

10 Loukogeorgakis SP, Panagiotidou AT, Broadhead MW, Donald A, Deanfield JE, MacAllister RJ. Remote ischemic preconditioning provides early and late protection against endothelial ischemia-reperfusion injury in humans: role of the autonomic nervous system. *J Am Coll Cardiol* 2005;**46**:450−6.

11 Poredoš P, Bešič H, Jeraj L. Relationship between endothelial function of micro- and macrocirculation in patients with peripheral arterial disease. *Vasa* 2017;**46**:17−22.

12 Kals J, Lieberg J, Kampus P, Zagura M, Eha J, Zilmer M. Prognostic impact of arterial stiffness in patients with symptomatic peripheral arterial disease. *Eur J Vasc Endovasc Surg* 2014;**48**:308−15.

13 Hwang MH, Yoo JK, Kim HK, Hwang CL, Mackay K, Hemstreet O, et al. Validity and reliability of aortic pulse wave velocity and augmentation index determined by the new cuff-based SphygmoCor Xcel. *J Hum Hypertens* 2014;**28**:475−81.

14 Abramson JH. WINPEPI updated: computer programs for epidemiologists, and their teaching potential. *Epidemiol Perspect Innov* 2011;**8**:1.

15 Husmann M, Jacomella V, Thalhammer C, Amann-Vesti B. Markers of arterial stiffness in peripheral arterial disease. *Vasa* 2015;**44**:341−8.

16 Zahner GJ, Gruendl MA, Spaulding KA, Schaller MS, Hills NK, Gasper WJ, et al. Association between arterial stiffness and peripheral artery disease as measured by radial artery tonometry. *J Vasc Surg* 2017;**66**:1518−26.

17 Mosimann K, Jacomella V, Thalhammer C, Meier TO, Kohler M, Amann-Vesti B, et al. Severity of peripheral arterial disease is associated with aortic pressure augmentation and subendocardial viability ratio. *J Clin Hypertens* 2012;**14**:855−60.

18 Brewer LC, Chai H-S, Bailey KR, Kullo IJ. Measures of arterial stiffness and wave reflection are associated with walking distance in patients with peripheral arterial disease. *Atherosclerosis* 2007;**191**:384−90.

19 Weber T, O'Rourke MF, Lassnig E, Porodko M, Ammer M, Rammer M, et al. Pulse waveform characteristics predict cardiovascular events and mortality in patients undergoing coronary angiography. *J Hypertens* 2010;**28**:797−805.

20 Palombo C, Kozakova M. Arterial stiffness, atherosclerosis and cardiovascular risk: pathophysiologic mechanisms and emerging clinical indications. *Vascul Pharmacol* 2016;**77**:1−7.

21 Schillinger M, Haumer M, Mlekusch W, Schlerka G, Ahmadi R, Minar E. Predicting renal failure after balloon angioplasty in high-risk patients. *J Endovasc Ther* 2001;**8**:609−14.

22 Zarbock A, Kellum JA. Remote ischemic preconditioning and protection of the kidney—a novel therapeutic option. *Crit Care Med* 2016;**44**:607−16.

23 Ismaeel A, Lavado R, Smith RS, Eidson JL, Sawicki I, Kirk JS, et al. Effects of limb revascularization procedures on oxidative stress. *J Surg Res* 2018;**232**:503−9.

24 Laude K, Beauchamp P, Thuillez C, Richard V. Endothelial protective effects of preconditioning. *Cardiovasc Res* 2002;**55**:466−73.

25 Secemsky EA, Schermerhorn M, Carroll BJ, Kennedy KF, Shen C, Valsdottir LR, et al. Readmissions after revascularization procedures for peripheral arterial disease: a nationwide cohort study. *Ann Intern Med* 2018;**168**:93−9.

26 Burdess A, Nimmo AF, Campbell N, Harding SA, Garden OJ, Dawson AR, et al. Perioperative platelet and monocyte activation in patients with critical limb ischemia. *J Vasc Surg* 2010;**52**:697−703.

27 Pedersen CM, Cruden NL, Schmidt MR, Lau C, Bøtker HE, Kharbanda RK, et al. Remote ischemic preconditioning prevents systemic platelet activation associated with ischemia-reperfusion injury in humans. *J Thromb Haemost* 2011;**9**:404−7.

28 Konstantinov IE, Arab S, Kharbanda RK, Li J, Cheung MMH, Cherepanov V, et al. The remote ischemic preconditioning stimulus modifies inflammatory gene expression in humans. *Physiol Genomics* 2004;**19**:143−50.

29 Heusch G, Gersh BJ. ERICCA and RIPHeart: two nails in the coffin for cardioprotection by remote ischemic conditioning? Probably not! *Eur Heart J* 2016;**37**:200−2.

30 Epps JA, Smart NA. Remote ischaemic conditioning in the context of type 2 diabetes and neuropathy: the case for repeat application as a novel therapy for lower extremity ulceration. *Cardiovasc Diabetol* 2016;**15**:1−17.

31 Jacomella V, Shenoy A, Mosimann K, Kohler MK, Amann-Vesti B, Husmann M. The impact of endovascular lower-limb revascularisation on the aortic augmentation index in patients with peripheral arterial disease. *Eur J Vasc Endovasc Surg* 2013;**45**:497−501.