Effect of permanent right internal mammary artery occlusion on right coronary artery supply: A randomized placebo-controlled clinical trial

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Background Natural, nonsurgical internal mammary artery (IMA) bypasses to the coronary circulation have been shown to function as extracardiac sources of myocardial blood supply. The goal of this randomized, placebo-controlled, double-blind trial was to test the efficacy of permanent right IMA (RIMA) device occlusion on right coronary artery (RCA) occlusive blood supply and on clinical and electrocardiographic (ECG) signs of myocardial ischemia.

Methods This was a prospective superiority trial in 100 patients with chronic coronary artery disease randomly allocated (1:1) to RIMA vascular device occlusion (verum group) or to RIMA sham procedure (placebo group). The primary study end point was RCA collateral flow index (CFI) as obtained during a 1-minute ostial RCA balloon occlusion at baseline before and at follow-up examination 6 weeks after the trial intervention. CFI is the ratio between simultaneous mean coronary occlusive divided by mean aortic pressure both subtracted by central venous pressure. Simultaneously obtained secondary study end points were the registration of angina pectoris and quantitative intracoronary ECG ST-segment shift.

Results CFI change during the follow-up period was +0.036 ± 0.068 in the verum group and –0.021 ± 0.097 in the placebo group (P = .0011). Angina pectoris during the same RCA balloon occlusions had disappeared at follow-up in 14/49 patients of the verum group and in 4/49 patients of the placebo group (P = .0091). Simultaneous intracoronary ECG ST-segment shift change revealed diminished myocardial ischemia at follow-up in the verum group and more severe ischemia in the placebo group.

Conclusions Permanent RIMA device occlusion augments RCA supply to the effect of diminishing clinical and electrocardiographic signs of myocardial ischemia during a brief controlled coronary occlusion. (Am Heart J 2020;230:1-2.)

Cardiovascular disease is the leading global cause of death, accounting for more than 17.6 million deaths per year in 2016, a number expected to grow to more than 23.6 million by 2030.[1] In the event of acute coronary syndrome, percutaneous coronary intervention (PCI) has been shown efficacious on outcome.[2] Conversely, PCI has not yet been proven beneficial on the course of chronic stable coronary artery disease (CAD).[3]

Recent guidelines on myocardial revascularization state that "prognostic and symptomatic benefits of myocardial revascularization critically depend on the completeness of revascularization,"[4] the statement of which is based on the adverse relationship between extent of myocardial ischemia and outcome.[5,6] Among patients with stable CAD undergoing coronary angiography, myocardial revascularization has been documented incomplete in more than one fourth (138 of 493 patients in the study by Williams et al[7]), in whom all-cause mortality has been found elevated to 5% per year.[7] Thus, novel treatment strategies for patients with incomplete revascularization are sought for aimed at reducing myocardial ischemia and angina pectoris, and consequently improving prognosis of stable CAD.

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).[8] Alternative sources of coronary blood supply consist of intercoronary anastomoses, that is, the coronary collateral circulation, whose benefit on survival has been demonstrated in chronic CAD.[9] Extracardiac coronary blood supply via

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Clinical trial registration: NCT03950947
Submitted April 23, 2020; accepted September 7, 2020.
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https://doi.org/10.1016/j.ahj.2020.09.006

the internal mammary arteries (IMAs) as natural, that is, native nonsurgical bypasses, has been described anatomically and conceptually[10-13] but not thoroughly examined for 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.[14,15]

Thus, the present randomized controlled clinical trial was designed to assess the effect of permanent right IMA (RIMA) device occlusion versus placebo on right coronary artery (RCA) occlusive blood supply (collateral flow index, CFI) and on clinical and electrocardiographic (ECG) signs of myocardial ischemia.

Methods

Study design and patients

This was a prospective, double-blind, placebo-controlled clinical trial with 1:1 randomized allocation to RIMA device occlusion (verum group) or RIMA sham procedure (placebo group) in 100 patients with chronic CAD undergoing diagnostic coronary angiography due to chest pain and diagnosed with RCA stenosis (Figure 1). The primary study end point was the intergroup difference in coronary collateral function 6 weeks after RIMA occlusion or sham procedure (difference in CFI; see below for calculation) as obtained during a single artificial, 1-minute ostial RCA balloon occlusion. Secondary study end points were changes during follow-up in angina pectoris and the quantitatively determined intracoronary (ic) ECG ST-segment shift during the identical 1-minute coronary occlusion. Criteria for study inclusion were age > 18 years, 1- to 3-vessel chronic stable CAD, and written informed consent for trial participation. Exclusion criteria were acute coronary syndrome, previous myocardial infarction in the vascular region undergoing CFI measurement, prior surgical coronary bypass, and severe hepatic or renal failure (creatinine clearance <15 mL/min/1.73 m^2).

The study was approved by the ethics committee of the Kanton of Bern, Switzerland (KEK 360/15), and all patients gave written informed consent to participate before the start of the baseline invasive examination.

This work was supported by the Swiss National Science Foundation (to C. S., grant number 32003B_163256).

The authors are solely responsible for the design and conduct of this study, all study 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. Central venous pressure (CVP) was measured by a 5F pigtail catheter as right atrial pressure via the right femoral vein.

Randomization and masking

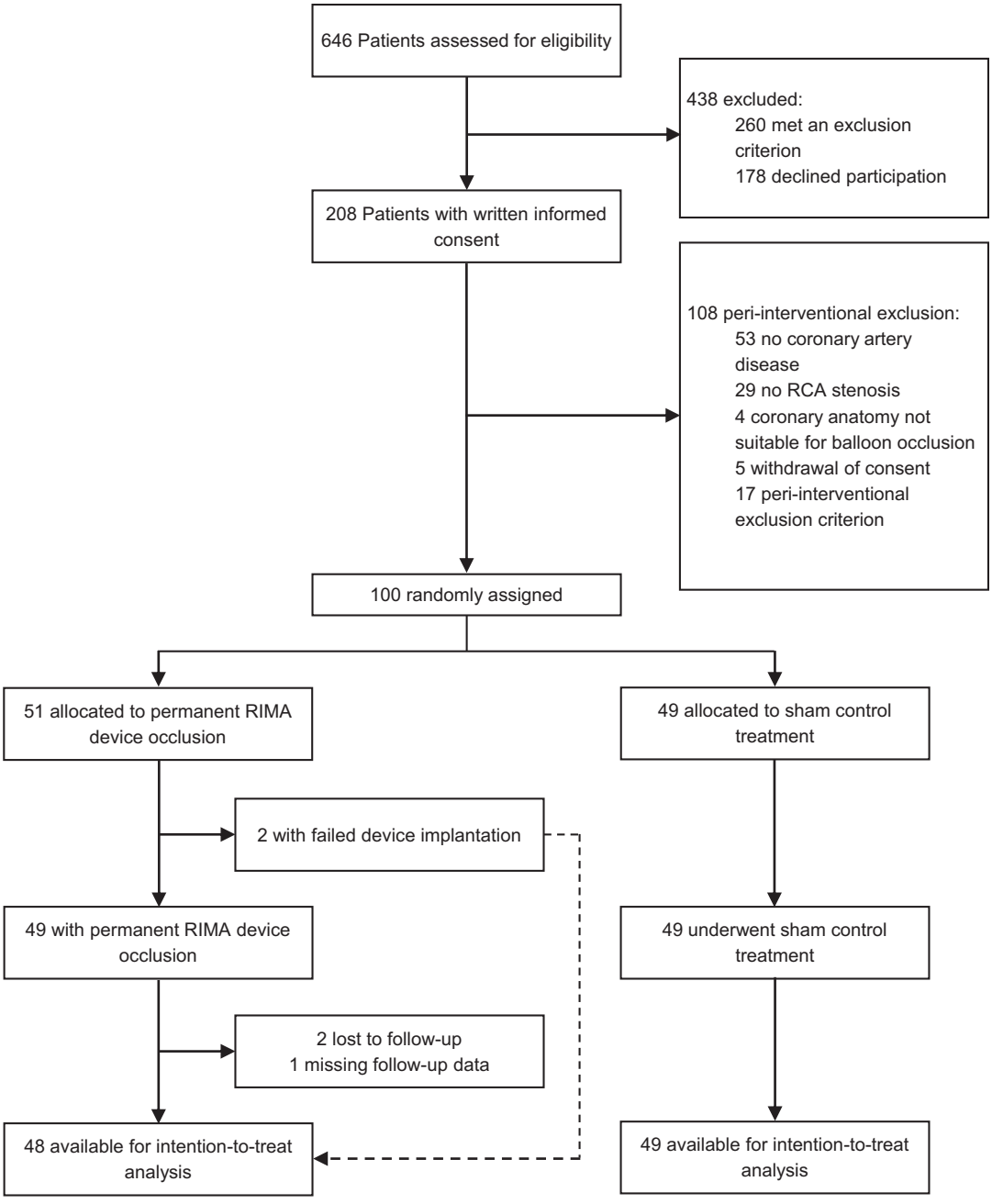
Randomized, computer-based allocation to the RIMA device occlusion or placebo group occurred after diagnostic coronary angiography and was stratified according to the clinical decision on whether or not PCI in the left coronary artery territory could be deferred until invasive follow-up examination at 6 weeks after study inclusion. PCI of the RCA was deferred in all but 4 patients in whom RCA stenosis was subtotal (2 patients in each group). Patients were not informed about group allocation until completion of all the follow-up study end point measurements. Naturally, the interventional operator was not blinded for the study procedure at baseline, nor was he blinded at follow-up examination because the device was instantaneously visible already during fluoroscopy. At the time of data analysis, the analyzing operator was unaware of a patient's group allocation.

Study end points

Primary study end point. Coronary occlusive collateral flow relative to normal antegrade flow through the nonoccluded coronary artery (CFI) was determined using coronary pressure measurements. A 0.014-in pressure monitoring angioplasty guidewire (PressureWire X Guidewire, Abbott, Chicago, IL) 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 examination). CFI was determined by simultaneous measurement of mean P_{ao} (mm Hg), the mean distal coronary artery pressure during RCA balloon occlusion (P_{occl}, mm Hg), and the mean CVP (mm Hg) (Figure 2) as measured during the last 10 seconds of the balloon occlusion. CFI was calculated as (P_{occl} − CVP) divided by (P_{ao} − CVP).[16] The accuracy of pressure-derived CFI measurements in comparison to ECG signs of myocardial ischemia during occlusion and to absolute myocardial perfusion measurements has been documented previously.[16,17] The difference of CFI during follow-up was calculated as CFI at follow-up examination minus CFI at baseline examination.

Secondary study end points. Signs of myocardial ischemia were obtained simultaneously with CFI measurements, that is, during the same 1-minute ostial RCA balloon occlusion. Myocardial ischemia was characterized by the presence or absence of angina pectoris as interrogated immediately after release of the angioplasty balloon occlusion at baseline and follow-up examination. The parameter change from baseline to follow-up examination was categorized as follows: angina pectoris disappeared, unchanged, or newly manifest. Additionally, ic ECG ST-segment shift in mV was recorded during the same 1-

Figure 1

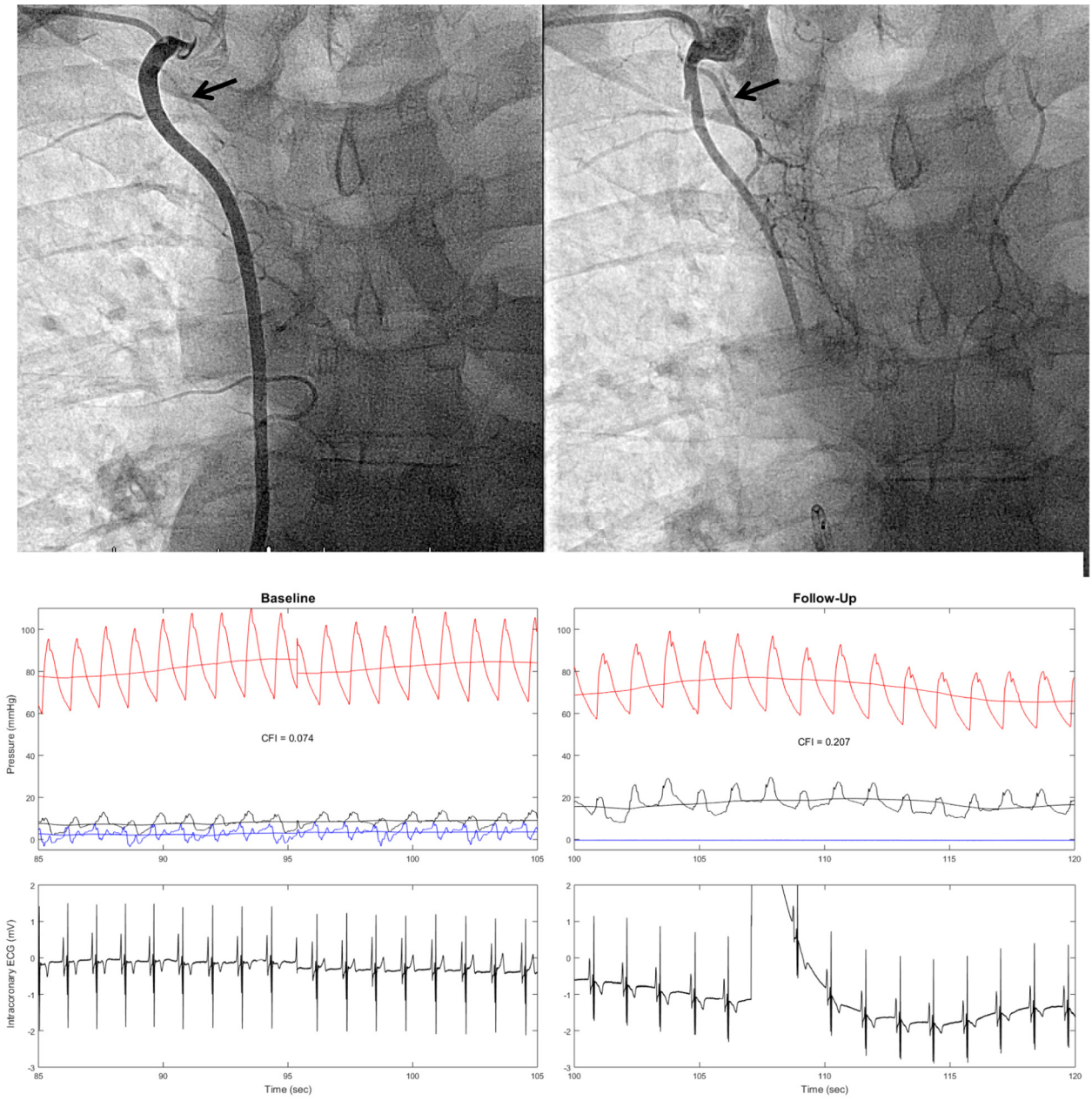


Trial profile.

minute RCA balloon occlusions (Figure 2). The ic ECG was obtained from the angioplasty pressure guidewire via a cross-clamp to a precordial lead. Quantitative ic ECG ST-segment shift was determined as the difference between ic ECG ST-segment shift (elevation or depression obtained at the J-point) during RCA occlusion minus ic ECG ST-segment shift immediately before RCA occlusion. The change in ic ECG ST-segment shift was determined as occlusive ic ECG ST-segment shift at follow-up minus ic ECG ST-segment shift at baseline examination.

Exploratory study end points. As exploratory end points, reactive hyperemia-induced fractional flow reserve

Figure 2



Upper panels: Angiograms (anteroposterior projection) of the right internal mammary artery (RIMA) before (left) and 6 weeks after its occlusion by a vascular plug at the level of the right atrium (marked by a pigtail catheter). The pericardiacophrenic branch of the RIMA (arrows) is barely visible at baseline. Its caliber is augmented at follow-up examination, and the pericardiacophrenic branch of the left IMA is also depicted. Lower panels: Simultaneous recordings during the 1-minute ostial RCA balloon occlusion from the same patient of phasic and mean P_{ao} (red curve), RCA P_{occl} (black curve), CVP (blue curve; sequential recording during follow-up examination), and intracoronary ECG (bottom, black curve) as obtained during baseline (left) and follow-up (right) examination. CFI = $(P_{occl} - CVP)/(P_{ao} - CVP)$.

(FFR) was obtained immediately after artificial RCA occlusion, and Canadian Cardiovascular Society (CCS) class of angina was interrogated at baseline and follow-up examination.

Study protocol

Immediately following right radial artery sheath insertion, 5,000 U of intravenous heparin plus 2 puffs of oral isosorbide dinitrate was given. Following diagnostic

coronary angiography and at the start of the invasive baseline and follow-up study procedure, all patients received an additional 5000 U of heparin intravenously. Among patients undergoing PCI of the left coronary artery at baseline examination (nondeferred PCI of stenotic lesions at an FFR ≤ 0.75), study end point measurement in the RCA was always performed after left coronary artery PCI. For RCA CFI and myocardial ischemia measurements, an adequately sized angioplasty balloon catheter was positioned in the ostial part of the RCA, whereas the pressure guidewire was placed distally. Coronary balloon inflation occurred at a pressure of 1-2 atm. Complete coronary occlusion was ascertained by angiography. During the 1-minute occlusion, simultaneous P_{occl}, P_{ao}, and CVP were recorded for the calculation of CFI (Figure 2). During the entire procedure, the ic ECG obtained from the guidewire was recorded. Immediately following CFI measurement, the patient was asked about the occurrence of angina pectoris during RCA balloon occlusion. Directly after RCA balloon deflation and without changing the sensor wire position, reactive hyperemia, that is, postocclusive FFR of the RCA, was obtained following RCA angiography. FFR was equal to distal coronary pressure divided by P_{ao}.

In both groups, radiographic imaging of the RIMA was performed using a 5F IMA catheter. In the placebo group, the baseline examination ended after RIMA angiography. In the verum group, a Radiofocus 0.032-in, 260-cm stiff guidewire (Terumo Corporation, Tokyo, Japan) was subsequently inserted into the IMA catheter and advanced with its tip to below the diaphragm. The IMA catheter was then engaged in the RIMA until its tip reached the level of the right atrium in anteroposterior projection. Subsequently, an appropriately sized (4-5 mm in diameter) Amplatzer vascular plug 4 (Abbott, Chicago, IL) was inserted via the IMA catheter into the RIMA and released at the level of the right atrium (Figure 2, top panel). Invasive follow-up examinations at 6 weeks after RIMA device occlusion consisted of RIMA radiographic imaging in both groups and of identical study end point measurements as described above.

Statistical analysis

Sample size calculation was performed using a 2-sided unpaired Student *t* test with the primary study end point of CFI change during the 6-week follow-up study period and was based on the following alternative hypothesis: CFI change from baseline to follow-up examination is higher in the verum than the placebo group. CFI change was estimated to be +0.020 in favor of the verum group at an SD of 0.035 yielding an effect size of 0.57,[15] at an α level of .05 and a power of 0.80. Accordingly, the calculated sample size was equal to 100 patients (50 per group). Between-group comparison of continuous demographic, clinical, angiographic, and hemodynamic variables and study end point variables was performed by unpaired Student *t* test. A χ^2 test was used for comparison of categorical variables among the study groups. Intraindividual comparison of CFI, ic ECG ST-segment shift, FFR, and heart rate obtained at baseline versus follow-up examination was performed by a paired Student *t* test. Statistical significance was defined at a *P* level < .05. Continuous variables are given as mean and SD.

Results

Fifty-one patients were randomly allocated to the RIMA device occlusion group (verum group) and 49 patients to the sham control group (placebo group) (Table I). A total of 3 patients in the verum group were lost either to failed study end point recording (n = 1) or to follow-up examination (n = 2) (Figure 1).

Patient characteristics and clinical data at baseline

Patients were younger in the verum than those in the placebo group (Table I). There were no statistically significant differences between the groups regarding gender, body mass index, CCS class of angina pectoris, and cardiovascular risk factor prevalence (Table I). Patients in the verum versus the placebo group had suffered more prior myocardial infarction in another than the RCA territory. Regarding cardiovascular medication, there was no difference between the groups, except for the less frequent use of calcium channel blockers and diuretics in the verum than the placebo group (Table I).

Hemodynamic and coronary angiographic data at baseline

There were no statistical differences between the groups in heart rate, systemic blood pressure, left ventricular end-diastolic pressure, left ventricular ejection fraction, and central venous pressure (Table II). Central venous pressure was directly obtained in 52 patients (26 each in both groups), and it was assumed equal to 5 mm Hg in 48 patients. The number of coronary arteries with stenotic lesions >50% was similar between the groups. RCA quantitative percent diameter stenosis was similar in both groups, and the number of chronic total RCA occlusions was identical.

RCA PCI was deferred until follow-up examination (after study end point measurement) in 96 patients; it was performed for clinical reasons at baseline in 2 patients of the verum group and in 2 patients of the placebo group. Left coronary artery (LCA) PCI was deferred in 24 patients each in the verum and placebo group (Table II). The LCA vessel (left anterior descending artery [LAD] or left circumflex coronary artery [LCX]) undergoing PCI or the LCA stenosis severity did not differ between the groups. Thrombolysis in Myocardial Infarction flow in

Table I. Patient characteristics at baseline examination.

	Overall	Verum	Placebo	*P* value
No. of patients		51	49	
Patients lost to follow-up, n	3	3	0	
Patient characteristics				
Age	68 ± 12	66 ± 13	71 ± 9	.0286
Female gender, n (%)	12 (12)	10 (10)	14 (14)	.49
Height (cm)	173 ± 8	173 ± 8	173 ± 7	.74
Weight (kg)	85 ± 17	87 ± 17	83 ± 16	.31
Body mass index (kg/m^2)	28 ± 5	29 ± 5	28 ± 5	.20
Angina pectoris before intervention (%)	63	67	59	.44
Duration of angina pectoris (m)	5 ± 6	4 ± 5	6 ± 8	.42
CCS class of angina pectoris	2.25 ± 0.88	2.32 ± 0.84	2.17 ± 0.93	.50
Diabetes mellitus (%)	38	41	34	.50
Arterial hypertension (%)	80	78	81	.69
Current smoking (%)	20	19	20	.92
Cumulative pack years of cigarettes	41 ± 26	37 ± 23	45 ± 29	.36
Dyslipidemia (%)	87	86	88	.83
Family history for CAD (%)	28	28	29	.90
Prior myocardial infarction (%)	46	59	33	.0092
Medical treatment				
Aspirin (%)	85	90	80	.24
Platelet inhibitor (%)	33	33	33	.94
Calcium channel-blocker (%)	31	20	43	.0122
β-Blocker (%)	65	71	59	.23
Nitrate (%)	17	14	20	.37
Oral anticoagulation (%)	17	22	12	.22
Statin (%)	79	84	74	.18
ACE inhibitor or ARB (%)	69	65	74	.34
Diuretics (%)	42	29	55	.0098

ACE, angiotensin-converting enzyme; *ARB*, angiotensin receptor blocker.

patients with nondeferred LCA PCI was equal to 3 in all of them. At baseline, RCA CFI tended to be lower in the verum than the placebo group (Table II). At baseline, angina pectoris during the same RCA occlusion occurred more often, and ic ECG ST-segment shift was larger in the verum than the placebo group (Table II).

Changes of coronary function and myocardial ischemia during follow-up

Primary study end point. At follow-up examination, RCA CFI tended to be higher in the verum than the placebo group (Table II). RCA CFI changed from 0.092 ± 0.078 at baseline to 0.128 ± 0.066 at follow-up in the verum group and from 0.123 ± 0.098 at baseline to 0.101 ± 0.077 at follow-up in the placebo group (Figure 3). RCA CFI change during follow-up was significantly higher in the verum than in the placebo group (Table II and Figure 4).

Secondary study end points. In the verum group, there was a net decrease of 10 cases with angina pectoris during RCA occlusion at follow-up versus baseline examination (net increase of 6 cases in the placebo group) (Table II). Angina pectoris during the 1-minute ostial RCA balloon occlusion had disappeared more often at the follow-up examination in the verum than in the placebo group (Figure 5). Ic ECG ST-segment shift during the identical RCA occlusion at follow-up was less pronounced in the verum than the placebo group (Table II), and there was a decrease in ic ECG ST-segment shift during follow-up in the verum group, whereas the respective change was positive during follow-up in the placebo group (Table II and Figure 6).

Exploratory study end points. RCA FFR tended to increase in the verum group, and it remained unchanged in the placebo group (Table II). CCS class of angina pectoris at follow-up was unchanged or worse in 20 and 30 patients of the verum and placebo group, respectively, and it improved in 28 and 19 patients of the verum and placebo group, respectively (P = .0540).

Procedural feasibility of RIMA closure

RIMA device closure in the verum group was successful in all but 3 patients (2 failed implantations, 1 aberrant implantation into a RIMA side branch). One case of proximal RIMA dissection occurred. These complications were left untreated without sequelae. During the 6 weeks of follow-up, all patients of the verum group remained asymptomatic with regard to the RIMA device closure.

Table II. Invasive parameters at baseline and follow-up examination.

	Overall	Verum	Placebo	*P* value
Heart rate (beat/min)	75 ± 15	76 ± 17	73 ± 13	.34
Systolic blood pressure (mm Hg)	123 ± 24	121 ± 23	125 ± 24	.40
Diastolic blood pressure (mm Hg)	63 ± 11	64 ± 12	61 ± 10	.15
Left ventricular end-diastolic pressure (mm Hg)	11 ± 7	11 ± 7	11 ± 7	.79
Left ventricular ejection fraction (%)	58 ± 10	58 ± 10	58 ± 10	.89
CVP (mm Hg)	6 ± 3	6 ± 3	6 ± 3	.41
Coronary angiographic parameters at baseline				
No. of diseased vessels	2.31 ± 0.75	2.35 ± 0.72	2.27 ± 0.79	.59
RCA percent diameter stenosis	48 ± 23	49 ± 25	47 ± 23	.70
RCA chronic total occlusion, n	8	4	4	.92
RCA PCI deferred, n (%)	96 (96)	49 (96)	47 (96)	.89
LCA PCI deferred, n (%)	48 (48)	24 (47)	24 (49)	.92
LCA treated by PCI				.56
LAD, n	36	19	17	
LCX, n	25	10	15	
LAD percent diameter stenosis	55 ± 20	55 ± 21	55 ± 23	.82
LCX percent diameter stenosis	44 ± 17	44 ± 15	44 ± 22	.95
RCA functional outcome parameters at baseline and follow-up				
RCA CFI @ baseline	0.108 ± 0.089	0.092 ± 0.078	0.123 ± 0.098	.09
RCA CFI @ follow-up	0.115 ± 0.073	0.128 ± 0.066	0.101 ± 0.077	.07
Delta CFI (follow-up minus baseline)	+0.007 ± 0.088	+0.036 ± 0.068	–0.021 ± 0.097	.0011
Angina pectoris during ostial RCA occlusion @ baseline, n	52	32	20	.0260
Angina pectoris during ostial RCA occlusion @ follow-up, n	48	22	26	.54
New angina pectoris during ostial RCA occlusion @ follow-up, n	14	4	10	
Ic ECG ST-shift during ostial RCA occlusion @ baseline (mV)	0.438 ± 0.465	0.525 ± 0.555	0.365 ± 0.350	.07
Ic ECG ST-shift during ostial RCA occlusion @ baseline (mV)	0.462 ± 0.496	0.352 ± 0.365	0.567 ± 0.570	.0312
Delta ic ECG ST-shift (follow-up minus baseline)	+0.024 ± 0.462	–0.173 ± 0.472	+0.202 ± 0.515	.0004
RCA FFR @ baseline	0.902 ± 0.096	0.900 ± 0.094	0.902 ± 0.097	.72
RCA FFR @ follow-up	0.908 ± 0.099	0.917 ± 0.065	0.896 ± 0.123	.29
Delta RCA FFR (follow-up minus baseline)	+0.005 ± 0.083	+0.014 ± 0.079	–0.011 ± 0.082	.11

Angiographic control of the RIMA in the verum group at follow-up revealed incomplete occlusion at the device in 16 of 49 cases. Among patients with incomplete occlusion, delta CFI was not statistically different from that in patients with complete device occlusion (+0.039 ± 0.058 and +0.028 ± 0.075, respectively; $P = .70$).

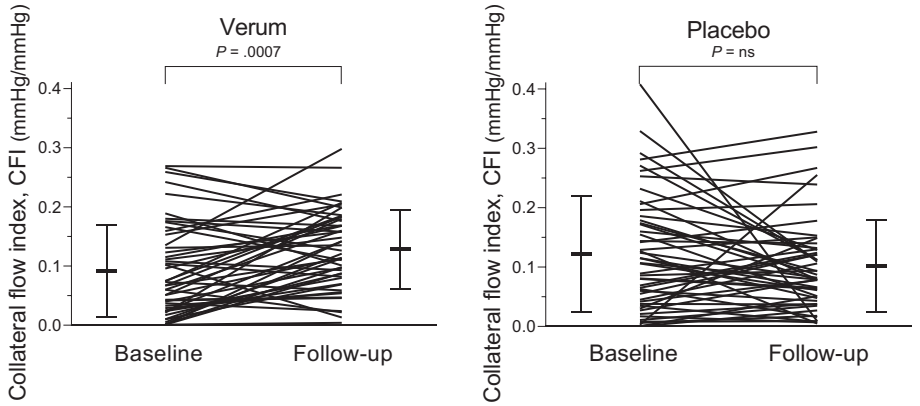
Discussion

The present randomized controlled trial found permanent RIMA device occlusion superior to RIMA sham treatment in terms of augmented RCA collateral function as obtained during a brief artificial ostial RCA occlusion 6 weeks after study intervention. Improved RCA supply in the RIMA occlusion group was reflected by more frequent angina pectoris relief and less severe ECG signs of myocardial ischemia during the same systematic 1-minute RCA occlusion.

Incomplete coronary revascularization

The results of the present trial offer a new and sustainable treatment option for patients with incomplete coronary revascularization (multivessel CAD, chronic total occlusion of the RCA following unsuccessful interventional treatment, no-option surgical candidates [18]) and, as such, for those with refractory angina pectoris. *Refractory angina pectoris* is defined as angina pectoris of more than 3 months' duration associated with reversible myocardial ischemia in the context of CAD which cannot be controlled by medical, coronary interventional, or surgical therapy.[19] Hence, the terms *incomplete revascularization* and *refractory angina pectoris* are closely related, whereby the former concerns a larger population because not all patients with incomplete revascularization suffer from angina pectoris. The prevalence of refractory angina amounts to 10%-12% of patients with chronic CAD,[20] and more than 25% of patients undergoing coronary angiography have been reported to receive incomplete revascularization.[7] Mortality of patients with refractory angina as well as those with incomplete revascularization is slightly elevated at 4%-5% per year.[7,20] Since the early 1990s, many therapeutic concepts have been proposed for the treatment of refractory angina pectoris such as therapeutic angiogenesis,[21] arteriogenesis,[22] stellate ganglion

Figure 3



Individual values of right coronary artery CFI (vertical axis) for patients in the verum (left) and the placebo group (right) as obtained at baseline and follow-up examination. Error bars indicate mean values and SD.

block, cardiac shockwave therapy,[23] myocardial ischemic preconditioning,[24] lower-limb external diastolic counterpulsation,[25] and coronary sinus reducer stent implantation.[26] Although some of these treatment modalities have not undergone sound efficacy testing, others have done so but proven inefficacious (angiogenesis).[21] Furthermore and except for coronary sinus reducer treatment, the other therapeutic options are not sustainable. They require repetitive applications for a lasting effect, thus reducing the tolerability of a procedure, especially if it is as strenuous and time-consuming as, for example, external counterpulsation with its daily 1-hour sessions.

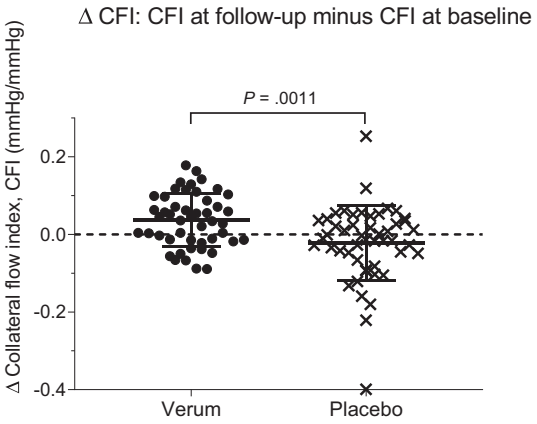
In comparison, in situ anatomical connections between the IMAs and the coronary circulation are the basis for a *sustainable* source of myocardial blood supply with the potential of partially substituting the diseased coronary circulation.[12] In principle, this applies also to the extracardiac source of collateral connections between the bronchial artery and the RCA, respectively, the left circumflex coronary artery (LCX).[27] However, these anastomoses are less accessible and less explored than the IMA–coronary artery network.

Extracardiac coronary artery supply

In contrast to the human intercoronary collateral arterioles and arteries called *endomural coronary anastomoses*,[22] the extracardiac coronary arterial anastomoses have received much less attention even though they have been known for a long time in healthy and diseased individuals.[10] Hudson et al discovered extracardiac anastomoses unintentionally 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.[10] Moberg et al later observed direct connections between these mediastinal arterial sources and atrial branches of the coronary circulation.[11] The pericardiacophrenic arterial branch is the first or second branch of the internal mammary arteries 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 but also of other IMA branches and the coronary arteries.[27,28]

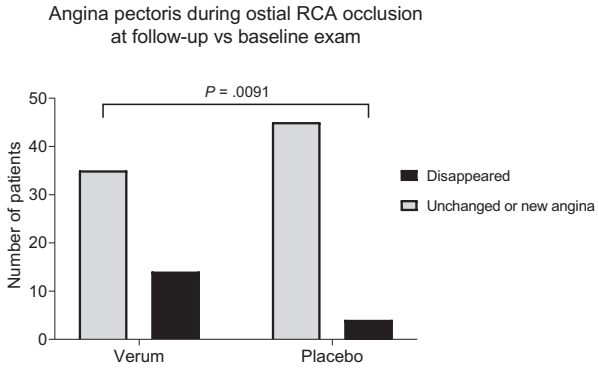
Because of the anatomical connection to both the upper and lower limb arterial circulation (subclavian arteries and external iliac arteries, respectively), the supply regions of the IMAs and their native, that is, nonligated, side branches are not at risk for ischemia. In fact, collateral perfusion pressure downstream of a proximal IMA balloon occlusion amounts to approximately 80% of normal perfusion pressure during IMA patency (own data). This physiologic piece of evidence explains the relatively low number of ischemic events following IMA coronary artery bypass grafting with the exception of hampered sternal wound healing as a consequence of extensive IMA side branch ligation. 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.[29] Following initial documentation of clinical success,[30] surgical IMA ligation has been reported inefficacious based on 2 very small (totaling 35 patients) but sham-controlled clinical trials,[31,32] the publication of which together with the advent of the heart-lung machine closed this option of

Figure 4



Individual changes of RCA CFI between baseline and follow-up examination (ΔCFI) for patients in the verum (filled circles, left) and the placebo group (crosses, right).

Figure 5



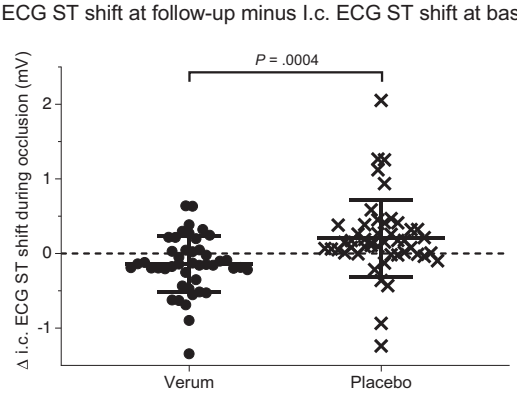
Number of patients in the verum and placebo group whose angina pectoris during the 1-minute ostial RCA occlusion disappeared, remained unchanged, or was newly manifest at follow-up versus baseline examination.

myocardial revascularization almost entirely. The physical basis of action of IMA ligation, flow diversion toward its side branches connecting to the heart, persisted only in the Vineberg procedure with its direct implantation of the disconnected IMAs into the freely exposed myocardium.

Permanent RIMA occlusion

Recently, there have been 2 clinical investigations supporting the physical concept of enhanced myocardial perfusion by increased resistance to IMA flow downstream of its pericardiacophrenic branch. First, *temporary* distal IMA with simultaneous ostial coronary artery balloon occlusion in 120 patients with CAD has found ischemia-reducing, enhanced extracardiac coronary artery supply via natural IMA bypasses.[14] Specifically, the CFI difference as obtained with versus without IMA occlusion was consistently positive during left IMA with LAD occlusion and during RIMA with RCA occlusion: +0.033 ± 0.044 and +0.025 ± 0.027.[14] Second, *permanent* RIMA device occlusion has been shown feasible and potentially efficacious on RCA occlusive, that is, collateral, function and on simultaneous signs of myocardial ischemia in an open, proof-of-concept study.[15] The rationale for selecting the RIMA rather than the LIMA to undergo permanent occlusion for feasibility testing has

Figure 6



Individual changes of ic ECG ST-segment shifts (vertical axis) between baseline and follow-up examination for patients in the verum (filled circles, left) and the placebo group (crosses, right).

been to largely minimize the risk of wasting a surgical bypass. At our institution, RIMA coronary artery bypass grafts account for 5%-8% of all coronary grafts. In addition, the distal occlusion site at the level of the right atrium would still allow the RIMA to be grafted onto the RCA.

The present randomized controlled and double-blind trial has been the rational consequence of the above-mentioned open-label study on the feasibility of permanent IMA occlusion.[15] Except for the 2 mentioned pathophysiologic studies on the topic of IMA occlusion, there have been no data from the literature allowing direct comparison of the primary study end point, that is, quantitative RCA collateral function. Considering the increase in RCA CFI of +0.025 ± 0.027 during temporary RIMA balloon occlusion,[14] the respective value of +0.036 ± 0.068 in the present trial is slightly higher though in a similar range. During 6 weeks of permanent RIMA occlusion, RCA CFI increase in our uncontrolled study amounted to +0.067 ± 0.094,[15] the difference of which to the present trial may be partly explained by the larger fraction of 16/48 patients showing incomplete RIMA occlusion when compared to 11/50 patients in the proof-of-concept study. Notwithstanding, permanent RIMA device occlusion in the present trial still proved to be efficacious on all predefined outcome parameters in spite of incomplete closure in one third of the verum group. In the scientific methodologic sense, incomplete RIMA occlusion tends to preserve the trial's null hypothesis of no treatment effect and as such strongly supports the trial results. Angina pectoris during the brief ostial RCA occlusion (1 of the secondary end points indicative of myocardial ischemia) disappeared more frequently in the verum than the placebo group, the result of which challenges the findings of the underpowered though sham-controlled IMA ligation studies mentioned above.[31,32] The importance of applying a controlled ischemic stimulus with identical duration and size of ischemia for assessing the symptom of angina pectoris becomes evident even within our trial when considering that the CCS class of angina was affected by RIMA occlusion to a lesser though still positive degree. Conversely, to test the effect of RIMA occlusion on a less systematically obtained primary outcome parameter such as the more authentic CCS class of angina would have required a more sizeable study population. The results of the other, simultaneously obtained quantitative parameter for gauging myocardial ischemia, ic ECG ST-segment shift, mirror the effect of RIMA occlusion on angina pectoris. The theoretical possibility that these consistently alleviated signs of myocardial ischemia would be the effect of remote ischemic preconditioning (by the RIMA vascular plug) is dismissible because RIMA occlusion does not cause ischemia due to its supply from the upper and lower extremity circulation. Also, the effect of RIMA occlusion on signs of myocardial ischemia was associated with augmented RCA collateral supply.

Study limitations

Incomplete coronary revascularization was not an eligibility criterion for the present study, although IMA occlusion conceptually aims at this patient population. However, at this early stage of controlled efficacy testing, patients with mild coronary atherosclerosis were also included, thus allowing ostial RCA balloon occlusion for end point measurement with technical ease, while at the same time assessing the effect of RIMA occlusion in a less symptomatic population, thus tending to conserve the trial's null hypothesis. According to the same methodologic principle, technical failure of device implantation in 3 patients supports the positive study findings because data were analyzed per intention to treat. Failure of RIMA

device implantation in those cases occurred for safety reasons to prevent long intervention times in the proximity of the neck vessels. Along the same methodologic line, the relatively short follow-up duration of 6 weeks versus, for example, a longer period of 6 months most likely supported the trial's null hypothesis of no treatment effect of RIMA occlusion.[33] For clinical reasons, a very small number of 4 patients (2 in each group) underwent PCI of the RCA at baseline. The concomitant coronary hemodynamic changes reduced the primary study end point CFI in both groups, thus having no net effect on the study results. Despite the randomized allocation of study participants to the treatment groups, a few clinical variables were unequally distributed: age, prior myocardial infarction in non-RCA territory, and treatment with calcium channel blockers and diuretics. Statistically (multivariate regression analysis), the unbalanced distribution of these covariables did not affect the study outcomes. The present trial's results may not be representative for nonwhite people and for the female gender.

Conclusions

Permanent RIMA device occlusion augments right coronary artery supply to the effect of diminishing clinical and electrocardiographic signs of myocardial ischemia during a brief controlled coronary occlusion.

Disclosures

None.

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