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Clinical Efficacy of Permanent Internal Mammary Artery Occlusion in Chronic Coronary Syndrome: a Double-Blind, Randomized, Sham-Controlled Trial

Running title: CLIMACCS Trial

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Abstract

The CLIMACCS trial, a randomized, sham-controlled trial tested the CLinical efficacy of permanent internal mammary artery (IMA) device occlusion on symptoms in patients with chronic coronary syndrome (CCS), on coronary artery occlusive blood supply, and on myocardial ischemia. This was a prospective trial in 101 patients with CCS randomly allocated (1:1) to IMA device occlusion (verum group) or to IMA sham intervention (placebo group). The primary study endpoint was the change in treadmill exercise time (ΔET in seconds, s) at 6 weeks after trial intervention. Secondary study endpoints were the changes in collateral flow index (CFI), and angina pectoris during a simultaneous 1-minute proximal balloon occlusion of a coronary artery. CFI is the ratio between simultaneous mean coronary occlusive divided by mean aortic pressure both subtracted by central venous pressure. In the verum and placebo group, exercise time changed from 398±176s to 421±198s in the verum group (p=0.1745), and from 426±162s to 430±166s in the placebo group (p=0.55); □ET amounted to +23±116s and +4±120s, respectively (p=0.44). CFI change during follow-up equalled +0.022±0.061 in the verum and-0.039±0.072 in the placebo group (p<0.0001). Angina pectoris at follow-up during the coronary balloon occlusion for CFI measurement had decreased or disappeared in 20/48 patients of the verum, and in 9/47 patients of the placebo group (p=0.0242). In conclusion, permanent IMA device occlusion tends to augment treadmill exercise time in response to heightened coronary artery occlusive blood supply, the fact of which is reflected by mitigated symptoms and signs of myocardial ischemia.

Introduction

Depending on the severity and frequency of angina pectoris, chest pain refractory to optimal medical therapy or to myocardial revascularization has been shown to range between 2-24% [1]. The cumulative 9-year mortality rate in a registry of patients with refractory angina pectoris has been reported 28% [2].Treatment options for refractory angina pectoris in chronic coronary syndrome (CCS) are, so far, limited to three methods: Percutaneous coronary intervention of chronic total occlusion(s) [3], coronary sinus constriction [4, 5], and application of external counterpulsation [6], whereby all of them have been tested in regard to symptom relief using –in part- a sham controlled trial design. Thus, novel treatment strategies for patients with CCS and refractory angina aimed at improving symptoms and prognosis via augmented myocardial blood supply are sought for.

In the event of coronary occlusion, myocardial ischemia is mostly influenced by its duration, and the presence or lack of alternative sources of blood supply to the ischemic region (collateral supply) [7]. Alternative sources of coronary blood supply consist of inter-coronary anastomoses, i.e., the coronary collateral circulation, whose benefit on survival has been demonstrated in CCS [8]. Extracardiac coronary blood supply via the internal mammary arteries (IMA) as natural, i.e., native non-surgical bypasses has been described anatomically and conceptually [9Picichè, 2011 #578], but not tested for clinical efficacy as a new therapeutic option. As proof of concept, our group has provided first evidence of myocardial ischemia-reducing extracardiac coronary artery supply during temporary as well as permanent IMA occlusion [10-12].

The present randomized controlled CLIMACCS trial was designed to assess the CLinical efficacy of permanent right or left IMA device occlusion on symptoms in patients with CCS, on coronary artery occlusive blood supply, and on myocardial ischemia.

Methods

Study design and patients

This was a prospective, double-blind, longitudinal (baseline and follow-up endpoint measurements), placebo-controlled, clinical superiority trial with 1:1 randomized allocation to IMA device occlusion (verum group) or IMA sham procedure (placebo group) of 101 patients with symptomatic CCS undergoing coronary angiography, and diagnosed with at least one coronary artery stenosis (figure 1).

Randomized allocation to the group undergoing baseline IMA device occlusion or to the placebo group was computer generated.

The primary study endpoint was the change in treadmill exercise time (ΔET in seconds, s) during 6 weeks of follow-up after trial intervention versus baseline. Secondary study endpoints were the respective changes in collateral flow index (CFI), and angina pectoris simultaneously obtained during a 1-minute proximal balloon occlusion of the coronary artery of interest. CFI is the ratio between simultaneous mean coronary occlusive divided by mean aortic pressure both subtracted by central venous pressure [13]. As further secondary study endpoint, the change in quantitatively determined intracoronary (i.c.) ECG ST-segment shift during the identical 1-minute coronary occlusion was measured.

Criteria for study inclusion were age ≥18 years, 1- to 3-vessel CCS, percutaneous coronary intervention (PCI) of the culprit coronary lesion deferrable for 6 weeks, and written informed consent for trial participation. Exclusion criteria were acute coronary syndrome, previous myocardial infarction in the vascular region undergoing secondary

endpoint measurements, prior surgical coronary bypass, severe hepatic or renal failure (creatinine clearance < 15ml/min/1.73m^2).

The study was approved by the ethics committee of the Kanton of Bern, Switzerland (KEK 2018-01480), and all patients gave written informed consent to participate before the start of the baseline invasive exam.

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The authors are solely responsible for the design and conduct of this trial, all trial analyses, the drafting and editing of the paper and its final contents.

Cardiac catheterization and coronary angiography

Patients underwent left heart catheterization and coronary angiography for diagnostic purposes from the right radial artery approach via a 6-in-5F introducer sheath. Biplane coronary angiography was performed followed by left ventriculography. Coronary artery stenoses were assessed quantitatively as percent diameter reduction using the guiding catheter for calibration. Aortic pressure (P_{ao}) was acquired via a 6F guiding catheter. If applicable, central venous pressure (CVP) was measured by a 5F pigtail catheter via the right femoral vein.

Randomisation and masking

Randomised, computer-based allocation to the IMA device occlusion or placebo group occurred after diagnostic coronary angiography. Patients were not informed about group allocation until completion of all the follow-up study endpoint measurements. The interventional operator (CS) was not blinded to the study procedure at baseline;

nor was he blinded at follow-up exam, since the device was instantaneously visible already during fluoroscopy. At the time of data analysis, the analysing operators (different from the interventional operator) were unaware of a patient's group allocation.

Study endpoints

Primary study endpoint: Treadmill exercise time (ET in seconds, s) was obtained during treadmill ergometry using an identical exercise protocol at baseline and follow-up. Selection of the exercise protocol was left at the discretion of the admitting clinical physician who was not involved in the study. Treadmill exercise tests were carried out immediately before (i.e., on the same day) the invasive procedures at baseline and follow-up exam. The exercise test was terminated according to the patient's request in the context of evolving symptoms or exhaustion. The change in ET (ΔET, s) and in secondary study endpoints was determined as difference between follow-up values minus baseline values.

Secondary study endpoints: Coronary occlusive collateral flow relative to normal antegrade flow through the non-occluded coronary artery (collateral flow index, CFI) was determined using coronary pressure measurements. A 0.014 inch pressure monitoring angioplasty guidewire (PressureWire^{TM} X Guidewire, Abbott, Chicago, Illinois, United States) was set at zero, calibrated, advanced through the guiding catheter, and positioned in the distal part of the vessel of interest (identical position at baseline and follow-up exam). CFI was determined by simultaneous measurement of mean aortic pressure (P_{ao}, mmHg), mean distal coronary artery pressure during ostial coronary artery balloon occlusion (P_{occl}, mmHg), and –in the minority of cases- mean central venous pressure (CVP, mmHg; figure 2) as measured during the last 10

seconds of the 1-minute coronary balloon occlusion. CFI was calculated as (P_{occl}-CVP) divided by (P_{ao}-CVP) [13]. The accuracy of pressure-derived CFI measurements in comparison to absolute myocardial perfusion measurements has been documented previously [14].

Symptoms and signs of myocardial ischemia were assessed simultaneous to CFI measurements, i.e., during the same 1-minute ostial coronary artery balloon occlusion. Myocardial ischemia was characterized by the presence or absence of angina pectoris, and by its intensity on a scale from 0-10 as interrogated immediately after release of the angioplasty balloon occlusion at baseline and follow-up exam. The parameter change from baseline to follow-up exam was analysed according to its intensity or dichotomized as follows: angina pectoris disappeared vs unchanged / newly manifest. Additionally, intracoronary ECG (icECG) ST-segment shift in mV was recorded during the same 1-minute coronary artery balloon occlusions (figure 2). IcECG was obtained from the angioplasty pressure guidewire via a cross-clamp to a precordial lead. Quantitative icECG ST-segment shift was determined as the difference between icECG ST-segment shift (elevation or depression obtained at the J-point) during coronary occlusion minus icECG ST-segment shift immediately before coronary occlusion.

Study protocol

Immediately following right radial artery sheath insertion, 5’000 units of intravenous heparin plus two puffs of oral isosorbidedinitrate were given. Following diagnostic coronary angiography and at the start of the invasive baseline and follow-up study procedure, all patients received an additional 5000 units of heparin intravenously.

The coronary artery of interest undergoing secondary endpoint measurements was selected according to the site of the most severe and most proximal stenotic lesion by visual assessment.

For coronary artery CFI and myocardial ischemia measurements, an adequately sized angioplasty balloon catheter was positioned in the ostial part of the coronary artery of interest while the pressure guidewire was placed distally. Coronary balloon inflation occurred at a pressure of 1-2 atmospheres. Complete coronary occlusion was ascertained angiographically using small volume contrast injections. During the 1-minute occlusion, simultaneous P_{occl}, P_{ao} and CVP (where applicable) were recorded for the calculation of CFI (figure 2). During the entire procedure, the icECG obtained from the guidewire was recorded. Immediately following CFI measurement, the patient was asked about the occurrence of angina pectoris during coronary balloon occlusion. Directly after coronary balloon deflation and without changing the sensor wire position, reactive-hyperaemia, i.e., post-occlusive FFR (=distal coronary pressure divided by P_{ao}) was obtained immediately following coronary angiography.

In both groups, radiographic imaging of the IMA was performed using a 5F IMA catheter (figure 3). The IMA of interest as study vessel was chosen according to the coronary artery undergoing endpoint measurements and PCI after follow-up measurements. The ipsilateral IMA was selected in case of the right coronary artery (RCA →RIMA) or left anterior descending artery (LAD →LIMA), respectively as the vessels of interest. In case of the left circumflex coronary artery (LCX) as the vessel of interest, the RIMA was chosen for device occlusion in the verum group (indeterminate effect according to Stoller et al. [10]). In the placebo group, the baseline exam ended after IMA angiography. In the verum group, the radial artery access was switched to

the left arm for LIMA occlusion. For both RIMA and LIMA device occlusion, a Radiofocus® 0.032inch, 260cm stiff guidewire (Terumo Corporation, Tokyo, Japan) was inserted into the IMA catheter and advanced with its tip to below the diaphragm. The IMA catheter was then engaged in the IMA until its tip reached the level of the right atrium in antero-posterior image projection. Subsequently, an appropriately sized (4-5mm in diameter) Amplatzer vascular plug 4® (Abbott, Chicago, Illinois, USA) was inserted via the IMA catheter into the IMA and released at the level of the right atrium (figure 3, middle panel). Invasive follow-up exams at 6 weeks after IMA device occlusion or sham procedure consisted of IMA radiographic imaging in both groups, and of identical study endpoint measurements as described above.

Statistical analysis

Sample size calculation was performed using a two-sided unpaired Student's t test with the primary study endpoint of ΔET during the 6-weeks follow-up study period, and was based on the following alternative hypothesis: ΔET from baseline to follow-up exam is higher in the verum group than in the placebo group. ΔET was estimated to be +18s in favour of the verum group at a standard deviation of 50s yielding an effect size of 0.36. At an alpha level of 0.05 and a power of 0.80, the calculated sample size was equal to 246 patients (123 per group).

Between-group comparison of continuous demographic, clinical, angiographic, hemodynamic variables, and study endpoint variables was performed by unpaired Student's t-test. A Fisher's exact test was used for comparison of categorical variables among the study groups. Intra-individual comparison of continuous parameters obtained at baseline versus follow-up exam was performed by a paired Student's t-test.

Data were analysed on an intention-to-treat basis. Statistical significance was defined at a p-level <0.05. Continuous variables are given as mean and standard deviation.

Results

Fifty patients were randomly allocated to the IMA device occlusion group (verum group), and 51 patients to the sham control group (placebo group; figure 1 and table 1). Two patients in the placebo group were lost to follow-up (figure 1). In the verum group, 34 patients underwent RIMA and 16 patients underwent LIMA device occlusion. Study recruitment was terminated after three years due to slow patient accrual.

Patient characteristics and clinical data at baseline

Three fourths of patients were on optimal anti-anginal medical therapy at trial inclusion. Twenty-seven of 101 patients did not receive optimal medical therapy. Of these patients, 20 were allocated to the IMA device occlusion, i.e., the verum group, and 7 to the placebo group (p=0.0121). At follow-up, the number of patients on optimal medical therapy remained unchanged in both study groups. Patients did not differ in their baseline medical characteristics between the study groups, except for angina pectoris, which occurred more often in the verum than the placebo group (table 1). Regarding cardiovascular medication, there was no difference between the groups, except for the less frequent use of diuretics in the verum than the placebo group (table 1).

Hemodynamic and coronary angiographic data at baseline

There were no statistical differences between the groups at baseline in heart rate, systemic blood pressure, left ventricular end-diastolic pressure, left ventricular ejection

fraction and central venous pressure (table 2). Central venous pressure was directly obtained at baseline in 14 patients (7 each in both groups), and it was assumed equal to 5mmHg in 86 patients.

The distribution of coronary arteries with stenotic lesions treated by PCI at follow-up was similar between the groups (table 2). Coronary artery quantitative percent diameter stenosis and the number of chronic total coronary occlusions were similar in both groups (table 2). Hemodynamic stenosis severity (FFR) was less severe in the verum than the placebo group.

PCI in all patients was deferred until after the follow-up measurements of all study endpoints.

At baseline, treadmill exercise time was similar, i.e., approximately 400s in both study groups (table 2). Coronary artery CFI at baseline was lower in the verum than the placebo group (table 2). At baseline, angina pectoris during the same ostial coronary artery occlusion as for CFI measurement was similarly severe among the groups, and i.c. ECG ST-segment shift was not statistically different in the verum and the placebo group (table 2).

Treadmill exercise time, coronary collateral function and myocardial ischemia during follow-up

Primary study endpoint: Treadmill exercise time increased from 398±176s to 421±198s in the verum group (p=0.1745), and it changed from 426±162s to 430±166s in the placebo group (p=0.55; table 2 and figure 4). The exercise time increment (ΔET) was +23±116s in the verum group and +4±120s in the placebo group (p=0.44; figure 5).

Secondary study endpoints:

Coronary artery CFI changed from 0.120±0.078 at baseline to 0.142±0.073 at follow-up in the verum group (p=0.0126), and from 0.168±0.127 at baseline to 0.126±0.103 at follow-up in the placebo group (p=0.0004; table 2 and figure 6). Coronary artery CFI change during follow-up was significantly higher in the verum than in the placebo group (table 2 and figure 7). During the 1-minute ostial coronary occlusion for CFI measurement, angina pectoris had disappeared at follow-up in 20 patients of the verum group, and in 9 patients of the placebo group (p=0.0242; figure 8). Similarly, angina pectoris over the 6 weeks follow-up had disappeared in 14 patients of the verum group and in 4 of the placebo group (p=0.0176; table 2).

There was a trend to a decrease in icECG ST-segment shift (as obtained simultaneously with CFI measurement) during follow-up in the verum group (p=0.1690), whereas the respective change was positive during follow-up in the placebo group (table 2 and figure 9).

The heart rate change during coronary occlusion (at follow-up minus baseline) was not statistically different among the study groups (table 2).

Procedural feasibility of IMA closure

IMA device closure in the verum group was successful in all but two patients (2 failed implantations). One case of proximal RIMA dissection occurred. This complication was left untreated without sequelae. During the 6 weeks follow-up, all patients of the verum group remained asymptomatic with regard to the IMA device closure.

Angiographic control of the IMA in the verum group at follow-up revealed incomplete occlusion at the device in 29 of 50 cases. Among patients with incomplete occlusion

exercise time increment was smaller though not statistically different in comparison to patients with complete occlusion (+17±117s and +32±129s, respectively; p=0.66).

Discussion

The present randomized controlled, double-blind clinical trial found a trend to prolonged treadmill exercise time six weeks after permanent IMA device occlusion (verum group), though the difference in exercise time *change* was not statistically different from the group receiving IMA sham intervention. Secondary study endpoints specific for myocardial ischemia, i.e., angina pectoris during a 1-minute coronary balloon occlusion had disappeared more often at the follow-up vs baseline exam in the verum than in the placebo group, the fact of which can be explained by the simultaneously augmented coronary supply in patients having undergone IMA device occlusion at baseline. The less frequent angina pectoris during coronary occlusion in patients of the verum group was mirrored by the more frequent disappearance of angina during the entire study period, i.e., during coronary artery patency.

Therapeutic options for refractory angina pectoris

Three quarters of the present trial's patients fulfilled by definition the diagnosis of refractory angina pectoris, since the symptom lasted for ≥3 months despite optimal medical therapy [1]. The multitude of therapeutic options listed even in a recent review on controlling refractory angina pectoris reflects its relevance as a health problem, and equally important, the ongoing search for a "cure" against it- [1]. Many therapeutic approaches have not been proven efficacious in the past, such as transmyocardial laser treatment [15], surgical unroofing of myocardial contractile bridges (during systole in a circulatory system, such as the coronary, in which flow is diastolic) [16], electrical spinal stimulation [1, 17], therapy with angiogenic substances [18, 19], or pluripotent stem

cells [20]. Methods having been shown effective on angina pectoris severity are ante- or retrograde PCI of chronic total coronary occlusion(s) with reduced myocardial supply causing ischemia [21], diastolic lower-limb external counterpulsation [6], and coronary sinus reducer stent implantation [4]. But so far, none of the mentioned therapeutic approaches for refractory angina has been documented effective on patients' *outcome* with refractory angina [1]. In addition and except for external counterpulsation and coronary sinus reducer therapy [4, 6], the placebo effect of the different therapeutic modalities on refractory angina has not been controlled for by a randomized trial. Furthermore, the only efficacious method with regard to improved exercise tolerance and angina pectoris relief, which is sustainable is coronary sinus reducer intervention [4].

The majority of patients in the present trial was on optimal medical therapy at study onset. Medical treatment remained unchanged during the course of the trial, and PCI was deferred in all patients until after the trial's follow-up endpoint measurements, i.e., six weeks following IMA device occlusion or IMA sham procedure. Thus, study endpoint changes during follow-up among patients of the present trial can be attributed to the experimental or to the sham procedure, the fact of which is particularly applicable to qualitative parameters such as exercise tolerance and the level of angina pectoris. The latter was positively influenced in the verum group of our trial, manifesting as more frequent disappearance of angina during follow-up in comparison to the sham or placebo group. Similar results have been obtained in the COSIRA trial (Coronary Sinus Reducer for Treatment of Refractory Angina, [4]). Of note, angina pectoris in the present trial was –primarily- assessed during a 1-minute ostial coronary balloon occlusion, i.e., most systematically using a uniform "stress test" (blocking epicardial antegrade coronary flow for a given time) equally applicable to all study participants. Angina

pectoris as obtained in this way disappeared more frequently in the verum than the placebo group (figure 8). The identical 1-minute coronary occlusion was employed for two other secondary, quantitative endpoint measurements (collateral function, CFI, and icECG ST-segment shift), thus providing information on the physiologic mechanism by which permanent IMA device occlusion could beneficially affect angina: by augmented coronary collateral supply (CFI increase; figure 7).

Since no intervention was performed during follow-up at the coronary circulatory level, the augmented occlusive coronary supply (CFI) in the verum group must have been due to the extracardiac source of anatomical anastomoses between the IMAs and the heart [9]. In parentheses, this does not explain the relevant decrease in CFI during follow-up in the placebo group, which –in the absence of an intervening PCI- remains elusive.

Extracardiac coronary artery supply

In contrast to the human inter-coronary collateral arterioles and arteries called endomural coronary anastomoses, extracardiac coronary arterial anastomoses have received much less attention though they have been known for a long time in healthy and diseased individuals [9]. Hudson et al. discovered naturally existing coronary bypasses by accident while injecting the coronary circulation with ink, and observing the dye dispersing to sites such as the pericardium, the pericardial reflections of the great vessels, and anterior mediastinal, phrenic, intercostal, esophageal and pericardiacophrenic arterial branches [9]. The pericardiacophrenic arterial branch is the first or second branch taking off the proximal IMAs at the second intercostal space. On angiography, it is easily recognizable by its unique motion pattern simultaneous to the

heart beat. Case reports have provided structural angiographic evidence of arterial connections between the pericardiacophrenic artery and the coronary arteries [22, 23].

The upper and lower limb arterial circulation is interconnected bilaterally via the IMAs. Thus, the supply regions of the IMAs and their native, i.e., non-ligated side branches are not at risk for ischemia in case of IMA occlusion. This can be appreciated by the fact that collateral perfusion pressure downstream of a proximal IMA balloon occlusion amounts to approximately 80% of normal perfusion pressure during IMA patency (own data). Hence, the relatively low number of ischemic events following IMA coronary artery bypass grafting is explained, and impaired sternal wound healing in response to extensive IMA side branch ligation supports the concept of upper- and lower-limb circulatory anastomosis via the IMAs. Before the advent of coronary bypass surgery, the *ligation* of the IMAs aiming at redirecting blood flow to the pericardiacophrenic branch was introduced as a treatment concept for angina pectoris by Fieschi [24]. The first sham-controlled clinical trial in the field of surgery among a total of 17 (sic!) patients has not found a difference in angina pectoris between those undergoing IMA ligation and the IMA sham group [25, 26], the publication of which together with the advent of the heart-lung-machine terminated this option of myocardial revascularization almost entirely. The physical basis of action of IMA ligation, i.e., flow diversion towards its side branches connecting to the heart, continued only in the Vineberg procedure with its stump implantation of the disconnected IMAs into the freely exposed myocardium.

Permanent left or right IMA occlusion

Recently, there have been three clinical investigations supporting the physical concept of enhanced myocardial perfusion by increased resistance –either temporary or permanent- to IMA flow downstream of its pericardiacophrenic branch [10-12]. The

primary study endpoint in all these investigations has been coronary collateral function during a brief ostial coronary balloon occlusion, i.e., CFI. The present randomized sham-controlled trial, on the other hand, investigated for the first time *clinical* efficacy of IMA device occlusion using the primary study endpoint of ΔET between the baseline and follow-up exam. ΔET in the verum and the placebo group was equal to +23s and +4s, respectively. Even though the intra-individual increments in exercise time among patients of the verum group surpassed the estimate used in this trial's sample size calculation on average by 5s, the *inter*-group difference in ΔET (projected to be 18s) did not reach statistical relevance due to the large variability in exercise times. In fact, the standard deviation found was more than twice as high as the projected 50s, to which heterogeneous exercise test protocols as well as patient gender might have contributed.

More importantly, the effect of the IMA sham procedure, i.e., the placebo effect on ΔET was largely different depending on the patient's vessel undergoing secondary endpoint measurements. While there was no placebo effect on ΔET among patients undergoing secondary endpoint measurements of the LAD and RCA, ΔET among LCX-patients amounted to practically identical values of +28s in the verum and +25s in the placebo group, respectively. This finding appears to be in agreement with that of an indeterminate effect related to LCX of (temporary) IMA occlusion documented in one of our earlier investigations on the topic [10], though the increase in ΔET in the placebo group remains elusive.

As a further source of variability affecting the primary study endpoint ΔET, incomplete IMA occlusion at follow-up may have played a role (with ΔET=+17s vs +33s in patients

with complete IMA occlusion; p=0.55). Among 29 of 50 patients of the verum group, angiographic control six weeks after device implantation revealed contrast medium directly injected into the IMA leaking beyond the device. Since trial data were analyzed according to the intention-to-treat principle, and since partial IMA occlusion tended to preserve the H0-hypothesis in our IMA-occlusion-superiority trial, incomplete IMA occlusion can be interpreted as a scientific strength rather than a limitation of the study. Practically speaking, intra-individual exercise times tended to be augmented in response to IMA device occlusion (see figure 4) despite the fact that in more than half the patients of the verum group, the vessel was only partially blocked at six weeks after implantation.

Study limitations

The main limitation of this trial is its premature termination, which occurred in the context of insufficient patient accrual, which itself was mainly influenced by the longitudinal trial design with an invasive follow-up exam and strict adherence to PCI deferral for six weeks. As an unintended corollary, more patients undergoing LCX than LAD or RCA endpoint measurements were recruited for the study, thus over-proportionally introducing “noise” into the data set. Equally important, it restricted the statistical power of the consistently more “responsive”, ipsilateral vessels, i.e., LAD (LIMA) and RCA (RIMA). Instead of one third the study population, 42% belonged to the LCX-group, which mostly affected the power of the RCA group (n=13 cases instead of 17). Thus and also in light of our former work showing robust efficacy for purely ipsilateral IMA occlusion [10], the LCX group should have been omitted and replaced by patients with LAD or RCA as culprit lesion. Sample size recalculation using the actually obtained data, i.e., including the LCX group (see table 2 for ΔET) would have required

600 patients per study group given an effect size d of 0.16 instead of the projected 0.36.

The underestimation of study endpoint variability during the trial's planning phase becomes also evident in regard to the secondary study endpoint of icECG ST-segment shift, the quantitative measure of myocardial ischemia. The degree of ischemia during coronary occlusion is not only influenced by the duration of the occlusion (held constant), the presence of microvascular disease, changing heart rate (no inter-group difference between baseline and follow-up), and by collateral supply (obtained as CFI) [7]. Another contributor to the amplitude of icECG ST-segment shift in mV is the size of ischemic myocardium, i.e., the area at risk. The area at risk is highly variable depending on the coronary artery and the myocardium downstream of the *ostial* occlusion (=experimental setup in our trial). Additionally, this variability is enhanced by the type of dominance of coronary supply. In the present trial, left coronary dominance was present in 9 of 100 cases with an almost identical distribution among the groups. The systematic ostial coronary occlusion site was chosen to render the ischemic areas for the different coronary arteries more homogenous when compared to varying occlusion sites. However and even with a systematically ostial occlusion site, the icECG ST-segment amplitude derived from the angioplasty sensor wire is sensibly influenced by its proximity position. This is particularly relevant in the context of potentially changing wire positions at the baseline vs follow-up exam. It is a limitation of the present study that insufficient care was taken to ascertain identical wire position between baseline and follow-up exams in all cases. Two cases from the placebo group with the most pronounced *decrease* in icECG ST-segment shift during follow-up (from 5.4 to 3mV, and from 1.5 to 0.4mV, respectively) in whom no change would be expected both showed a much more proximal wire position at follow-up vs baseline

exam (in both cases proximal to the bifurcation of ramus interventricularis posterior and posterolateral branch at follow-up and distal at baseline). Excluding these two cases from the analysis would have resulted in a significant difference in icECG ST-segment shift between the study groups (less ischemia in the verum group; p=0.05); the data shown *in*clude the mentioned cases.

C o n c l u s i o n

Permanent IMA device occlusion tends to augment treadmill exercise time in response to heightened coronary artery occlusive blood supply, the fact of which is reflected by mitigated symptoms and signs of myocardial ischemia.

Disclosures

None

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Figures

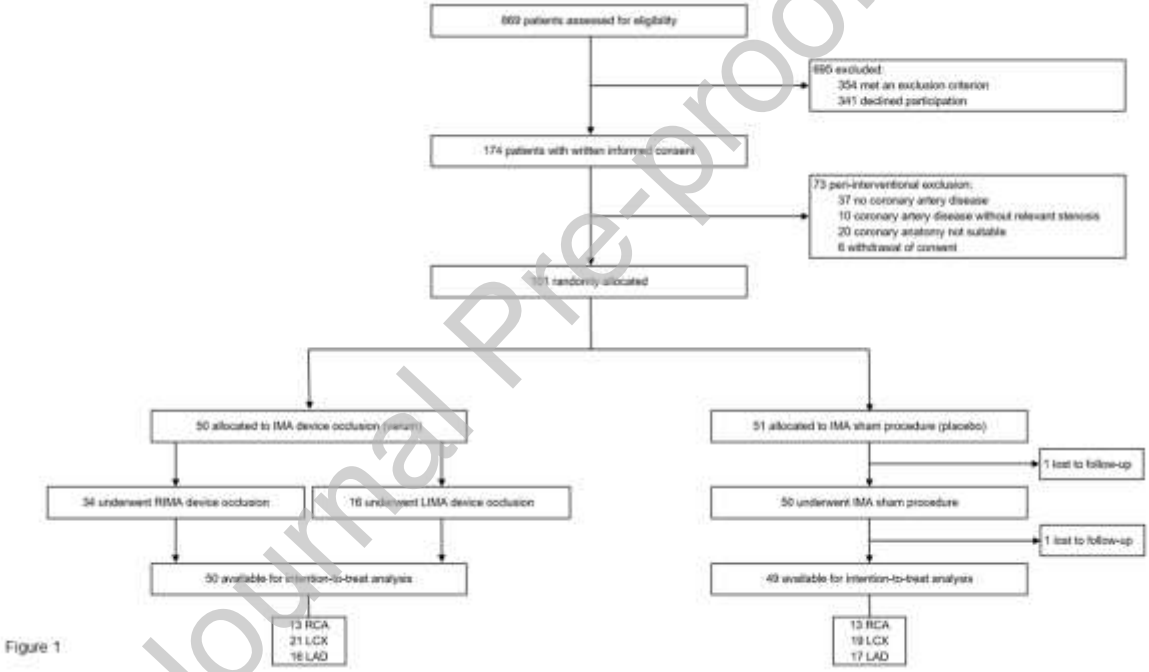

Figure 1 Trial profile.

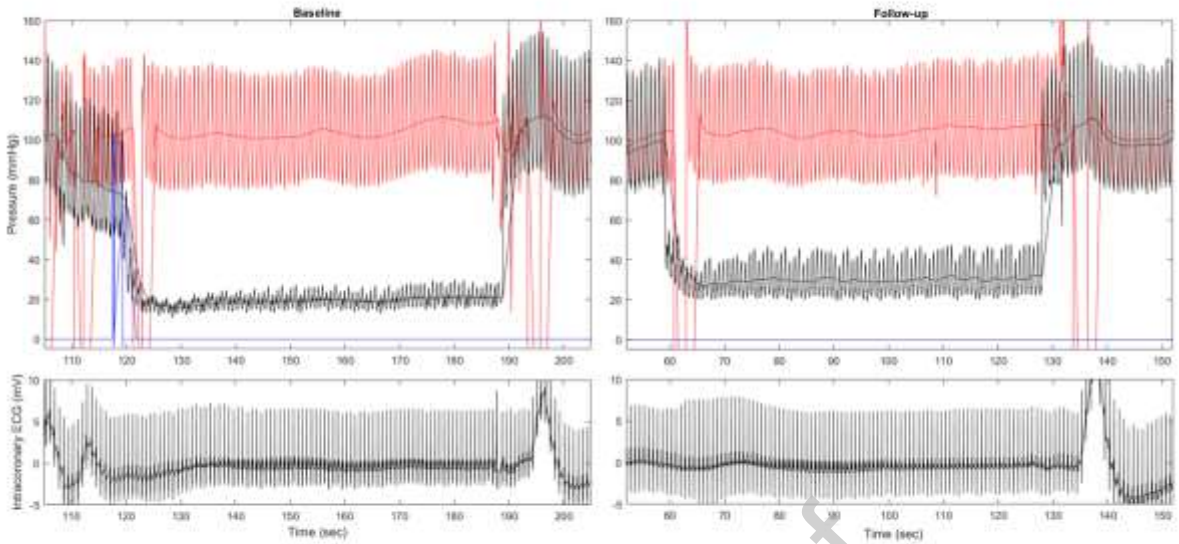

Figure 2

Figure 2 Simultaneous recordings during the 1-minute ostial coronary balloon occlusion of phasic and mean aortic pressure (P_{ao}, red curve), coronary occlusive pressure (P_{occl}, black curve), central venous pressure (CVP, not recorded in this case, assumed to be equal to 5mmHg) and intracoronary ECG (bottom, black curve) as obtained during baseline (left) and follow-up (right) exam. Collateral flow index, $CFI=(P_{occl}-CVP)/(P_{ao}-CVP)$.

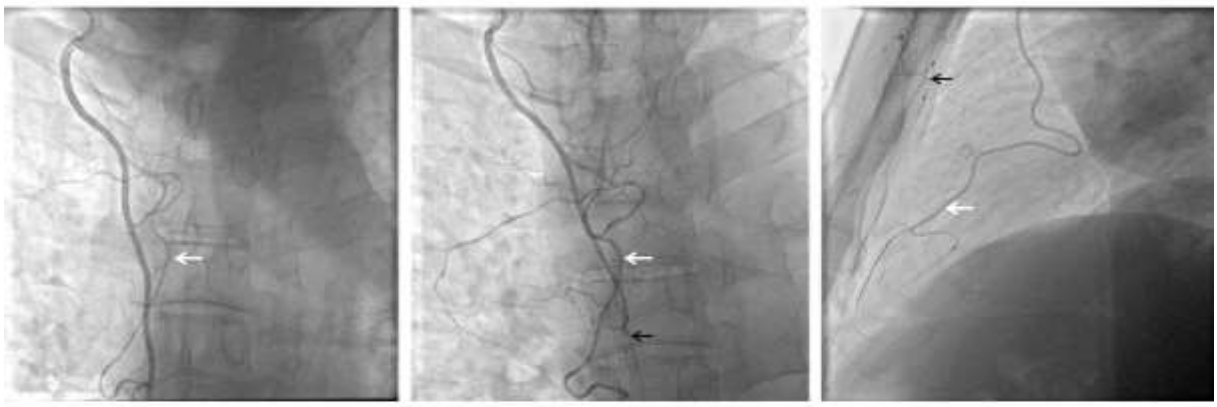

Figure 3

Figure 3 Right internal mammary artery angiographies at baseline (left panel) and follow-up exam (middle and right panel) in antero-posterior and lateral (right panel) projection. The pericardiacophrenic branch of the internal mammary artery (device-occluded in the middle and right panels; black arrow) is indicated by the white arrow.

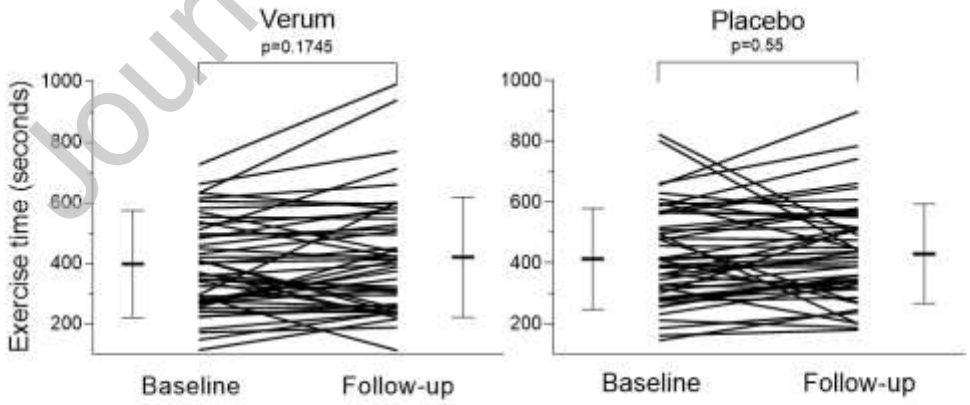

Figure 4

Figure 4 Individual values of exercise time (vertical axis) for patients in the verum (left) and the placebo group (right) as obtained at baseline and follow-up exam. Error bars indicate mean values and standard deviation.

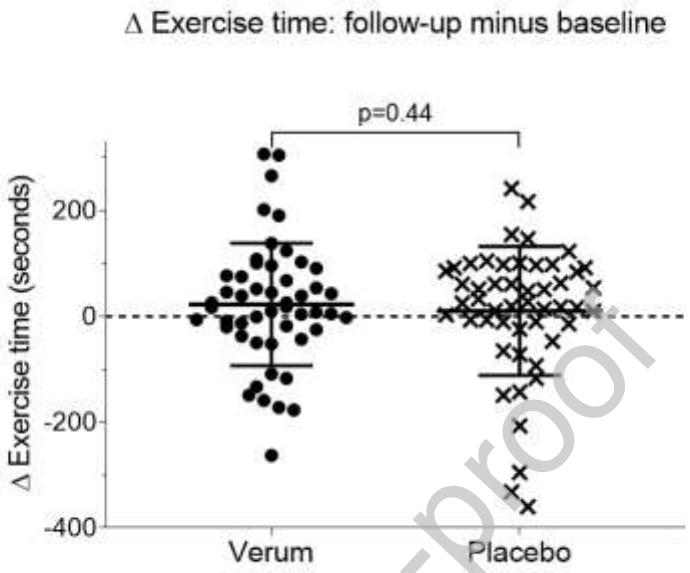

Figure 5

Figure 5 Individual changes of treadmill exercise time between baseline and follow-up exam (ΔET) for patients in the verum (filled circles, left) and the placebo group (crosses, right). Error bars indicate mean values and standard deviation.

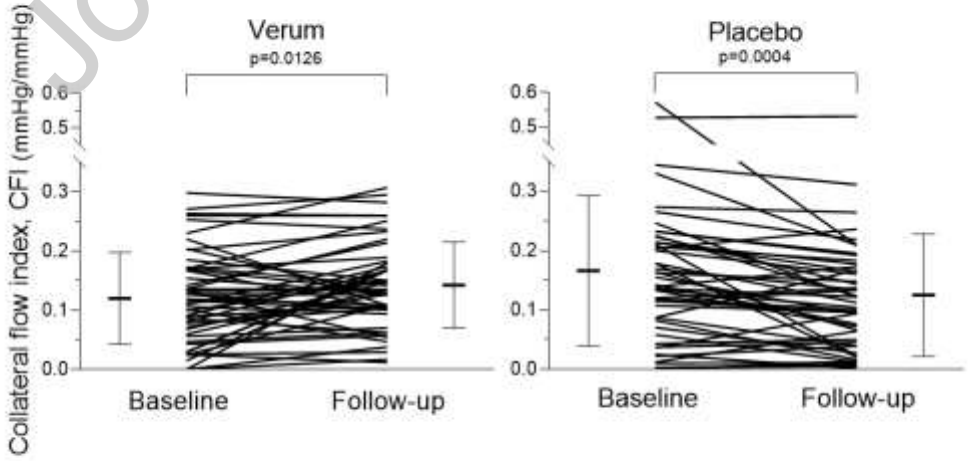

Figure 6

Figure 6 Individual values of coronary artery collateral flow index (CFI, vertical axis) for patients in the verum (left) and the placebo group (right) as obtained at baseline and follow-up exam. Error bars indicate mean values and standard deviation.

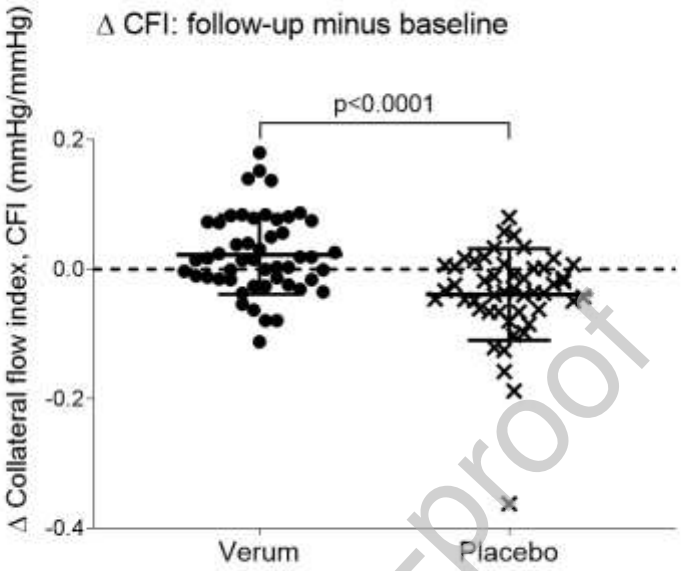

Figure 7

Figure 7 Individual changes of coronary collateral flow index between baseline and follow-up exam (ΔCFI) for patients in the verum (filled circles, left) and the placebo group (crosses, right). Error bars indicate mean values and standard deviation.

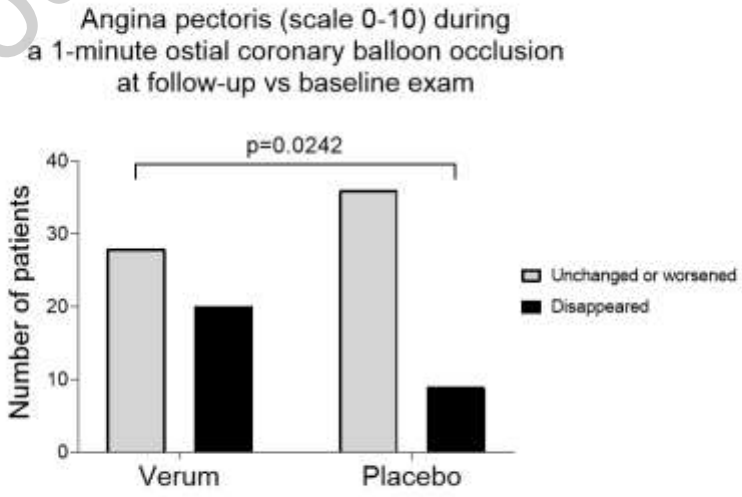

Figure 8

Figure 8 Number of patients in the verum and placebo group whose angina pectoris during the 1-minute ostial RCA occlusion disappeared, remained unchanged or worsened at follow-up vs baseline exam.

Table 1 Patient characteristics at baseline examination

	Overall	Verum	Placebo	p-value
Number of patients	101	50	51	
Patients lost to follow-up, n	2	0	2	
Patient characteristics				
Age (years)	70±9	70±9	70±8	0.88
Female gender (%)	13	16	10	0.55
Height (cm)	173±8	172±9	174±8	0.19
Weight (kg)	85±17	84±19	86±15	0.32
Body mass index (kg/m^2)	28±5	28±5	28±4	0.59
Angina pectoris before intervention (%)	55	69	42	0.0088
Duration of angina pectoris (months)	7±14	5±6	10±20	0.24
Canadian cardiovascular society class of angina pectoris before intervention	1.84±0.69	1.82±0.81	1.86±0.47	0.81
Diabetes mellitus (%)	41	40	40	0.99
Arterial hypertension (%)	77	76	77	0.81
Current smoking (%)	16	16	15	0.99
Cumulative pack years of cigarettes	34±22	27±17	39±25	0.11
Dyslipidemia (%)	82	86	77	0.30
Family history for CAD (%)	25	22	29	0.49
Prior myocardial infarction (%)	38	42	35	0.54
Medical treatment				
Aspirin (%)	77	76	77	0.99
Platelet inhibitor (%)	19	24	15	0.55
Calcium channel-blocker (%)	31	24	38	0.19
Beta-blocker (%)	55	49	62	0.23
Nitrate (%)	12	16	8	0.36
Oral anticoagulation (%)	14	14	15	0.31
Statin (%)	78	78	77	0.99
ACE inhibitor or ARB (%)	72	70	75	0.65
Diuretics (%)	37	26	48	0.0357

Abbreviations: ACE = angiotensin converting enzyme, ARB = angiotensin receptor blockers
CAD = coronary artery disease

Table 2 Invasive parameters at baseline and follow-up examination

	Overall	Verum	Placebo	p-value
Heart rate (beats per minute)	76±11	76±12	76±11	0.96
Systolic blood pressure (mmHg)	122±24	122±24	121±24	0.97
Diastolic blood pressure (mmHg)	65±12	65±12	66±13	0.76
Left ventricular end-diastolic pressure (mmHg)	10±5	11±5	10±5	0.20
Left ventricular ejection fraction (%)	60±12	60±13	60±12	0.82
Central venous pressure, CVP (mmHg)	5±2	5±2	5±2	0.42
Coronary angiographic parameters at baseline				
Coronary artery treated by PCI (all deferred)				0.90
Left anterior descending artery (LAD), n	33	16	17	
Left circumflex coronary artery (LCX), n	40	21	19	
Right coronary artery (RCA), n	26	13	13	
Number of diseased vessels	2.1±0.8	2.0±0.8	2.2±0.8	0.13
Coronary artery percent diameter stenosis	46±18	45±21	48±16	0.33
Fractional flow reserve, FFR	0.867±0.109	0.890±0.104	0.842±0.110	0.0312
Chronic total occlusion, n	7	6	1	0.11
Exercise time (seconds, s)				
Exercise time @ baseline (s)	412±169	398±176	426±162	0.41
Exercise time @ follow-up (s)	425±182	421±198	430±166	0.79
Delta Exercise time (follow-up - baseline, s)	+14±118	+23±116	+4±120	0.44
Coronary artery functional outcome parameters				
Collateral flow index, CFI @ baseline	0.143±0.107	0.120±0.078	0.168±0.127	0.0275
Collateral flow index, CFI @ follow-up	0.134±0.089	0.142±0.073	0.126±0.103	0.36
Delta CFI (follow-up minus baseline)	-0.009±0.073	+0.022±0.061	-0.039±0.072	<0.0001
Angina pectoris grade during ostial coronary artery occlusion @ baseline (0-10)	2.7±2.8	3.0±2.9	2.3±2.7	0.23
Angina pectoris grade during ostial coronary artery occlusion @ follow-up (0-10)	2.7±2.8	2.6±2.7	2.8±3.0	0.78
Delta angina pectoris grade during coronary artery occlusion (follow-up minus baseline)	-0.1±2.3	-0.6±2.4	+0.4±2.0	0.0304
Angina pectoris disappeared during follow-up	18	14	4	0.0176
I.c. ECG ST-shift during ostial coronary artery occlusion @ baseline (mV)	1.175±0.991	1.174±0.997	1.176±0.996	0.99
I.c. ECG ST-shift during ostial coronary artery occlusion @ follow-up (mV)	1.185±1.096	1.054±1.004	1.325±1.181	0.23

Delta i.c. ECG ST-shift (follow-up minus baseline)	+0.014± 0.846	-0.102±0.577	+0.138± 1.053	0.1690
Delta heart rate during coronary artery occlusion (follow-up minus baseline)	+2±13	+1±9	+3±17	0.33

Conflicts of Interest

We have no conflicts of interest to declare for any of the authors.