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Long-Term Evaluation of a Selective Retrograde Coronary Venous Perfusion Model in Pigs (*Sus Scrofa Domestica*)

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The lack of suitable target vessels remains a challenge for aortocoronary bypass grafting in end-stage coronary heart disease. This study aimed to investigate the arterialization of cardiac veins as an alternative myocardial revascularization strategy in an experimental long-term model in pigs. Selective retrograde perfusion of a coronary vein (aorta to coronary vein bypass, retrobypass) before ligation of the ramus interventricularis paraconalis (equivalent to the left anterior descending artery in humans) was performed in 20 German Landrace pigs (*Sus scrofa domestica*). Retroperfusion of the left anterior descending vein was performed in 10 pigs (RP+) but not in the other 10 (RP–), and the vena cordis magna was ligated (L+) in 5 pigs in each of these groups but left open (L–) in the remaining animals. Hemodynamic performance (for example, cardiac output) was significantly better in the group that underwent selective retroperfusion with proximal ligation of vena cordis magna (RP+L+; 4.1 L/min) compared with the other groups (RP+L–, 2.5 L/min; RP–L+, 2.2 L/min; RP–L–, 1.9 L/min). Long-term survival was significantly better in RP+L+ pigs (112 ± 16 d) than in all other groups. Histologic follow-up studies showed significantly less necrosis in the RP+L+ group compared with all other groups. Venous retroperfusion is an effective technique to achieve long-term survival after acute occlusion of the left anterior descending artery in a pig model. In this model, proximal ligation of vena cordis magna is essential.

Abbreviations: L, ligation; RP, retroperfusion.

In cardiac surgery, the lack of suitable target vessels remains a challenge for coronary artery bypass grafting in end-stage coronary heart disease. Because coronary veins do not develop atherosclerosis, these vessels are potential targets for alternative revascularization strategies.[2,9,25,31] Coronary retroperfusion was first suggested in 1898.[35] In those experiments, cardiac contractility was sustained in a feline model by delivering oxygenated blood through the coronary sinus. Further experimental studies were made in 1943, in which the coronary sinus in a canine model was arterialized by using an autologous carotid artery as a conduit between the dogs' descending aorta and the coronary sinus.[39] Another author independently evaluated coronary retroperfusion in dogs by directly anastomosing the common carotid artery to the coronary sinus, followed by partial occlusion of the coronary sinus (Beck II procedure) to reduce the shunt volume. [3,4,5] This method was attempted in humans but was abandoned due to high mortality caused by the edema and hemorrhage in the postcapillary venules that resulted from the elevated pressure.[7,9,16,33] Currently, the venous vasculature is used frequently for effectively delivering cardioplegic solutions through the coronary sinus during surgical procedures requiring cardioplegic heart arrest. The goal underlying permanent retrograde perfusion through the coronary sinus is to perfuse the ischemic myocardium from proximal to the occlusion or stenosis.

The current study aimed to investigate arterialization of venous vessels as an alternative myocardial revascularization strategy. We hypothesized that selective retrograde perfusion of the vein concomitant to the left anterior descending artery in combination with proximal ligation would preserve hemodynamic function after ligation of the in a long-term selective retroperfusion model in pigs.

Materials and Methods

Animals. This study used 20 male, German Landrace pigs (Schmidt's Farm, Langensendelbach, Germany), which received humane care in strict compliance with the *Principles of Laboratory Animal Care* as formulated by the National Society for Medical Research[32] and the *Guide for the Care and Use of Laboratory Animals*.[22] All procedures were performed in accordance with the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes[13] and the German Animal Protection Law of 1998,[17] and IACUC approval was obtained from the local Veterinary Office (Regierungspräsidium Mittelfranken, Ansbach, Germany; permission no. 54–2531.31–30/06). As described previously,[19] the animals were housed at the Friedrich-Alexander University's Animal Research Center (Franz Penzoldt Center of Animal Sciences, Erlangen, Germany). The pigs had ad libitum access to water and were fed a commercial diet (4 mm, V4133-000 SSNIFF, Ssniff Spezialdiaeten, Soest, Germany). Swine were housed in pairs and separated only temporarily for safety

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or space reasons. Hay was provided daily. A room temperature of 18.5 to 21.5 °C and humidity of 50% to 70% were maintained. The pigs were acclimated for at least 2 wk and carefully checked for preexisting diseases before undergoing surgical procedures. Food was withheld for 8 h before surgery.

Anesthesia and monitoring. Healthy male pigs (age, 111.2 ± 31.9 d; weight: range, 35.1 to 55.2 kg; median, 40.4 kg) were premedicated intramuscularly with ketamine hydrochloride (20 mg/kg; Ketavet, Pfizer, Karlsruhe, Germany), azaperone (4 mg/kg; Stresnil, Janssen-Cilag, Neuss, Germany), midazolam hydrochloride (1 mg/kg, Midazolam, Ratiopharm, Ulm, Germany), and atropine (0.01 mg/kg; Atropin, Braun, Melsungen, Germany), as described previously.[19] In brief, after loss of consciousness, the spontaneously breathing pigs were transferred to the operating theater. A marginal vein in 1 ear was cannulated with a 32-mm 20-gauge intravenous catheter (Venflon 2, Braun) for fluid and drug administration. After 3 min of preoxygenation, anesthesia was supplemented by rapid intravenous infusion of ketamine (10 mg/kg; Ketavet, Pfizer) and bolus infusion of propofol (1 to 2 mg/kg; Disoprivan, Pfizer); 1 min later, the pigs were endotracheally intubated with a cuffed tube. After induction of unconsciousness, sufficient anesthesia was determined by hemodynamic and clinical observation as described previously.[19,36] An adequate level of anesthesia was maintained by inhaled isoflurane and intravenous fentanyl.

Ventilation was performed with a respirator in volume-control mode (Fabius, Dräger, Lübeck, Germany) at a frequency of 20 to 25 breaths per minute, tidal volume of 10 to 12 mL/kg, positive end-expiratory pressure of 5 mbar, and inspired oxygen fraction at 0.5. Leads for 3-lead electrocardiography were attached. Body temperature was monitored by using a rectal probe thermometer and maintained at 37 ± 1 °C by warm infusions, a heating pillow and a room temperature of 25 °C. Central venous catheterization of the right jugular vein was accomplished by using a 7-French, 30-cm multilumen catheter (Arrow, Reading, PA) for additional infusions and blood sampling and hemodynamic monitoring was performed by using PiCCO technology (Pulsion Medical Systems, Munich, Germany), as described previously.[19] After exposure of the heart through a median sternotomy, catheterization of the pulmonary artery and measurement of left atrial pressure were performed as previously described.[19,28,41] Blood samples were obtained for analyses of oxygen tension, acid–base balance, and electrolyte levels (ABL800 Flex and Hemoximeter OSM3, Radiometer, Copenhagen, Denmark).

Experimental design. We allocated the 20 pigs into 4 groups of 5 pigs each. In each group, acute ischemia was induced by ligation of the ramus interventricularis paraconalis (equivalent to the left anterior descending artery) in the middle of the sulcus interventricularis. By using a beating heart technique, an aorta-to-coronary–vein bypass (retrobypass) was created (Figure 1). The hemodynamic effect of selective retrograde perfusion of a coronary vein was studied, either with or without proximal ligation of the vena cordis magna. To this end, the retrobypass and drainage of blood into the vasuclature were identified angiographically (Figure 2).

Intraoperative angiograms were obtained by using mobile X-ray imaging (Arcadis Avantic, Siemens, Medical Solutions, Erlangen, Germany), with 50 to 70 mL iomeprol (Imeron 350, Altana Pharma, Konstanz, Germany) as the contrast medium.

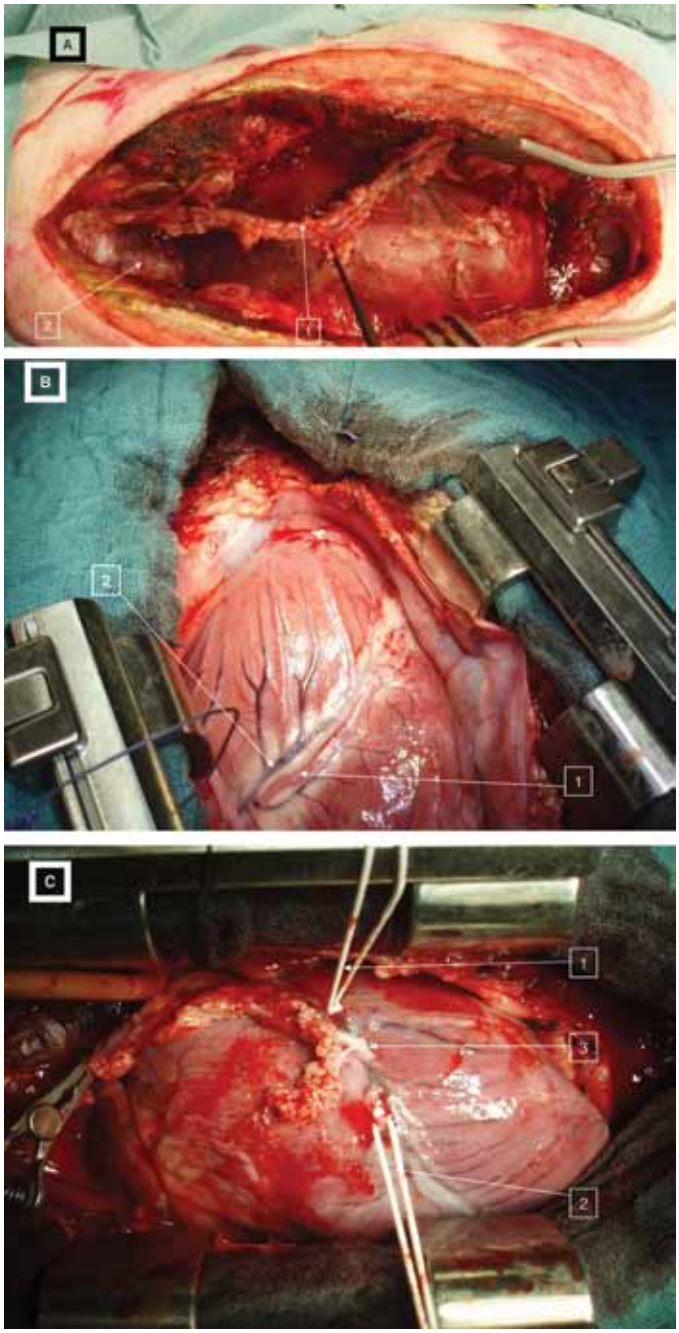

Figure 1. The operating field as seen from the perspective of the surgeon; cranial is to the left. (A) After median sternotomy and harvesting of the (1) left internal thoracic artery. (B) The facies sternalis of the heart is shown; cranial is downward. The (1) right interventricularis paraconalis (equivalent to the ramus interventricularis anterior, RIVA) and (2) vena interventricularis anterior are shown. (C) After creation of the retrobypass (3: end-to-side anastomosis of the left internal thoracic artery to the vena interventricularis anterior); vessel loops have been placed around the (1) vena interventricularis anterior and (2) Right interventricularis paraconalis (equivalent to the ramus interventricularis anterior, RIVA). Cranial is to the left.

Surgical procedures. A median incision and sternotomy were performed in anesthetized pigs, and the heart was exposed by using pericardial stay sutures. Heparin (200 IU/kg) was admin-

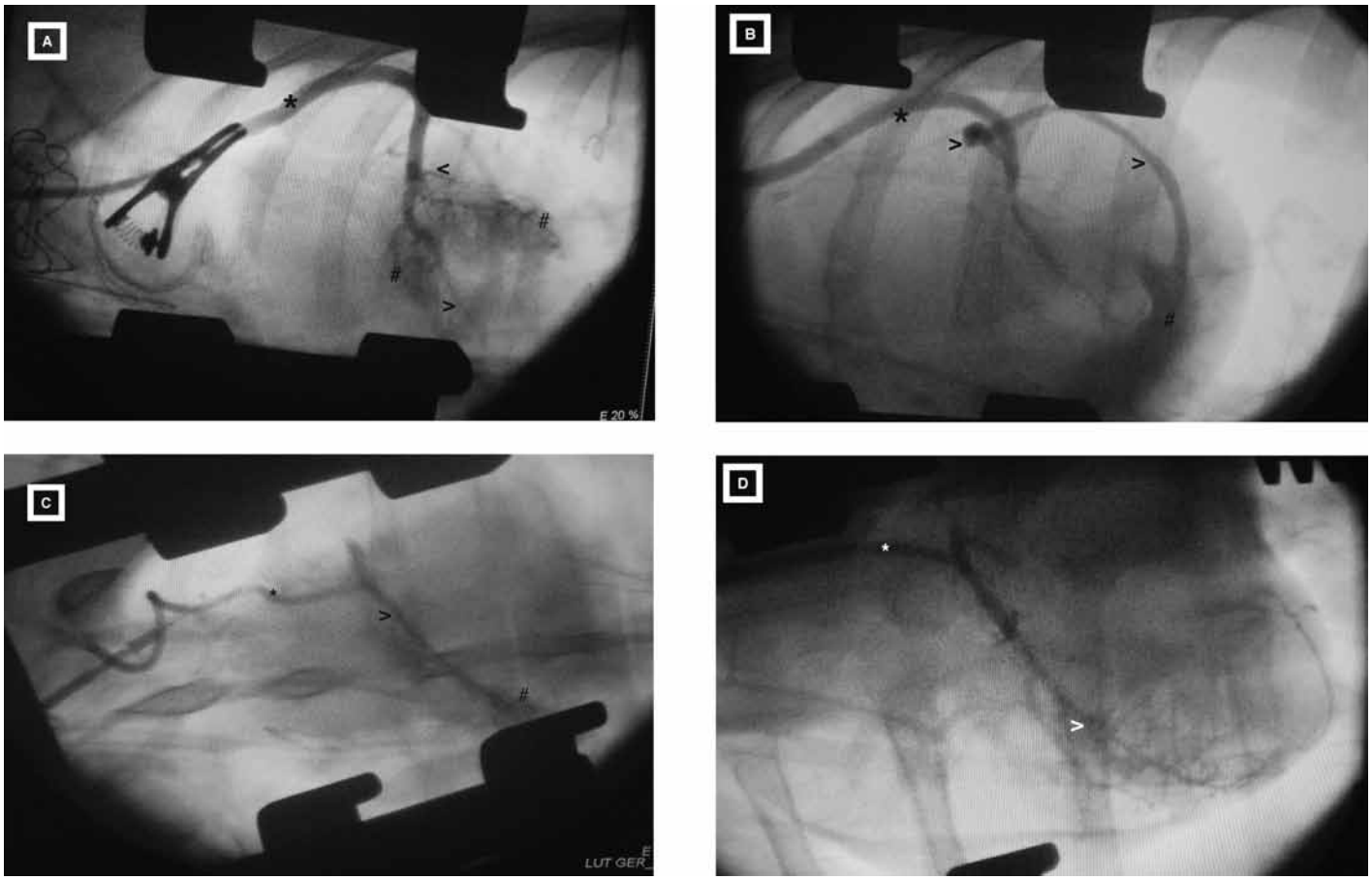

Figure 2. (A) Intraoperative angiogram of the retrobypass (*, left internal thoracic artery); cranial is to the left. The (>) vena interventricularis anterior and (#) venous plexus are filled with contrast material. The vena cordis magna has been ligated proximally to the anastomosis (<). (B) Intraoperative angiogram; cranial is to the left. Without ligation of the vena cordis magna, (*) the left internal thoracic artery immediately fills the (>) vena cordis magna and (#) sinus coronarius. (C, D) Postoperative venograms of representative retrobypasses. The vena interventricularis anterior and venous plexus are filled with contrast material.

istered, and the activated clotting time (Hemochron Jr Whole-Blood Coagulation System, International Technidyne, Edison, NJ) was kept above 200 s. The arteria thoracica interna sinistra (equivalent to the left internal thoracic artery) was dissected from the thoracic wall (Figure 1). The ramus interventricularis paraconalis was identified in the middle of the sulcus interventricularis, encircled with a tourniquet, and held open until the start of the experiment. The left anterior descending vein was identified at the point where it connects to the vena cordis magna; (Figure 1), vessel loops were placed at this point and at 5 cm distal (toward the apex) to the proposed anastomotic site. The arteriovenous anastomosis was created by using 8-0 polypropylene sutures in an off-pump technique (Figure 1). The anastomotic site of the retrobypass and thus the effective drainage of blood into the vena interventricularis anterior was checked angiographically with and without ligation of the vena cordis magna (Figure 2). Transesophageal echocardiography (Acuson CV70, Siemens) was performed intraoperatively.

In all 20 pigs, the left anterior descending artery was ligated in the middle of the sulcus interventricularis by using 5-0 polypropylene sutures, and hemodynamic performance was observed for 6 h with (RP+) or without (RP–) selective retrograde perfusion through the retrobypass, during which time the left anterior descending vein was proximally either ligated (L+) by closing the vessel loop or left open (L–). Efficiency of the retrobypass was evaluated by coronary angiography and online pressure measurement. Hemodynamic performance (electrocardiographic changes, cardiac output, mean arterial pressure, mean pulmonary artery pressure, heart rate, stroke volume, and ejection fraction) was monitored with and without retrograde perfusion through the retrobypass.

After the end of the primary observation period (6 h), the chest was closed in a standard technique by using steel wires and polyglactin 910 sutures for subcutaneous adaptation and 4-0 poliglecaprone 25 sutures for skin closure. The pericardium and, if necessary, pleural cavities were drained by using standard 24-French chest drains. The central venous catheter and any drains were removed at the end of the operation. All animals received sufficient analgesic therapy by using different analgesic regimes: ropivacain (2 mg/kg; Naropin 2%, Astra- Zeneca, Wedel, Germany) intraoperatively for blockade of the parasternal intercostals nerves; buprenorphine (0.02 mg/kg SC; Temgesic, Essex Pharma, Munich, Germany) for the first 3 postoperative days; and metamizol (40 mg/kg IM; Vetalgin, Intervet, Unterschleissheim, Germany) for the first 3 postoperative days. In accordance with our standard procedure, analgesics (buprenorphin, metamizol or

carprofen) were given 3 times daily for 3 d and then as necessary. A single oral dose of carprofen (4 mg/kg; Rimadyl, Pfizer) was given during the first 3 postoperative days if needed. After they had been breathing spontaneously for at least 30 min, swine were extubated and transferred to the observation unit in the housing facility. An infrared light was used to keep the pigs' body temperature within the physiologic range. Swine had free access to water and were fed the next morning after surgery.

During surgery, swine with intractable cardiocirculatory depression or refractory rhythm disturbances (groups RP–L–, RP–L+, and RP+L–) were euthanized during deep anesthesia by barbiturate injection (80 mg/kg pentobarbital sodium; Eutha 77, Essex Pharma, Munich, Germany). Cardiac arrest was induced by infusion of Bretschneider cardioplegic solution (Custodiol, Koehler Chemie, Alsbach-Haehnlein, Germany). The hearts were explanted and histopathologically examined. At the end of the observation period (100 ± 10 d), all swine were euthanized under deep anesthesia as described, and the hearts were explanted for histopathologic examination. Biopsies were taken from the myocardial region perfused by the left anterior descending artery and prepared for further studies.

Histomorphometric analysis. Explanted hearts were perfused and fixed with formaldehyde (10% neutral buffered formalin, which is approximately 3.7% formaldehyde in PBS). Fixed hearts were cut into 1-cm slices in an apicobasal direction. Samples taken from each of these slices were prepared for staining by hematoxylin and eosin and Sirius red. The area of necrosis within the left ventricular area was determined histochemically by using Sirius red and hematoxylin and eosin as described previously.[26,27] By using planimetry (AnalySIS, Soft Imaging Systems, Olympus, Soft Imaging Solutions, Munster, Germany), the area of necrosis within the left ventricular area was obtained.[34]

Laboratory measurements. The concentration of cardiac troponin I was determined automatically (Access 2, Beckman Coulter, Krefeld, Germany). The cutoff point was 0.07 ng/mL. The analytic specificity for swine cardiac troponins has been published elsewhere.[15]

Cardiac CT angiography. Swine underwent cardiac computed tomographic angiography at 30 d after surgery. They were premedicated intramuscularly with ketamine hydrochloride, azaperone, midazolam hydrochloride, and atropine as described earlier. A marginal vein in one ear was cannulated with a 32-mm 20-gauge intravenous catheter (Venflon 2, Braun) for fluid and drug administration. Blood was taken for measurement of cardiac enzymes. After loss of consciousness, the spontaneously breathing pigs were transferred to the Institute of Medical Physics (Director, Professor WA Kalender), and computed tomographic angiography was performed as previously published elsewhere.[14]

Statistical analysis. Data were analyzed by using SigmaStat statistical software (Systat Software, San Jose, CA). All data are presented as mean ± 1 SD. Two-way ANOVA for repeated measurements was used to compare variables within and between groups. A P value of less than 0.05 was considered statistically significant.

Results

Survival time. In the retroperfusion group with ligation of the great cardiac vein (RP+L+ group), cumulative survival was 562 d (range, 96 to 138 d; mean ± 1 SD, 112 ± 16 d; n = 5 animals). In all other groups, long-term survival could not be assessed. Swine in which the vena cordis magna remained open (RP–L– and RP+L– groups) did not survive for longer than 1 h after ligation of the left anterior descending artery. Swine the RP–L+ group did not survive longer than 2 h (Table 1).

Intraoperative angiography. Intraoperative angiograms confirmed competent anastomoses in all pigs in the RP+L– and RP+L+ groups. After initiation of venous retroperfusion, effective retrograde flow was visible angiographically only if the vena cordis magna was ligated (RP+L+ group; Figure 2 A). Blood flow was directed immediately to the coronary sinus in RP+L– pigs (Figure 2 B).

Myocardial enzyme release. Troponin I release at 1 h was significantly ($P < 0.05$) lower in pigs with retroperfusion and ligation of the vena cordis magna (RP+L+ group; 7.04 ± 2.1 ng/mL) than in the RP–L– (35.3 ± 6.1 ng/mL), RP–L+ (46.8 ± 4.9 ng/mL), and RP+L– (29.4 ± 4.1 ng/mL) groups (Table 1). In the prolonged time course of the RP+L+ group (2, 4, 6, and 24 h and 30 d after surgery), troponin I declined after 4 h and subsequently reached preoperative values (Figure 3).

Hemodynamic performance. Parameters of hemodynamic performance declined after ligation of the left anterior descending artery in swine lacking retroperfusion (RP–L+ and RP–L– groups) and those in which the great cardiac vein was left open (RP+L– animals). Only in pigs with retroperfusion and a ligated great cardiac vein (RP+L+ group) did hemodynamic variables remain unchanged from preoperative values (Table 1, Figure 4).

Left ventricular ejection fraction, measured planimetrically by using transesophageal echocardiography, declined from 59% preoperatively to 24% in RP–L– pigs, from 62% to 20% in RP–L+ animals, and from 64% to 23% in the RP+L– group. In contrast, the intraoperative left ventricular ejection fraction in the RP+L+ group (51%) did not differ significantly from that preoperatively but was significantly ($P < 0.05$) higher than the intraoperative measurements of the other 3 groups. Similar changes occurred in left ventricular end-diastolic pressure, which increased significantly compared with preoperative values in the RP+L–, RP–L+, and RP–L– groups but not the RP+L+ group (Table 1).

In all groups, changes in cardiac output, the clinically most important parameter, reflected changes in stroke volume (Table 1). The effect of ligation of the great cardiac vein on cardiac output is in Figure 4.

Electrocardiographic changes and rhythm disorders. All pigs showed signs of myocardial ischemia (elevation of the ST segment, ventricular extrasystole as a sign of electrical instability due to ischemia) after ligation of the left anterior descending artery, but the changes were nonsignificant in the RP+L+ group only (Table 1). In addition, mean arterial pressure was maintained throughout the observation period in the RP+L+ group. All other groups showed a significant ($P < 0.05$) decline of mean arterial pressure compared with baseline values for the same group.

Postoperative angiography. Computed tomographic angiography at 30 d after surgery confirmed the presence of competent retrobypasses in all RP+L+ swine (Figure 5).

Histopathologic examination. One-factor ANOVA showed that the necrotic area in the RP+L+ group (1.1% ± 0.25%) was significantly ($P < 0.05$) smaller than that in the RP–L– (32.4% ± 4%), RP+L– (19.83% ± 3%), and RP–L+ (21.6% ± 2%) groups (Figure 6).

Table 1. Hemodynamic and other cardiac variables (mean ± 1 SD, n = 5) before (preoperative) and 60 min after ligation of the left anterior descending artery

	Preoperative				After ligation			
	RB–L–	RB–L+	RB+L–	RB+L+	RB–L–	RB–L+	RB+L–	RB+L+
Cardiac output (L/min)	4.4 ± 1.4	4.8 ± 1.1	5.1 ± 1.3	4.8 ± 0.9	1.9 ± 0.8[a]	2.2 ± 0.3[a]	2.5 ± 0.9[a]	4.3 ± 0.7[b]
Heart rate (bpm)	72 ± 7	82 ± 12	80 ± 10	74 ± 9	97 ± 16[a]	91 ± 11[a]	99 ± 17[a]	79 ± 8[b]
Stroke volume (mL)	61.2 ± 5	58.8 ± 8	63.3 ± 9.0	64.6 ± 7	19.4 ± 9[a]	24.3 ± 7[a]	25.4 ± 6[a]	49.4 ± 8[b]
Ventricular extrasystole (bpm)	2 ± 1	0 ± 1	1 ± 1	0 ± 1	14 ± 4[a]	13 ± 5[a]	9 ± 3[a]	4 ± 2[b]
Mean arterial pressure (mm Hg)	69 ± 6.2	72 ± 2.1	70 ± 5.4	73 ± 8.3	34 ± 11[a]	32 ± 6[a]	35 ± 4[a]	62 ± 8[b]
Left ventricular end-diastolic pressure (mm Hg)	8.2 ± 2.1	7.8 ± 1.1	9.1 ± 2.0	8.7 ± 5.2	14.3 ± 3.4[a]	16.4 ± 3.7[a]	17.4 ± 7.2[a]	9.8 ± 2.9[b]
Mean pulmonary arterial pressure (mm Hg)	26 ± 5	22 ± 3	21 ± 2	24 ± 5	46 ± 5[a]	49 ± 6[a]	43 ± 9[a]	29 ± 4[b]
Central venous pressure (mm Hg)	12 ± 2	14 ± 1	15 ± 2	13 ± 3	24 ± 3[a]	21 ± 3[a]	23 ± 5[a]	15 ± 3[b]
Ejection fraction (%)	59.4 ± 2.1	62.2 ± 3.1	64.2 ± 2.9	60.6 ± 2.9	24.2 ± 2.3[a]	20.2 ± 2.2[a]	23.2 ± 3.3[a]	51 ± 2.7[b]
Ventricular extrasystole (bpm)	2 ± 1	1 ± 2	1 ± 2	2 ± 1	14 ± 8[a]	18 ± 4[a]	12 ± 3[a]	4 ± 2[b]
ST segment elevation (mm)	0.2 ± 0.1	0.1 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	14.5 ± 3.2[a]	12.2 ± 4.1[a]	11.5 ± 3.3[a]	2.1 ± 1.9[a,b]
Troponin I (ng/mL)	0.34 ± 0.19	0.17 ± 0.06	0.26 ± 0.15	0.44 ± 0.24	35.3 ± 6.1[a]	46.8 ± 4.9[a]	29.4 ± 4.1[a]	7.04 ± 2.1[b]

Mean survival time after ligation of the left anterior descending artery: RB–L–, 64 min; RB–L+, 67 min; RB+L–, 70 min; RB+L+, 112.4 ± 16.2 d ($P < 0.05$ compared with values for all other groups).
RB, perfusion through retrobypass (+, present; –, absent); L, ligation of left anterior descending vein (+, present; –, absent)
[a]$P < 0.05$ compared with baseline value for same group and parameter
[b]$P < 0.05$ compared with postligation values for the same parameter for the RB–L–, RB–L+, and RB+L– groups.

Discussion

The coronary venous system has been in the focus of scientific evaluation for more than 100 y.[1,3,4,5,7,20,24,35,38] Currently efforts are being made to apply coronary venous retroperfusion methods for clinical treatment of ischemic myocardium. Due to improved understanding of the efficiency and safety of retroperfusion,[11] retroinfusion techniques can lead to marked recovery of previously infarcted myocardial tissue and enhance cardiac function.[23] Until now, the coronary sinus was used routinely to deliver cardioplegic solutions in clinical situations.[27] In experimental studies in dogs,[42] pigs,[8,33,40] and sheep[37] and in human clinical studies, retroperfusion of the coronary sinus has been used to improve myocardial perfusion and postischemic systolic and diastolic function in many surgical procedures, including off-pump coronary artery bypass grafting[8] and percutaneous intermittent coronary sinus occlusion.[29,30]

The improved pathophysiologic understanding of the global retroperfusion techniques has led to technical modifications, including those for regional, selective, and segmental venous retroperfusion. The importance of pressure in the adaptation process of the coronary veins has been shown in a canine model, in which damage to the venous endothelium begins at a pressure of 60 mm Hg.[18] This idea of adaptation and remodeling of the venous vasculature has been studied intensively; these studies revealed that different degrees of remodeling can be observed across the left ventricular wall.[11,12] The authors proposed occlusion of the coronary vein first, to allow time for the venous vasculature to adapt to the increased pressure, followed 2 wk later by retroperfusion with exposure to arterial pressure.[12] This staged procedure had been proposed earlier but had been abandoned because of hemorrhage and rupture of small venules.[3,4,5]

The rather unsystematic clinical experience of cardiac surgeons with regional retroperfusion has been reviewed previously.[21] Among 117 patients with coronary artery disease and unsuitable target vessels, surgeons unintentionally bypassed the coronary vein. Because the vein was not ligated proximally in these cases, drainage of blood through the coronary sinus was not prevented, and flow reversal in the vein concomitant to the left anterior descending artery was not established. In 35% of planned coronary venous bypass procedures, the vena cordis magna was ligated, and patients experienced relief of symptoms.[6,21]

Clinical use of retroperfusion is not widespread because results from animal studies in dogs,[18] pigs,[8,33,40] and sheep[37] and clinical studies have been controversial.[10] Therefore, we performed a long-term study in pigs, in which we applied selective retroperfusion by using an acute infarction model through ligation of the ramus interventricularis paraconalis (equivalent to the left anterior descending artery in humans). We studied the effect of selective retrograde perfusion of the vena interventricularis anterior through retrobypass by analyzing hemodynamic and other parameters. As expected, we found that occlusion of the left anterior descending artery at its midpoint reduced cardiac output and worsened cardiac and circulatory parameters, including ejection fraction, end-diastolic pressure, stroke volume, and mean arterial pressure, and led to electrocardiographic changes (ST elevation) that were consistent with myocardial ischemia. In addition, all pigs in all groups manifested rhythm disturbances, consistent with occlusion of the left anterior descending artery.

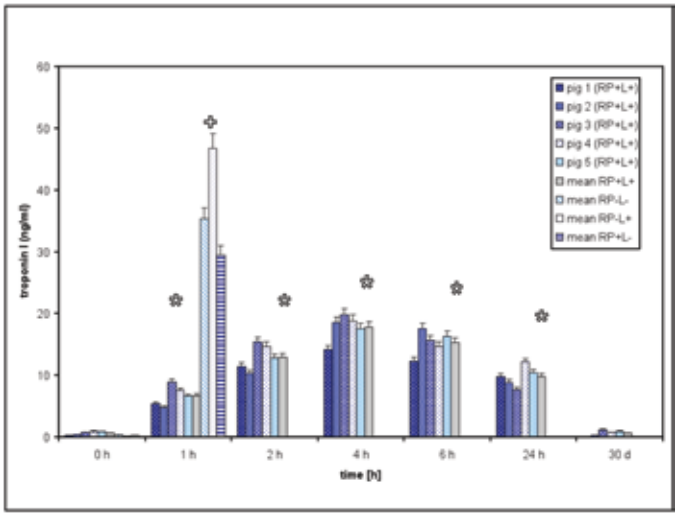

Figure 3. Changes in myocardial enzyme release: effect of retroperfusion with ligation of left anterior descending vein. Stippled bars represent individual animals of the RP+L+ group; the solid gray bar represents the mean value (error bar, 1 SD) for this group. Cross-hatched bars represent the mean values of the other 3 groups, for which limited data points were available due to limited survival time. RP, perfusion through the retrobypass (+, present; –, absent); L, ligation of left anterior descending vein (+, present; –, absent); *, significantly ($P < 0.05$) different from preoperative value; +, significantly ($P < 0.05$) different from the mean value of group RP+L+.

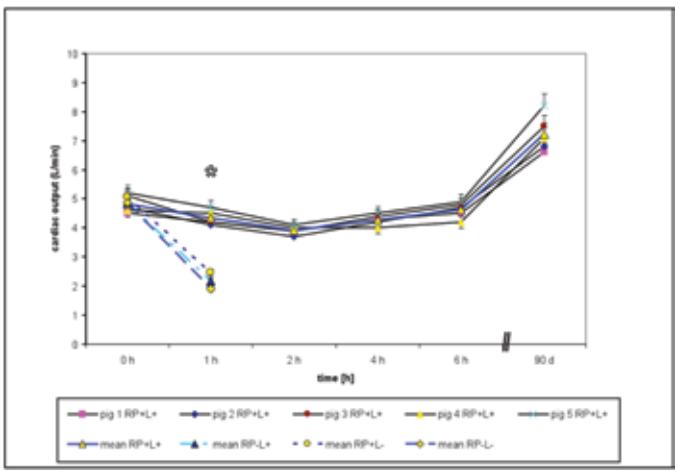

Figure 4. Changes in cardiac output after ligation of the left anterior descending artery: effect of retroperfusion with ligation of the vena cordis magna (error bar, 1 SD). RP, perfusion through retrobypass (+, present; –, absent); L, ligation of left anterior descending vein (+, present; –, absent); *, significantly ($P < 0.05$) different from preoperative value.

Selective retroperfusion prevented hemodynamic deterioration only when it was combined with proximal ligation of the vena cordis magna (equivalent to the left anterior descending vein in humans). When selective retroperfusion was performed in addition to proximal ligation of the vena cordis magna, arterialized blood was prevented from flowing into the coronary sinus (bypassing the heart) and was redirected to the ischemic myocardium (flow reversal). In our acute infarction model, selective retroperfusion led to improved hemodynamic stability, an indirect sign of sufficient myocardial oxygen supply. The serum concen-

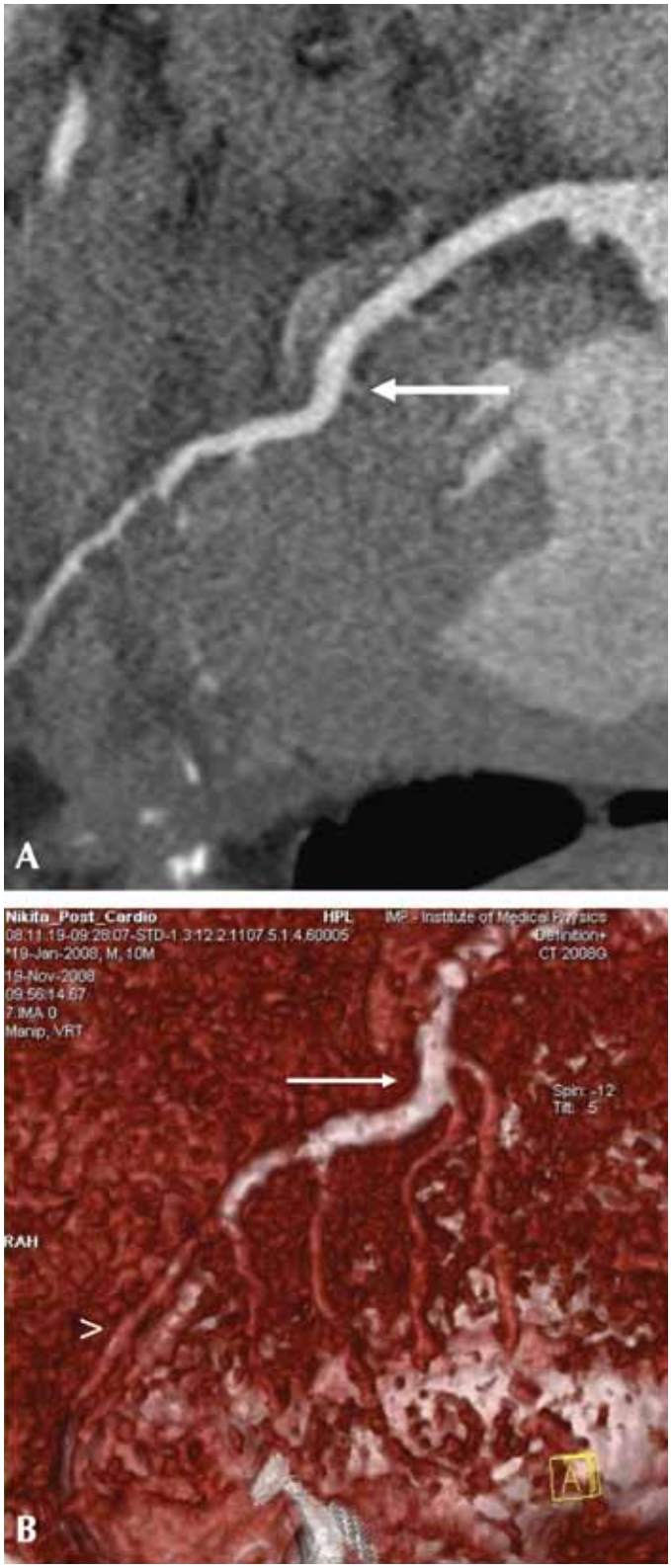

Figure 5. (A) Postoperative computed tomographic angiogram of the retrobypass of the (*) left internal thoracic artery. (B) 3D reconstruction of the filling of the vena interventricularis anterior through the retrobypass.

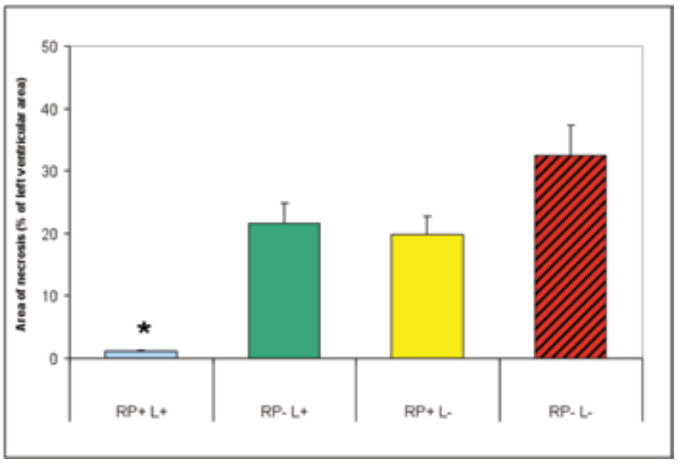

Figure 6. Area of necrosis in the left ventricle. Swine that underwent retrobypass and ligation of left anterior descending vein (RP+L+)had significantly ($P < 0.05$) less necrosis than did those without retrobypass (RP–L–, RP–L+) or ligation of the left anterior descending vein (RP–L–, RP+L–).

trations of cardiac troponin I that we measured further supported this conclusion. These clinical parameters are consistent with the histologic studies. The use of the retrobypass in combination with ligation of the vena cordis magna significantly reduced the area of necrosis. For the first time, we have shown that regional venous retrobypasses can be performed in a long-term pig model. For long-term survival of the swine, simultaneous ligation of the vena cordis magna is mandatory.

Despite its results, the current study had several limitations. Because the juvenile pig hearts we used were free of coronary artery disease, our experimental model of acute occlusion of the left anterior descending artery differs from the scenario in human patients, in whom extensive coronary artery disease can lead to development of collateral flow and thus limit the extent of subsequent ischemia. However, our experimental results likely remain directly relevant for patients with acute single-vessel disease without sufficient collateral flow.

In this long-term swine model of selective retroperfusion, the negative hemodynamic effects of ligation of the left anterior descending artery were prevented by regional retroperfusion. This benefit was achieved by means of an aorta-to-coronary–vein bypass only when the vena cordis magna was ligated and flow reversal was established. Therefore, elimination of the venous connection to the coronary sinus (for example, the vena cordis magna) is crucial when using this model of selective retroperfusion. We have demonstrated, for the first time, in a long-term large animal model that retrobypass in combination with ligation of the vena cordis magna (equivalent to the left anterior descending vein in humans) maintains stable hemodynamic function. This success may allow this technique to become a useful alternative not only in experimental settings involving retroperfusion in pigs but also in the treatment of human patients lacking eligible target vessels for aortocoronary bypass grafting in end-stage coronary heart disease.

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