Selective arterialization of a cardiac vein in a model of cardiac microangiopathy and macroangiopathy in sheep

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Objective: Some patients with significant arteriosclerosis of the heart are not amenable to revascularization of a coronary artery because they have a combination of microangiopathy and significant macroangiopathy. We investigated the benefit of arterialization of a cardiac vein under these circumstances in an acute animal model.

Methods: In the hearts of 8 sheep, microspheres were injected into the left coronary artery; 60 minutes later, a stenosis of the left anterior descending artery was performed. After 45 minutes, retrograde venous revascularization was performed by sewing the left internal thoracic artery to the concomitant vein of the left anterior descending artery in a beating-heart technique. For flow reversal, the vein was ligated proximally to the anastomosis. The efficiency of the bypass graft was evaluated by coronary angiography and flow measurement. Cardiac output, electrocardiography, and mean arterial blood pressure were assessed in each phase of the experiment.

Results: The ischemic state of the myocardium was confirmed by a significant decrease of cardiac output, stroke volume, and mean arterial blood pressure, and a significant elevation of the ST segment in the electrocardiography. After retrograde venous revascularization was established, cardiac output and stroke volume increased and ST elevations decreased. The grafts showed adequate flow (26.15 ± 2.08 mL/min), and reversed blood flow in the grafted vein was proved by coronary angiography.

Conclusion: Retrograde venous revascularization is possible and improves cardiac function in a state of acute ischemia caused by a combination of microangiopathy and macroangiopathy.

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Despite constant advances in surgical and interventional therapy of coronary artery disease, there remains a group of patients who are not amenable to these traditional treatment strategies. Cardiologists meet this challenge by introducing new therapeutic approaches such as the application of growth factors, gene therapy, and methods of percutaneous venous revascularization.[1-3] Cardiac surgeons developed the technique of laser revascularization.[4] There is another technical approach that was suggested by Pratt[5] in 1898 and that found its way into practical use in coronary heart surgery for a short period of time in the 1970s: to nourish the heart through the coronary veins. The results of experiments in animal models and outcome of follow-up examinations of patients who experienced venous revascularization were as controversial as the opinions of surgeons about this method.[6-15] However, some patients who are not eligible for coronary artery bypass grafting may be suitable for venous revascularization. Therefore, in this acute study we created a coronary microangiopathy combined with the conditions of a coronary macroangiopathy to investigate the benefit of the arterialization of a cardiac vein

Abbreviations and Acronyms
ECG = electrocardiogram
LAD = left anterior descending
LCA = left coronary artery

under these circumstances, which has not been examined before (as a model for a patient with small-vessel disease and additional proximal stenosis).

Materials and Methods

Eight sheep of both sex, weighing 60 to 65 kg, were used in the experiment. After induction of anesthesia the right femoral artery was cannulated, the left coronary artery (LCA) was visualized by standard catheterization technique (Figure 1, A), and 8000 microbeads (diameter: 100 μm) in 5 mL of 0.9% sodium chloride solution were injected into the LCA. During the next 60 minutes through a median sternotomy, the left internal thoracic artery was prepared. A constantly inflated small balloon (volume: 4 mL) was put on the surface of the proximal part of the left anterior descending (LAD) artery and fixed by sutures stitched in the myocardium around the vessel to induce stenosis greater than 65% by compressing the LAD top down. (The degree of the stenosis was verified by conventional heart catheterization technique.) Forty-five minutes after stenosis, the anastomosis of the left internal thoracic artery on the concomitant vein of the LAD was performed in a beating-heart technique distally to the stenosis of the LAD. To reverse venous flow direction, the vein was ligated proximally to the anastomosis. During the next 60 minutes, coronary angiography and flow measurements of the bypass were performed. Finally the LAD stenosis was reopened, and measurements were taken after 15 minutes.

The following parameters were assessed in each phase of the experiment: cardiac output (measured by a transonic flow probe attached to the ascending aorta), stroke volume, heart rate, electrocardiogram (ECG), mean arterial pressure, and coronary angiography. Creatine kinase and cardiac specific creatine kinase were measured at the beginning of the experiment and after injection of the microspheres to reveal changes of the laboratory findings after this step. Digital subtraction angiography was used to show the distribution of contrast agent at the different stages of the study.

All experiments were approved by the Regierungspräsidium Leipzig, the institution of the University of Leipzig responsible for laboratory animal care, and performed in accordance with the "Principles of Laboratory Animal Care" and the "Guide for the Care and Use of Laboratory Animals," defined in the German law of animal protection of 1998. All data are presented as mean ± standard error of mean. Statistical evaluation was performed by using the Kolmogorov–Smirnov test followed by the Friedman repeated-measures analysis of variance on ranks and Dunn's test. The paired t test was used for laboratory findings.

Results

Compared with baseline, the injection of microbeads resulted in a reduction of cardiac output, stroke volume, and mean arterial pressure (Table 1). The heart rate stayed the same. The ECG showed an elevation of the ST segment (Figure 2, *B*) from baseline (Figure 2, *A*), and there was an elevation of creatine kinase and cardiac specific creatine kinase, which was significant for creatine kinase (Table 1). Digital subtraction angiography revealed a lesser content of

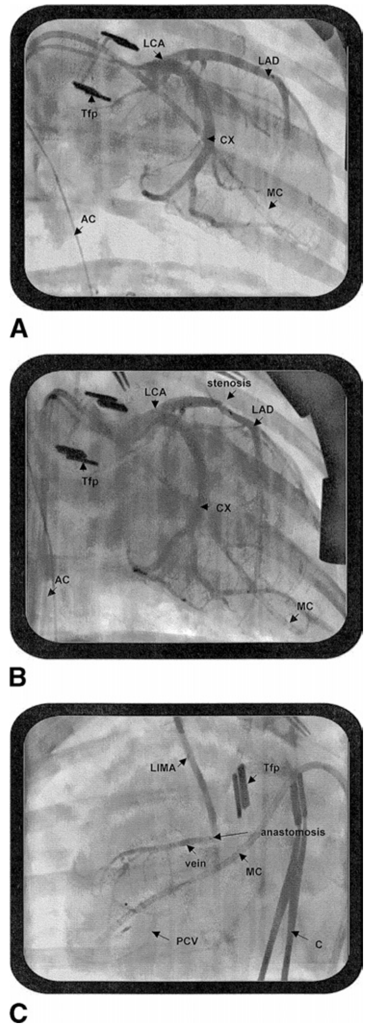

Figure 1. Angiograms taken during the experiment: The angiographic catheter is introduced into the LCA where contrast fluid is injected, which fills the LCA and its branches, the Ramus circumflexus, and the LAD without any pathologic changes (A) at the beginning of the experiment and with stenosis (B). The transonic flow probe is placed on the ascending aorta, and a catheter for measurement of changes of left ventricular volume is introduced (not used in this experiment). *C*, The contrast fluid has filled the left internal thoracic artery, and after passing the anastomosis, the cardiac vein that accompanies the LAD artery. There is a connection (∗) of this vein with a venous vessel on the back of the heart (posterior cardiac vein). A clamp (C), used for fixation, is also visible. *LCA*, left coronary artery.

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TABLE 1. Trends of parameters during the experiment

Parameter	Baseline	Microspheres	Stenosis	Bypass	LAD open
Cardiac output (L/min)	2.35 ± 0.16	1.95 ± 0.12	1.7 ± 0.19*	2.26 ± 0.18	2.68 ± 0.21
Stroke volume (mL/min)	22.13 ± 1.43	20.06 ± 1.94	17.75 ± 2.1*	24.88 ± 2.45	26.25 ± 1.83
Heart rate (beats/min)	106.5 ± 5.48	110.88 ± 3.94	102.63 ± 6.08	93.38 ± 5.16	106.88 ± 6.87
Mean arterial pressure (torr)	78.25 ± 4.25	69.25 ± 2.74	59.13 ± 3.74*	56.75 ± 5.08	54.88 ± 5.79
Creatine kinase (μmol/L/s)	13.20 ± 2.05	24.34 ± 3.57*	/	/	/
Cardiac specific Creatine kinase (μmol/L/s)	6.66 ± 0.50	7.19 ± 0.63	/	/	/

LAD, Left anterior descending. Trends of parameters during the experiment (LAD). Data are presented as mean standard ± error of mean. *There is a significant change of value compared with the measurement at the beginning of the experiment ($P \leq .05$).

contrast agent in the region supplied by the LCA after injection of the microbeads.

Tightening a balloon on the LAD resulted in a stenosis of 80.88% ± 2.86% (Figure 1, *B*). It caused a significant reduction of cardiac output, stroke volume, and mean arterial pressure compared with baseline (Table 1). Heart rates showed no significant changes. The ECG demonstrated a significant progression of the elevation of ST segments from baseline as well (Figure 2, *C*).

After arterialization of the cardiac vein was established, cardiac output and stroke volume increased, approaching significance (P = .08) (Table 1). Mean arterial pressure decreased slightly but not significantly, as well as the heart rate. In the ECG, ST segment elevations from baseline showed a clear tendency of regression (Figure 2, *D*). Coronary angiography showed the reversed blood flow in the cardiac vein after arterialization (Figure 1, *C*). The bypass grafts, with a flow of 26.15 ± 2.08 mL/min, restored 77.5% ± 37.2% of the original cardiac function. (This statement is based on the following calculation: cardiac output and stroke volume were measured after venous revascularization and after reopening of the LAD stenosis. Improvement of values were compared, and the bypass on the cardiac vein obtained 77.5% of the improvement, which was achieved by removing the stenosis on the LAD.) Digital subtraction angiography images of the region, perfused by the bypass, demonstrated restituted enrichment of contrast fluid.

Finally, release of the LAD stenosis resulted in complete restoration of cardiac output and stroke volume, even at a higher level than it was at the start of the experiment. Mean arterial pressure decreased slightly, and the heart rate returned to its basic value (Table 1). In the ECG, ST elevations from baseline showed a further regression to a level between the basic value at the start of the experiment and the value measured after injection of the microbeads (Figure 2, *E*).

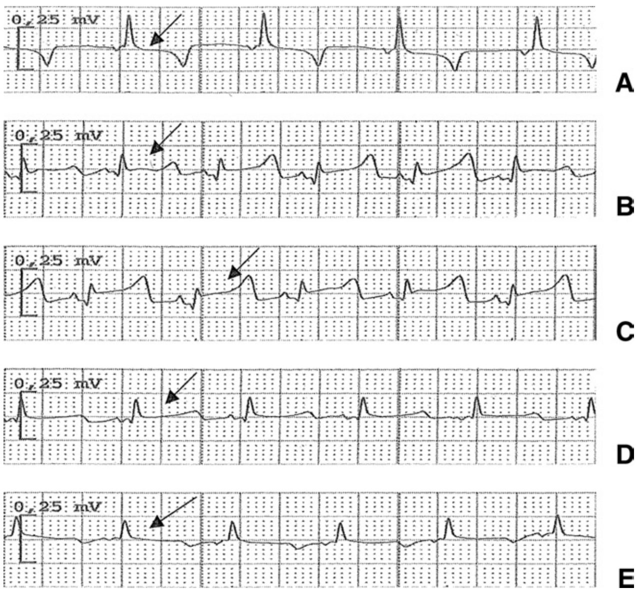

Figure 2. Limb lead II is chosen to demonstrate the normal ECG at the start of the experiment (A), the elevation of the ST segment after injection of the microspheres (B), its progression after stenosis of the LAD artery (C), the regression of the ST segment elevations after establishing venous revascularization (D), and its return to nearly normal after reopening the LAD artery (E). ***ECG*****, electrocardiogram;** ***LAD*****, left anterior descending.**

Discussion

In the past few decades, there has been in an increase in the number of patients with coronary heart disease who are not eligible for standard procedures (eg, coronary artery bypass grafting and percutaneous coronary angioplasty). Clinical trials investigating treatment with angiogenesis factors and gene therapy[1] have been initiated, and new devices for creating cardiac arteriovenous fistulas percutaneously[2,3] have been introduced. Whereas injection of growth factors requires an adequate arterial inflow, which is often not existent in the hearts of these "no option patients," new catheter devices to create a fistula between a coronary artery and the accompanying vein or, as performed in animal experiments, a coronary vein and the left ventricle, are difficult to handle, may be expensive, and hold all the risks

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of catheterization of a severely altered vessel. In addition to these new procedures, the efficiency of which will have to be investigated in long-term trials, we think that some patients might profit from the revival of an "old" method: retrograde venous revascularization. All previous animal models[6-12,14,15] that systematically examined arterialization of a cardiac vein imitated only the macroangiopathy of a coronary artery. Therefore, we investigated the efficiency of a coronary venous bypass graft under the conditions of a combination of cardiac microangiopathy with a significant macroangiopathic stenosis of a coronary artery, which is frequently found in diabetic angiopathy.

Our hypothesis, the creation of a model imitating an acute ischemic situation caused by a combined angiopathy, was supported by the observation of significant elevations of ST segments in the ECG as a typical symptom of ischemia accompanied by a significant decrease of cardiac output, stroke volume, and mean arterial pressure. Digital subtraction angiography revealed a lesser content of contrast agent in the affected myocardial region. We are aware that in real disease the process of microangiopathy is more complex and involves surrounding tissue, but in our model, as well as in the disease, capillary perfusion is reduced. Also, other investigators have demonstrated that the injection of microbeads creates a significant change in heart function.[16]

After establishment of venous revascularization, the reversal of blood flow in the vein connected to the arterial graft was proved by the flow of contrast fluid. We suppose that the majority of the arterial blood provided by the bypass vessel reaches the capillary bed, nourishes the myocardium,[6] and drains through the arteriosinusoidal and thebesian vessels into the heart caves. The drainage could not be made visible by the contrast fluid, probably because of the slow passage of blood through these vessels. Digital subtraction angiography showed restituted enrichment of contrast fluid in the region of the revascularized vein as a sign of improved regional perfusion. Other indications of the efficiency of the coronary venous bypass graft are the regression of ST segment elevations in the ECG, as described previously,[7] and the improvement of the hemodynamic situation. Stroke volume and cardiac output increased by improving the contractility of the heart muscle and not by increasing the heart rate, because this parameter did not show any relevant changes through the whole experiment. Mean arterial blood pressure did not return to normal after revascularization. This might be an effect of reactions of the vegetative nervous system and the long operation time with an open chest, although we tried to prevent the status of hypovolemia and its vegetative consequences by keeping the central venous pressure in a certain range (10-12 torr) throughout the experiment. After the LAD was reopened, cardiac output was even higher than its basic value at the beginning. The reason for this may be a hyperemia caused by retrograde venous revascularization. To sum up these hemodynamic parameters, the coronary venous bypass graft with an adequate flow restored $77.5\% \pm 37.2\%$ of the myocardial function compared with its basic value before the ischemic state.

These observations suggest that retrograde venous revascularization is a safe and efficient method to improve the function of a heart in an acute state of ischemia caused by a combination of macroangiopathy and microangiopathy. However, future studies are needed to investigate whether this revascularization technique also leads to improvement on a more chronic time scale and especially whether the oxygen supply during and apart from exercise can be maintained with this method. Only a long-term study on restenosis and functionality will establish whether this type of revascularization may be as helpful as suggested by the results of the acute investigations and whether it could be regarded not as an alternative to replace an aortocoronary artery bypass graft operation, if it is feasible, but as a last therapeutic option for a group of patients who are not eligible for any other standard procedure: patients with small vessel disease, diffuse arteriosclerosis, distal stenosis, or dissected vessels, or patients who have undergone multiple stenting of the coronaries.

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