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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.
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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.

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3. Measurements

3.1. Invasive endpoints

The pressure-derived collateral flow index (CFIp) is the primary endpoint of the study.

The main hypothesis of this trial, whether ECP leads to an improvement of the coronary collateral circulation (positive outward remodeling = arteriogenesis), is investigated using the CFIp, currently the gold-standard for assessment of collateral blood flow [25]. There are no units for the index whereas a value above 25% represents a sufficient network of collaterals [14]. CFIp expresses the maintained blood flow during coronary occlusion via connecting collateral arteries relative to normal antegrade flow during vessel patency (see Fig. 3).

CFIp is determined by simultaneous measurement of mean aortic pressure (P_a, mm Hg), the distal coronary artery pressure during balloon occlusion (P_w, mm Hg) and the central venous pressure (P_v, mm Hg). CFIp is calculated upon the next equation [26]:

$$\mathrm{CFIp} = \frac{P_w - P_v}{P_a - P_v}.$$

Secondary endpoint as well as inclusion criterion in the study is the pressure derived fractional flow reserve (FFR), an index that allows a functional evaluation of the severity of a stenosis. FFR is defined as the ratio of the maximal blood flow achievable in a stenotic vessel to the normal maximal flow in the same vessel, which represents the fraction of maximum flow that can be still maintained despite the presence of the stenosis. It is calculated from the equation [23]:

$$\mathrm{FFR} = \frac{P_d - P_v}{P_a - P_v}.$$

The other invasive secondary endpoint is the index of the myocardial microcirculatory resistance (IMR). IMR compared to coronary flow reserve (CFR) provides a more reproducible assessment of the microcirculation if epicardial stenosis is evident [27]. Since all patients in the current study protocol have at least one significant residual stenosis, IMR has been chosen as a functional endpoint. Assuming that collateral arteries are present when a stenosis exists, the contribution of the collateral circulation is taken into account for the calculation of IMR upon the next equation [27]:

$$\mathrm{IMR} = P_a \times T_{mn} \times \left(\frac{P_d - P_w}{P_a - P_w}\right).$$

P_a, P_d and T_{mn} are estimated under maximal vasodilation whereas P_w is obtained under the brief coronary occlusion.

3.2. Protocol of the invasive measurements

Invasive procedures are performed in the catheterization laboratory of the Franz-Volhard-Klinik, Helios Klinikum Berlin. The procedure is performed on a standard angiography suite (Hicor, Siemens, Erlangen, Germany). All pressures are measured in mm Hg. The aortic pressure (P_a) is measured in the ascending aorta by the guiding catheter. The central venous pressure (P_v) is measured with a catheter placed in the right atrium. Pressures distal to the stenosis (abbreviated as P_d under adenosine or P_w during occlusion) and thermodilution curves are obtained by using the PressureWire® (Radi Medical systems, Uppsala, Sweden). The PressureWire® is a 0.014 in. guidewire equipped with a sensor suitable for simultaneously pressure and temperature measurements.

Steady state hyperemia for assessment of FFR and IMR is achieved with administration of adenosine (Adenoscan® 30 mg/10 ml, Sanofi-Aventis) through a large antecubital vein at 140 μg kg^{-1} min^{-1} [28].

During catheterization the patient is under continuous ECG and blood-pressure monitoring. The right femoral approach is used in all patients. A 6-French (F) guiding catheter without side holes is being inserted and advanced initially to the left ventricle for the measurement of the left ventricular end-diastolic pressure. Afterwards, a 5F catheter is being inserted in the femoral vein and advanced into the

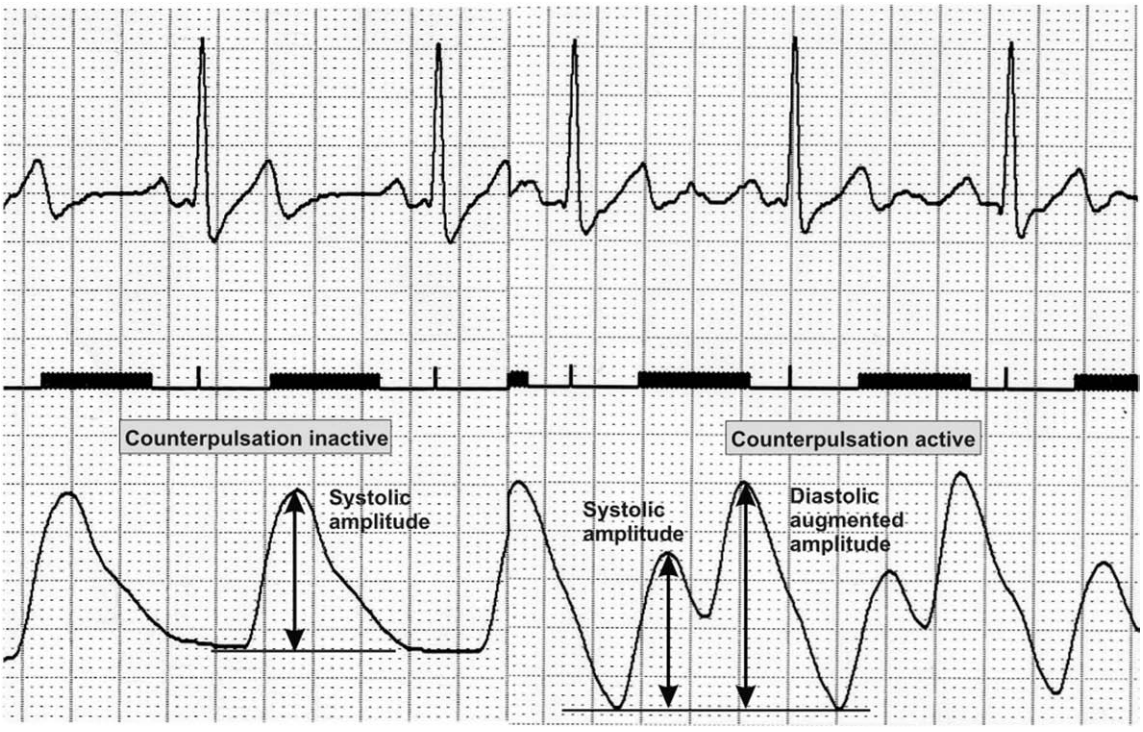

Fig. 1. Plethysmographic curves of a patient. Hemodynamic waveforms at rest (counterpulsation inactive) and during ECP (counterpulsation active) through finger plethysmography. Effectiveness or D/S ratio = peak diastolic amplitude / peak systolic amplitude.

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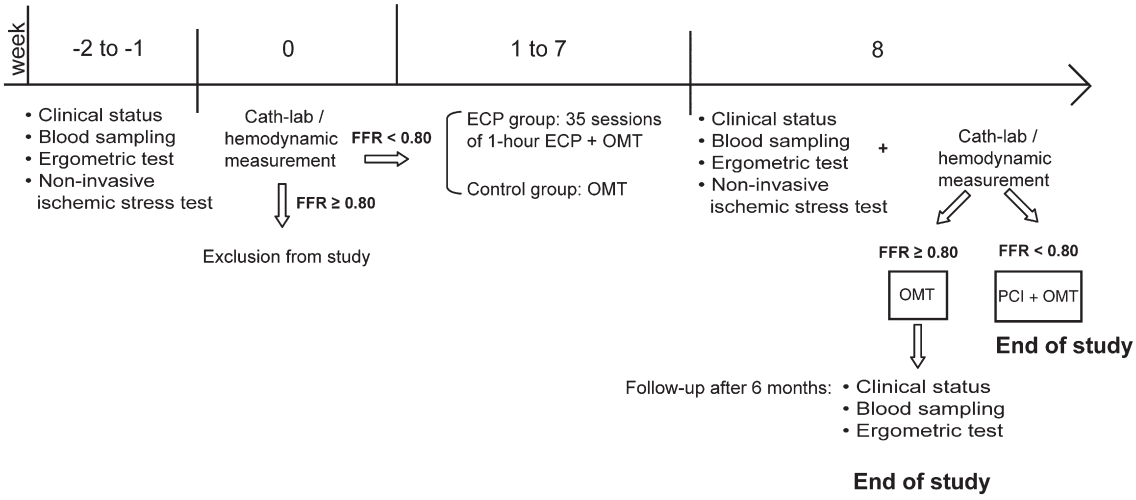

Fig. 2. Flow-chart of the study. ECP: external counterpulsation therapy, OMT: optimal medical treatment, PCI: percutaneous intervention, FFR: fractional flow reserve.

right atrium to record the P_v. Weight adjusted heparin is administered intravenously. 0.2 mg nitroglycerine is given intracoronary and repeated, if needed, every 20 min throughout the cardiac catheterization to prevent coronary spasm that might occur due to the injection of contrast agent. Biplane coronary diagnostic angiography is performed. Quantitative angiography for estimation of the percent diameter stenosis (%) is performed offline. If the stenosis is angiographically characterized as significant but low-risk type A stenosis [21] the procedure is continued with the pressure measurements. To avoid a possible vasoconstriction caused by injection of the contrast agent, an interval of 10 min is allowed before continuation with the hemodynamic measurements. The pressure wire is set at zero, calibrated and advanced to the tip of the guiding catheter where, if needed, is equalized to the aortic pressure. Thereafter the wire is advanced through the guiding catheter distal to the stenosis. The measurements start with the thermodilution at rest and under hyperemia. Three injections of 3 ml saline into the guiding catheter are performed; a deviation of <15% of Tmean is accepted for analysis. Subsequently hyperemia with adenosine is induced. After 2 min, a steady state hyperemia is to be expected [29]. Thereafter and under continuous administration of adenosine the three saline injections are repeated. Thermodilution curves, transit mean times (T_{mn}) and pressure values are recorded at rest and under hyperemia. If FFR ≥0.80 the patient is not eligible for inclusion and the study protocol is terminated at this time point. Further diagnostic or therapeutic procedures for these patients are performed, if needed, independent of the study protocol. If FFR <0.80, the patient is included and the study protocol is continued with assessment of the primary endpoint, the CFIp.

The pressure wire remains in position serving as a guide wire, and an adequately sized balloon is placed right proximal to the stenosis in the non-stenotic segment. The balloon is inflated at low pressure (1 to 3 atm) until the antegrade coronary flow is interrupted. The transient complete occlusion is controlled via the real-time pressure measurement display and by injection of contrast dye. CFIp is determined at the end of a 1 min occlusion [30]; earlier deflation is done if a patient develops excessive anginal symptoms or ST-elevation is documented. After deflation of the balloon time is allowed for normalization of the pressures to the baseline values. Finally the target vessel is examined with dye injection to rule out potential dissections.

3.3. Clinical secondary endpoints

The CCS and NYHA classifications are obtained to assess exercise induced angina and dyspnea at exercise. Anginal episodes and use of on demand nitroglycerine are documented in a daily basis from the patient and reported to the study nurse or physician. Patients who undergo no PCI at week 8 are assessed clinically in a follow-up 6 months after completion of the main study protocol.

3.4. Exercise test

A symptom-limited bicycle ergometric test is performed at weeks 0, 8 and at the 6-month's follow-up. An ergometric system from General Electric is used (Kiss and eBike L). Continuous monitoring of symptoms, 12-canal electrocardiogram and heart rate is performed. Blood pressure is periodically measured at 2-min intervals. The test starts at 50 W and continues with a raise of 25 W every 2 min. The examination is terminated due to emergence of modest to severe angina or dyspnea, exhaustion or presence of other indications according to the guidelines [31]. The achievable workload, rate-pressure product, exercise duration and maximal heart rate and severity of electrocardiographic changes are recorded for the study analysis.

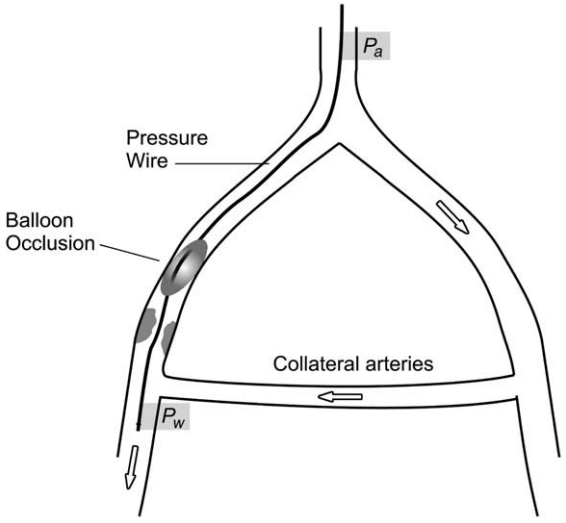

Fig. 3. Coronary artery model for the assessment of the collateral flow index. The brief occlusion with a PCI balloon serves the interruption of the antegrade flow and enables the measurement of the collateral flow. P_a: aortic pressure, P_w: pressure during brief balloon occlusion.

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3.5. Detection of pro-arteriogenic and endothelial factors in blood samples

Blood samples to evaluate blood count, inflammatory and paracrine parameters, coagulation status and lipid profile are obtained at baseline (week 0) and after 7 weeks (week 8) and are immediately analyzed. Further blood samples collected at weeks 0, 4, 8 and after 6 months are stored at −80 °C for later analysis. Factors promoting arteriogenesis like hepatocyte growth factor (HGF), basic-fibroblast growth factor (bFGF) and the Granulocyte-Macrophage-Colony Stimulating Factor (GM-CSF) will be assessed. Furthermore, shear-stress depended markers of endothelial function will be estimated (extracellular superoxide dismutase — ecSOD, E-selectin and ICAM-1). The pooled samples will be tested through commercially available Enzyme Linked Immunosorbent Assays (Elisa).

3.6. Sample size and statistics

The strongest evidence for ECP related improvement of myocardial blood flow due to adaptive collateral arterial growth is mainly based in previous PET studies [6,32]. The methodological error of CFIp and FFR measurement was taken into account by reviewing prospective trials [23,33].

Based on the aforementioned studies reporting perfusion changes after ECP treatment the power calculations are based on the following assumptions: one-tailed test for increase in myocardial blood flow in the ischemic region, significance level of 5%, desired power to detect change 80%, a mean change of myocardial blood flow respectively to the collateral blood flow in ischemic myocardial region of at least+ 15%. These assumptions are in proximity to other estimates of significant increase of perfusion after ECP treatment mostly detected by SPECT.

Based on these assumptions a sample size of 12 patients is required for the ECP group. Taking a drop out rate of 30–40% into account, a total of 16 patients has been planned for inclusion. Because in published data on the natural course of the collateral circulation [10,13] a reduced variance had been observed, a 2:1 ratio for the control group has been planned, resulting in a sample size of 7 patients (6 + 1 expected drop out). Statistical significance is defined at $p<0.05$.

4. Discussion

Our own experimental data on the role of shear stress in inducing the proliferation of collateral arteries, supported by clinical studies in the area of external counterpulsation prompted us to design this trial. At the time point of inclusion all patients are candidates for percutaneous coronary intervention. It is not our intention to withhold patients from standard interventional procedures. The decision if a PCI has to be performed is taken during the final catheterization, after the FFR measurement, without taking the CFIp into account. Consequently, the treatment option for the stable coronary artery disease patients in the study could be modified after the ECP treatment. If a reduction of the significance of the stenosis and improvement of the clinical symptoms occur after ECP, a conventional pharmaceutical treatment without coronary intervention may be suggested.

The hypothesis of our trial is based on the concept of arteriogenesis generated by the research group of Schaper and experimental data dating back in the 1970 to 1990s. Jacobey and Rosenzweig had demonstrated first in animal experiments the pro-arteriogenic impact of external counterpulsation in the heart: in a canine model with acute and chronic myocardial ischemia external counterpulsation induced enhanced epicardial and subendocardial collateralization. Moreover the infarct size of the counterpulsation group was significantly reduced in comparison to the control group [34,35].

External counterpulsation treatment provokes –due to the pulsatile inflation of the air cuffs– an increase up to 109% of the average blood velocity in the coronary bed compared to rest [4]. This indicates a proportional increase of shear stress according to the formula: $\tau\ (\mathrm{dyn/cm^2}) = 4\eta V / R^3\pi$ (τ = shear stress, η = blood viscosity, V = blood flow velocity, R = vessel's radius). When a severe coronary stenosis occurs, blood flow and shear stress are elevated in the peripheral arterial anastomoses connecting the low-pressure territories distal to the stenosis.

Up to date direct evidence for the growth of collateral arteries in response to ECP is lacking mainly due to the non-specific methodology which has been used for collateral assessment. Urano and colleagues [3] found no change of the Rentrop score of collateral arteries despite the demonstrated reduction of ischemic defects in scintigraphy. However, it has been shown that angiographic endpoints do not correlate with myocardial perfusion [36]. Hemodynamic measurements for the assessment of the collateral flow are superior compared to the angiographic methods [25]. Thus in the current trial a functional assessment of the collateral arteries is performed. The Doppler-wire- and pressure-wire-obtained collateral indices (CFIv and CFIp) are currently the gold-standards for assessment of the collateral arteries. The flow-derived collateral index (CFIv) may be influenced by changes of the heart rate and aortic pressure as long as the flow velocity during occlusion and during vessel patency are not recorded simultaneously [26]. In contrary, the CFIp index is not depended on the hemodynamics. For clinical trials like this, where repetitive CFI measurements are performed in different points of time, an index independent of the hemodynamic condition of the patient may be preferred. Furthermore, the use of a pressure wire (instead of a Doppler wire) enables the calculation of the FFR. For these reasons the CFIp was selected as the primary endpoint to assess collateral arteries.

The presence of a severe stenosis is a prerequisite for adaptive arteriogenesis and growth of collateral arteries. In our study, patients with significant residual stenoses are recruited. We decided to use the FFR as an established method to assess the significance of the coronary stenosis. Due to their functional inferiority angiographic endpoints were not included in the trial. FFR is a lesion-specific index of the functional severity of coronary stenosis and correlates well with the findings from a variety of non-invasive stress-tests [28]. A FFR <0.75 indicates a stenosis in need for revascularization whereas a value greater than 0.80 excludes ischemia in 90% of the cases and is the cut-off point to defer intervention [28]. Thus, FFR acts in this study-setting as a criterion for inclusion as well as a secondary endpoint. From this point of view and taking into account that only patients with hemodynamic significant stenosis are eligible to enter the study we decided to recruit patients if they fulfill both criteria: positive stress-test and FFR <0.80.

The FFR takes into account the contribution of collaterals as long as the distal coronary pressure during maximal hyperemia reflects both antegrade and retrograde coronary blood flow [37]. Consequently, it is hypothesized that an improvement of the collateral flow reflects changes of the FFR index, assuming that the severity of the stenosis does not change upon the ECP therapy. To evaluate a possible progression or regression of the coronary stenosis during the 7 week period QCA is performed. In addition to QCA, IMR is estimated to assess the status of the coronary microcirculation which could also potentially influence the FFR values. An alteration of the distal microvascular resistances could influence the adenosine-induced dilation and therefore the distal pressure and the FFR. In this case, a change of the FFR could partially reflect a change of the cardiac microcirculation [38]. By assessing the IMR during both invasive measurements we evaluate a) the effect of ECP on coronary microcirculation and b) whether changes of FFR are influenced by changes of the distal microcirculation.

5. Conclusion

The present study is merely designed as a “proof-of-concept” study to test the hypothesis whether arteriogenesis may be stimulated non-invasively via external counterpulsation. Up to now there are no clinical

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data available which provide a direct evidence of the effect of ECP on myocardial collateral function. In earlier studies only inferior surrogate markers such as angiography and PET imaging were used. The Art.Net.2 Trial will provide for the first time novel functional data in terms of gold-standard endpoints (CFIp) in the field of therapeutic arteriogenesis in stable angina pectoris. If the hypothesis is proven, a novel therapeutic option for patients unable to undergo endurance training will be available. Furthermore, patients who are unable for further revascularization procedures may benefit from this therapy. From this point of view, ECP may be a preventive therapy for stable angina pectoris.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [39].

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