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Assessment of the effect of external counterpulsation on myocardial adaptive arteriogenesis by invasive functional measurements — design of the arteriogenesis network trial 2 ☆

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ABSTRACT

Background: Stimulation of collateral artery growth is a promising therapeutic option for patients with coronary artery disease. External counterpulsation is a non-invasive technique suggested to promote the growth of myocardial collateral arteries via increase of shear stress. The Art.Net.2 Trial tests invasively and functionally for the first time the hypothesis whether a treatment course with external counterpulsation (over 7 weeks) can induce the growth of myocardial collateral arteries.
Methods: This study is designed as a prospective, controlled, proof-of-concept study. Inclusion criteria are (1) age 40 to 80 years, (2) stable coronary disease, (3) a residual significant stenosis of at least one epicardial artery and (4) a positive ischemic stress-test for the region of interest. As primary endpoint serves the pressure-derived collateral flow index (CFIp), the invasive gold-standard to assess myocardial collateral pathways. CFIp is determined by simultaneous measurement of mean aortic pressure (P_a, mm Hg), distal coronary occlusive (wedge) pressure (P_w, mm Hg) and central venous pressure (P_v, mm Hg). The index is calculated as $CFIp = (P_w - P_v)/(P_a - P_v)$. The pressure derived fractional flow reserve (FFR) and the index of microcirculatory resistance (IMR) are assessed as secondary invasive endpoints to investigate the effect of ECP on the myocardial vasculature. The non-invasive secondary endpoints include symptoms (CCS and NYHA classification), treadmill-testing and analysis of shear-stress related soluble proteins.
Conclusions: The Art.Net.-2 Trial will report within the next months whether direct evidence can be brought that ECP promotes coronary collateral growth in patients with stable angina pectoris.

1. Introduction

Enhanced external counterpulsation has been introduced during the last 3 decades as a non-invasive alternative approach to active physical exercise in patients suffering from severe coronary artery disease (CAD). Several prospective clinical trials have demonstrated a clear therapeutic benefit including improvement of clinical status and exercise performance as well as an improved quality of life [1–3]. However, the exact mechanisms of action of external counterpulsation remain unclear.

During ECP the aortic and intracoronary average and diastolic blood flow and pressure are increased while systolic pressure is decreased [4]. This increase in blood flow results in increased shear stress in the arterial system [5] suggesting also an improvement of the shear stress in the coronary artery bed [4]. The proposed mechanism by which ECP alleviates angina includes improvement of peripheral and coronary endothelial function, improvement of ventricular function, favorable peripheral effects similar to that of physical training and the recruitment and proliferation of collateral arteries [3,6–8].

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The latter process, termed arteriogenesis, is initially triggered by physical forces: in the presence of a stenosis blood flow and consequently endothelial shear stress are increased across the lumina of pre-existing anastomotic arteries. Shear stress is a major trigger of arteriogenesis [9]. Clinical studies demonstrated a clear positive correlation between collateral formation and physical activity [10,11]. A well-developed coronary collateral system minimizes the loss of myocardium in case of myocardial infarction [12] and reduces the long-term cardiac mortality [13]. However, only one third of the patients with CAD and residual stenosis or occlusions possess adequate collateral networks [14].

ECP is therefore an attractive therapeutic option for the non-invasive stimulation of collateral growth. Previous trials using positron emission tomography and myocardial scintigraphy have demonstrated increased myocardial perfusion after ECP [3,6,15]. However, the data about the effect of ECP on myocardial perfusion are still controversial [16,17]. Furthermore, it remains unclear whether the improvement of myocardial perfusion is directly related to improved collateralization, improved coronary endothelial function or both.

None of the previous studies has used a specific method for the assessment of collateral vessels. In the majority of the trials physical exercise tests (e.g. treadmill SPECT) were used to evaluate the effect of ECP on myocardial blood flow. By using these methods a possible contribution of the coronary endothelium to the coronary blood flow cannot be excluded. Furthermore these tests were mostly performed at the same levels of exercise (same double product) before and after ECP. In this case reduced myocardial oxygen demand due to a peripheral training effect could also be a possible mechanism for the attenuation of perfusion defects [8].

In the current clinical trial we therefore decided to use functional invasive endpoints allowing a conclusive assessment of the effect of ECP on coronary collateral artery growth in patients with stable coronary artery disease. Thus the pressure-derived collateral flow index, currently the gold-standard for the invasive assessment of collateral arteries, is the primary endpoint of the study.

2. Methods

2.1. Study population

Patients between 40 and 80 years of age, suffering from stable coronary artery disease are considered for screening and potential recruitment into the trial. Those with a significant narrowing of a coronary artery (>70%) and a correlating positive ischemic stress-test eligible for invasive coronary angiography and/or coronary intervention are candidates for inclusion. In addition, patients whose present coronary status is unknown but who have a positive stress-test and are advised to undergo a diagnostic coronary angiography are also considered for inclusion. The last inclusion criterion, the FFR, is assessed during the baseline cardiac catheterization. Only patients with FFR <0.80 are recruited in the trial. All inclusion and exclusion criteria of the study are summarized in Table 1.

2.2. Study design

The study is conducted in accordance with the principles of the declaration of Helsinki. The investigational protocol has been approved by the ethics committee for human studies at the Charité Universitaetsmedizin Berlin. Written informed consent is obtained from all patients prior to the invasive procedure.

At the time of the ethical approval in September 2006, the first study protocol was planned to include a counterpulsation group (treatment group) as well as a control group with low-pressure counterpulsation (pressure of 80 mm Hg) based on the assumption that sham-ECP does not have any relevant effect on coronary hemodynamics [2,18]. However the ethical committee withheld approval to this strategy and proposed the use of published data referring to the natural time course of the coronary collateral circulation. Meanwhile the COURAGE Trial [19] was published, providing evidence that coronary intervention – especially in this patient population eligible to take part in the Art.Net.2 Trial – can be deferred safely. Based on this a positive votum of the ethical committee for the inclusion of a prospective control group has been obtained. The trial is conducted as an intention to treat, prospective non-randomized controlled proof-of-concept study.

Patients who fulfill the inclusion criteria undergo a voluntary ECP treatment of 30 min to confirm that they tolerate the therapy. Patients who do not approve the method or are not able to follow the time course of the daily ECP treatment are recruited into the control group. The clinical symptoms of the patients are assessed twice within 3 weeks. Clinical evaluation is based on the Canadian Cardiovascular Society grading scale (CCS) for angina pectoris and the New York Heart Association (NYHA) functional class for dyspnea at exertion. A questionnaire on the daily and physical activities of the patients is filled out. From this point of time and until the study protocol is completed patients are instructed not to modify their daily (physical) activities. Oral antihypertensive medication may be adjusted to meet the guideline recommendations [20]. In patients who have not already undergone a myocardial stress-testing (scintigraphic imaging, stress-echocardiography or stress perfusion magnetic resonance imaging of the heart) a cardiac magnetic imaging (CMI) with adenosine stress-test is performed. During the baseline coronary angiography, if the existence of at least one angiographically significant stenosis of type A according to AHA/ACC [21] is confirmed, the hemodynamic significance of the stenosis is evaluated via fractional flow reserve (FFR). Taking into account that all patients have already a positive ischemic stress-test at the time of catheterization, they are recruited in the study if FFR <0.80 [22,23]. If FFR ≥0.80 the patient is excluded from the study.

Table 1
Inclusion and exclusion criteria.

Inclusion criteria	• 40 to 80 years of age • Stable coronary vessel disease • Angiographically visual significant stenosis (>70%) of at least one epicardial coronary artery • Positive imaging stress-test (myocardial scintigraphy, stress-echo, adenosine or dobutamine stress cardiac magnetic imaging) for the region of interest (ROI) • Fractional flow reserve (FFR) <0.80
Exclusion criteria	• Unstable angina • Severe kinking of coronary vessels or vessel anatomy unfavorable for pressure measurements • Previous Q-wave infarction in the area assessed for coronary collaterals • Ischemic or non-ischemic left ventricle dysfunction with an Ejection Fraction (EF) less than 35% • Tricuspid and aortic valve insufficiency insufficiency>moderate and aortic valve stenosis>moderate • Relevant stenosis of the aorta abdominalis or aorta thoracica, coarctatio aortae • Atrial fibrillation, severe hypertension with systolic pressure >180 mm Hg • Symptomatic angiopathy of the lower limb (neuropathy, vasculitis, ankle pressures <100 mm Hg), chronic venous insufficiency > grade III, symptomatic varicosis, thrombosis, occlusion of vena cava inferior, phlebitis • Lesions of the lower extremity (ulcera, big scar, etc.) or symptomatic orthopaedic disease (hip, knee) • Prepoliferative or proliferative diabetic retinopathy • Anticoagulation with International Normalised Ratio (INR) >3 or INR <<3 and disturbed homeostasis • Asthma bronchiale, severe systemic disease, pregnancy, mental retardation or dementia • Acute renal insufficiency, progressive renal insufficiency, chronic renal insufficiency — KDOQI ≥ III

After the baseline coronary angiography the main phase of the trial, lasting 7 weeks, begins. In the ECP group the ECP therapy is performed using the standard treatment course which comprises 60 min of therapy five times weekly for a period of seven weeks (35 h). The enhanced external counterpulsation (EECP®) device (TS3, Vasomedical, New York, USA) consists of a computer module, the air compressor, three pairs of pneumatic cuffs and a treatment table. The cuffs, wrapped around the calves, lower thighs, and upper thighs are sequentially inflated with compressed air from distal to proximal in early diastole and rapidly deflated at the onset of the systole. The hemodynamic changes are registered by finger plethysmography and the systolic-to-diastolic effectiveness ratio (D/S ratio) is automatically calculated (Fig. 1). ECP is performed with cuff-pressures between 200 and 260 mm Hg depending on the toleration to the therapy by the patients and the achieved hemodynamic effect with a target D/S ratio >1.0 [24]. Clinical symptoms, blood pressure and heart rate are registered at every treatment session.

The control group receives during the 7 week period an optimal medical treatment according to the COURAGE Trial [19]. The therapeutic goals are to improve clinical symptoms and reduce cardiovascular risk factors and poor health behaviors. To compensate for the non-therapy related effect (increased daily activity in the ECP treatment group due to walk in treatment, regular contact to the study-team), the control group has 5 days/week an appointment within our clinic over seven weeks in terms of counseling or non-study related diagnostics: ultrasound, ankle-brachial index, 24 h blood-pressure measurements, ergometric test, 24 hour ECG reading, weekly advisory by a dietary consultant. The control group is being seen by the study-physician twice weekly to assess CAD related symptoms. In the 8th week, after having completed the study-course, the follow-up with the identical to week 0 non-invasive tests and invasive measurements is performed. During this catheterization the decision to treat the stenosis with PCI/stent is taken. Taking into account the clinical status of the patient, the non-invasive stress-test, the FFR measurement and according to the current guidelines [22] an intervention is performed for all FFR values under 0.75 and for most of the patients with 0.75<FFR<0.80. If FFR ≥0.80 no intervention is performed. A flow-chart of the study is presented in Fig. 2.