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ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

Peripheral ARtery Atherosclerotic DIsease and SlEep disordered breathing (PARADISE) trial — protocol for an observational cohort study

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Abstract

Background: Peripheral arterial disease (PAD) is in fact a group of disease entities with different symptoms and course but a common underlying cause, i.e. atherosclerosis. Atherosclerosis is known to be aggravated by several cardiovascular risk factors, including obstructive sleep apnoea (OSA).

Aim: Following paper is a protocol for the Peripheral ARtery Atherosclerotic DIsease and SlEep disordered breathing (PARADISE) trial, which aims to describe the prevalence of OSA in PAD patients scheduled for revascularisation, and to determine the effect of OSA on the procedure outcomes.

Methods: The PARADISE study is an observational cohort trial. It plans to include 200 consecutive patients hospitalised for revascularisation due to PAD. In every patient an overnight sleep study will be performed to diagnose sleep disorders. According to the results of the test, patients will be divided into two groups: group A — patients with OSA, and group B — patients without OSA (control group). All patients will also be screened for classical and non-classical cardiovascular risk factors. In some of the patients, during surgery, a fragment of atherosclerotic plaque will be collected for further testing. Patients will be followed for one year for adverse events and end-points. Primary end-point of the study will be the failure of revascularisation defined as recurrence or new onset of the symptoms of ischaemia from the treated region, a need for re-operation or procedure revision, or recurrence of ischaemia signs on the imaging tests.

Discussion: The data obtained will help determine the incidence of OSA in the population of patients with PAD. The authors expect to show that, as with other cardiovascular diseases associated with atherosclerosis, also in patients with PAD the incidence of undiagnosed OSA is high and its presence is associated with elevated cholesterol, inflammatory markers, and higher prevalence of arterial hypertension and poor control of other cardiovascular risk factors. In addition, due to increased oxidative stress and vascular endothelial injury associated with OSA, patients afflicted with this condition will not only have more advanced atherosclerotic lesions, but also in their histopathological examination their atherosclerotic plaque will exhibit evidence of greater instability and adverse morphology. We also expect to show that in patients with OSA, achieving correct control of cardiovascular risk factors will be more difficult. The study may improve PAD control through assuring better multispecialty care in PAD patients.

Key words: peripheral artery disease, obstructive sleep apnoea, clinical trial protocol

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INTRODUCTION

Peripheral arterial disease (PAD) is in fact a group of disease entities with different symptoms and courses but a common underlying cause, i.e. atherosclerosis. Regardless of the location of the arteriosclerosis, the course of its formation is similar in each case. The process begins in vessels in which vascular endothelial dysfunction occurs due to flow disruption and increased shear stress caused by flowing blood or on-going inflammatory reaction. With time, the lipid plaque develops markedly and progresses in the surrounding cells and extracellular matrix, in the last stage giving atherosclerotic plaque that permanently narrows the lumen of the vessel [1, 2].

For PAD, the two main goals of therapy are the most important. First, the need to reduce the onerous symptoms, and to reduce the increased cardiovascular (CV) risk [3]. Some of the drugs traditionally used in alleviating intermittent claudication have a modest effect, and the field of application is limited according to current guidelines [3]. Second, in patients with PAD, particular attention is paid to the control of CV risk factors. This is due to the fact that the more extensive the atherosclerosis is, the greater the risk of CV death, stroke, and heart attack [4].

On the other hand, obstructive sleep apnoea (OSA) is one of the most common sleep disorders that can occur at any age [5]. The essence of OSA is the collapse of the upper respiratory tract, primarily due to a decrease in the muscle tone of their walls. In addition to the obvious impact on patients' quality of life, including sleep quality and daytime sleepiness, OSA also has a significant impact on the risk of CV events. This relationship has already been described in so much detail that OSA is currently considered, in addition to classical factors such as dyslipidaemia, hypertension, obesity, and older age, as a CV risk factor [6].

The observed dependence is due to the multidirectional, complex effect of OSA on almost all CV risk components. The most important ones include arterial hypertension, including resistant hypertension, and atherosclerotic diseases such as stroke or heart attack. Oxidative stress, chronic inflammation, and hypertension caused by OSA translate into damage to vascular endothelium and slowly promote the development of atheromatous plaques and consequently, for example, myocardial infarction [7, 8]. This not only negatively affects the quality of life of the patient, but is also a sign that atherosclerosis has already covered other vascular placements — in this case the pelvic arteries and the penis [9, 10].

In patients with OSA, each subsequent apnoea results in deeper hypoxia and hypercapnia. Over the course of the night, patients with OSA develop several to several hundred long-term hypoxia events, which must cause changes throughout the CV system. Hypoxia causes a number of changes at both cellular and molecular levels. It was found to be related to changes in the CD4+ / CD8+ T cell count, increased neutrophil counts, and increased secretion of proinflammatory cytokines (increase in interleukin — IL-1b and IL-6). Repetitive episodes of hypoxia can fix such changes in the immune system [11–13]. In addition, hypoxia is associated with a change in cervical voltages, which directly affects blood pressure, and leads to increased production of reactive oxygen species, which in turn stimulate changes in intracellular calcium. It leads to further changes in the function of cardiomyocytes, the cardiac conduction system, and endothelial cells. At present, more questions about the OSA's association with the prognosis of patients with PAD remain open, as are the answers to the OSA and PAD relationship, and their impact on the efficacy of treatment for both diseases.

METHODS/DESIGN

Study design

This study is an observational cohort study. The study plans to include 200 consecutive patients hospitalised in the Department of General and Endocrine Surgery of the Medical University of Warsaw for revascularisation due to PAD (including stenting or endarterectomy of the carotid artery and stenting, local endarterectomy, or lower limb artery bypass). Patients will have been previously qualified for this type of treatment by vascular surgeons, and the presence of PAD must be confirmed by clinical findings. In every patient, an overnight sleep study will be performed using a portable device for diagnosing sleep disorders. According to the results of the test, patients will be divided into two groups: group A — patients with OSA, and group B — patients without OSA (control group) (Fig. 1).

Aims of the study

- Determining the prevalence of OSA in the population of patients undergoing revascularisation due to PAD.
- Assessment of the prevalence of CV risk factors in patients with coexisting PAD and OSA.
- Determining the effect of OSA on the extent of atheromatous lesions and the composition and morphology of atherosclerotic plaque taken from the examined patients.
- Assessment of the effect of OSA on long-term effectiveness of revascularisation and risk of adverse CV events in patients with PAD.

Overview

In the first stage of the study, during hospitalisation in the preoperative period, in the Department of General and Endocrine Surgery, in all patients included in the study, in addition to standard patient examination, the collection of information on CV risk factors will be made.

From each patient, 10 mL of venous blood will be collected for assessment of biomarkers of atherogenesis and inflammation, including growth factors, cholesterol, C-reactive protein, interleukin, and others. All patients will also be tested for sleep apnoea. At the next stage of the study, from patients undergoing revascularisation, a small portion of the atherosclerotic plaque from the treated vessel will be collected.

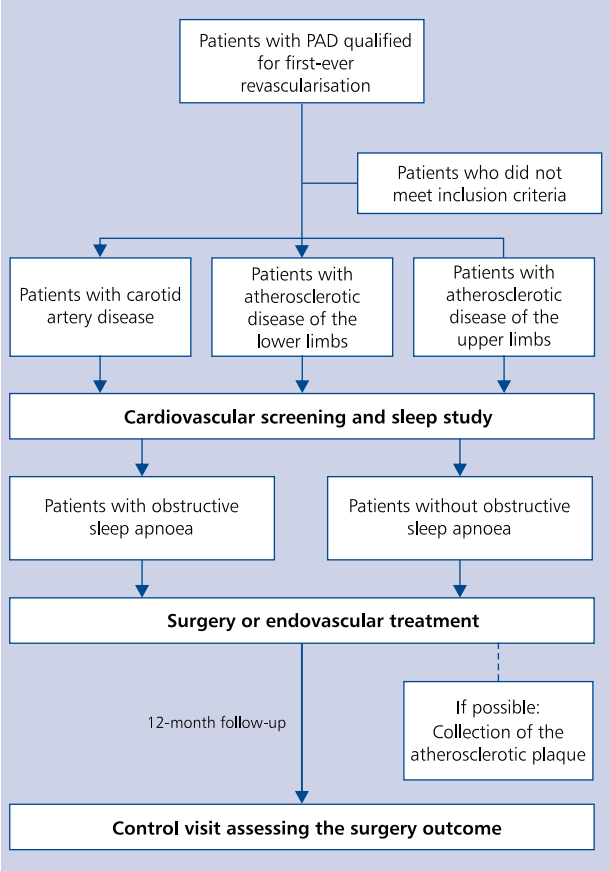

Figure 1. Study design; PAD — peripheral arterial disease

Participant inclusion criteria

- Men and women aged ≥ 18 years.
- Qualified to a first-ever surgical revascularisation because of PAD prior to the study enrolment.
- Obtained informed consent.

Exclusion criteria

- Lack of consent to participate in the study.
- Past revascularisation or amputation due to PAD.
- Current use of continuous positive pressure airways due to OSA.
- Contraindications to the study for sleep apnoea.
- Disqualification from surgery.
- Coexisting illness with a predicted survival rate < six months.
- Age > 85 years.
- Body mass index < 18.5 kg/m^2.
- Any physical, mental, or social condition impairing the ability to participate in the trial.

Study measurements

Primary end-point

The primary end-point of the study will be the failure of revascularisation defined as recurrence or new onset of the symptoms of the ischaemia from the treated region, a need for re-operation or procedure revision, or recurrence of ischaemia signs on the imaging tests.

Sleep study

All patients included in the study will be studied with overnight polysomnography irrespective of their daytime and night-time symptoms. Polysomnography will be performed using devices recording > four channels, including channels to detect respiratory movements or respiratory effort, airflow, heart rate, electrocardiogram, and oxygen saturation (Embletta Gold; Flaga, Reykjavik, Iceland). All sleep study results will be scored manually, according to the current guidelines, by a physician qualified in sleep medicine. Apnoea is defined as a reduction of airflow of ≥ 90% of pre-event baseline lasting ≥ 10 s. Hypopnoea is defined as a ≥ 30% drop in maximal airflow lasting ≥ 10 s, associated with ≥ 3% oxygen desaturation from pre-event baseline [5]. OSA is diagnosed based on the apnoea-hypopnoea index (AHI, the number of apnoeas and hypopnoeas per hour) and categorised into three severity classes: mild OSA — AHI ≥ 5 and < 15 per hour; moderate OSA — AHI ≥ 15 and < 30 per hour, and severe OSA — AHI ≥ 30 per hour.

Diagnosis of cardiovascular risk factors

Cardiovascular risk factors were in this protocol also defined as in the previous studies [14].

- Arterial hypertension: repeatedly elevated blood pressure (> 140/90 mm Hg) or taking antihypertensive drugs.
- Diabetes: a random plasma glucose > 200 mg/dL (11.1 mmol/L), or fasting plasma glucose > 126 mg/dL (7.0 mmol/L), or 2-h plasma glucose > 200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test or taking antidiabetic drugs.
- Heart failure: the presence of signs and symptoms typical of heart failure or reduced ejection fraction (< 40%).
- The metabolic syndrome was defined according to modified ATP-III criteria.
- Myocardial infarction: according to the medical records after another hospitalisation and/or signs of new ischaemia in physical examination, electrocardiography, or echocardiography.

Non-classical cardiovascular risk factors

Diagnosis of other, non-classical CV risk factors will be made using standardised, previously used questionnaires. All enrolled patients will complete the form in calm conditions, adapted to the situation, which ensures comfort and discretion. The filled questionnaires will be scored by researchers, assuring the anonymity of patient data. Used tools will include inter alia.

Evaluation of sexual dysfunction using the international index of erectile function (IIEF), a 15-item self-administered questionnaire, designed to provide reliable data on erectile

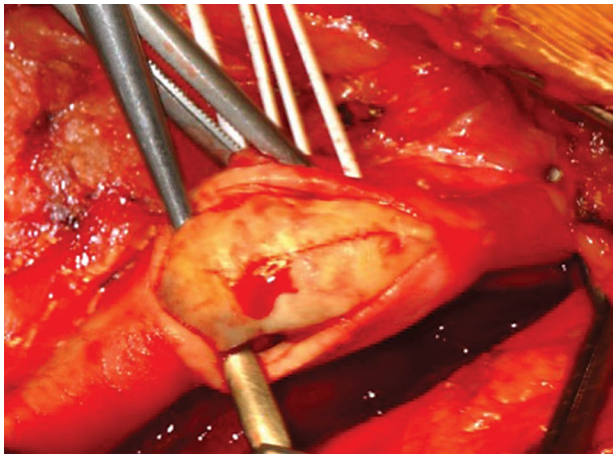

Figure 2. Picture taken during the collection of atherosclerotic plaque

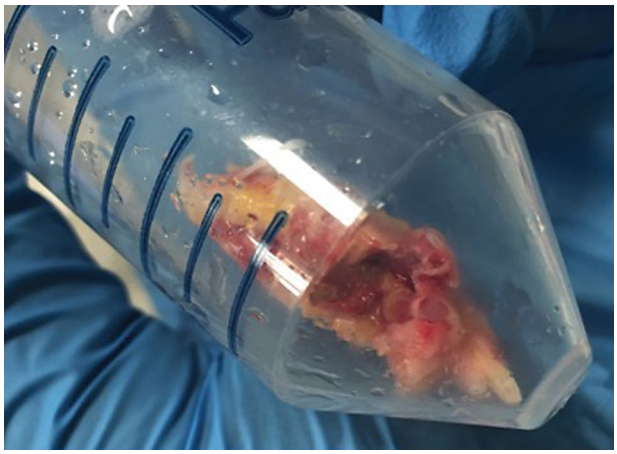

Figure 3. Fragment of atherosclerotic plaque collected from a patient

dysfunction (ED) [15]. The IIEF has been validated and shown to assess ED with sensitivity of 98% and a specificity of 88% [16]. The IIEF describes five main domains of male sexual function: erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction. Responses on each item are based on the patient's experience during the last four weeks, and are scored on a five-point scale where lower values represent poorer sexual function. Each domain of male sexual function was scored separately. For the ED domain, erectile dysfunction was classified as scores of 25 or less. For orgasmic function a value of eight or less was considered a dysfunction, for sexual desire — eight or less, for intercourse satisfaction — 12 or less, and for overall satisfaction — eight or less.

The incidence of depression will be established based on a questionnaire designed for this purpose — Beck Depression Inventory II (BDI-II) [17]. The BDI-II questionnaire consists of 21 questions aiming to evaluate the incidence of subjective symptoms of depression. The questionnaires are evaluated on a point scale, with the maximum of 63 points suggesting a very strong probability of depression, while 0 shows the lack of subjective symptoms of depression. The high sensitivity and specificity of the scale have been extensively described in the literature, confirming the value of the BDI-II in the diagnosis of mood disorders [17].

Blood samples collection and biochemical assessment

Blood samples will be collected prior to the surgery. The biological material will be taken from the subject from 10 h to 12 h after the last intake of food or fluid of any calorific value. A venous blood sample of 10 mL will be collected from respondents in a sitting position. After taking a sample of venous blood it will be centrifuged to obtain serum/plasma samples up to 2 h after blood collection. Biochemical analysis will be made on site in a local hospital laboratory according to the standard protocol. The rest of the unused samples will be frozen at –20°C and then transferred to –80°C for storage and further tests.

Collection and testing of the atherosclerotic plaque

In patients in whom surgery conditions will allow it, a sample of atherosclerotic plaque will be collected. The material will only cover fragments of atherosclerotic plaque that are classified by the operator as medical waste and will not be associated with a break in the continuity of healthy vessels. Collection of the specimen will only take place if the technical conditions permit, and the procedure itself will not entail any danger to the health or life of the patient and will not necessitate the prolongation or modification of the technique of the procedure. The material will be preserved in formaldehyde in standard conditions until further testing. A portion of the material will be further processed and preserved for further histopathological and biochemical examinations aimed at assessing the composition and morphology of atherosclerotic lesions.

Follow-up and duration of the study

After discharge from the hospital, each patient will be contacted via telephone or will have an outpatient clinical visit scheduled for evaluation at one year after the revascularisation procedure.

Adverse events and procedure efficacy will be investigated using open questions and a semi-structured questionnaire, with questions on general symptoms and the presumed effects of the procedure. If applicable, standard laboratory tests and diagnostic imaging will be used to identify procedure efficacy and adverse events, such as bleeding, wound infection, etc.

Ethical and legal issues

The PARADISE study was approved by the Bioethics Commission by the Medical University of Warsaw (KB/196/2015). The

approval concerned the questionnaire and all the procedures and measurements, including polysomnography studies, blood tests, and the storage of biological material for further scientific research. Before enrolment in the study, each participant will sign an informed consent. All data are blinded for the researchers by assigning a unique identification number for each participant to ensure confidentiality of personal data collected during the survey. The same number was assigned to all questionnaires and all blood samples originating from a specific individual. The data blinding assures anonymous storage of samples and data processing by researchers, statisticians, and controlling bodies.

Data management

The data are entered in a password-protected computer system by researchers not otherwise involved in the protocol. The database is backed up each 15 min in a computer located remotely at the university and in an international data safety company. No third parties have access to the study data.

Statistical analysis

Data will be tested for normality using the Kolmogorov-Smirnov test. Continuous data will be presented as mean and 95% confidence intervals, with statistical comparisons performed with the Mann-Whitney test or Student's t-test. For categorical variables a comparison will be made using either the χ^2 or Fisher exact tests. A Pearson correlation will be used to determine the correlation coefficient between variables. A one-way analysis of covariance (ANCOVA) will be used to determine associations between relevant variables while controlling for relevant cofactors. A p value of less than 0.05 will be considered statistically significant. Statistical analyses will be performed using SPSS (SPSS version 21, Inc., Chicago, IL).

DISCUSSION

The data obtained will help determine the incidence of OSA in the population of patients with PAD. We expect to show that, as with other CV diseases associated with atherosclerosis, also in patients with PAD the incidence of undiagnosed OSA is high and its presence is associated with elevated cholesterol, inflammatory markers, and higher prevalence of arterial hypertension and poor control of other CV risk factors. Probably, the incidence of OSA will be higher in patients with elevated body mass index. In addition, due to increased oxidative stress and vascular endothelial injury associated with OSA, patients afflicted with this condition will not only have more advanced atherosclerotic lesions, but also in their histopathological examination their atherosclerotic plaque will exhibit evidence of greater instability and adverse morphology. We also expect to show that in patients with OSA, achieving correct control of CV risk factors will be more difficult. OSA patients will require higher doses of stronger hypoglycaemic or antihypertensive drugs. Also, distant results of revascularisation in patients with OSA are presumed to be worse (more frequent recurrences and the need for another procedure) than in those who do not experience sleep apnoea. We also expect that in adverse observation adverse CV events will occur more frequently in patients with OSA than in the rest of the group.

Our work will have not only scientific implications but also practical. After selecting patients with increased CV risk, including those with OSA, we will be able to cover both cardiac and surgical care at an earlier stage. Multidisciplinary care is associated in most cases with better control of risk factors for atherosclerosis, which is the basis for the prevention and treatment of both PAD and other CV diseases. As a consequence, we hope that, as far as possible, we will improve the overall health and prognosis of patients.

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Availability of data and materials: *The study sample is small, and data sharing raises significant confidentiality issues. No data sharing has been planned at this time.*

Conflict of interest: *none declared*

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PARADISE (*Peripheral ARtery Atherosclerotic DIsease and SlEep disordered breathing*) — protokół obserwacyjnego badania kohortowego

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Streszczenie

Wstęp: Choroba tętnic obwodowych (PAD) jest w istocie grupą schorzeń z różnymi objawami i przebiegiem, ale wspólną przyczyną, którą stanowi miażdżyca tętnic. Miażdżyca jest pogłębiana przez kilka różnych czynników ryzyka sercowo-naczyniowego, w tym obturacyjny bezdech senny (OSA).

Cel: Niniejszy artykuł stanowi protokół badania PARADISE (*Peripheral ARtery Atherosclerotic DIsease and SlEep disordered breathing*), które ma na celu określenie częstości występowania OSA u pacjentów z PAD zakwalifikowanych do zabiegu rewaskularyzacji oraz określanie wpływu OSA na wyniki zabiegu.

Metody: PARADISE jest obserwacyjnym badaniem kohortowym. Planuje się włączenie 200 kolejnych pacjentów hospitalizowanych w celu rewaskularyzacji z powodu PAD. U każdego chorego zostanie przeprowadzone badanie snu w celu zdiagnozowania zaburzeń snu. Zgodnie z wynikami testu zostaną oni podzieleni na dwie grupy: grupa A — pacjenci z OSA; grupa B — pacjenci bez OSA (grupa kontrolna). Wszyscy pacjenci będą badani pod kątem klasycznych i nieklasycznych czynników ryzyka sercowo-naczyniowego. Od niektórych chorych podczas zabiegu zostanie pobrany fragment blaszki miażdżycowej, która posłuży do dalszych analiz. Pacjenci będą obserwowani przez 1 rok pod kątem zdarzeń niepożądanych i z góry sprecyzowanych punktów końcowych. Głównym punktem końcowym badania są: niepowodzenie rewaskularyzacji definiowane jako nawrót lub nowy początek objawów niedokrwienia z obszaru poddanego procedurze, konieczność ponownej operacji lub ponowienia procedury lub nawrót objawów niedokrwienia w badaniach obrazowych.

Dyskusja: Uzyskane dane pomogą określić częstość występowania OSA w populacji pacjentów z PAD. Autorzy oczekują, iż wykażą, że podobnie jak w przypadku innych chorób sercowo-naczyniowych związanych z miażdżycą tętnic, także u osób z PAD częstość występowania nierozpoznanej OSA jest wysoka, a jej obecność wiąże się z podwyższonym stężeniem cholesterolu, markerów zapalnych oraz wyższą częstością występowania nadciśnienia tętniczego i złej kontroli innych czynników ryzyka sercowo-naczyniowego. Ponadto, ze względu na zwiększony stres oksydacyjny i naczyniowe uszkodzenie śródbłonka związane z OSA, pacjenci z tym schorzeniem będą nie tylko dotknięci bardziej zaawansowanymi zmianami miażdżycowymi, ale w badaniu histopatologicznym ich blaszka miażdżycowa będzie wykazywać większą niestabilność i niekorzystną morfologię. Można przypuszczać również, że u chorych na OSA uzyskanie prawidłowej kontroli czynników ryzyka sercowo-naczyniowego będzie trudniejsze. Badanie może poprawić kontrolę PAD poprzez zapewnienie lepszej opieki wielospecjalistycznej pacjentom z PAD.

Słowa kluczowe: choroba tętnic obwodowych, obturacyjny bezdech senny, protokół badania

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