Dissertation

Auricular Nerve Stimulation in Peripheral Arterial Disease Patients

submitted by

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Graz, July 2017 (Gerald Hackl)

Declaration

“I hereby declare that this dissertation is my own original work and that I have fully acknowledged by name all of those individuals and organizations that have contributed to the research for this dissertation. Due acknowledgement has been made in the text to all other material used. Throughout this dissertation and in all related publications I followed the guidelines of “Good Scientific Practice and Ombuds Committee at the Medical University of Graz.“

Dr.med.univ. Gerald Hackl

Graz, July 2017

Disclosures

This doctoral thesis was the basis for the praparation of a manuscript, which has been published in VASA – The European Journal of Vascular Medicine.[1] The published manuscript was draftet by the doctoral candidate, Gerald Hackl. Therefore, significant parts of the doctoral thesis are similar to the published manuscript (with permission of VASA – The European Journal of Vascular Medicine).

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The author of the dissertation hereby confirms that he has permission to reproduce the illustrations and tables used in this work. If necessary, these were provided with the corresponding references.

Dedication

There are many people who have accompanied me on my way. Some were temporary companions, others remain life-long. I do not want to cite here any individuals, since the probability is too great to forget someone important. The only thing I would like to mention is my thanks to my wife Martina, my son Julian and my daughter Valentina. I will always keep you in my heart.

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Abbreviations and Definitions

PAVK	Periphere arterielle Verschlusskrankheit
WIQ	Walking impairment questionnaire
SF-36	Short form-36 health survey
CI	Confidence interval
PAOD	Peripheral arterial occlusive disease
ABI	Ankle-brachial index
BMG	Bundesministerium für Gesundheit
WHO	World health organization
LMIC	Low and medium income countries
HIC	High income countries
TBI	Toe-brachial index
CTA	Computed tomography angiography
MRA	Magnetic resonance angiography
DSA	Digital subtraction angiography
CO2 Angio	Carbon dioxide angiography
DUS	Color-coded duplex sonography
AAA	Abdominal aortic aneurysm
CFA	Common femoral artery
CIA	Common iliac artery
EIA	External iliac artery
SFA	Superficial femoral artery
TASC	Transatlantic Inter-Society Consensus Document
PTA	Percutaneous transluminal angioplasty
ACE-I	Angiotensin converting enzyme inhibitor
TCM	Traditional chinese medicine
AV Block III°	Atrioventricular Block Grade III
CONSORT	Consolidated Standards of Reporting Trials
HRQoL	Health related quality of life
G-test	Graded treadmill test
C-test	Continuous treadmill test
IBM-SPSS	International Business Machines Corporation-Statistical Package for Social Sciences

ARB	Angiotensin receptor blocker
eGFR	Estimated glomerular filtration rate
CRP	C-reactive protein
Nt-proBNP	N-terminal-prohormone brain natriuretic peptide
QoL	Quality of life
ECG	Electrocardiography

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Zusammenfassung

Ziele: Die Stimulierung von Nerven am äußeren Ohr wurde bereits bei verschiedenen Erkrankungen zur Schmerztherapie erfolgreich eingesetzt. In der vorliegenden Studie wurde untersucht, ob mittels Elektroakupunktur am äußeren Ohr eine neue konservative Behandlungsalternative bei Claudicatio intermittens im Rahmen einer peripheren arteriellen Verschlusskrankheit (PAVK) etabliert werden könnte.

Methoden: In dieser prospektiven, doppelblinden Studie wurde eine Ohrakupunktur mit einem Elektroakupunkturgerät bei 40 PAVK-Patienten im Fontaine-Stadium IIb durchgeführt. 20 Patienten wurden in die Verum-Gruppe mit einem voll funktionsfähigen Elektroakupunktur Gerät randomisiert, die anderen 20 Patienten erhielten ein Schein-Gerät (Kontrollgruppe). Pro Patient wurden 8 Zyklen (1 Zyklus = 1 Woche) der Elektroakupunktur durchgeführt. Der primäre Endpunkt wurde definiert als eine Verdoppelung der maximalen (absoluten) Gehstrecke (+100%) in einer standardisierten Laufbandergometrie. Sekundäre Endpunkte waren eine signifikante Verbesserung der Gesamtpunktzahl des Walking Impairment Questionnaires (WIQ) sowie Verbesserungen der Lebensqualität erhoben mittels des Short-Form 36 Health Survey (SF-36).

Ergebnisse: Es lagen keine signifikanten Unterschiede in den Basisdaten zwischen den beiden Vergleichsgruppen vor. Die initiale Gehstrecke nahm in beiden Gruppen signifikant zu (Verum Gruppe: 182 [95% CI 128-236] Meter bis 345 [95% CI 227-463] Meter [+90%], p <0,01; Kontrollgruppe: 159 [95 % CI 109-210] Meter bis 268 [95% CI 182-366] Meter [+69%], p=0,01). Zwölf Patienten (60%) in der Verum-Gruppe und fünf Patienten (25%) aus der Kontrollgruppe erreichten den primären Endpunkt einer Gehstreckenverdoppelung (p=0,05). Der Gesamt-Score des WIQ nahm in der Verum-Gruppe signifikant zu (+22%, p=0,01), in der Kontrollgruppe hingegen nicht (+8%, p=0,56). Mittels des SF-36 wurden signifikante Verbesserungen in 6 von 8 Kategorien in der Verum-Gruppe, und nur in einer von 8 Kategorien in der Kontrollgruppe objektiviert.

Schlussfolgerungen: Die Elektroakupunktur des äußeren Ohres scheint speziell im Zeitalter von zunehmend invasiven und mechanisch komplexen Behandlungen für PAVK Patienten eine einfach durchzuführende Therapieoption zu sein.

Abstract

Objectives: Auricular nerve stimulation has been proven effective in the treatment of pain in different diseases. We investigated if a conservative therapeutic alternative for claudication in peripheral arterial occlusive disease (PAOD) via electroacupuncture of the outer ear can be established.

Methods: In this prospective, double blinded trial an ear acupuncture using an electroacupuncture device was carried out in 40 PAOD patients in Fontaine stage IIb. 20 patients were randomized to the verum group using a fully functional electroacupuncture device, the other 20 patients received a sham device (control group). Per patient, 8 cycles (1 cycle = 1 week) of electroacupuncture was administered. The primary endpoint was defined as a significantly increased maximal (absolute) walking distance (+100%) after 8 cycles of electroacupuncture in a standardized treadmill testing. Secondary endpoints were a significant improvement of the total score of the Walking impairment questionnaire (WIQ) as well es improvements in Quality of Life using the Short Form 36 health survey (SF-36).

Results: There were no differences in baseline characteristics between the two groups. The initial walking distance significantly increased in both groups (verum group: 182 [95%CI 128-236] meters to 345 [95%CI 227-463] meters [+90%], p<0.01; control group: 159 [95%CI 109-210] meters to 268 [95%CI 182-366] meters [+69%], p=0.01). Twelve patients (60%) in the verum group and five patients (25%) in controls reached the primary endpoint of doubling walking distance (p=0.05). Total Score of WIQ significantly improved in the verum group (+22%, p=0.01) but not in controls (+8%, p=0.56)**.** SF-36 showed significantly improvements in 6 of 8 categories in the verum group and only in 1 of 8 in controls.

Conclusions: Electroacupuncture of the outer ear seems to be an easy-to-use therapeutic option in an age of increasingly invasive and mechanically complex treatments for PAOD patients.

Introduction

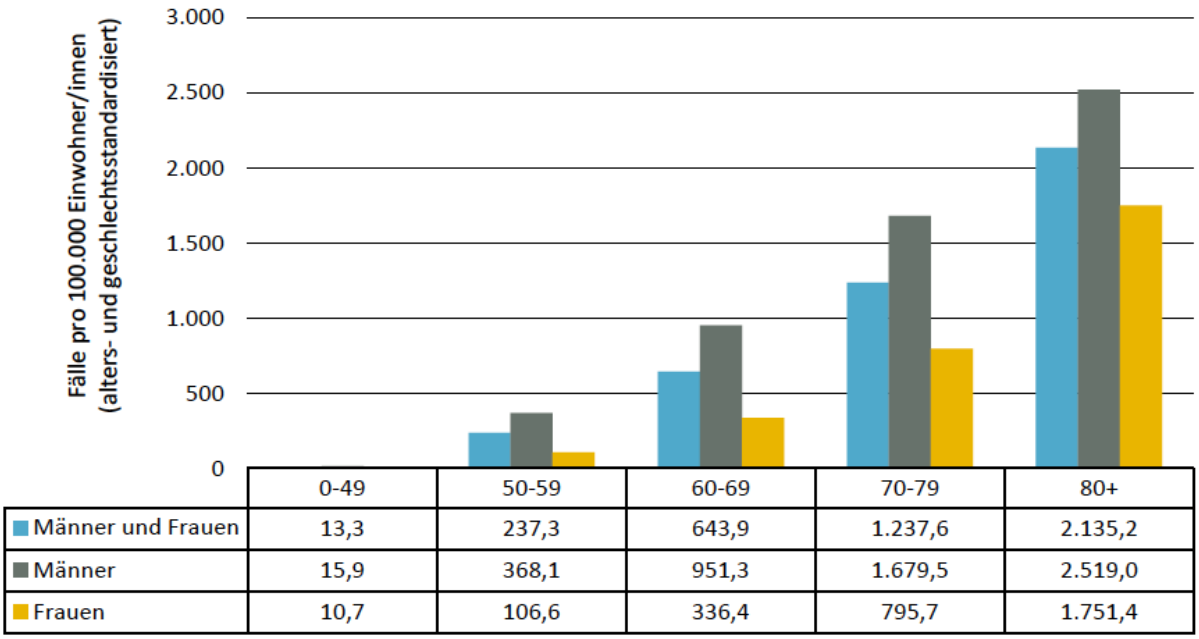
Overview of peripheral arterial occlusive disease

Atherosclerosis is an acquired inflammatory, systemically appearing disease of the arteries with manifestation in the range of various organ systems.[2] Its most common form is the peripheral arterial occlusive disease (PAOD) which is often a sign of generalized atherosclerosis.[3] In general, PAOD describes stenosing and occluding processes of the peripheral arteries. In the narrower sense, PAOD is understood as chronic atherosclerosis in the area of the pelvic and leg arteries.[4]

Epidemiology

The prevalence of PAOD grows dramatically in accordance with increasing age. Thus, a prevalence of 6% could be observed in patients over 60, whereas in case of 70-year-olds the prevalence had already increased to 15-20%.[3]

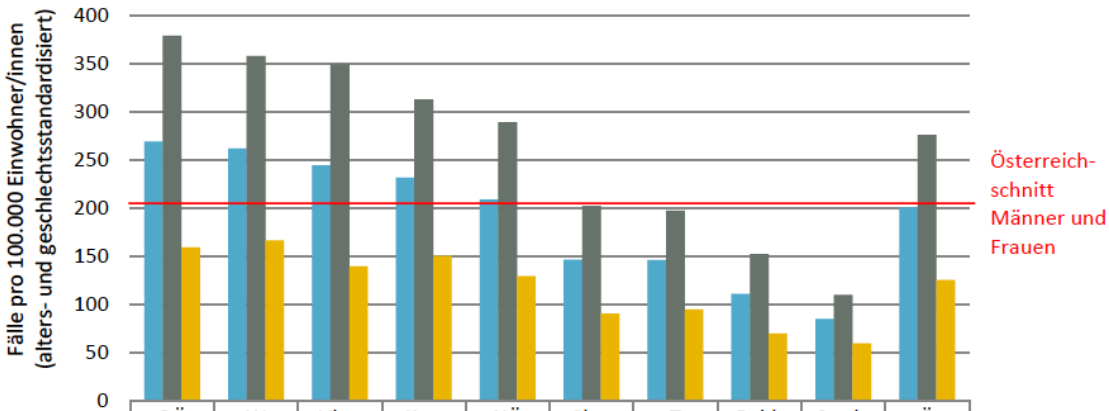
In the annual report of 2015 of the Austrian ministry of health about cardiovascular diseases, data from 2011 that were collected in Austrian health institutions in the framework of diagnosis- and performance-documentation were presented. Thereby, approximately 25,000 PAOD cases per year were documented in Austria. The incidence rate of men is approximately 2.2 times higher than the one of women (276 vs. 125 people per 100,000 inhabitants). Furthermore, the occurrence of PAOD is clearly dependent on age. A sharp increase of incidents can be observed from the age of 50 onwards. In all age groups, the number of incidents is higher in case of males as compared to females. Thus, 64% of PAOD cases occur in patients over 70, and only 4% in patients under 50. Furthermore, the high rate of asymptomatic PAOD makes an adequate determination of epidemiology problematic. Moreover, incidence rates based on diagnosis- and performance-documentation of the Austrian health institutions, as well as death statistics, provide only an incomplete picture because the diagnosis of PAOD does not necessarily lead to mandatory inpatient treatment.[4] For instance, the getABI-study could objectify that almost 20% of patients in German family practices had an ankle-brachial index (ABI) <0.9.[2] Figure 1 illustrates the rate of incidents in accordance with age and sex in Austria.[4]



	0-49	50-59	60-69	70-79	80+
Männer und Frauen	13,3	237,3	643,9	1.237,6	2.135,2
Männer	15,9	368,1	951,3	1.679,5	2.519,0
Frauen	10,7	106,6	336,4	795,7	1.751,4

Figure 1: PAOD incidence rate in accordance with age and sex in Austria 2011.[4] Reproduced from Griebler et al with permission of Bundesministerium für Gesundheit.

With regards to regional differences of the PAOD incidence rate in Austria, it can be established that the number is highest in Upper Austria, Vienna, and Vorarlberg, and lowest in Burgenland and Styria. Considering the regional aspect, it remains true that men have a higher incidence rate in all Austrian federal states than women. Figure 2 illustrates the PAOD incidence rate in the Austrian federal states.[4]



	OÖ	W	Vbg.	Ktn.	NÖ	Sbg.	T	Bgld.	Stmk.	Ö
Männer und Frauen	269,2	262,0	244,5	231,6	209,1	146,3	146,0	110,9	84,7	200,7
Männer	379,4	357,9	349,6	313,1	289,0	202,2	197,6	152,1	109,8	276,1
Frauen	159,1	166,1	139,4	150,2	129,2	90,4	94,5	69,7	59,5	125,4

Figure 2: PAOD incidence rate according to age and sex in the Austrian federal states 2011.[4] Reproduced from Griebler et al with permission of Bundesministerium für Gesundheit.

Internationally, it is assumed that when all clinical stages are considered, more than 200 million people are suffering from PAOD. Compared internationally, Austria as a European country constitutes an area with high prevalence.[5] See Figure 3.[5]

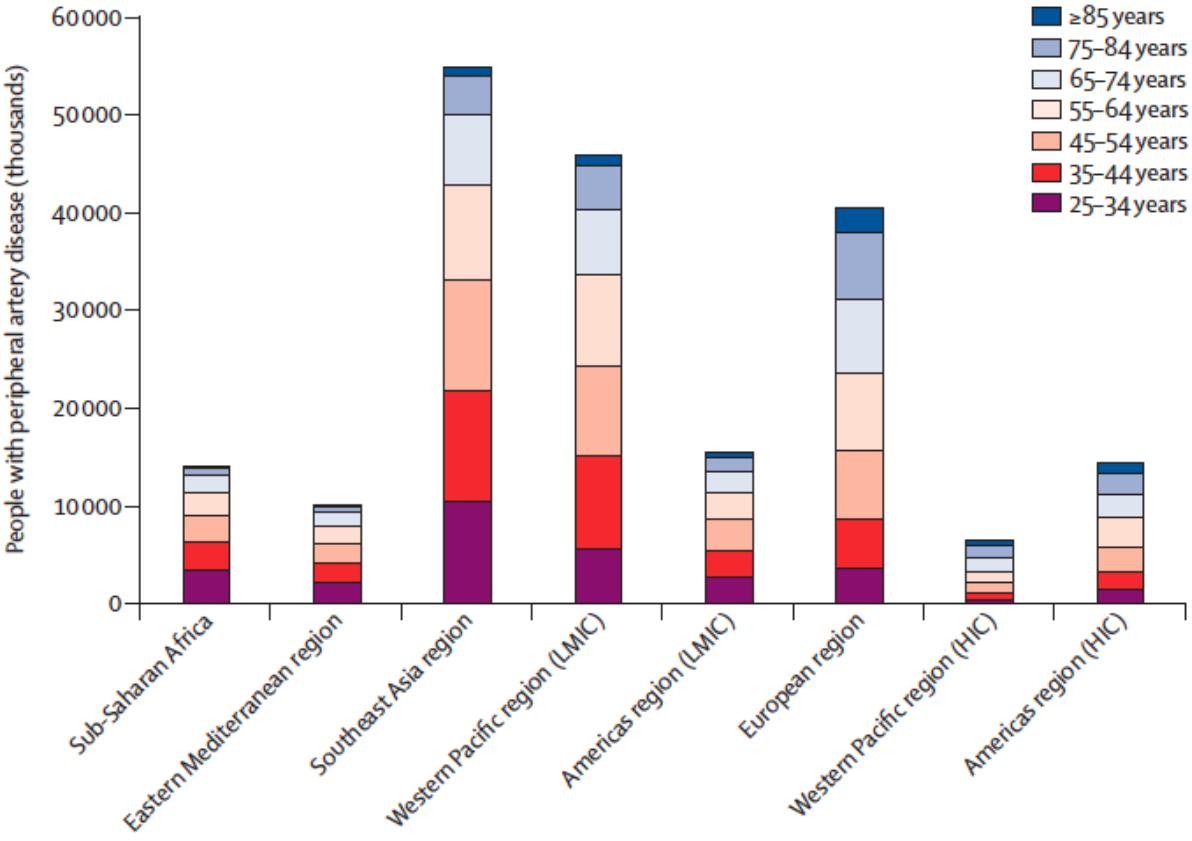


Figure 3: Estimation of PAOD cases depending on age in eight WHO regions in the year 2010. LMIC = low and medium income countries HIC = high income countries.[5] Reproduced from Fowkes FG et al. with permission of Elsevier.

Etiology

The influence of certain risk factors encourages the occurrence of PAOD. Thus, the traditional cardiovascular risk factors of PAOD were mainly identified as increasing age, male sex, positive family anamnesis, diabetes mellitus, arterial hypertension, and hyper/dyslipidemia.[6-9] Next to these traditional risk factors, further risk factors, such as race, ethnicity, elevated C-reactive protein, fibrinogen, leukocytes and interleukin-6, genetics, hypercoagulable states of altered blood levels of D-dimer, homocysteine, lipoprotein, and an abnormal waist-to-hip ratio, could be identified [6,10]. Due to these numerous and frequently avoidable risk factors, the early diagnosis of PAOD is essential to improve quality of life, as well as to prevent further functional impairment, and to reduce mortality and morbidity from coronary artery disease and cerebrovascular disease.[11]

Pathophysiology

The arterial blood circulation in the human organs is controlled by the tone of the precapillary resistance vessels. In healthy individuals, muscular activity leads to an increase in blood circulation in the sense of hyperactive hyperemia via a dilation in the peripheral arterial flow area and a subsequent reactive decrease of the peripheral resistance. Thereby, the resistance vessels can dilate up to 10- to 20-fold. In case of PAOD patients, the chronic and slow decrease of blood circulation is compensated by neoangiogenesis which results in the formation of collaterals. If there is only insufficient compensation due to higher-grade arterial stenosis or progressing PAOD, which is particularly the case in muscular activity, this results in a prolonged and intensified decrease of post-stenotic blood pressure. If the post-stenotic blood pressure falls below approximately 50mmHg in the process, sufficient tissue perfusion can no longer be assured. Depending on the manifestations, this eventually leads to the clinical expression of claudicatio intermittens, ranging from ischemic resting pain to the occurrence of necroses.[12]

Clinical characteristics and stages

The clinical severity is classified into *Fontaine*-stages I - IV, as well as into *Rutherford*-stages 0 - 6. Thereby, *Fontaine*-stage I (*Rutherford* 0) constitutes asymptomatic PAOD. In *Fontaine*-stage II (*Rutherford* 1 -3) the leading symptom of an intermittent claudication is expressed. Furthermore, *Fontaine*-stage II can be sub-classified into stage IIa (*Rutherford* 1) without limitations of lifestyle and a painless walking distance of >200 meters respectively, as well as stage IIb (*Rutherford* 2 - 3) with limitations of lifestyle and a painless walking distance of <200 meters (= lifestyle limiting PAOD). As opposed to the subsequent *Fontaine*-stages III and IV (*Rutherford* 4 - 6), ischemic resting pain as well as development of necroses are not yet present.[12]

Fontaine-stages	*Rutherford-classification*
I – Asymptomatic	0 - Asymptomatic
II – Claudication	1 – Mild Claudication
A – Mild Claudication	2 – Moderate Claudication
B – Severe Claudication	3 – Severe Claudication
III – Ischemic Rest Pain	4 – Ischemic Rest Pain
IV – Ulceration or Gangrene	5 – Minor Tissue Loss
	6 – Ulceration of Gangrene

Table 1: Comparison of *Fontaine-stages* and *Rutherford-classification*.[12]

Diagnosis

Anamnesis is of great importance for the diagnosis of PAOD. The prototypical claudicatio pain is an easily reproduced muscle pain dependent on exertion, which fades quickly after a few minutes of rest. Depending on the location of the vascular lesion, the pain may occur in the gluteal area, the thigh-, calf-, and feet muscles.[13] Due to the characteristic symptoms it is possible to differentiate a cox- and/or gonarthrosis, a claudicatio venosa or polyneuropathy with the help of a structured anamnesis.[14]

The clinical examination starts with an inspection. Hereby, the skin temperature, skin color, and production of perspiration need to be assessed. Furthermore, necroses/gangrene, muscle atrophies, deformities, and edemas should be considered. By palpating the pulse on both sides and comparing it, pathological processes can already be limited to one segment. Auscultation with a stethoscope is most suitable to detect 60-85% stenoses of the vessel lumen for physical reasons. These stenoses cause post-stenotic turbulences because of the increased speed of blood flow in the stenosis, which can be auscultated as systolic murmurs.[12] For the Ratschow-test the patient is lying on her/his back. While the legs are vertically lifted, rolling motions of the foot in the ankle joint are performed for two minutes. After that, the patient sits up and allows the legs to hang down in a vertical direction. The reactive hyperemia is judged. Hyperemia should take place within 15 seconds, and be followed by the filling of the veins within 20 seconds. In case of unilateral

circulatory disturbance, the result is delayed reactive hyperemia, which can be clinically easily observed if the sides are compared.[15] There are no big studies that provide evidence for the Ratschow-test, but clinical experience rates this simple examination as effective.[13] Thus, the combination of anamnesis, comparative pulse palpitation of both sides, and auscultation lead to a detection rate for clinically relevant stenosis in over 80% of the cases.[16] Further frequently used, non-invasive diagnostic methods are treadmill ergometry, pulse oscillography, the ankle-brachial index (ABI), the toe-brachial index (TBI), as well as the color-coded duplex sonography (DUS). Treadmill ergometry is essentially best suited to judge the compensation, the clinical degree of severity, as well as to monitor the progress after therapeutic measures in Fontaine stage II. Thereby, the relative (start of complaints) and absolute (maximally possible) walking distance are measured under standardized conditions. In the process, the ABI is determined while resting before the examination, and again immediately after the treadmill ergometry. A decrease of the ABI by 20% is proof of the diagnosis.[17-19] During pulse oscillography, oscillations are detected with the help of electric pulse sensors. The smaller the amplitude distal of the stenosis, the more severe the degree of PAOD is. The method is clinically relevant in the judgment of reduced acral perfusion.

The ABI is a parameter that can be used to assess the peripheral arterial circulation. The assessment of the ABI with the help of the non-invasive Doppler-pressure measurement is not only simple, quick, and reliable, but also has a high significance in assessing the vessel status. The ABI is calculated by using the quotient of systolic ankle artery pressure and systolic arm artery pressure. Physiological values range from >0.9 to <1.3. Values over >1.3 suggest mediasclerosis, which is particularly frequent in case of diabetics.[17] An ABI <0.9 is seen as threshold value for the diagnosis of PAOD. It was claimed that an ABI <0.9 has a sensitivity of 95% for the presence of a stenosis of at least 50%, and a specificity of almost 100%.[13,20-22] Patients with an ABI <0.8 exhibit symptoms of claudicatio intermittens under exertion. Patients with an ABI <0.3 generally suffer from ischemic resting pain due to a critically reduced perfusion of the extremity.[23] Table 2 depicts the degree of PAOD severity according to the ABI.[12]

ABI	Severity of PAOD
>1.3	False high values (suspicion of mediasclerosis)
>0.9	Normal condition
0.75 – 0.9	Slight PAOD
0.5 – 0.75	Moderate PAOD
<0.5	Severe PAOD (critical limb ischemia)

Table 2: Degree of PAOD severity according to the ABI.[12]

Diabetes mellitus and PAOD show high coincidence.[24-26] In case of coexistent diabetes, the ABI is frequently >1.3 because of incompressible arteries in the context of mediasclerosis. As mediasclerosis barely affects the digital arteries, the toe brachial index (TBI) can be used instead of the ABI in order to assess the peripheral circulation. The pressure of toe arteries is approximately 30mmHg and, therefore, lower than the systolic ankle artery pressure. This is why the TBI is only pathological at values <0.7. The German S3 guideline for PAOD recommends measuring the TBI if the ABI is not conclusive, as well as in case of diabetics with an ABI >1.3 as a complementing method.[13]

The DUS has great significance in the context of non-invasive PAOD diagnosis. It is comprised of a color-coded B-image sonography combined with a Doppler sonography. A physiological Doppler curve is bi- or triplephased. If the Doppler curve is monophased, this indicates the presence of a stenosis >75% proximal of the measuring point. The Doppler frequency spectrum shows an intrastenotic increase of systolic and diastolic speeds in case of stenosis greater than 50%. The color duplex technology enables a color-coded representation of the arterial flow signal inside the vessel lumen. This procedure enables the diagnosis of low- as well as high grade arterial stenosis, and occlusions in case of missing color-coding.[12] Computed tomography angiography (CTA) and magnetic resonance angiography (MRA) are used as radiologic-diagnostic methods. These are particularly well suited to plan revascularizing interventions, although the CTA still has weaknesses in differentiating between calcified occluded lumen and perfused lumen in the area of the calf arteries.[15]

In case of invasive imaging, the digital subtraction angiography (DSA) is used. For diagnostic purposes, the DSA is only rarely used today. Generally, the DSA is combined with therapeutic intervention (in particular balloon angioplasty and stenting). Furthermore, the DSA is considered as gold standard in diagnostic imaging.[13,15] Figure 4 provides an overview of the diagnostic algorithm for PAOD according to the German S3 guideline.[13]

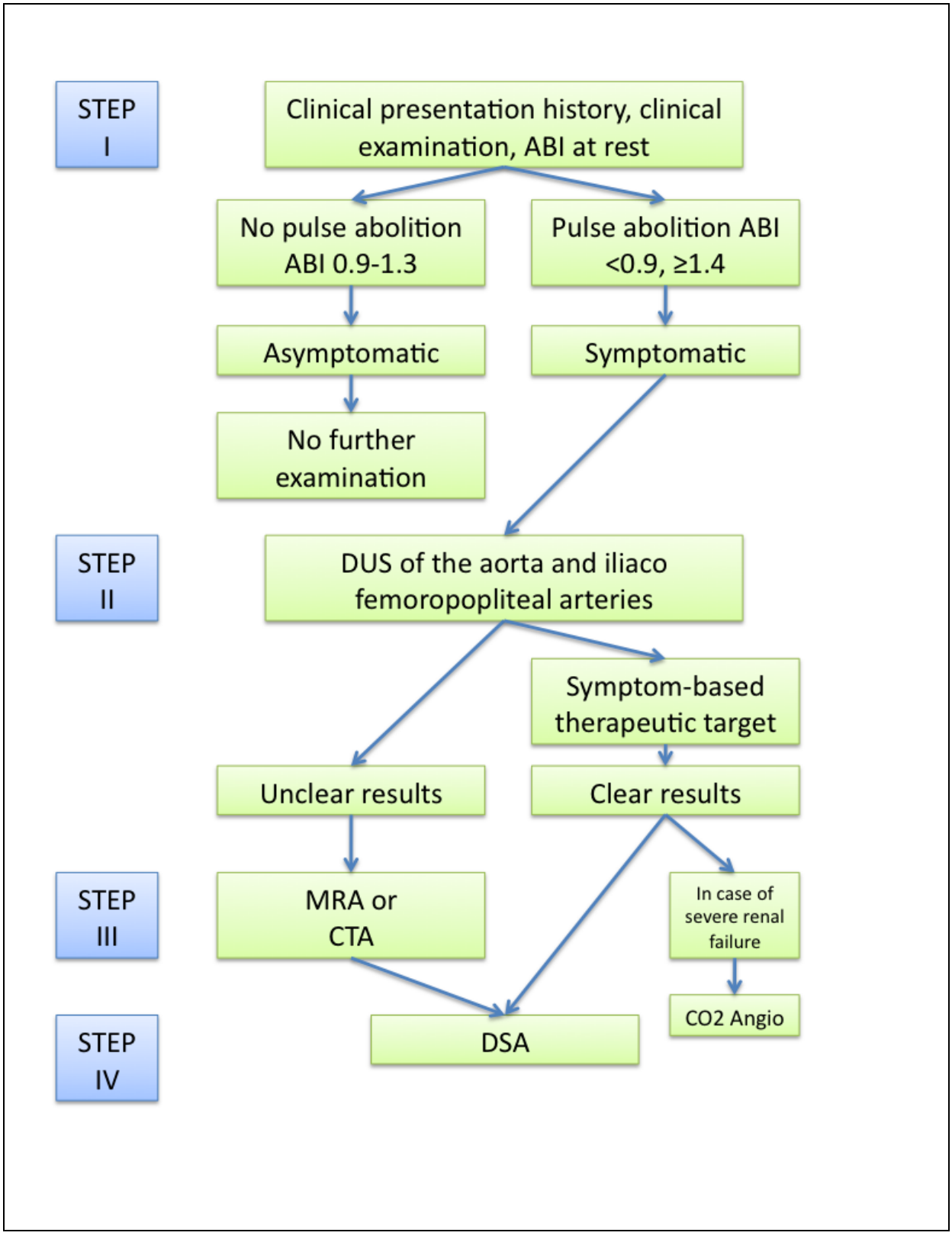


Figure 4: Diagnostic algorithm for PAOD.[13] ABI: ankle-brachial-index; MRA: contrast-enhanced magnetic resonance angiography; CO2 Angio: carbon dioxide angiography; CTA: computed tomographied angiography; DSA: digital subtraction angiography; DUS: color-coded duplex sonography.

Therapy

PAOD therapy distinguishes conservative from revascularizing methods. The two therapeutic options always need to be closely connected.

Base aspects of conservative therapy are, first and foremost, the modification of risk factors, treatment of co-morbidities, and supervised exercise therapy.[13] If intermittent claudication is present, it is of great importance to conduct regular, and if possible structured, walking training, as this does not only maintain mobility, but also has been shown to improve the quality of life.[13,27] In case of critical limb ischemia, pain reduction and the avoidance of amputation take center stage. In both clinical situations, intermittent claudication as well as critical limb ischemia, it is necessary to reduce cardio- and cerebrovascular complications. Acetylsalicylacid and statins are the standard pharmacological options for the therapy of PAOD patients.[13] In the treatment of PAOD, there is no definite LDL goal value.[28] Patients who additionally suffer from arterial hypertension should strive for blood pressure values under 140/90mmHg. Contrary to previous ideas, beta blockers are no longer seen as contraindication. Furthermore, it was discussed that the continued medication with ACE-inhibitors led to an improvement of walking distances.[13,29]

Vasoactive substances, such as cilostazol and naftidrofuryl, are also associated with an improvement of the quality of life in the presence of intermittent claudication and if structured walking training is impossible.[30,31]

Revascularizing treatment of PAOD distinguishes between endovascular and operational-surgical interventions. A revascularizing strategy should always be employed in case of critical limb ischemia. Revascularization should, however, only take place in case of intermittent claudication if despite the best possible conservative treatment no improvement of symptoms could be achieved, and if a vessel specialist prefers the option of revascularization after evaluating the risks and gains.[32,33] During the decision-making process, existing co-morbidities, expertise of the vascular center, the patient's preference, and, very importantly, the anatomical preconditions of the vascular lesions should be considered.[13,32] In 2007, a classification of lesions for the treatment of PAOD was made within the framework of an international conference, the transatlantic inter-society classification. The classification is shown in Table 3.[34] ESC recommendations for the

revascularization of patients with aorto-iliac, femoro-popliteal, and infrapopliteal lesions are shown in the following tables 4, 5, 6.[32]

Aorto-iliac lesions	
Lesion type	Description
Type A	- Unilateral or bilateral stenosis of CIA - Unilateral or bilateral single short (≤3 cm) stenosis of EIA
Type B	- Short (≤3 cm) stenosis of infrarenal aorta - Unilateral CIA occlusion - Single or multiple stenosis totaling 3-10 cm involving the EIA not extending into the CFA - Unilateral EIA occlusion not involving the origins of internal iliac or CFA
Type C	- Bilateral CIA occlusions - Bilateral EIA stenoses 3-10 cm long not extending into the CFA - Unilateral EIA stenosis extending into the CFA - Unilateral EIA occlusion that involves the origins of internal iliac and/or CFA - Heavily calcified unilateral EIA occlusion with or without involvement of origins of internal iliac and/or CFA
Type D	- Infra-renal aorto-iliac occlusion - Diffuse disease involving the aorta and both iliac arteries requiring treatment - Diffuse multiple stenosis involving the unilateral CIA, EIA and CFA - Unilateral occlusions of both CIA and EIA - Bilateral occlusions of EIA - Iliac stenosis in patients with AAA requiring treatment and not amenable to endograft placement or other laesions requiring open aortic or iliac surgery
Femoral-popliteal lesions	
Lesion type	Description
Type A	- Single stenosis ≤10 cm in length - Single occlusion ≤5 cm in length
Type B	- Multiple lesions (stenoses or occlusions), each ≤5 cm - Single stenosis or occlusion ≤15 cm not involving the infra geniculate popliteal

	artery - Single or multiple lesions in the absence of continuous tibial vessels to improve inflow for a distal bypass - Heavily calcified occlusion ≤5 cm in length - Single popliteal stenosis
Type C	- Multiple stenoses or occlusions totaling >15 cm with or without heavy calcifications - Recurrent stenoses or occlusions that need treatment after two endovascular interventions
Type D	- Chronic total occlusion of CFA or SFA (>20 cm, involving the popliteal artery) - Chronic total occlusion of popliteal artery and proximal trifurcation vessels

Table 3: Lesion classification according to the TransAtlantic Inter-Society Consensus for the Management of PAOD (TASC II).[34] CIA = common iliac artery; EIA = external iliac artery; CFA = common femoral artery; AAA = abdominal aortic aneurysm; SFA = superficial femoral artery.

Recommendations	Class[a]	Level[b]
When revascularization is indicated, an endovascular-first strategy is recommended in all aorto-iliac TASC A-C lesions.	**I**	**C**
A primary endovascular approach may be considered in aorto-iliac TASC D lesions in patients with severe comorbidities, if done by an experienced team.	**IIb**	**C**
Primary stent implantation rather than provisional stenting may be considered for aorto-iliac lesions.	**IIb**	**C**

Table 4: Recommendations for the revascularization of patients with aorto-iliacal lesions.[32] (a: Class of Recommendation. b: Level of Evidence). TASC = Transatlantic Inter-Society Consensus Document.

Recommendations	Class[a]	Level[b]	Ref[c]
When revascularization is indicated, an endovascular-first strategy is recommended in all femoro-popliteal TASC A-C lesions.	**I**	**C**	**-**
Primary stent implantation should be considered in femoro-popliteal TASC B lesions.	**IIa**	**A**	**285, 286, 291**
A primary endovascular approach may also be considered in TASC D lesions in patients with severe comorbidities and the availability of an experienced interventionist.	**IIb**	**C**	**-**

Table 5: Recommendations for the revascularization of patients with femoro-popliteal lesions.[32] (a: Class of Recommendation. b: Level of Evidence. c: References in Eur Heart J 2011;32:2851-906.). TASC = Transatlantic Inter-Society Consensus Document.

Recommendations	Class[a]	Level[b]
When revascularization in the infrapopliteal segment is indicated, an endovascular-first strategy should be considered.	**IIa**	**C**
For infrapopliteal lesions, angioplasty is the preferred technique, and stent implantation should be considered only in the case of insufficient PTA.	**IIa**	**C**

Table 6: Recommendations for the revascularization of patients with infrapopliteal lesions.[32] (a: Class of Recommendation. b: Level of Evidence). TASC = Transatlantic Inter-Society Consensus Document; PTA = percutaneous transluminal angioplasty.

The table below summarizes the treatment strategies according to the present Fontaine stage.[13]

	Fontaine-stage			
Therapeutic strategy	**I**	**II**	**III**	**IV**
Risk factor management: Smoking cessation, antidiabetic / antihypertensive therapy, statins	+	+	+	+
Antiplatelet agents: Acetylsalicylic acid or Clopidogrel	(+)	+	+	+
(Supervised) exercise therapy	+	+		
Pharmacotherapy: Cilostazol or Naftidrofuryl		+		
Wound care				+
Endovascular therapy		+*	+	+
Surgical therapy		+*	+	+
Legend: + Recommendation; * depending on appropriate individual morphology and patient preference				

Table 7: Treatment strategies according to the *Fontaine-stages*.[13]

Auricular acupuncture

Acupuncture originates from traditional Chinese medicine (TCM) and is predominantly used to treat chronic pain. It is based on life energies of the body which circulate in the body on defined channels, meridians, and which are claimed to have a regulating influence on all bodily functions.[35] Auricular acupuncture is a branch of traditional acupuncture and has been established as independent treatment strategy in the past 60 years.[36] Thereby, the surface of the ear constitutes a reflex zone on which the entire body is anatomically represented. It is, therefore, possible to influence the whole body (for instance spine, intestine, urogenital system) by stimulating the according points, usually by using needles. The applied stimuli are transferred to the central nervous system, which seems to enable effective treatment of various forms of pain.[36] Figure 9 shows the anatomy of the outer ear according to the concept of the „inverted fetus“.[37]

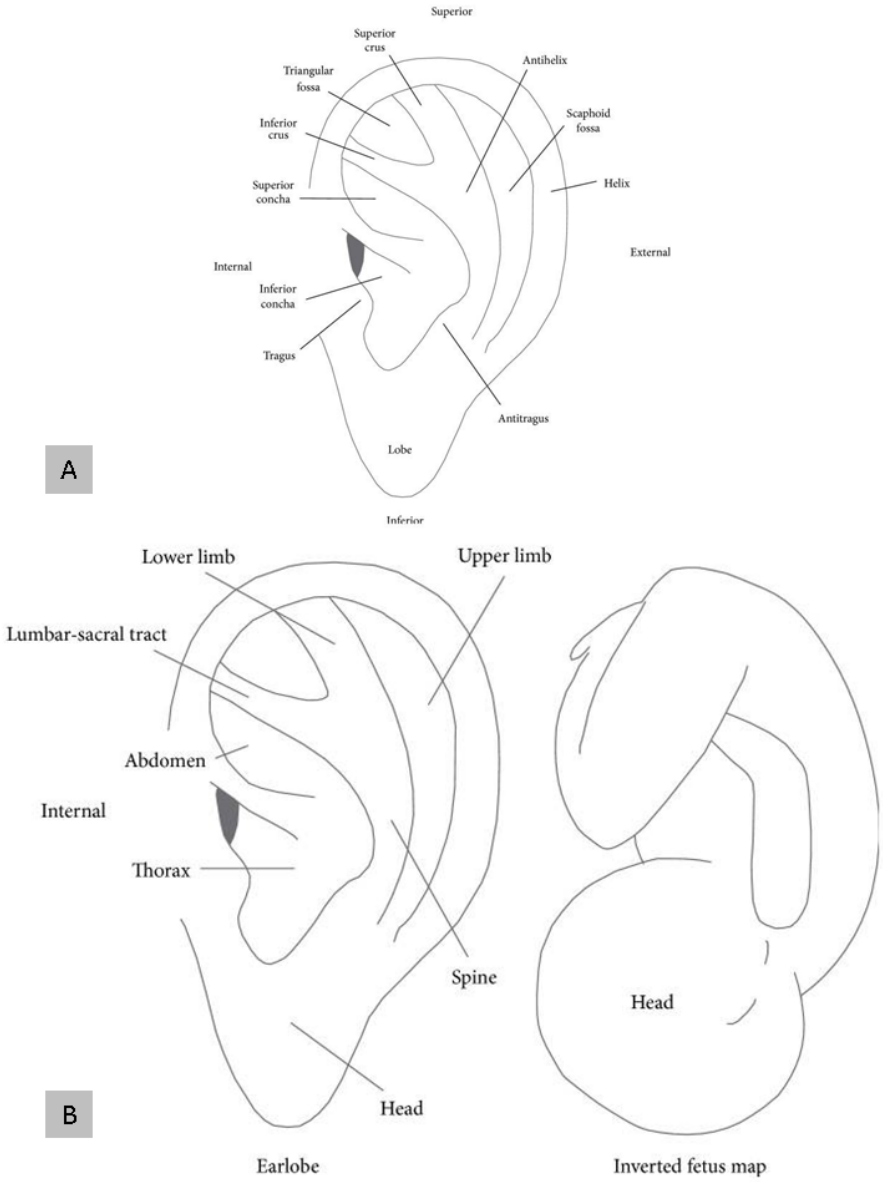


Figure 5: A: Anatomical structure of ear. B: Ear map as like an inverted fetus.[37] Reproduced from How PW et al. with permission of Hindawi.

In the past, attempts at enhancing the stimuli applied during acupuncture by using electric stimulation have increased. This so-called electroacupuncture seems to be superior to conventional acupuncture in case of chronic pains, such as knee osteoarthritis.[38] The stimulation of afferent nerve fibers utilizing a portable, battery-operated electroacupuncture device to be applied on the outer ear could already be shown to influence the walking distance of PAOD patients positively in an uncontrolled case series.[39] Also in the treatment of chronic low back pain the use of electrical stimulation of auricular acupuncture significantly improved long-term clinical outcome.[40]

Study aim

There are only a small number of therapeutic interventions available for patients with insufficient improvements after revascularization or exercise training, as well as for patients lacking the possibility for revascularization.

The aim of this study was to ascertain in a double-blinded randomized trial if transcutaneous auricular nerve stimulation in the area of the Fossa triangularis utilizing an electroacupuncture device is an effective conservative therapeutic alternative for lifestyle-limiting PAOD.[1]

Material and methods

Study design and patient population

In this prospective, double blinded trial the stimulation of afferent nerve fibers of the outer ear using an electroacupuncture device was carried out. The device is shown in Figure 7 (photo courtesy of the *Ducest Medical GmbH*).

In total, 40 patients with lifestyle-limiting PAOD in *Fontaine*-stage IIb were included. Per patient, 8 cycles of electroacupuncture were administered. A cycle consisted of 5 days, during which the device was implanted into the auricular region by means of an acupuncture needle (double needle, made of titanium, length 2mm, diameter 0.4 mm, distance between needles 2.5 mm), and thus was enabled to send electrical impulses to the *Ramus auricularis nervi vagii* in the *Fossa triangularis*. After 5 days the patients removed the device independently. Two days later, the re-application for another cycle on the opposite ear took place. The duration of device application constituted, therefore, a time-frame of 8 weeks (one week = one cycle = five days electroacupuncture + two days pause). Following a similar study, a stimulation period of 8 weeks was deemed sufficient.[40] In order to test the increase in walking distance at baseline (before the first device application), as well as after 4 and 8 weeks, a treadmill ergometry was performed. In addition, the WIQ as well as the SF-36 were used to assess changes of complaints. In order to avoid training effects, patients were asked not to change their daily activities. Furhtermore, arterial stiffness was measured at baseline and after 8 weeks.

Inclusion criteria were a written informed consent and a lifestyle-limiting PAOD due to calf-pain in *Fontaine-stage IIb* existing for at least 6 months. The diagnosis of a lifestyle-limiting PAOD was made by a vascular specialist according to valid guidelines.[13] Furthermore, at least one hemodynamically relevant vascular obstruction or vascular occlusion in the arterial femoro-popliteal area had to be verified with radiological imaging (MRA, CTA, DUS or DSA). Relevant exclusion criteria were a known symptomatic diabetic polyneuropathy, claudicatio spinalis, atrial fibrillation, therapy with prostanoids within the last 6 months, structured exercise training within the last 6 months, myocardial infarction within the last 6 months, stroke / transitory ischemic attack within the last 6 months, pregnancy, any kind of paralyses of the limbs, other implanted devices (pacemaker, implanted

cardioverter defibrillator, cardiac resynchronization therapy, implanted analgesics pump) as well as a known malignant neoplasia. Moreover, patients were not included in the trial if the walking distance was limited by other causes than intermittent claudication (e.g. dyspnoea or chest pain). In accordance with this double-blinded, two-sided study, 20 patients received a modified device which equaled a sham (control group). The other patient group (n=20) was provided with a fully functional device (verum group). The company *Biegler Medizinelektronik GmbH, Mauerbach, Austria, A-3001* was responsible for the production of the electroacupuncture devices. The blinding has been conducted by a clinical trial specialist who was not involved in patient care, and who had no access to the study data.[1]

The study as well as all related research was conducted at the division of angiology of the department of internal medicine, Medical University of Graz, Austria. The study was approved by the Institutional Review Board of the Medical University of Graz, Austria (EK Nr. 25-028 ex 12/13) and followed the guidelines of good scientific practice and the local ombuds committee.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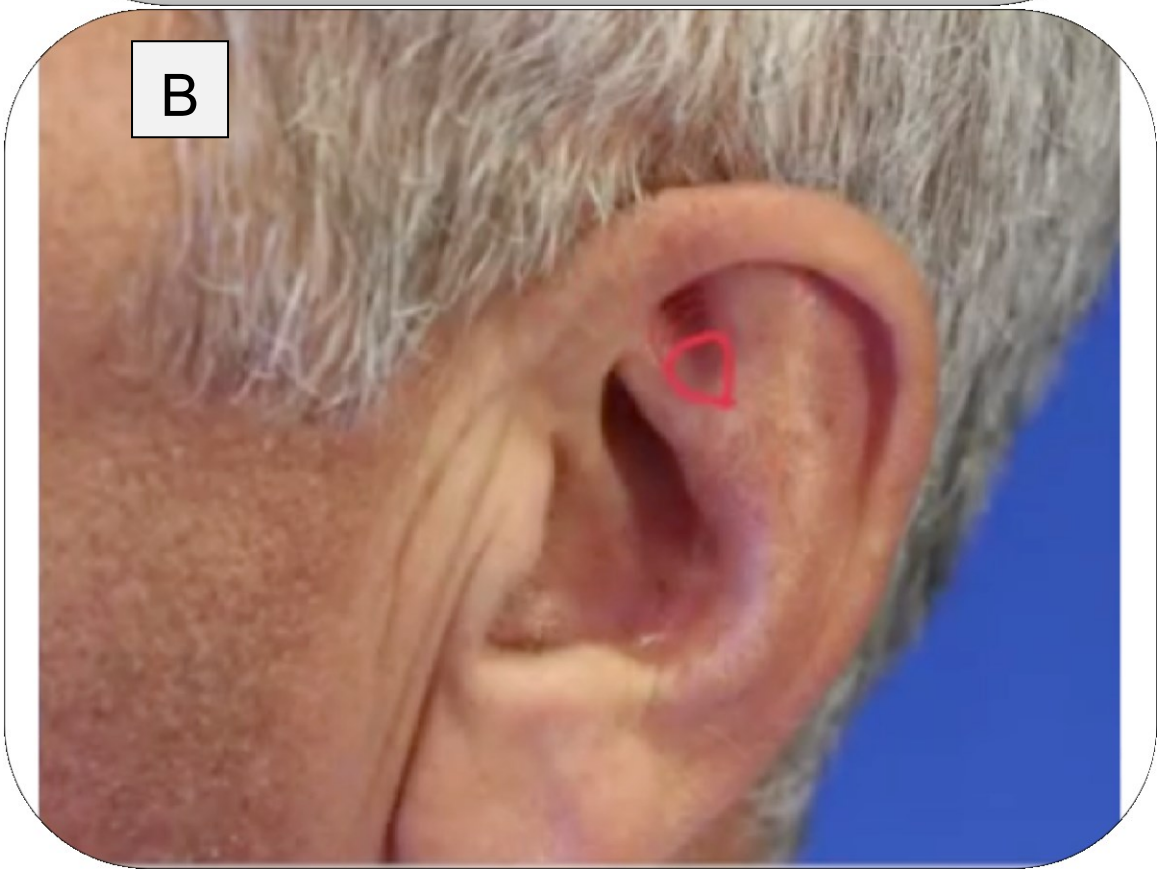
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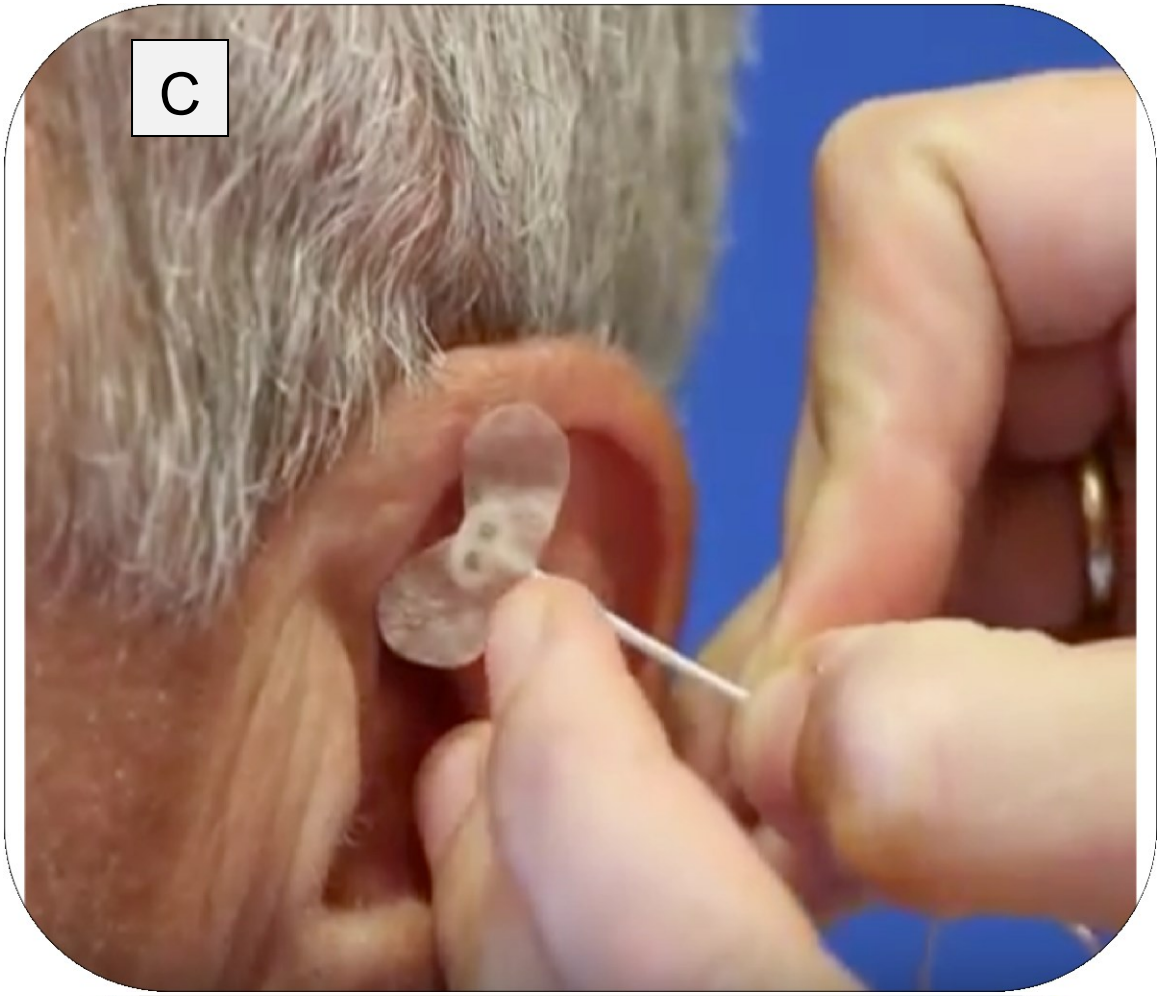
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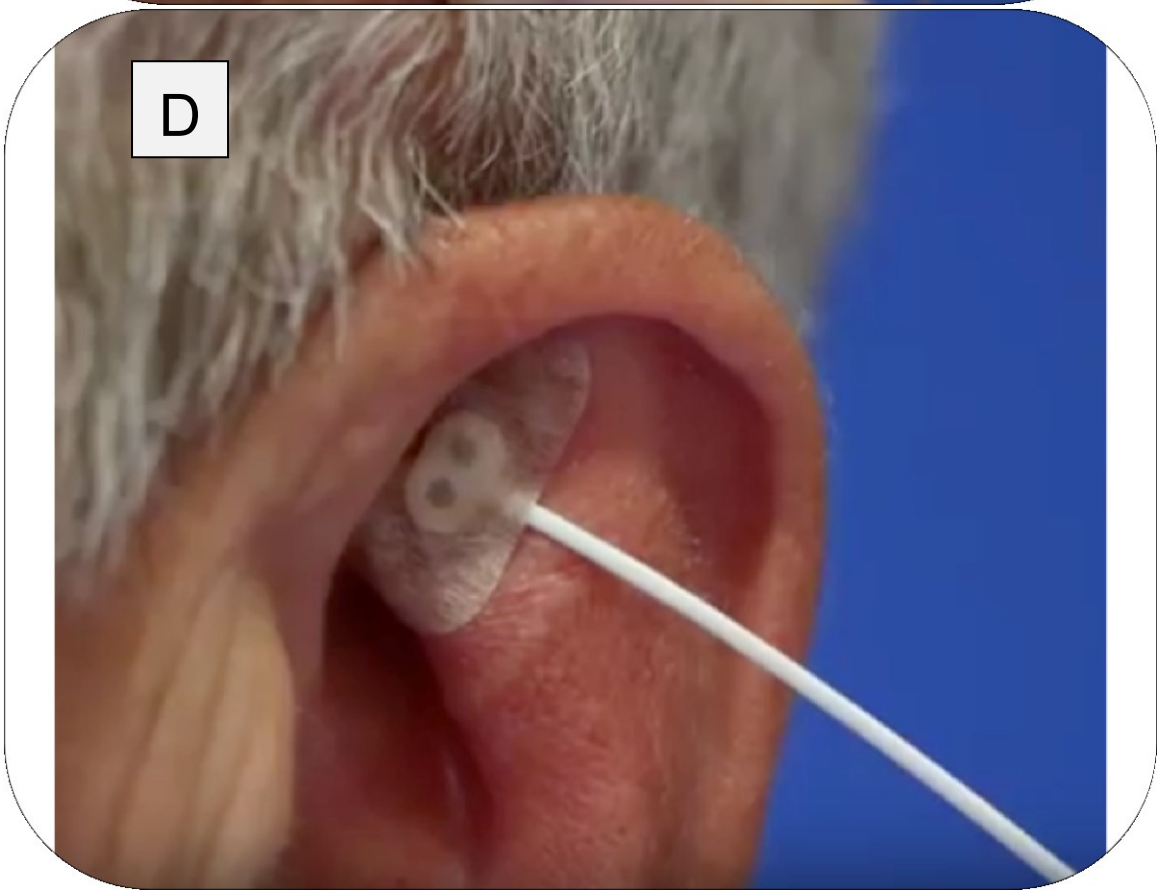
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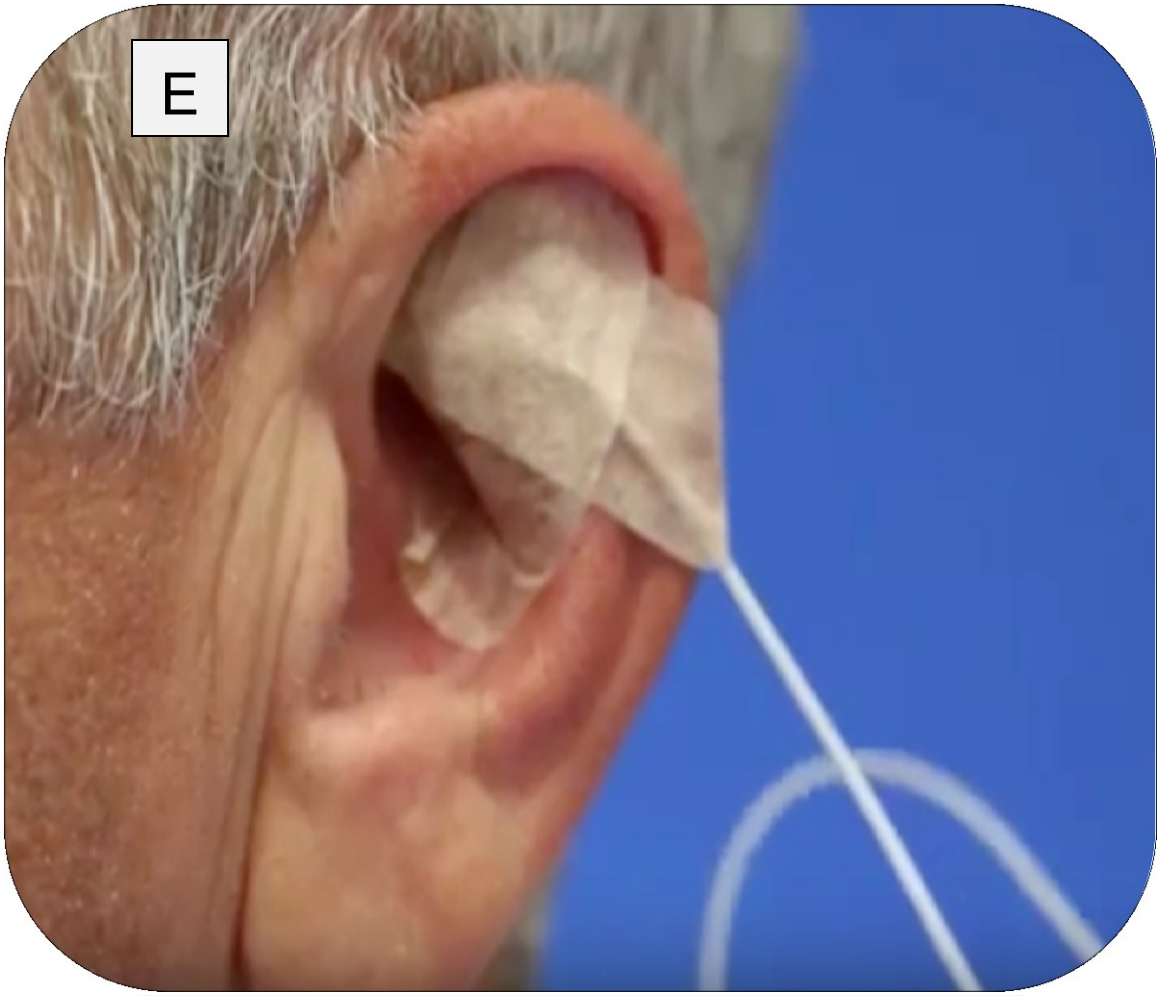
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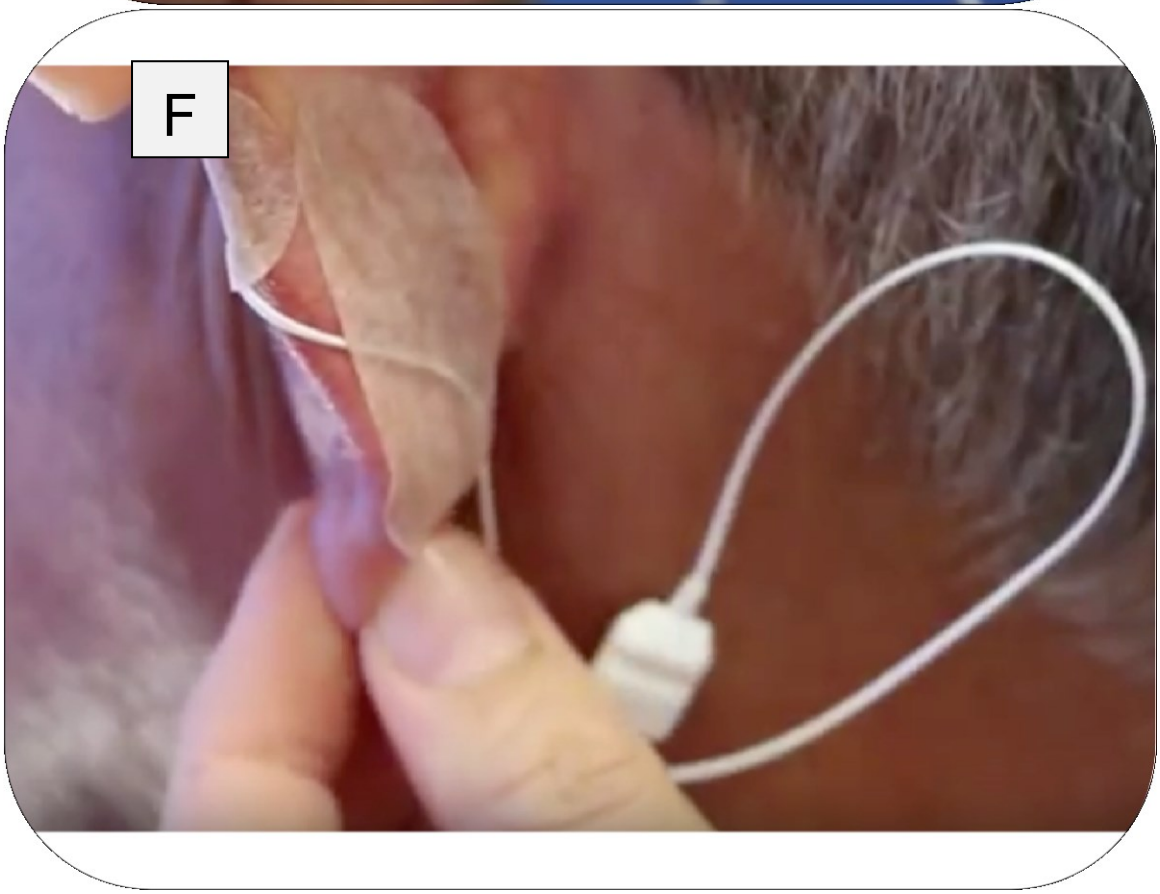
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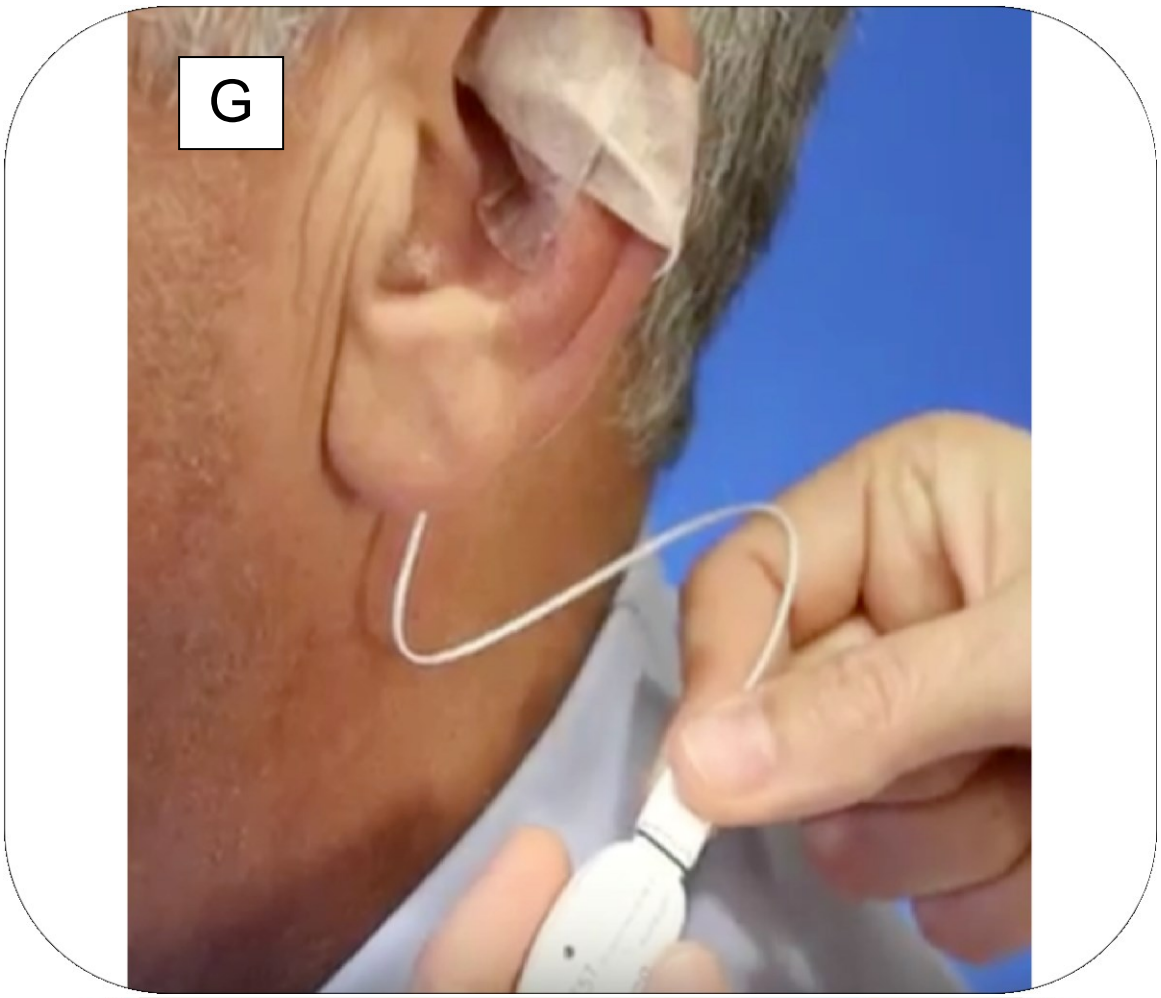
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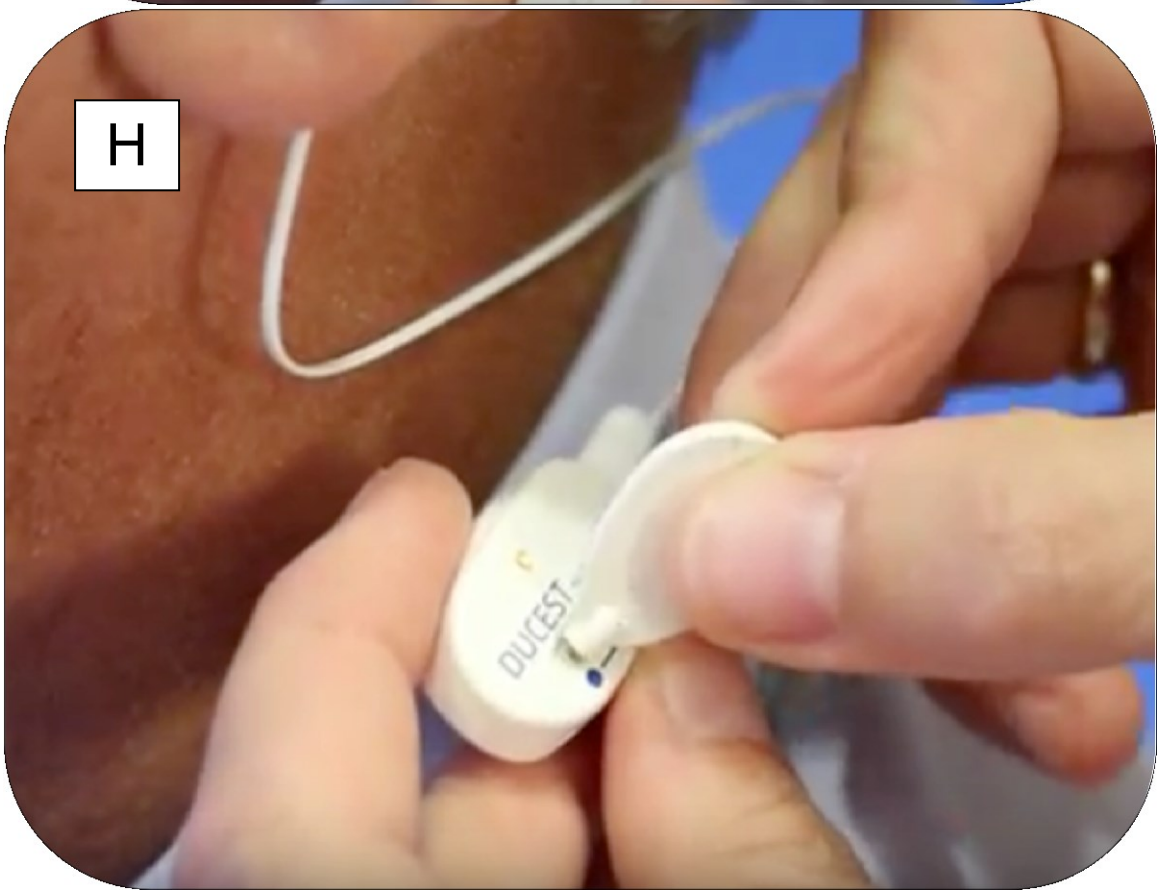
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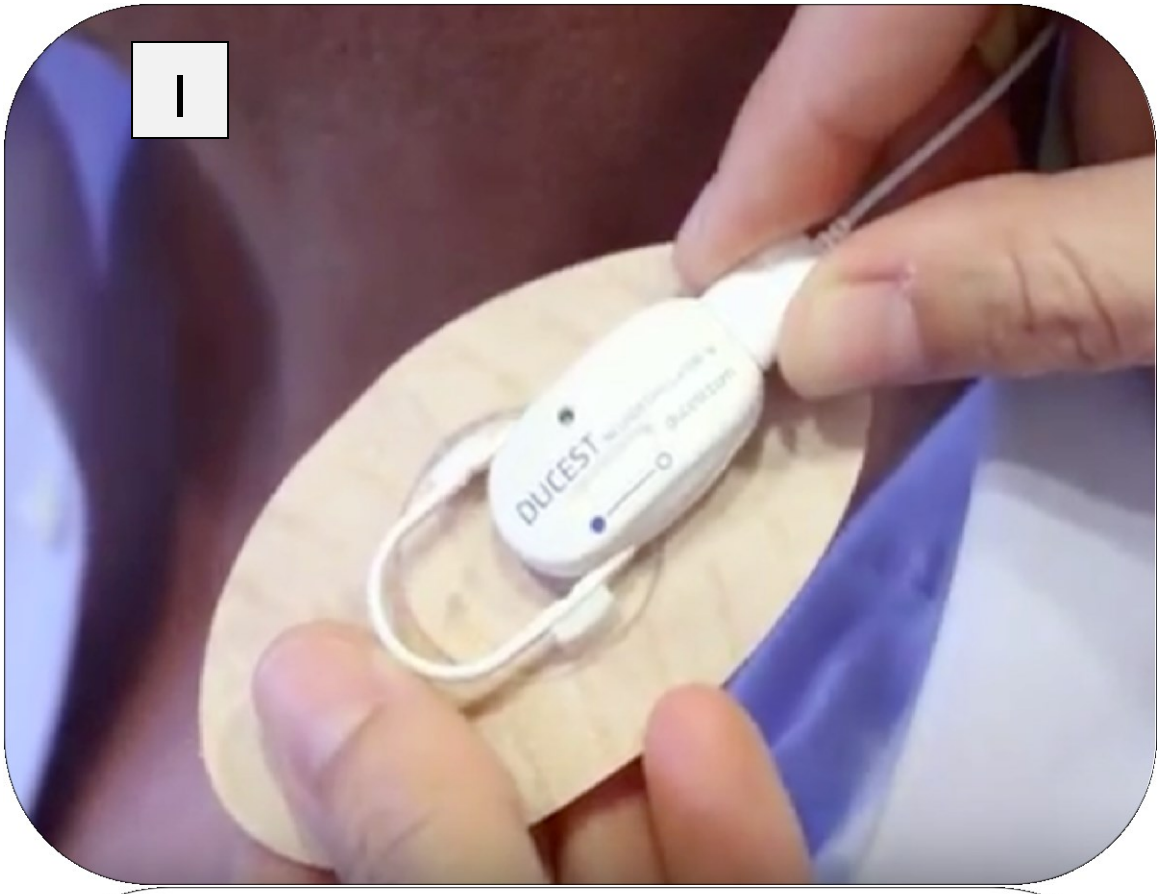
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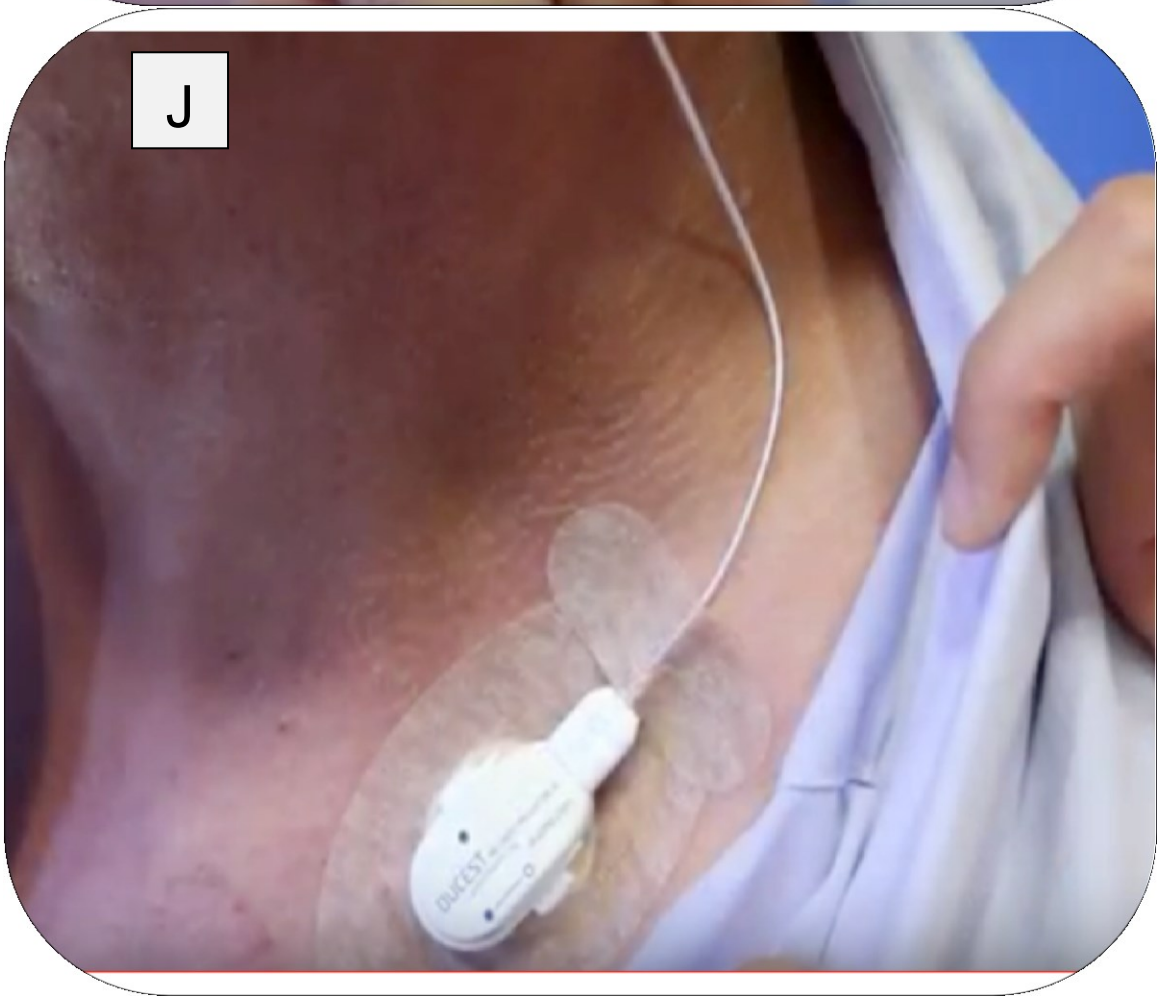
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Figure 6: Application of the device.

A. Various elements of a set (acupuncture needle with cable, device, holding clip, magnet pin, fixing plaster, disinfectant)
B. Outer ear with red marked *Fossa triangularis*
C. Placement of the acupuncture needle
D. Fixed acupuncture needle
E. Fixation from the front
F. Fixation from behind
G. Connection of the needle unit with the device
H. Adjusting stimulation intensity
I. Attachment of the device to the holding clip
J. The applied device

The device

The product was a portable, miniaturized, 3 V battery powered device that was used to stimulate the *Ramus auricularis nervi vagii* of the outer ear with an acupuncture needle. The needle unit consisted of a cable and an acupuncture needle. The needle unit was designed for one-time use (1 cycle), the device for use twice (2 cycles). The product was activated by plugging the needle unit into the device. Following activation, the display became unlit after 20 minutes and the keys were locked so no changes in settings could be made by the patients. The maximum dimensions of the device were width x height x depth 34 x 7 x 20 mm, the weight was 4.41 g including the battery. Using a special adhesive carrier, the device was attached to the body in the area of the *Trigonum clavipectorale* of the stimulated ear. The needle unit was fixed to the neck with a transparent patch so that it led to the outer ear almost invisibly. The starting signal was a series of unipolar square pulses. The pulse frequency was 1 Hertz, the pulse duration 200 µs, and the pulsed current ranged between 0-1,2 mA (adjustable in 16 levels at the maximum tension of 10 Volt). The current was chosen in a way that made the electric impulses noticeable for the patient without causing any pain. During the first application habituation effects took place within a few minutes, so that the electric stimulus could no longer subjectively be perceived. An operating duration of 40 minutes followed by a pause of 20 minutes took place in the verum. The sham device of the control group was visually identical to the verum device. After activation, however, the sham device only stimulated for 20 minutes before it switched off. Subsequently, the stimulation of the sham device was switched on every 12 hours for 1 minute. Thereby, the patient was given non-effective electric stimulation in order to minimize distinction between verum and sham. To check the blinding, patients were asked before unblinding whether they believed they had been given a verum or sham device. This question could be answered with "I believe to have received a verum", "I believe to have received a sham", or "I am not sure".[1]
Figure 7 shows the device (photo courtesy of the *Ducest Medical GmbH*).

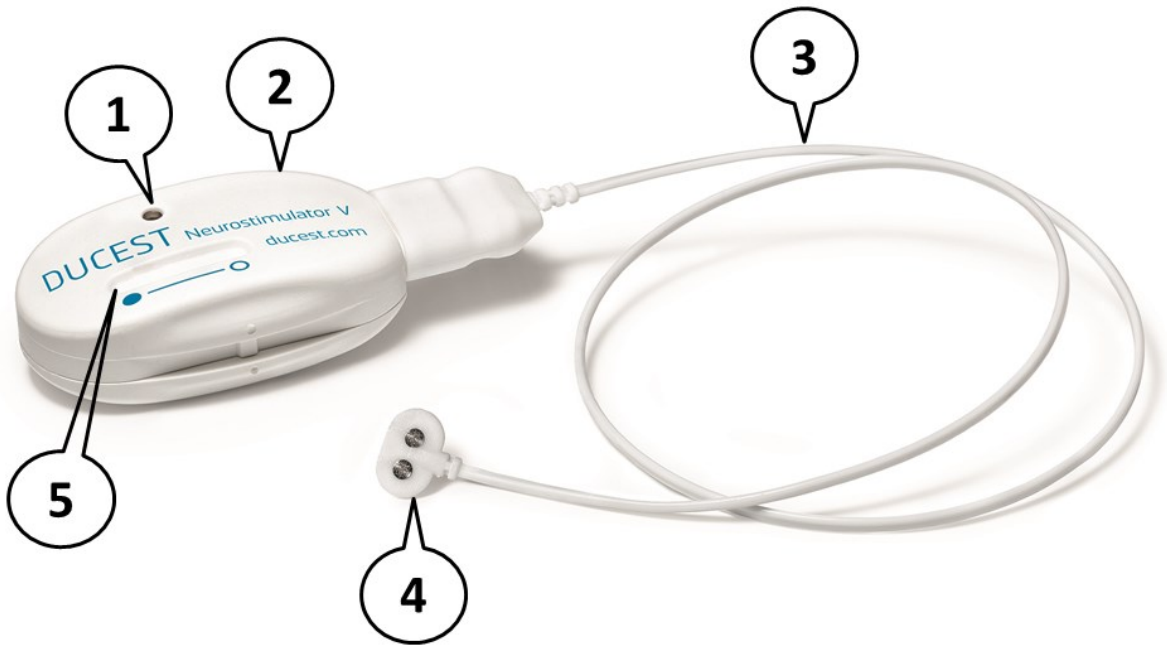

Figure 7: The device. *Ducest Neurostimulator V*®. Reproduced from the *Ducest Medical GmbH* with permission of the *Ducest Medical Gmbh*.

1: Control light

2: Processor for development of the electrical stimulus

3: Cable between the processor and the acupuncture needle

4: Twofolded acupuncture needle for placement in the *Fossa triangularis*

5: Guide channel to adjust the preferred intensity

Study endpoints

Primary endpoint: Significantly more frequent doubling of the maximum (absolute) walking distance (+100%) after 8 cycles (8 weeks) in the verum group compared to controls. Secondary endpoints: Statistically significant improvement of the total score of WIQ as well as statistically significant improvement of Health Related Quality of Life (HRQoL) based on SF-36 after 8 cycles (8 weeks) of therapy. Another secondary enpoint were statistically significant changes in arterial stiffness (aortic and brachial augmentation index, carotid-femoral pulse wave velocity) after 8 weeks between the groups.[1]

Treadmill testing

To objectify the walking distance, a treadmill ergometry *(Lode Valiant, Berger Medizintechnik GmbH, Gleisdorf, Austria)* using appropriate software *(CardioSoft, Version 6.7, GE Medical Systems GmbH, Munich, Germany)* was conducted. In the process, a graded treadmill test (G-test) was used under standard conditions. In accordance with the *Gardner* protocol, the test began at a 0% incline which was consecutively increased by 2% every 2 minutes. The speed remained constant at 3.2 km/hour.[41] The G-test has been preferable over a continuous test (C-test) with constant incline and speed because it has the highest reliability for the detection of the absolute walking distance in case of intermittent claudication.[42] Prior to the initial treadmill ergometry, the examiner demonstrated the correct walking technique. During the load, clinging to the lateral boundaries of the treadmill was avoided.[43] The absolute walking distance was quantified on the basis of the distance traveled at the end of the load test. The display of the walking distance was not visible to the patient.[1,43]

Figure 8: The treadmill ergometry.

WIQ

The WIQ was developed and validated specifically for patients with claudication to assess treatment effects on claudication-limited walking ability.[44]
In the present study the WIQ in German language using the European metric system was executed at baseline and after 8 weeks.[45] The questionnaire was self-administered by the patients and consisted of the 3 domains: walking distance (7 items), walking speed (4 items) and stair climb (3 items). For each separate domain a subscore was calculated. Each subscale had a range of 0% to 100% computed from the score of the respective domain divided by the maximum score of the domain multiplied by 100. The total score was defined as the mean of the three subscores.[1,44]

SF-36

The SF-36 health questionnaire is a disease-specific measuring instrument for assessing the HRQoL.[46] The SF-36 covers 8 dimensions, which are conceptually classified into the areas of "physical health" (Physical Function, Role Physical, Bodily Pain, General Health) and "mental health" (Mental Health, Role Emotional, Social Function, Vitality).[1] The questionnaire has proven useful in comparing general and specific populations, estimating the relative burden of different diseases, differentiating the health benefits produced by a wide range of different treatments, and screening individual patients.[47] Also in PAOD patients, especially in claudicants, the questionnaire has already been used to assess their HRQoL.[48] In the current study SF-36 was executed at baseline and week 8.[1]

Arterial stiffness

The vascular stiffness was measured using the *Vascular Explorer® (Enverdis GmbH, Jena, Germany)*. Two special blood pressure cuffs were used for this purpose. One cuff was applied to the upper limb and another to the lower limb. Then the carotid-femoral pulse wave velocity, the aortic- and the brachial- augmentation index were

automatically calculated by means of a photoplethysmography. The values were displayed on a standardized print out. All measurements were performed in supine position in the morning after 10 minutes of rest in a silent and 22-24°C temperatured room. Smoking was ommited for at least 6 hours.[1] Further information on the method were published elsewhere.[49,50]

Statistics

We performed an Intention-to-treat analysis. Descriptive statistics were conducted via explorative data analysis. To evaluate the distribution of continuous variables a Shapiro-Wilk test was used. In case of normal distribution a t-test was used to evaluate differences between the verum and control group. In case of non-parametrical data, a Mann Whitney U test was utilized. Qualitative variables were compared via crosstabs, as well as Chi Square and Fisher exact tests if indicated. Associations between variables were described using Pearson's correlation coefficients. To quantify the improvements in walking distance in each group from baseline to week 4 and week 8, Friedman tests were applied. Changes of WIQ and SF-36 were analyzed with Wilcoxon signed-rank Tests. Statistical analyses were exectued via IBM-SPSS version 23.0.[1]

Sample size calculation and randomization

The primary endpoint in the sense of a placebo effect was assumed to be up to 30% in the control group.[51,52] As there was no relevant preliminary data for electroacupuncture in PAOD patients an additional achievement of the primary endpoint in 50% of the verum participants compared to controls was assumed (+100% walking distance in 80% of the verum participants in total). In case of two sided testing for two independent samples using fisher´s exact test, a probability value of less than 0.05, a study power of 80%, and a possible dropout rate of 15%, a total sample size of 20 patients per group (40 patients total) was regarded as sufficient.

The devices (recognizable as verum or sham) were delivered by the manufacturing company to the randomizing person who was a clinical trial specialist, working at the Center for Clinical Research at the Medical University of Graz. The randomizer assigned the devices to the study participants after randomization in a 1:1 ratio using the research randomizer on http://www.randomizer.org with stratification for diabetics as well as beta-blocker therapy.[53] It was noted whether the device was a verum or a sham. The note was kept in a sealed envelope. The devices were then delivered to the clinical examiner, who used them on the patients without knowing whether the

device was a verum or a sham. The delivery and opening of the envelope to the clinical examiner took place after the study participant had completed the study, or had to leave the study prematurely for various reasons.[1]

Results

In the verum group one drop out occurred after two weeks of therapy because wearing the device was perceived as uncomfortable. The control group had two drop outs in total. One of these two patients suffered from progressive dizziness after three weeks of therapy. Within the following examinations, extended cerebral metastatic spread originating from a bronchial carcinoma was detected. The second premature study termination in the control group was caused by an AV Block III° that made the implantation of a pacemaker necessary (Figure 9).[1]

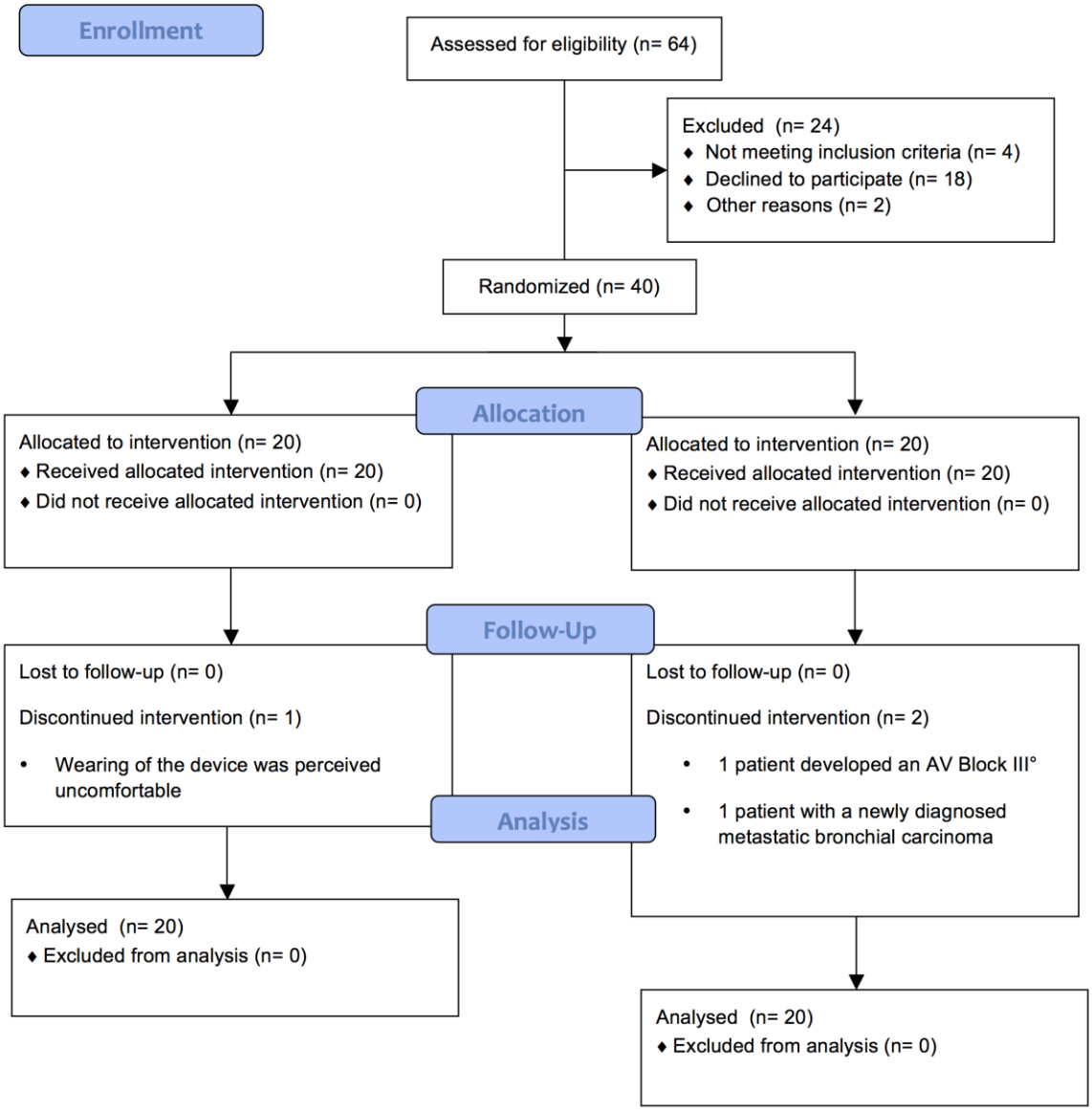

Figure 9: CONSORT Flow Diagram.[1] Reproduced from Hackl G et al. with permission of VASA.

Patients' baseline characteristics for each group are shown in Table 8.[1] No statistically significant differences could be observed.

	Control (n=20)	Verum (n=20)	p-Value
Men, n (%)	11 (55)	15 (75)	0.32
Age (yrs), mean (± SD)	66 (± 8)	65 (± 9)	0.71
Coronary artery disease, n (%)	8 (40)	9 (45)	1.00
Prior Myocardial infarction, n (%)	6 (30)	4 (20)	0.72
Prior Stroke, n (%)	5 (25)	2 (10)	0.41
Arterial hypertension, n (%)	20 (100)	20 (100)	1.00
Diabetics, n (%)	7 (35)	6 (30)	1.00
Body mass index (kg/m^2), mean (± SD)	27 (± 3)	29 (± 4)	0.07
Hypercholesterolaemia†, n (%)	18 (90)	18 (90)	1.00
Smokers, n (%)	8 (40)	8 (40)	1.00
Prior malignant neoplasia, n (%)	0 (0)	1 (5)	1.00
Complaint-causing lesion‡, n (%)			
Common femoral artery	5 (25)	8 (40)	0.50
Superficial femoral artery	10 (50)	8 (40)	0.75
Popliteal artery	4 (20)	1 (5)	0.17
Femoro-popliteal Bypass	1 (5)	3 (15)	0.61
Duration of lifestyle-limiting claudication (months), median (25^{th}-75^{th} percentile)	16 (6-108)	24 (6-120)	0.62
Medication, n (%)			

Beta-blockers	14 (70)	12 (60)	0.74
Alpha-blockers	4 (20)	2 (10)	0.66
ACE-I/ARB	12 (60)	10 (50)	0.75
Platelet aggregation	16 (80)	18 (90)	0.66
Oral anticoagulation	4 (20)	2 (10)	0.66
Statins	20 (100)	20 (100)	1.00
Insulin	3 (15)	3 (15)	1.00
Oral antidiabetics	3 (15)	4 (20)	1.00
Ankle brachial index*, mean (± SD)			
Dorsal pedis artery	0.60 (± 0.37)	0.52 (± 0.35)	0.51
Posterior tibial artery	0.56 (± 0.33)	0.50 (± 0.39)	0.64
Baseline laboratory values, median (25^{th}-75^{th} percentile)			
Hemoglobin g/dL	13.8 (12.7-14.0)	14.3 (13.5-14.7)	0.17
Platelets g/L	226 (213-279)	237 (188-280)	0.99
Leucocytes *10^9/L	7.4 (6.4-8.7)	6.8 (6.4-7.6)	0.20
eGFR mL/min/1.73 m^2	78 (40-88)	76 (61-92)	0.36
CRP mg/L	3.7 (1.3-5.8)	2.1 (1.1-5.2)	0.25
Nt-pro-BNP pg/ml	165 (79-275)	85 (43-213)	0.14

Table 8: Patients`characteristics.[1] Reproduced from Hackl G et al. with permission of VASA.

† Low density lipoprotein > 100 mg/dl before statin mediaction

‡ Unilateral symptoms

* Measured on the affected leg in resting position

All patients were asked for their estimated walking distance at baseline. The average was 194 [95% CI 135-254] meters and correlated significantly with the average initial walking distance measured on the treadmill ergometer (171 [95% CI 135-206] meters), r=0.42, p=0.01.

The mean initial walking distance on the treadmill ergometer of the verum group was 182 [95% CI 128-236] meters. After 4 weeks of electroacupuncture, the average walking distance was 274 [95% CI 182-366] meters (+51%) (p=0.01). After 8 weeks of therapy, the average walking distance increased to 345 [95% CI 227-463] meters (+90% from baseline) (p<0.01). In the control group, the mean initial walking distance was 159 [95% CI 109-210] meters. After 4 weeks (mean) 205 [95% CI 151-258] meters (+29 %) (p=0.06) and after 8 weeks (mean) 268 [95% CI 182-366] meters (+69% from baseline) (p=0.01). A comparison between the increase in walking distance of the two groups did not show a significant difference (p=0.46, Figure 10).[1]

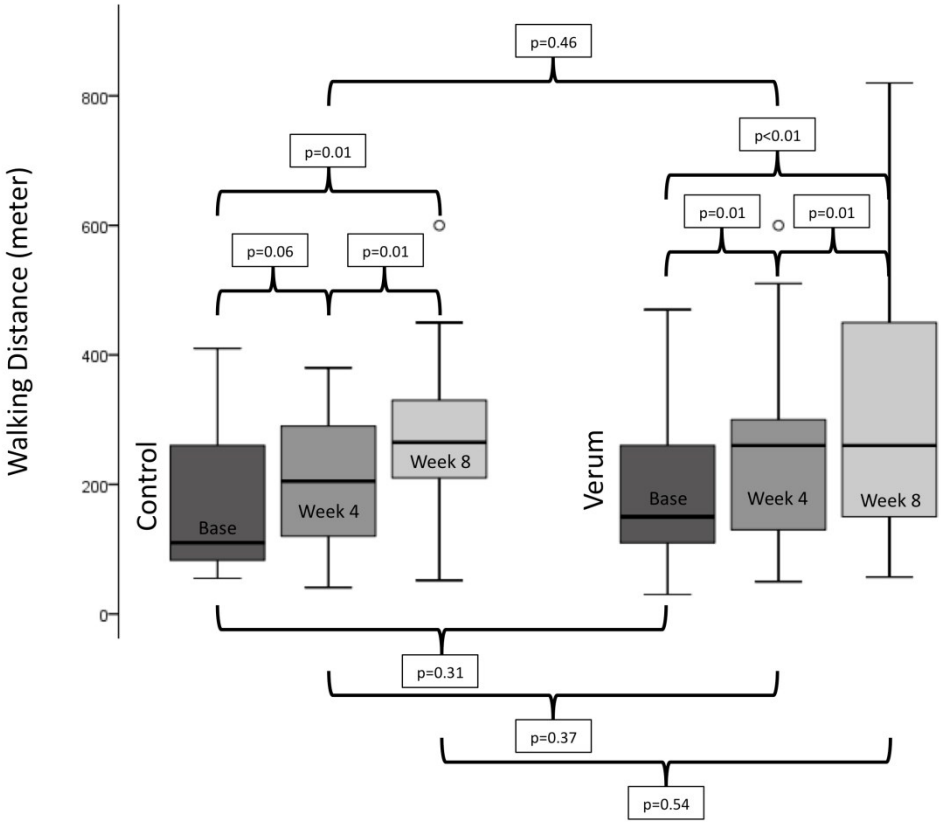

Figure 10: Boxplots demonstrating the walking distances at different time points. The boxes represent the 25th to 75th percentile. The whiskers indictae the 1.5x Interquartile-range.[1] Reproduced from Hackl G et al. with permission of VASA.

The primary endpoint of doubling the walking distance was reached in case of 12 out of 20 patients (60%) in the verum group, and in 5 out of 20 patients (25%) in the control group. The resulting p-value was at the significance level (p=0.05).[1]

The total score of the walking impairment questionnaire after 8 weeks was significantly associated with the absolute walking distance at week 8 (r=0.55, p<0.01). The following changes were observed in the verum group after 8 weeks: walking distance +8% (p=0.31), walking speed +36% (p=0.01), stair climb +26% (p=0.03), total score +22% (p=0.01). Changes in controls were as follows: walking distance +6% (p=0.66), walking speed +3% (p=0.75), stair climb +17% (p=0.12), total score +8% (p=0.56) (Table 9).[1]

WIQ categories	Verum* (Baseline)	Verum* (Week 8)	p-value†	Changes (%)
Walking distance	60 (± 22)	65 (± 24)	0.31	+8
Walking speed	39 (± 18)	53 (± 20)	0.01	+36
Stair climb	51 (± 26)	64 (± 27)	0.03	+26
Total	**50 (± 20)**	**61 (± 21)**	**0.01**	**+22**
	Control* (Baseline)	Control* (Week 8)		
Walking distance	53 (± 26)	56 (± 28)	0.66	+6
Walking speed	39 (± 21)	40 (± 24)	0.75	+3
Stair climb	52 (± 30)	61 (± 32)	0.12	+17
Total	**48 (± 23)**	**52 (± 25)**	**0.56**	**+8**

Table 9: Results of the WIQ.[1] Reproduced from Hackl G et al. with permission of VASA.

*Means (± Standard deviation)

†Baseline vs. Week 8 (Wilcoxon signed-rank test)

SF-36 showed the following changes after 8 weeks in the verum group: Physical Function +26% (p=0.01), Role Physical +239% (p=0.01), Bodily Pain +33% (p=0.02), General Health +10% (p=0.44), Mental Health +20% (p=0.01), Role Emotional +105% (p=0.01), Social Function -4% (p=0.68), Vitality +10% (p=0.20). Changes in controls were: Physical Function +13% (p=0.12), Role Physical -12% (p=0.38), Bodily Pain +46% (p=0.01), General Health +9% (p=0.29), Mental Health 0% (p=0.87), Role Emotional -5% (p=0.68), Social Function +10% (p=0.30), Vitality -4% (p=0.63) (Table 10).[1]

Categories	Baseline	Week 8	p-value†	Changes (%)
Physical Funtion				
Verum*	51 (± 14)	64 (± 15)	0.01	+26
Control*	48 (± 21)	54 (± 25)	0.12	+13
Role Physical**				
Verum*	18 (± 27)	61 (± 44)	0.01	+239
Control*	43 (± 36)	38 (± 32)	0.38	-12
Bodily Pain				
Verum*	42 (± 19)	56 (± 22)	0.02	+33
Control*	37 (± 24)	54 (± 24)	0.01	+46
General Health				
Verum*	52 (± 16)	57 (± 19)	0.44	+10
Control*	56 (± 19)	61 (± 18)	0.29	+9
Mental Health				
Verum*	65 (± 17)	78 (± 18)	0.01	+20
Control*	68 (± 21)	68 (± 22)	0.87	0

Role Emotional				
Verum*	42 (± 19)	86 (± 32)	0.01	+105
Control*	60 (± 45)	57 (± 46)	0.68	-5
Social Function				
Verum*	80 (± 27)	77 (± 28)	0.68	-4
Control*	69 (± 28)	76 (± 28)	0.30	+10
Vitality				
Verum*	49 (± 20)	54 (± 18)	0.20	+10
Control*	55 (± 22)	53 (± 19)	0.63	-4

Table 10: Results of the SF-36 questionnaire.[1] Reproduced from Hackl G et al. with permission of VASA.

*Means (± Standard deviation)

**p-value of Role Physical between verum and controls at baseline =0.04 (Mann Whitney U test)

† Baseline vs. Week 8 (Wilcoxon signed-rank test)

Changes of “Physical Health” differed significantly between verum and control group after 8 weeks (p=0.04; subgroups: Physical Function [p=0.31], Role Physical [p=0.01], Bodily Pain [p=0.52], General Health [p=0.80]). Significant changes between verum and control group were also observed for “Mental Health” (p=0.03; subgroups: Mental Health [p=0.04], Role Emotional [p=0.31], Social Function [p=0.48], Vitality [p=0.25]). Furthermore, “Physical health” was significantly associated with “mental health”(r=0.42, p=0.01) as well as with absolute walking distance after 8 weeks (r=0.37, p=0.03).[1]

With respect to arterial stiffness, baseline values were not significantly different between the groups whereas a significant difference after 8 weeks in the aortic- as well as in the brachial- augmentation index could be observed ($p<0.01$ and $p<0.01$). The carotid-femoral pulse wave velocity was lower in the verum group after 8 weeks than in the control group, but the difference was not statistically significant ($p=0.11$).
Regarding to the blinding, the following results were objectified in the verum group: 9 patients (45%) believed they were given a verum, 1 patient (5%) believed in a sham, and 10 patients (50%) were undecided. Control group patients answered as follows: 6 patients (30%) believed they were given a verum and 2 patients (10%) thought they had received a sham. In the control group, as well, 12 patients (60%) were unsure. A statistical comparison of the three possible answers between the two groups did not yield a significant difference ($p=0.57$).[1]

Discussion

In the present study the acupuncture was executed in the *Fossa triangularis* to stimulate the *Ramus auricularis nervi vagii* in this area.

The *Ramus auricularis nervi vagii* is a nerve consisting of only afferent fibers that lead to the *Nucleus tractus solitarii*. As it is easily accessible due to its location on the outer ear it is a point suitable for the transcutaneous stimulation of the *Nervus vagus*.[54] This is followed by a switch to efferent vegetative nerve fibers, which enter the periphery. In this study it has been assumed that via this efferent autonomic nerve fibers from the *Nucleus tractus solitarii* an influence on the vasomotion in peripheral vessels and collateral vessels results.[55] Vasomotion is a rhythmically coordinated change in vascular diameter by contraction of smooth muscle cells, especially in small arteries and arterioles.[56] Various factors, especially the autonomous vegetative nervous system, influence the occurrence and extent of vasomotion in different ways.[57] Furthermore, the use of electroacupuncture has already shown in several animal studies that somatosensory inputs result in hemodynamic responses of small vessels.[58,59] The observed changes in vascular stiffness in this study would support this thesis. It has also been published that in the treatment of spinal stenosis acupuncture seems to have effects on QoL.[60] Therefore, several mechanisms like the induction of endogenous opiod relief or an increase in pain threshold have been discussed.[60,61] Also a transient change in the nerves blood flow during electroacupuncture could decrease complaints in this disease entity.[60,62] This mechanisms could potentially play a role in the electroacupuncture treatment of PAOD too.[1]

Interestingly, a significant increase in walking distance could be achieved whether a sham or verum device was used for acupuncture. Although the increase in walking distance by +21% was more pronounced in case of the verum group if compared to the control group, the difference between the two groups was statistically not significant. It appears that the observed increase in walking distance is most likely due to the known analgesic effects through acupuncture in the area of the *Fossa triangularis*, even without the application of additional electric stimuli. The reason for this is most likely the immediate vicinity of the *Ramus auricularis nervi vagii* to the well-known ear acupuncture point „shen-men“, which is also known as „heavenly

gate".[63] Traditional Chinese medicine in particular, has substantial data indicating that acupuncture of the „shen-men" point is associated with an improvement of complaints in case of anxiety, stress, depression, insomnia, pain, as well as addiction and detoxification.[64,65] Therefore, it would have been interesting to include a third group, without any acupuncture, as a control group.[1]

The primary endpoint of doubling the walking distance was achieved by 60% of the verum group patients, and by 25% of the control group. The primary endpoint was, however, not achieved by 40% of the verum group. This may be potentially attributed to the frequent non-responsiveness of the complex and intra-individual innervation in the area of the *Fossa triangularis*.[66] However, the *Fossa triangularis* is protected by the *Helix*, and was therefore perceived to be the most suitable location for acupuncture.[1] Stimulation in the area of the *Anthelix* or *Cymba conchae* would have been interesting as well because a stronger afferent vagus stimulation than in the *Fossa trinagularis* could be observed in these areas.[66] Additionally, a potential localization for stimulation might be found in the *Tragus* area, as a recent study on atrial fibrillation patients could show.[67] Due to the protrusions of the ear at the *Tragus* above, more frequent dislocations of the acupuncture needle were to be expected. With respect to the *Cymba conchae* 100% innervation by the *Ramus auricularis nervi vagii* was found in this area.[66] Due to the depth and narrowness of the *Cymba conchae* it was difficult to sufficiently affix the acupuncture needle to this area.

With regards to the increase in walking distance in both groups, a training effect is to be considered, although the study tried to minimize this effect. As a certain training effect was generally assumed, doubling of the walking distance was chosen to reach the primary endpoint.[1]

In comparison to vasodilatory substances such as Cilostazol, electroacupuncture seems to be comparable with an increase in walking distance of about 160 meters. Thus, the intake of Cilostazol 100mg twice a day over a period of several weeks only objectified an average increase of the walking distance of only 100 meters in a graded treadmill test.[68] The increase in walking distance that could be observed in

the verum group is also comparable to the one of a supervised walking training, the effect of which is an increase of about 150 meters.[32]

Furthermore, it seems that within the calculation of case numbers for the study the effect of electroacupuncture with an additional achievement of the primary endpoint of +50% in comparison to the control group was over-estimated. This led to a sample size of 20 patients per group, which was presumably too small. At the time the study was planned, no adequate comparative literature for the calculation of sample sizes was available.[1]

For the use of the total score of WIQ it was even published that, in case of claudicants, it can be used instead of a treadmill ergometry in order to assess the functional walking ability.[68] In the present study, the total score of WIQ was significantly improved by +22% in the verum group. This improvement is similar to results after walking training.[70] In the present study, the total score of WIQ was significantly correlated with the absolute walking distance. This once more underscores the clinical significance of this easily done questionnaire, in particular if the total score is used.[69] On the other hand, the observed significant increase in walking distance on treadmill ergometry in case of both groups could not be verified using the WIQ category "walking distance" as the increase of 8% in the verum group and 6% in controls was not statistically significant. However, only modest correlations between observed therapeutic effects and changes of the WIQ are known from other clinical trials.[1,71,72]

With regards to the surveyed HRQoL via the SF-36, the verum group showed a significant improvement in 6 of 8 categories after 8 weeks. In the control group, however, only significant improvements in the area of bodily pain could be achieved. Upon further investigation of the SF-36, a significant difference between verum and control group was observed in the category “role physical” at baseline. This significant difference results primarily from the low baseline values in the verum group. The reason for this poor physical role in verum group participants can not be clearly explained. Maybe this is due to the small sample sizes per group, which play an important role when using the SF-36.[73] Furthermore, the increase to a similar absolute value as in the control group after 8 weeks eventually led to massive

improvements in this category by >200 %. This also seems to influence the total category “physical health” to a certain degree. Interestingly, the subscales "general health" and "social function" do not show any relevant changes. This could be attributed to the fact that the subscale "general health" pays greater attention to emotional responses than to physical capabilities. Furthermore, the subscale "general health" consistently relates to social functions which may also be foregrounded by the lack of improvement on the subscale "social function".[74] Similar studies in PAOD patients could not objectify relevant influences on these subscales as well.[1,75,76]

Conclusion

In conclusion, we believe that our results are promising in an age of increasingly invasive and mechanically complex therapeutic options for PAOD patients. It seems to be possible to improve the complaints of intermittent claudication by using electroacupuncture in an easy way. It would also be possible to teach patients to self-apply the mentioned therapeutic device, which makes the method even more attractive.[1]

Limitations

The present study is a single center study with a small sample size. In order to investigate the present endpoints, in particular the increase in walking distance, further prospective and multi-centric studies utilizing larger patient cohorts should be conducted. In case of future studies, the inclusion of a third control group without any therapy in order to detect potential training effects would be of interest. Furthermore, a long-term follow-up would have been interesting concerning potential lasting effects. As there were no significant differences with regards to walking distance between verum and control group, other statistical analyses according potential confounders in the sense of regression analysis were not indicated. These would, however, become relevant when planning future studies. Finally, in future studies the primary endpoint should consider the absolute walking distance rather than only doubling as in the present study.[1]

Future perspectives

Within the framework of the present study further parameters were collected, which were not yet evaluated when drafting this thesis.

For example, the collected data on heart rate variability might be of interest. The heart rate variability was recorded within the scope of this study by means of 24 hour elctrocardiography (ECG) records. Heart rate variability is understood to mean physiological fluctuations in heart rate. Limited heart rate variability is a known and prognostically poor cardiovascular risk factor.[77]
Due to the afferent vagal stimulation performed in this study, a positive influence on the heart rate variability would be conceivable.

The heart rate variability measurements were combined with a 24 hour blood pressure measurement. As mentioned in the introduction, arterial hypertension is a known cardiovascular risk factor.[6-9] One of the basic pathophysiological parameter of essential arterial hypertension is sympathetic hyperactivity. Therefore, it would also be of interest to see whether antihypertensive effects can be observed with electroacupuncture.

Thus, these parameters are further interesting factors to investigate effects of electroacupuncture even more detailed with regard to their efficacy in PAOD patients.

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Appendix

Excerpt from the case report form

Laufbandergometrie (bei 3,2 km/h mit 12% Steigung)	
Symptom	**Gehstrecke (Meter)**
Eintreten von Claudicatio intermittens ab... **(Relative Gehstrecke)**	
Auftreten anderer Symptome ab... Welche?	
Abbruch der Belastung bei... **(Absolute Gehstrecke)**	

Abbruch wegen (bitte ankreuzen)

Claudicatio intermittens	
Dyspnoe	
Muskulärer Erschöpfung	
Stenokardien	
Andere Ursache Welche?	

Abbruch durch (bitte ankreuzen)

Untersucher	
Patient	

ABI RECHTS nach Belastung		
RR rechts	mmHg	
ATA	mmHg	
ATP	mmHg	

ABI LINKS nach Belastung		
RR links	mmHg	
ATA	mmHg	
ATP	mmHg	

Fragebogen zum Gesundheitszustand (SF-36)

(SF- 36 = Short Form 36, Fragebogen zur Erhebung des Gesundheitszstandes mit 36 Fragen)

1. Wie würden Sie Ihren Gesundheitszustand im Allgemeinen beschreiben ?
(Bitte kreuzen Sie nur eine Zahl an)

Ausgezeichnet	1
Sehr gut	2
Gut	3
Weniger gut	4
Schlecht	5

2. Im Vergleich zum vergangenen Jahr, wie würden Sie Ihren derzeitigen Gesundheitszustand beschreiben ?
(Bitte kreuzen Sie nur eine Zahl an)

Derzeit viel besser als vor einem Jahr	1
Derzeit etwas besser als vor einem Jahr	2
Etwa so wie vor einem Jahr	3
Derzeit etwas schlechter als vor einem Jahr	4
Derzeit viel schlechter als vor einem Jahr	5

3. Im folgenden sind einige Tätigkeiten beschrieben, die Sie vielleicht an einem normalen Tag ausüben. Sind Sie durch Ihren derzeitigen Gesundheitszustand bei diesen Tätigkeiten eingeschränkt ? Wenn ja, wie stark ?
(Bitte kreuzen Sie in jeder Zeile nur eine Zahl an)

TÄTIGKEITEN	Ja, stark eingeschränkt	Ja, etwas eingeschränkt	Nein, überhaupt nicht eingeschränkt
a. anstrengende Tätigkeiten, z.B. schnell laufen, schwere Gegenstände heben, anstrengenden Sport treiben	1	2	3
b. mittelschwere Tätigkeiten, z.B. einen Tisch verschieben, staubsaugen, kegeln, Golf spielen	1	2	3
c. Einkaufstaschen heben oder tragen	1	2	3

d. mehrere Treppenabsätze steigen	1	2	3
e. einen Treppenabsatz steigen	1	2	3
f. sich beugen, knien, bücken	1	2	3
g. mehr als 1 Kilometer zu Fuß gehen	1	2	3
h. mehrere Straßenkreuzungen weit zu Fuß gehen	1	2	3
i. eine Straßenkreuzung weit zu Fuß gehen	1	2	3
j. sich baden oder anziehen	1	2	3

4. Hatten Sie in den vergangenen 4 Wochen aufgrund Ihrer körperlichen Gesundheit irgendwelche Schwierigkeiten bei der Arbeit oder anderen alltäglichen Tätigkeiten im Beruf bzw. zu Hause ?
(Bitte kreuzen Sie in jeder Zeile nur eine Zahl an)

SCHWIERIGKEITEN	JA	NEIN
a. Ich konnte nicht so lange wie üblich tätig sein	1	2
b. Ich habe weniger geschafft als ich wollte	1	2
c. Ich konnte nur bestimmte Dinge tun	1	2
d. Ich hatte Schwierigkeiten bei der Ausführung (z.B. ich mußte mich besonders anstrengen)	1	2

5. Hatten Sie in den vergangenen 4 Wochen aufgrund seelischer Probleme irgendwelche Schwierigkeiten bei der Arbeit oder anderen alltäglichen Tätigkeiten im Beruf bzw. zu Hause (z.B. weil Sie sich niedergeschlagen oder ängstlich fühlten) ?
(Bitte kreuzen Sie in jeder Zeile nur eine Zahl an)

SCHWIERIGKEITEN	JA	NEIN
a. Ich konnte nicht so lange wie üblich tätig sein	1	2
b. Ich habe weniger geschafft als ich wollte	1	2
c. Ich konnte nicht so sorgfältig wie üblich arbeiten	1	2

6. Wie sehr haben Ihre körperliche Gesundheit oder seelischen Probleme in den vergangenen 4 Wochen Ihre normalen Kontakte zu Familienangehörigen, Freunden, Nachbarn oder zum Bekanntenkreis beeinträchtigt?
(Bitte kreuzen Sie nur eine Zahl an)

Überhaupt nicht	1
Etwas	2
Mäßig	3
Ziemlich	4
Sehr	5

7. Wie stark waren Ihre Schmerzen in den vergangenen 4 Wochen ?

(Bitte kreuzen Sie nur eine Zahl an)

Ich hatte keine Schmerzen	1
Sehr leicht	2
Leicht	3
Mäßig	4
Stark	5
Sehr stark	6

8. Inwieweit haben die Schmerzen Sie in den vergangenen 4 Wochen bei der Ausübung Ihrer Alltagstätigkeiten zu Hause und im Beruf behindert ?
(Bitte kreuzen Sie nur eine Zahl an)

Überhaupt nicht	1
Etwas	2
Mäßig	3
Ziemlich	4
Sehr	5

9. In diesen Fragen geht es darum, wie Sie sich fühlen und wie es Ihnen in den vergangenen 4 Wochen gegangen ist. (Bitte kreuzen Sie in jeder Zeile die Zahl an, die Ihrem Befinden am ehesten entspricht). Wie oft waren Sie in den vergangenen 4 Wochen...
(Bitte kreuzen Sie in jeder Zeile nur eine Zahl an)

BEFINDEN	Immer	Meistens	Ziemlich oft	Manchmal	Selten	Nie
a. ...voller Schwung	1	2	3	4	5	6
b. ...sehr nervös	1	2	3	4	5	6
c. ...so niedergeschlagen, daß Sie nichts aufheitern konnte?	1	2	3	4	5	6
d. ...ruhig und gelassen	1	2	3	4	5	6
e. ...voller Energie?	1	2	3	4	5	6
f. ...entmutigt und traurig	1	2	3	4	5	6
g. ...erschöpft	1	2	3	4	5	6
h. ... glücklich	1	2	3	4	5	6
i. ...müde	1	2	3	4	5	6

9. Wie häufig haben Ihre körperliche Gesundheit oder seelischen Probleme in den vergangenen 4 Wochen Ihre Kontakte zu anderen Menschen (Besuche bei Freunden, Verwandten usw.) beeinträchtigt?
(Bitte kreuzen Sie nur eine Zahl an)

Immer	1
Meistens	2
Manchmal	3
Selten	4
Nie	5

10. Inwieweit trifft jede der folgenden Aussagen auf Sie zu ?

(Bitte kreuzen Sie in jeder Zeile nur eine Zahl an)

AUSSAGEN	Trifft ganz zu	Trifft weitgehend zu	Weiß nicht	Trifft weitgehend nicht zu	Trifft überhaupt nicht zu
a. Ich scheine etwas leichter als andere krank zu werden	1	2	3	4	5
b. Ich bin genauso gesund wie alle anderen, die ich kenne	1	2	3	4	5
c. Ich erwarte, daß meine Gesundheit nachläßt	1	2	3	4	5
d. Ich erfreue mich ausgezeichneter Gesundheit	1	2	3	4	5

Walking Impairment Questionnaire (WIQ-German)

(Fragebogen zur Erfassung der Gehstrecke; WIQ – German: deutsche Version)

Die nachfolgenden Fragen beziehen sich auf die Gründe für Ihre Gehbehinderung. Wir möchten wissen, wie stark die nachfolgend angeführten Beschwerden und Probleme im Verlauf der vergangenen Woche zu Ihrer Gehbehinderung beigetragen haben. Bitte sagen Sie uns, wie schwierig oder anstrengend das Gehen für Sie war.

PAVK spezifische Fragen:

- **Schmerzen oder Krämpfe in Waden, Oberschenkel oder Gesäß ?**
  - Bein: rechts / links / beidseitig
  - Schwierigkeitsgrad:
    - Keine (4)
    - Leichte (3)
    - Mittelgradig (2)
    - Stark (1)
    - Sehr stark (0)

Schmerz oder Engegefühl in der Brust

- Ausmaß der Beschwerden:
  - Keine (4)
  - Leichte (3)
  - Mittelgradig (2)
  - Stark (1)
  - Sehr stark (0)

Kurzatmigkeit

- Ausmaß der Beschwerden:
  - Keine (4)
  - Leichte (3)
  - Mittelgradig (2)
  - Stark (1)
  - Sehr stark (0)

Herumspazieren im Hausinneren

- Schwierigkeiten beim Gehen:
  - Keine (4)
  - Leichte (3)
  - Mittelgradig (2)
  - Stark (1)
  - Sehr stark (0)

Gehstrecke 15 Meter

- Schwierigkeiten beim Gehen:
  - Keine (4)
  - Leichte (3)
  - Mittelgradig (2)
  - Stark (1)
  - Sehr stark (0)

Herzklopfen

- Ausmaß der Beschwerden:
  - Keine (4)
  - Leichte (3)
  - Mittelgradig (2)
  - Stark (1)
  - Sehr stark (0)

Sonstige Beschwerden

- Ausmaß der Beschwerden:
  - Keine (4)
  - Leichte (3)
  - Mittelgradig (2)
  - Stark (1)
  - Sehr stark (0)

Sonstige Beschwerden bitte anführen:

Gehstrecke 50 Meter

- Schwierigkeiten beim Gehen:
  - Keine (4)
  - Leichte (3)
  - Mittelgradig (2)
  - Stark (1)
  - Sehr stark (0)

Gehstrecke 90 Meter

- Schwierigkeiten beim Gehen:
  - Keine (4)
  - Leichte (3)
  - Mittelgradig (2)
  - Stark (1)
  - Sehr stark (0)

Gehstrecke 200 Meter

- Schwierigkeiten beim Gehen:
  - Keine (4)
  - Leichte (3)
  - Mittelgradig (2)
  - Stark (1)
  - Sehr stark (0)

Gehstrecke 300 Meter

- Schwierigkeiten beim Gehen:
  - Keine (4)
  - Leichte (3)
  - Mittelgradig (2)
  - Stark (1)
  - Sehr stark (0)

Gehstrecke 450 Meter

- Schwierigkeiten beim Gehen:
  - Keine (4)
  - Leichte (3)
  - Mittelgradig (2)
  - Stark (1)
  - Sehr stark (0)

100 Meter bei schnellem Gehtempo

- Schwierigkeitsgrad:
  - Keine (4)
  - Leichte (3)
  - Mittelgradig (2)
  - Stark (1)
  - Sehr stark (0)

100 Meter rennen oder joggen

- Schwierigkeitsgrad:
  - Keine (4)
  - Leichte (3)
  - Mittelgradig (2)
  - Stark (1)
  - Sehr stark (0)

100 Meter langsames Gehen

- Schwierigkeitsgrad:
  - Keine (4)
  - Leichte (3)
  - Mittelgradig (2)
  - Stark (1)
  - Sehr stark (0)

100 Meter bei mittlerem Gehtempo

- Schwierigkeitsgrad:
  - Keine (4)
  - Leichte (3)
  - Mittelgradig (2)
  - Stark (1)
  - Sehr stark (0)

1 Stockwerk

- Schwierigkeitsgrad:
  - Keine (4)
  - Leichte (3)
  - Mittelgradig (2)
  - Stark (1)
  - Sehr stark (0)

2 Stockwerke

- Schwierigkeitsgrad:
  - Keine (4)
  - Leichte (3)
  - Mittelgradig (2)
  - Stark (1)
  - Sehr stark (0)

3 Stockwerke

- Schwierigkeitsgrad:
  - Keine (4)
  - Leichte (3)
  - Mittelgradig (2)
  - Stark (1)
  - Sehr stark (0)