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EDITORIAL

Chronic refractory angina pectoris: recent progress and remaining challenges

Johannes Waltenberger[1,2]*

[1]Department of Cardiovascular Medicine, Division of Cardiology, University Hospital Münster, Münster, Germany; and [2]Cells-in-Motion Cluster of Excellence, EXC 1003–CiM, University of Münster, Münster, Germany

This editorial refers to 'Adenoviral intramyocardial VEGF-D$^{\Delta N \Delta C}$ gene transfer increases myocardial perfusion reserve in refractory angina patients: a phase I/IIa study with 1-year follow-up'†, by J. Hartikainen *et al.*, on page 2547.

Refractory angina, also described as chronic refractory angina pectoris (CRAP), classically occurs in patients with advanced, often diffuse coronary artery disease (CAD) that failed to be completely revascularized by percutaneous coronary intervention (PCI) and/or coronary artery bypass graft (CABG) with remaining angina pectoris symptoms despite maximized pharmacological intervention. In the majority of patients with CRAP, myocardial ischaemia can be detected by perfusion imaging using either cardiac magnetic resonance imaging (CMR), stress echocardiography, myocardial scintigraphy, or positron emission tomography (PET).

Chronic refractory angina pectoris has been a field of intense research and innovation during the past three decades. A number of novel modalities have been explored and introduced accordingly (*Figure 1*), in addition to significant improvement of PCI based on the introduction of novel technical equipment and skills.

Promoted from the early 1990s on, one of the first concepts for reducing chronic ischaemia and for symptomatic improvement of CRAP patients has been therapeutic angiogenesis and therapeutic arteriogenesis using local delivery of growth factor therapy, as either protein or as gene therapy.[1] The study by Hartikainen *et al.*[2] in the present issue of the journal is the latest contribution of its kind and will be commented on in detail below.

Various innovative treatment modalities can improve myocardial perfusion in patients with CRAP

Enhanced external counterpulsation (EECP) was introduced in the 1990s and validated thereafter.[3] Coronary perfusion is enhanced during diastole by elevating the diastolic blood pressure based on the external compression of the lower extremites using inflatable cuffs. In addition, this procedure may stimulate therapeutic angiogenesis in the partially ischaemic heart.

Another promising and targeted approach to improve regional myocardial perfusion is cardiac shockwave therapy (CSWT). The repeated application of external shockwaves targeting—echo-based—the area of proven ischaemia can locally stimulate therapeutic angiogenesis. Convincing clinical data have been presented recently.[4]

A major step forward in the successful treatment of patients with CRAP was the introduction of novel PCI guide wires, balloons, and microcatheters that allowed a safe and permanent opening of totally and chronically occluded conronary arteries (CTOs). The knowledge of how to use these devices has been accumulated and is now available for both antegrade and retrograde revascularization of CTOs.[5] This concept has greatly contributed to improve the symptoms of selected patients with CRAP.[5] It remains to be demonstrated in a prospective randomized trial, however, whether CTO-PCI in CRAP patients does improve survival of these patients, although data from registries[6] suggest this.

A very interesting alternative concept to improve myocardial perfusion in chronic myocardial ischaemia and to reduce symptoms in patients with CRAP has been introduced recently by using a coronary sinus reducing device.[7] Regional myocardial perfusion is improved by redistributing blood into the ischaemic myocardium secondary to reducing the venous outflow from the coronary sinus.

Although tremendous progress has been made in the field of somatic gene transfer in recent years, the final proof of efficient and succesful gene therapy to stimulate therapeutic angiogenesis and therapeutic arteriogenesis remains to be demonstrated.[8] The study by Hartikainen *et al.*[2] now suggests some efficacy, at least with regard to the improvement of regional myocardial ischaemia, using advanced PET-based imaging.

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* Corresponding author. Department of Cardiovascular Medicine, Division of Cardiology, University Hospital Münster, Albert-Schweitzer-Campus 1, Building A1, D-48149 Münster, Germany. Tel: +49 251 834 3201, Fax: +49 251 834 3204, Email: waltenberger@email.de

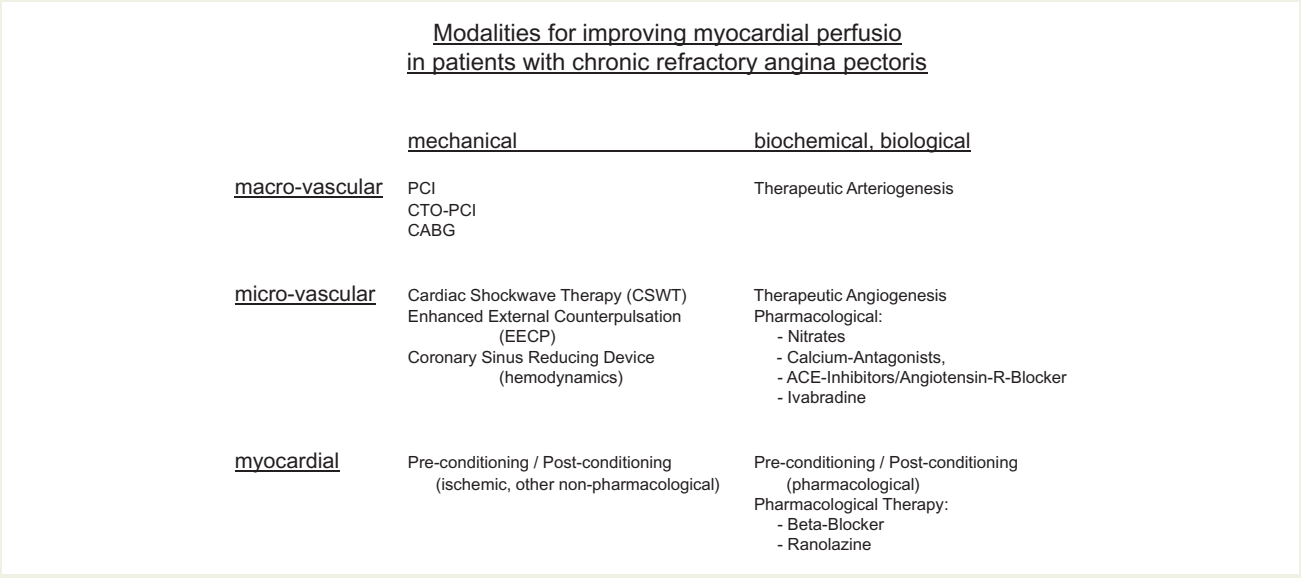

Figure 1 Modalities for improving myocardial perfusion in patients with chronic refractory angina pectoris.

Another crucial step on the long journey to the succesful implementation of vascular gene therapy

About 25 years ago, vascular gene therapy had created a hype in the cardiovascular community. The identification and characterization of vascular-specific growth factors such as vascular endothelial growth factor-A (VEGF-A) along with the availability of gene transfer modalities such as adenoviral vectors or other forms of recombinant DNA delivery ('naked DNA') had triggered several phase I/II trials in both myocardial and peripheral ischaemia. Those trials aimed at implementing proangiogenic and proarteriogenic gene therapy for either ischaemic heart disease, refractory angina pectoris, or peripheral limb ischaemia.[1]

The growth factor VEGF-A turned out to be a specific and reliable stimulator of vascular growth.[1] Alternative approaches had been testing fibroblast growth factor-2 (FGF-2) and other vascular growth factors. However, gene transfer technology was in its infancy and did not work the way in which it should. Along with the unavailability of reliable local delivery or local targeting strategies, the outcomes of controlled trials have been rather disappointing so far.[8]

While the field started to focus on cell therapy rather than on gene therapy, the group at the A.I. Virtanen Institute in Kuopio had continuously been working on improving adenoviral vascular gene transfer along with the identification of novel vascular growth factors throughout the years.[9]

In their latest study, Hartikainen *et al.* now provide data from testing adenoviral gene transfer of 10 injections of a variant of VEGF-$D^{\Delta N \Delta C}$ in the heart of patients with refractory angina.[2] VEGF-D is known to stimulate both angiogenesis and lymphangiogenesis, and has several potential advantages over other peptide growth factors, as outlined by the authors. Myocardial perfusion reserve (MPR) was assessed using PET imaging as a primary readout. MPR increased in the treatment group as well as in the control group; however, the increase was not statistically significant in the control group.

While this clearly represents a step forward in the establishment of vascular gene therapy for reducing myocardial ischaemia, a few critical questions remain.

i. What was the exact definition used for chronic refractory angina in the patient selection of this trial? Does this definition discriminate between atypical and typical angina as established in the ESC guidelines on stable angina.[10] Moreover, can patients with a component of non-cardiac chest pain be excluded with certainty?
ii. Has medical antiangiogenic treatment been optimized and maximized in all patients? Ranolazine or ivabradine have not been mentioned in the list of drug therapy.[10] Likewise, the intensity of nitrate use had not been monitored in the curent trial as was done in other trials on CRAP.[4] In any case, optimized medical therapy at the time of patient inclusion in the study would be important to minimize variability of the clinical outcome during the course of the study.
iii. Is regional myocardial perfusion an adequate endpoint of a trial for CRAP? Previous studies of similar size studying CRAP patients had been able to document a reduction in myocardial perfusion as well,[4] and this had been correlated with reduction in symptoms. Nevertheless, a reduction of angina symptoms would be the most important goal to be achieved in these patients that warrant therapeutic improvement.
iv. Is a randomization design of 4:1 (treated vs. control) adequate for a phase I/II trial? This is certainly a crucial point in the study by Hartikainen *et al.*, which concludes that the improvement in CCS (Canadian Cardiovascular Society) class reached statistical significance in the treatment group, but not in the control group. However, this conclusion is potentially biased as the average reduction in symptoms (CCS class) was rather similar in both groups. The reason why the improvement in the control group was not statistically significant may be based on the fact that the control group was much smaller (n = 6) compared with the treatment group (n = 24), therefore making this phase I/II study rather sensitive for being driven by any play of chance. On the other hand, we should be aware that this study has not been powered for any solid conclusion regarding efficacy. This will be the subject of the phase II trial that has been set up based on the safety data from the current trial (see below).

v. The small number of individuals in this study should call for caution in interpreting any other 'outcome' data including any correlation with the potential biomarker Lipoprotein(a).

The data generated by Hartikainen *et al.* are certainly encouraging as they provide a solid basis for a larger prospective and randomized phase II trial on adenoviral VEGF gene therapy in patients with chronic refractory angina pectoris, which is already set up at https://clinicaltrials.gov (NCT03039751). The remaining open questions raised by Hartikainen *et al.* should be solved there.

Conflict of interest: none declared.

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