Coronary ARteriogenesis with combined Heparin and EXercise therapy in chronic refractory Angina (CARHEXA):

A phase 3 double-blind, placebo-controlled, parallel group study

December 25, 2012

ABSTRACT

Background: Although experimental studies on the stimulation of coronary arteriogenesis have been promising, not a single drug has been proved to be applicable in clinical practice, either due to lack of efficacy or because of undesired side effects. Encouraging results have been obtained with combination of heparin (H)) coupled with a stress inducing ischemia and augmenting shear stress, such as exercise.

Aim: to establish the coronary arteriogenetic efficacy of H combined with exercise in patients with intractable coronary artery disease.

Methods: We will recruit 60 "no-option" patients with chronic stable angina refractory to optimal medical management, and not suitable for percutaneous and/or surgical revascularization therapy. As further inclusion criteria eligible patients are able to exercise (and enter a cardiac rehabilitation program). In a prospective, randomized, double-blind study design these "no-option" patients will be allocated (30 for each of the 2 groups) to one of 2 treatment groups: 1) standard physical rehabilitation (i.v. placebo 10 min prior to each of 2 exercise session per day for 5 days a week for 2 weeks); 2) drug-primed physical rehabilitation (same modality as 1, but with H, 100 UI/Kg up to a maximum of 5.000 IU iv, 10 min prior to the exercise). All patients will undergo exercise stress echo (with wall motion score index, coronary flow reserve on left anterior descending and global longitudinal strain evaluation) and cardiac CT (with coronary collateral assessment) both before and after the therapy cycle.

Endpoints. Clinical and imaging (by blinded observers) assessment will be performed before and after treatment. ***Primary clinical endpoint*** is Canadian Cardiovascular Society (CCS) angina severity, ranging from class 1 (mild) to 4 (severe). ***Secondary stress imaging functional endpoint*** is peak Wall Motion Score Index (WMSI) at stress echo (ancillary endpoints: global longitudianl strain and coronary flow reserve). ***Tertiary imaging endpoint*** is Coronary Collateral Circulation Score at cardiac CT.

Epidemiological and clinical background

The optimal treatment of coronary artery disease (CAD) involves reducing the ischemic burden, lowering the risk of future adverse cardiac events, and relieving symptoms of angina pectoris. Medical and mechanical therapies have played a major role in reducing the morbidity and mortality associated with ischemic heart disease. Despite the success of these conventional therapies, there are patients with coronary artery disease (CAD) who continue to experience angina despite maximal medical and revascularization therapy. Therapeutic angiogenesis represents a novel treatment option for these "no-option" patients with refractory ischemic coronary disease. A growing body of evidence has revealed the potential of therapeutic angiogenesis with gene, protein, or cell-based therapies. The goal of therapeutic angiogenesis is to induce the formation of new vessels that can enhance blood flow to areas that no longer have adequate blood supply. Although cardiovascular mortality attributable to ischemic heart disease has recently declined, it is still the leading cause of death in the Western countries. The associated morbidity and mortality of ischemic heart disease produces a considerable burden on the healthcare system. The number of patients with chronic stable angina has been estimated to be 16,500,000 (*Gibbons et al, 2003*). Given the ongoing obesity epidemic, increased incidence of diabetes mellitus, and an aging population, this impressive number will likely continue to grow. With a better understanding of the patho-physiology of ischemic heart disease over the last several decades, there have been tremendous advances in the treatment of CAD. Novel pharmacological agents, improved revascularization techniques, and better risk assessment tools have enabled healthcare practitioners to manage patients with ischemic heart disease more efficiently. Despite these advances, there is a growing population of patients who continue to be disabled by chronic angina. Healthcare providers have numerous treatment options to provide angina relief for these patients. Current guidelines for chronic stable angina recommend quitting smoking, blood pressure control, intensive lipid-lowering therapy, adequate physical activity, achievement of ideal body weight, and diabetes control. Medications routinely prescribed include anti-platelet therapy, statins, angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, calcium channel blockers, nitrates and more recently ranolazine. Revascularization either with percutaneous coronary intervention or surgical bypass is part of the management of chronic CAD as well. When standard treatment measures are inadequate to control angina, novel approaches are needed. The European Society of Cardiology has defined refractory angina as a "chronic condition (>3 months) characterized by the presence of angina caused by coronary insufficiency in the presence of CAD which cannot be controlled by a combination of medical

therapy, angioplasty, and coronary bypass surgery" (*Mannheimer C et al, 2002*). Although the epidemiology of refractory angina is unclear and descriptive epidemiological studies are urgently needed, recent data indicate that the number of patients with refractory angina not amenable to revascularization on optimal medical therapy ("no-option" patients) is at least 150,000 per year in the US alone (*Williams B et al. 2010*).

The clinically elusive goal of therapeutic coronary arteriogenesis

Patients with severe CAD commonly develop collateral flow to ischemic myocardial territories that ameliorate or in some cases, eliminate myocardial ischemia. However, there are many patients in whom this patho-physiological angiogenic response is inadequate to control angina symptoms. After birth, new blood vessel formation proceeds via angiogenesis or arteriogenesis. Angiogenesis (capillary sprouting) results in higher capillary density. Arteriogenesis (rapid production of collateral arterioles) is potentially able to significantly alter the outcome of coronary and peripheral artery disease. The processes share some growth factors but differ in many respects. Arteriogenesis is by far the most efficient adaptive mechanism for the survival of the internal organs such as heart because of its ability to conduct, after adaptive growth, relatively large blood volumes per unit of time. An increase in the number of capillaries, the results of stimulated angiogenesis, is unable to do this (*Buschmann I and Schaper W, 1999*).

The goal of therapeutic angiogenesis is to enhance the formation of new vessels that can provide arterial blood flow to myocardial regions with inadequate blood supply. Therapeutic angiogenesis can be accomplished using three approaches: gene therapy delivered locally (FGF and VEGF); cytokines stimulating angiogenesis (MP1, PIGF, etc); hematopoietic/angiogenic stem cells. Although experimental studies on the stimulation of arteriogenesis has been promising, not a single drug have been proved to be applicable in clinical practice, either due to lack of efficacy or because of undesired side effects (*Schirmer et al 2009*).

Pharmacologic approaches to enhance coronary arteriogenesis.

Our approach is based on the combination of pharmacological stimuli (with heparin) on top of a 2-week cycle of physical rehabilitation (in patients capable to exercise). The rationale for this chemical-physical cocktail stems from the fact that increase in shear stress (achieved with exercise), or heparin – when used alone - have no significant coronary arteriogenetic effect, which is consistently present, and clinically significant, when the two stimuli are coupled (*Fujita M et al. 1988*). The basic principle of heparin treatment is potentiation of angiogenic growth factors, which

are overexpressed by increased shear stress at the site of pre-existing collateral vessels as a result of exercise or pacing. Although the precise mechanisms by which heparin potentiates arteriogenesis remain to be completely elucidated, heparin administration combined with exercise (*Tateno S et al 2001*) has great potential in treating patients with effort angina who are not indicated for conventional reperfusion therapy.

Study hypothesis

In the large and expanding population of "no-option" patients with refractory angina, a clinically significant coronary arteriogenetic effect can be obtained through a combination of pharmacological (heparin) and physical (rehabilitation exercise program) stimuli, when used in combination.

Overall study design

We will recruit 60 patients with chronic stable angina refractory to medical management, and not suitable for percutaneous and/or surgical revascularization therapy. As additional criterion for treatment eligibility, patients will have exercise capacity allowing to enter a rehabilitation program. In a prospective, randomized, open-label study design these "no-option" patients will be allocated (30 for each group) to 2 treatments: 1) standard physical rehabilitation (2 exercise session per day for 5 days a week for 2 weeks); 2) drug-primed physical rehabilitation (same modality as 1, but with H, 100 UI/Kg up to a maximum of 5.000 IU iv, 10 min prior to the exercise). All patients will undergo exercise stress echo (with wall motion score index, coronary flow reserve on left anterior descending and global longitudinal strain evaluation) and cardiac CT (with coronary collateral assessment) both before and after then therapy cycle.

Inclusion criteria: patients with documented coronary artery disease not amenable of further treatment and belonging to the “no-option” category (see above definition), with symptoms consistent with angina pectoris.

Exclusion criteria: patients with unstable angina, recent acute myocardial infarction, uncontrolled hypertension, haemodynamically significant valvular heart disease, bronchial asthma and neurologic and/or orthopedic illnesses that limit exercise capacity will be excluded. Patients receiving vitamin K antagonist will be excluded. Patients should not be actively involved in programmes of cardiac rehabilitation or exercise training.

All medications will remain unaltered during the study

Clinical and imaging (by blinded observers) assessment will be performed before and after treatment. ***Primary clinical endpoint*** is Canadian Cardiovascular Society (CCS) angina severity, ranging from class 1 (mild) to 4 (severe). ***Secondary stress imaging functional endpoint*** is peak Wall Motion Score Index (WMSI) at stress echo (ancillary endpoints: global longitudianl strain and coronary flow reserve). ***Tertiary imaging endpoint*** is Coronary Collateral Circulation Score at cardiac CT.

Detailed Work Plan

The overall architecture of the project is structured into work-packages (WP) that will be run by separate teams, in parallel with each other:

WP0- Study design and statistical plan

WP1- Patient recruitment and treatment

WP2-Assessment of treatment effect on inducible ischemia by stress echo

WP3- Assessment of Coronary Collateral Circulation by MDCT

WP0- Study design and Statistical plan

Sample size calculation. The study is sized to detect with 80% power a clinically significant difference in the chosen endpoints with alpha=0.05. For primary endpoint, a Canadian Class Angina = 2.5, with 0.5 standard deviation, and with an expected, clinically significant improvement of 0.5 will lead to a sample size of 16 patients per arm (94 % power with 25 patients per arm). For secondary endpoint, a peak WMSI = 1.4, with 0.25 standard deviation, and with an expected, clinically significant improvement of 0.2 will lead to a sample size of 25 patients per arm. Overall a drop-out rate of 20 % is expected, and therefore 60 patients will be initially considered and 50 are expected to complete the trial (25 for each arm)

Statistical plan: All continuous data will be given as mean+ SD. Baseline characteristics between the groups will be analyzed by Student t test for continuous data and chi-square/Fisher exact test for categorical data. Outcomes at follow-up examinations will be analyzed with chi-square test (for angina class) and paired Student t test (for approximately normally distributed data such as Wall Motion score index). Differences are considered statistically significant at a 2-sided P value of

<0.05. Electronic Case Report form preparation, ad interim and final data analysis will be performed by the Biometry Unit of the Institute of Clinical Physiology.

Core lab reading: All imaging data will be read by a single reader blinded to patient identity and study conditions.

Expected results: The group treated with active drug therapy will show a significant improvement of clinical, functional and perfusion indices when compared to standard rehabilitation therapy

WP1- Patient recruitment and treatment

CARHEXA is a prospective, randomized, single-center study: clinical enrollment and data collection will be done by Belgrade Unit. The Belgrade center has a recent tradition of clinical and scientific excellence in the field of diagnosis and treatment of coronary artery disease and has the facilities required to complete the study.

Ethical Committee submission will be presented at local authority by the Belgrade Unit, also responsible of clinical enrollment and data collection. We will recruit 60 patients with chronic stable angina refractory to medical management and not suitable for percutaneous and/or surgical revascularization therapy (see the above definition of "no-option" patients). In a prospective, randomized, open-label study design these "no-option" patients will be allocated (30 for each of the 2 groups) to one of 2 treatment groups: 1) standard physical rehabilitation (2 exercise session per day for 5 days a week for 2 weeks) with placebo (iv saline 10 min prior to exercise) ; 2) drug-primed physical rehabilitation (same modality as 1, but with H, 100 UI/Kg up to a maximum of 5.000 IU iv, 10 min prior to the exercise).

The Canadian Cardiovascular Society (CCS) classification of angina severity, ranging from class 1 (mild) to class 4 (severe), is used routinely in patients with coronary artery disease and is a recognized marker for disease progression.

The SAQ is a 19- item questionnaire that measures 5 clinically important dimensions of health in patients with CAD: angina frequency, angina stability, physical limitations, treatment satisfaction, and disease perception/QOL. Each domain has a score ranging from 0 to 100, with higher scores indicating less disease burden. The quality of life assessed with SAQ has been shown to correlate with long-term survival and hospitalization for acute coronary syndrome among patients with chronic CAD *(Spertus JA et al, Circulation 2002).*

Intravenous injections will be given by a study nurse not involved in the process of data acquisition and analysis.

WP2: Assessment of treatment effect on inducible ischemia by Stress Echo

Background: Stress echocardiography is an established technique for the diagnostic and prognostic evaluation of coronary artery disease. Wall motion score index assesses in a semi-quantitative way the extent of inducible ischemia, which is related to the anatomic and prognostic severity of underlying coronary artery disease. Noninvasive external pacing has the same accuracy as other physical and pharmacological stressors, and can be the first-choice option in patients with permanent pacemaker (*Sicari et al. 2009*).

Methods: All patients will undergo a resting echo and a stress echo, with either heparinized exercise (Group 1) or exercise (Group 2), according to standard clinical protocol (*Sicari R et al, Eur Heart J 2009*). Resting echo will assess all left ventricular function and remodeling indices, as previously described (Bolognese L et al, Circulation 2004). No change in underlying optimal conventional medical therapy will be done, except for clinically driven reasons, during the study period. Wall Motion Score Index (each segment from 1=normal to 4=dyskinetic in a 17 segment model of left ventricle) will be calculated at baseline and peak stress following the standard protocols of European Association of Echocardiography. In all patients a quantitative assessment of longitudinal strain by 2D speckle tracking will be performed.

WP3: Assessment of Coronary Collateral Circulation by MDCT

Cardiac CT will be performed to assess coronary collateral circulation in all patients before and after 2-week exercise. A collateral circulation will be graded by coronary CT *angiography* score where 0-2 means poorly developed collaterals and score 3 will be considered as well developed collaterals (0 = absence of distal filling; 1 = partial distal filling, with a length less than one-third of the segment; 2 = partial distal filling, with a length between one-third and two-thirds of the segment; 3 = complete or partial distal filling, with a length longer than two-thirds of the segment). CT angiography scores correspond fully to Rentrop classificatio. Also we will look for change in growth of baseline bridging collaterals at 2 weeks (0 = not present, 1 = present).

References

Barron HV, et al. Effects of the repeated administration of adenosine and heparin on myocardial perfusion in patients with chronic stable angina pectoris. Am J Cardiol 2000; 85: 1-7

Bolognese L, et al. Impact of microvascular dysfunction on left ventricular remodeling and long-term clinical outcome after primary coronary angioplasty for acute myocardial infarction. Circulation. 2004;109:1121-6.

Bombardini T, Picano E: The coronary angiogenetic effect of heparin: experimental basis and clinical evidence. Angiology 1997; 48: 969-76

Buschmann I, Schaper W. Arteriogenesis Versus Angiogenesis: Two Mechanisms of Vessel Growth. News Physiol Sci. 1999;14:121-125

Fujita M, et al. Improvement of treadmill capacity and collateral circulation as a result of exercise with heparin pretreatment in patients with effort angina. Circulation. 1988;77:1022-9

Gibbons RJ, et al. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1999 Guidelines for the management of Patients with Chronic Stable Angina. Circulation 2003; 107: 149 – 158

Mannheimer C, et al. The problem of chronic refractory angina; report from the ESC Joint Study Group on the Treatment of Refractory Angina. Eur Heart J. 2002;23:355-70

Meier P, et al. Myocardial salvage through coronary collateral growth by granulocyte colony-stimulating factors in chronic coronary disease: a controlled randomized trial. Circulation 2009; 120 ; 1355-1363

Picano E et al. Noninvasive pacemaker stress echocardiography for noninvasive diagnosis of coronary artery disease: a multicenter study JACC 2002; 40: 1305- 1310

Picano E, Michelassi C. Chronic oral dipyridamole as a “novel” antianginal drug: the collateral hypothesis. Cardiovascular research 1997; 33: 666-670

Picano E. on behalf of the Persantine In Stable Angina (PISA) study. Dipyridamole in chronic stable angina pectoris. A randomized, double blind, placebo-controlled, parallel group study. Eur Heart J 2001; 22: 1411- 23

Rentrop KP, Cohen M, et al. Changes in collateral filling after controlled coronary artery occlusion by an angioplasty balloon in human subjects. J Am Coll Cardiol. 1985;5:587–592.

Schirmer SH, et al. Stimulation of collateral artery growth: travelling further down the road to clinical application. Heart. 2009; 95:191-7.

Sicari R, et al.; European Association of Echocardiography. Stress Echocardiography Expert Consensus Statement--Executive Summary: European Association of Echocardiography (EAE) (a registered branch of the ESC). Eur Heart J. 2009;30:278-89.

Tateno S, et al. Alleviation of myocardial ischemia after Kawasaki disease by heparin and exercise therapy. Circulation. 2001;103:2591-7

Traupe T, et al. Assessment of the human coronary collateral circulation. Circulation. 2010;122:1210-20

Williams B, et al. Patients with coronary artery disease not amenable to traditional revascularization: prevalence and 3-year mortality. Catheter Cardiovasc Interv 2010; 75:886-91

Wykrzykowska JJ, et al. Imaging myocardial angiogenesis. Nat Rev Cardiol. 2009;6:648-58.