The Heart Surgery Forum #2007-1219
11 (2), 2008 [Epub April 2008]
doi: 10.1532/HSF98.20071219

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Selective Retrograde Venous Revascularization of the Myocardium when PCI or CABG Is Impossible: Investigation in a Porcine Model

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ABSTRACT

We investigated the possibility of nourishing the myocardium through selective retrograde coronary venous bypass grafting (CVBG) with an off-pump technique and evaluated various methods of monitoring the physiological effects of this procedure. In a porcine model, the left internal mammary artery (LIMA) was anastomosed to the left anterior descending coronary vein (LAD vein) in an off-pump procedure. The LAD vein was ligated proximal to the anastomosis. The LAD artery was ligated proximally. The physiological effects were monitored using microdialysis, tissue oxygen tension, blood flow in LIMA, blood samples, and hemodynamic and histological analyses. As controls, 5 pigs underwent surgery involving only LAD artery ligation without CVBG. CVBG with LAD ligation was performed in 16 pigs; 12 survived CVBG and were monitored for 2-2.5 hours while in sinus rhythm, a 75% salvage rate after an otherwise lethal LAD artery occlusion. Immediately after LAD artery ligation, the anterior wall of the left ventricle became cyanotic and hypokinetic. Over time it regained color and contractility as flow in the LIMA increased. Microdialysis showed a significant increase in lactate. Initially tissue oxygen tension decreased, but with time some recovery was seen. Cardiac troponin T was elevated. Histological analysis showed ischemic changes. In control pigs, microdialysis was performed for 1.5 hours up to LAD artery ligation, after which all pigs died in ventricular fibrillation arrest. No increase in lactate was observed. These results indicate that after LAD artery occlusion, CVBG can nourish the myocardium to a certain extent and prevent death in the majority of cases, although varying degrees of ischemia remain.

Received December 14, 2007; accepted February 2, 2008.

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INTRODUCTION

Most patients with coronary artery disease can be treated with either coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI) either electively, or acutely after acute myocardial infarction. With occluded vessels, however, PCI may be impossible. In some patients with extensive atherosclerotic coronary disease and/or coronary arteries of very small caliber, as often found with chronic occluded vessels [Mukherjee 1999], it may be impossible to perform CABG or to completely revascularize the myocardium. Along these sick arteries run healthy veins, however; thus revascularization of the venous system with retrograde flow into the capillary vascular bed may be a way to supplement the blood flow to the myocardium, in both acute and chronic settings.

In 1898 Pratt suggested the concept of nourishing the myocardium through the venous system [Pratt 1898]. More than 60 years ago, at the Cleveland Clinic, Ohio, Beck introduced the concept of arterialization of the coronary venous system. He performed aortocoronary sinus bypasses in patients suffering from chest pain [Beck 1948]. Although some patients benefited from this surgery, its use was eventually abandoned because of the high mortality rate. In the mid-1970s the concept of selective coronary venous bypass grafting (CVBG) was introduced. Experiments were primarily done in dogs and sheep [Bhayana 1974; Gardner 1974; Hochberg 1979]. Hochberg and colleagues performed a bypass between the aorta and the left anterior descending (LAD) coronary vein in dogs, which survived for more than 3 months [Hochberg 1979]. These results indicated that CVBG could be used to nourish the myocardium, but the method gained little attention. In 1986 Hochberg et al sent out questionnaires to 41 surgeons who had performed planned CVBG (accidental revascularizations of a coronary vein were excluded). The data from the questionnaires revealed that 93% of the patients were long-term survivors, with symptomatic improvement described in 22 of 25 evaluated patients [Hochberg 1986]. In recent years only anecdotal cases of clinical CVBG have been described [Kulik 2004; Sadaba 2004].

The strategy for coronary revascularization has changed, with more patients being offered PCI and fewer patients

being referred for surgical evaluation. With the consequent increased comorbidity in the patients offered bypass surgery, the scenarios described above, in which PCI and CABG may not be possible, are becoming increasingly common. We therefore re-explored the CVBG technique with the aim of applying modern less invasive techniques for revascularization (off-pump), as well as using modern equipment to monitor the physiological impact of the procedure with a view to offering the technique to patients at a later stage.

We chose to use off-pump techniques because weaning from extracorporeal circulation after cardioplegic arrest of a heart in which complete revascularization cannot be expected may be impossible. In addition, physiological measurements in an experimental setting are likely to be influenced by ischemia introduced by cardioplegic arrest as well as extracorporeal circulation itself. With the use of off-pump techniques, our experimental measurements were expected to more accurately reflect only the effects of the altered circulation.

MATERIALS AND METHODS

Animals and Ethics

All experiments were performed in compliance with national rules for humane experimental animal care and use, and with license from the Animal Experiments Inspectorate of the Danish Ministry of Justice (license number 2002/561-577). Twenty-one female domestic pigs from a local source that regularly supplies animals for experimental surgery were used. The animals weighed 35 to 40 kg.

Anesthesia

After fasting overnight the pigs were premedicated with 0.50 mg/kg midazolam intramuscularly. Anesthesia was induced with a mixture of zolazepam (11.90 mg/mL), tiletamine (11.90 mg/mL), xylazine (12.38 mg/mL), ketamine (14.29 mg/mL), and methadone (2.38 mg/mL). The mixture was injected intramuscularly at a dose of 0.1 mL/kg. The pigs were intubated with an endotracheal tube and ventilated with 3 L/min FiO_2 74%. Anesthesia was maintained by isoflurane (3%) and intravenous administration of fentanyl at 400 µg/h. All intravenous administrations were given through an auricular vein. To minimize arrhythmia all pigs were given an intravenous bolus of amiodarone 300 mg before the chest was opened. The pigs were killed with pentobarbital (60 mg/kg).

CVBG Surgery

Through a median sternotomy the left internal mammary artery (LIMA) was harvested as a pedicled graft, and the pigs were heparinized with 10.000 IU heparin. Two ligatures were placed, one around the LAD coronary artery (LAD artery) right after its division from the left main coronary artery, and one around the LAD coronary vein (LAD vein) at the same level as the LAD artery ligature (Figure 1).

Initially both ligatures were left untied to allow a steady-state period of at least 80 minutes after insertion of the microdialysis probes, after which an anastomosis between the LIMA and the LAD vein was performed using off-pump techniques, including an Octopus® tissue stabilizer (Medtronic; Minneapolis, MN, USA) and temporary occlusion of the coronary vein. A transit-time probe (Medi-stim A/S, Oslo, Norway) was placed around the LIMA and blood volume flow was continuously monitored.

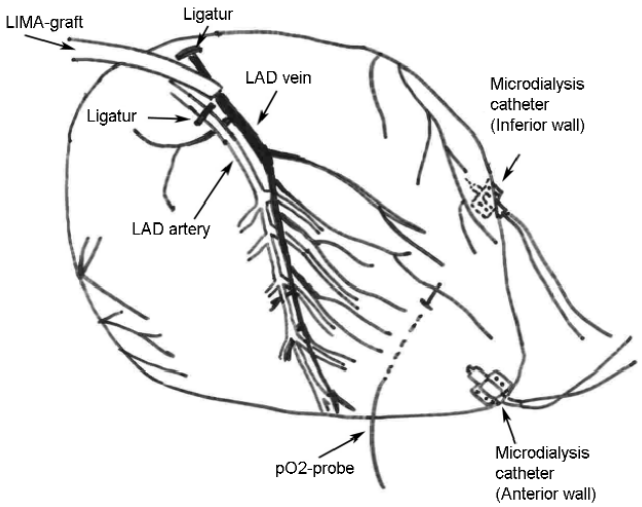

Figure 1. Experimental set-up. LAD artery, left anterior descending coronary artery; LAD vein, left anterior descending coronary vein; LIMA, left internal mammary artery.

The LIMA was unclamped and the flow measured with the unobstructed arteriovenous shunt open. Then the ligature around the LAD vein was tied to stop the direct arteriovenous shunt to the coronary sinus. Finally, the ligature around the LAD artery was tied so that the anterior wall of the left ventricle was dependent on blood flow from the LIMA graft running retrograde through the LAD vein.

Sham Operation

Five pigs, used as controls to assess the effect of LAD ligature, underwent the same procedure, except that the LIMA-to-LAD vein anastomosis was omitted, and the LAD artery was first ligated after 80 minutes steady state plus 1.5 hours of microdialysis (total 170 minutes).

Microdialysis

Before the CVBG operation, 2 microdialysis probes were inserted into the myocardium using a split-sheath introducer. One probe was placed in the anterior wall of the left ventricle (intervention wall) and the other in the inferior wall of the left ventricle (reference wall). A microdialysis pump with 2 syringes (CMA/102, CMA microdialysis AB, Stockholm, Sweden) and probes with a 10 mm membrane were used (CMA/20, CMA microdialysis AB). The molecular cut-off point for the dialysis membrane was 20 kDa. The probes were perfused at 0.3 µL/min using Ringer chloride. With this microdialysis perfusion rate there was a delay of 20 minutes between the interventions on the heart and the perfusate collection. After CVBG and LAD artery occlusion, the first sample was taken after 20 minutes to correct for the delay

in the outlet tube. After this the sampling interval was 30 minutes. Samples were analyzed for concentration of lactate using a CMA/600 microdialysis analyzer (CMA microdialysis AB).

Tissue Oxygen Tension and Hemodynamics

A flexible pO_2 probe (Revoxode, product no. CC1.2, Licox CMP instruments, GMS, Mielkendorf, Germany) with a 5-mm pO_2-sensitive tip was inserted into the anterior wall of the left ventricle for continuous monitoring of oxygen tension.

Mean arterial pressure, central vein pressure, and heart rate were monitored through surgically inserted intraarterial and intravenous catheters in a carotid artery and a jugular vein. Electrocardiogram (ECG) was monitored by lead II.

Blood Samples

For analysis of cardiac troponin T (cTnT), venous blood was collected from the last 6 CVBG pigs and from 4 control pigs. Blood was collected from a central vein catheter using heparinized test tubes. In CVBG pigs samples were collected before sternotomy, immediately after the LIMA-to-LAD vein anastomosis was performed, and 1 and 2 hours after retrograde perfusion was initiated. In control pigs samples were collected before sternotomy, after insertion of microdialysis probes, and at 1 and 2 hours of microdialysis. After centrifugation plasma was stored at –80°C. The samples were analyzed for cTnT using an Elecsys 2010 analyzer (Roche, Copenhagen, Denmark).

Histology

Immediately after the CVBG pigs were killed, transmural myocardial biopsy samples were collected from the anterior wall (intervention wall) and from the inferior wall of the left ventricle (reference wall). The biopsy specimens were fixated in 10% buffered formalin, stained with hematoxylin-eosin, and examined by use of light microscopy.

Statistical Analysis

Results are presented as mean ± 1 SEM. Logarithm-transformed values of the areas under the lactate concentration curve (AUC) for each animal were calculated. Mean logarithm-transformed AUCs were compared between CVBG and control pigs, and between intervention and reference walls using Mann Whitney U and Wilcoxon signed-rank tests, as appropriate. AUCs were calculated from –20 minutes to 90 minutes when CVBG and control pigs were compared, owing to the shorter observation period in the control pigs. Mann Whitney U and Wilcoxon signed-rank tests were used, as appropriate, to compare mean values at specific time points between CVBG and control pigs and between intervention and reference walls. Hemodynamic parameters and oxygen tension were analyzed using the Wilcoxon signed-rank test. A P value of <0.05 was considered significant.

RESULTS

Of the 16 pigs that underwent venous revascularization, 4 died shortly after the anastomosis was performed and were excluded from further analysis. Three of these had a poor flow in the LIMA graft (less than 15 mL/min after 5 minutes). The anastomosis was redone in all 3 pigs without improved blood flow. Subsequently the animals developed ventricular fibrillation.

One pig had a low mean arterial blood pressure (29-34 mm Hg) that occurred at induction of anesthesia, and cardiac arrest occurred 105 minutes after CVBG. During data processing we found that 1 pig had a cTnT increase to 0.277 µg/L in serum and a lactate increase to 34,825 µmol/L in microdialysate from the anterior wall of the left ventricle. These findings were interpreted as consistent with a myocardial infarct, and this pig was excluded from further analysis.

The 11 included pigs were monitored up to 2.5 hours after the anastomosis was performed. Five control animals received ligation of the LAD artery without CVBG and developed ventricular fibrillation and died within 5 to 15 minutes.

Myocardial Appearance and Contractility

When LAD artery ligation was performed in the 11 CVBG pigs, we observed a color change between the LAD vein and the LAD artery. The LAD vein appeared arterialized, whereas the LAD artery became dark, indicating that it contained deoxygenated blood. The intervention wall became cyanotic, with a sharp demarcation line to areas supplied from other arteries. The wall was initially clearly hypokinetic. In every animal, however, recovery of contractility and color, although slow and incomplete, was observed throughout the experiment.

Microdialysis

In the control pigs the results of the microdialysis for lactate of the anterior and inferior walls of the left ventricle were similar over the time period leading up to LAD ligation and consequent death (Figure 2). The mean values were used in the further calculations.

The logarithm-transformed AUC for lactate differed significantly between the intervention walls and the reference walls in the CVBG pigs ($P = 0.008$). The lactate concentration in the microdialysates from the intervention walls was 2032 µmol/L ± 249 µmol/L before CVBG. After CVBG an increase in lactate concentration to 7430 µmol/L (range, 6493-19030 µmol/L) was observed ($P = 0.0302$). Peak values were reached within 30-60 minutes. The lactate concentration in the microdialysate from the unaffected reference walls of the left ventricle was stable around 2636 µmol/L (range, 2201-3703 µmol/L) throughout the experiment. The logarithm-transformed AUC for the reference walls was not significantly different from the AUC of the control pigs ($P = 0.211$).

Oxygen Tension and Hemodynamics

Study results for oxygen tension and hemodynamics are shown in Figure 3. In the CVBG pigs, tissue oxygen tension decreased after ligation of the LAD artery (from 63.0 ± 12.8 mm Hg to 5.6 ± 2.26 mm Hg 10 minutes after ligation, $P = 0.0078$), but with time, as the LIMA flow slowly increased, some recovery was seen (26.8 ± 7.9 mm Hg at 120 minutes).

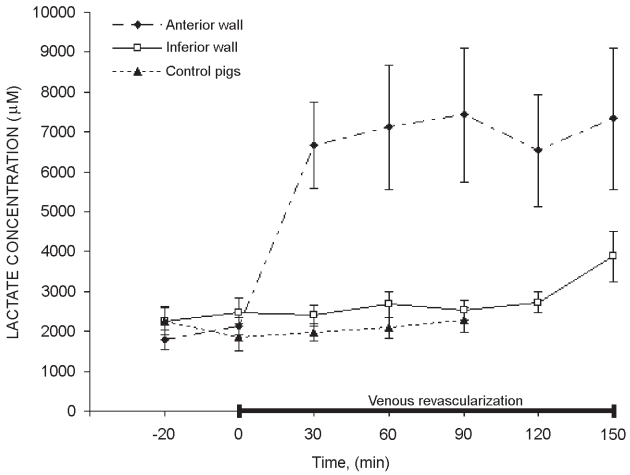

Figure 2. Results of microdialysis. Intervention wall = the area of the left ventricle supplied by the left anterior descending coronary artery; Reference wall = the area of the left ventricle supplied by the right coronary artery/circumflex coronary artery; Control pigs = values from the anterior and inferior walls presented as a mean value; Time 0 = ligation of the left anterior descending coronary artery in the CVBG pigs (ligation of the left anterior descending coronary artery in the control pigs was performed after end of microdialysis). Bars represent 1 SEM.

In both CVBG and control pigs the mean arterial pressure and central vein pressure were stable over time.

Blood Sample Analysis for cTnT

cTnT data are shown in Figure 4. A cTnT increase was seen after CVBG. In all 6 CVBG pigs cTnT continued to rise during the observation period. In the control pigs cTnT was

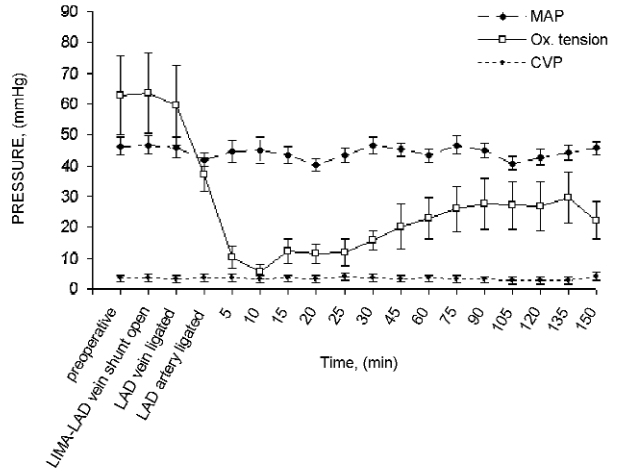

Figure 3. Hemodynamic values in CVBG pigs. MAP, mean arterial pressure; CVP, central vein pressure; Ox. Tension, oxygen tension in the anterior wall; LAD artery, left anterior descending coronary artery; LAD vein, left anterior descending coronary vein; LIMA, left internal mammary artery. Bars represent 1 SEM.

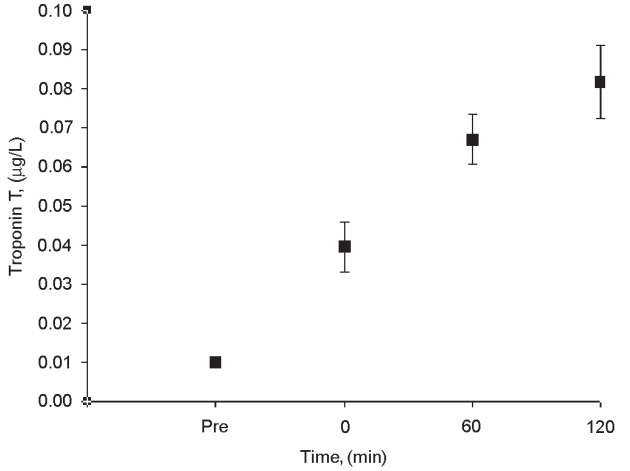

Figure 4. Serum cardiac troponin T levels in CVBG pigs. *Pre* = before sternotomy; *0* = ligation of the left anterior descending coronary artery. Bars represent SEM.

0.011 µg/L (range, 0.01-0.016 µg/L) during the 170 minutes of microdialysis.

Graft Flow

Graft flow (Figure 5) in the LIMA graft of the 11 CVBG pigs was 123 ± 17.6 mL/min before ligation of the LAD vein proximal to the anastomosis. Following LAD vein ligation (occlusion of the direct arteriovenous fistula) the LIMA flow was reduced to 38.0 ± 4.3 mL/min. During the observation period the flow slowly increased to 56.1 ± 9.2 mL/min.

Histology

The anterior walls were characterized by varying degrees of ischemic damage, including focal intracellular edema,

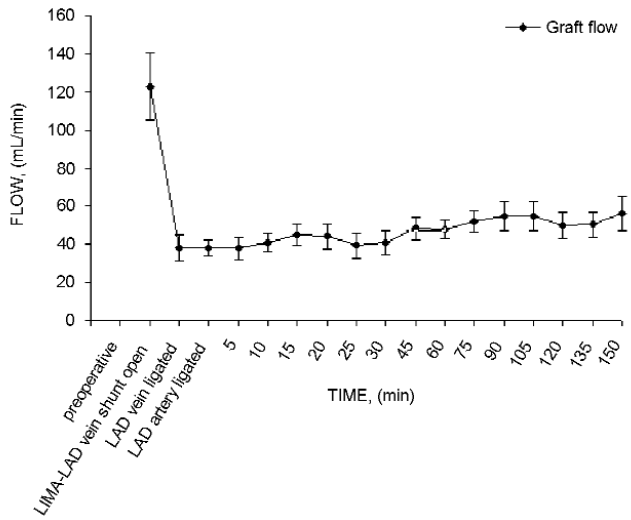

Figure 5. Flow in the left internal mammary artery conduit anastomosed to the left anterior descending (LAD) coronary vein. LIMA, left internal mammary artery. Bars represent 1 SEM.

vacuolization, and leukocyte infiltration, proceeding to focal necrosis with manifest signs of myocardial ischemia with granulocyte infiltration and myocytolysis. The inferior walls showed similar changes at a significantly reduced degree, with focal edema and leukocyte infiltration but without necrosis.

DISCUSSION

The main objective of this experiment was to evaluate the possibility of nourishing a part of the myocardium through selective retrograde revascularization of a coronary vein. This technique could have relevance for patients with coronary arteries inaccessible for PCI and CABG, a group that includes cases characterized by recurrent restenotic lesions after PCI, CABG failures, and diffuse coronary artery disease with multiple peripheral lesions. A previously explored option for these patients was percutaneous or surgical transmyocardial laser revascularization. These methods, however, lack consistent evidence of benefit [Almeda 2003]. Because atherosclerosis does not affect the venous system, we hypothesized that CVBG might be a way to revascularize the myocardium in patients with severe end-stage coronary artery disease.

In our model a massive ischemic event was induced when the LAD artery was ligated. Nevertheless, the flow to the LAD vein through the LIMA seemed to keep the anterior wall of the left ventricle viable. Because a direct arteriovenous fistula through normal run-off from the LAD veins was not possible owing to proximal ligation of the LAD vein, the LIMA flow could theoretically take 3 courses, passing directly into the Thebesian veins, emptying into the heart chambers; passing through vein collaterals into other veins on the heart surface, connecting to the coronary sinus; or passing retrogradely through the coronary veins into the myocardial capillaries, finding its way to the venous system, possibly through the Thebesian veins.

Because all control pigs died within 15 minutes after LAD artery ligation whereas CVBG kept 75% of the pigs alive, some flow through the myocardial capillaries maintaining viability of the myocardium (the last option mentioned above) must have occurred. The observation of return to near-normal color and contractility of the anterior wall with time, as well as increasing LIMA flow and tissue oxygen tension, may indicate that myocardial perfusion increased even during the first few hours after CVBG. Longer follow-up, ideally including survival studies, would be needed to address this further.

Finding ischemic changes in the intervention wall tissue samples was not unexpected. Prior to the experiment the pigs had healthy, normal coronary perfusion, which was obstructed and replaced by a nonphysiologic retrograde perfusion via the LAD vein. Except in 1 CVBG pig (excluded from further analysis), we found minimal cTnT increases that did not reach the threshold for considering myocardial infarction in humans (0.1 μg/L) within the 2 hours of observation. Because cTnT slowly increases over time following myocardial injury, the difference in the time frame between the CVBG pigs and the control pigs must be considered. However, the finding of increased cTnT levels in the CVBG pigs (compared to the control pigs) indicates that the cTnT rise was not exclusively caused by insertion of the microdialysis probe, but that CVBG did not fully compensate the ischemic injury, as confirmed at microscopic evaluation. We did not observe stabilization or decrease in cTnT during the observation period. It is possible that values consistent with myocardial infarction would be reached after a longer observation period.

Microdialysis appeared to be an appropriate way to assess metabolic changes in the myocardium. Lactate concentration is a well-known marker of ischemia [Wikström 1995; Mantovani 2006]. In the intervention wall an increase in lactate concentration was found after 30 minutes of establishing CVBG, and after LAD ligation. This increase may be caused by ischemia or increased metabolism. The observed loss of contractility and change in color immediately after CVBG and LAD ligature supports the view that although CVBG provides sufficient myocardial perfusion to hinder death, some degree of ischemia remains present after LAD ligation.

If CVBG is applied in patients who already have severe coronary artery disease, we do not know whether or how lactate concentration will be affected. In future CVBG patients, the coronary arteries will naturally remain untouched. Under these conditions an increase in lactate will not be expected, and if found would be considered an unwanted side effect of CVBG. In this respect lactate may be a useful indicator of the effects of the procedure.

The histological evaluation revealed manifest signs of myocardial ischemia in the anterior wall of the left ventricle, a finding that is not surprising because the experiment was done on previously healthy pigs sustaining a massive ischemic event.

Clinically, in patients with severely stenotic or occluded and ungraftable arteries even a small contribution to myocardial perfusion from CVBG could be beneficial. In 3 of our animals the graft flow was insufficient even though the anastomosis was redone, a situation that may have been due to differences in venous anatomy. Both inter individual and interspecies anatomic variation of the venous system could be limiting factors in the use of CVBG in humans. To pursue whether CVBG is a realistic clinical option, further experimental animal survival studies, including long-term survival, are needed. These studies are ongoing in our laboratory.

In conclusion, after LAD artery occlusion all control pigs developed ventricular fibrillation within 15 minutes, whereas 75% of the CVBG pigs survived 2-2.5 hours, until killed. These results indicate that CVBG may be a way to revascularize and nourish the myocardium after an acute ischemic event that cannot be treated with PCI or CABG. Measurements of oxygen tension, lactate concentration through myocardial microdialysis, and serum cTnT seem to be good indicators of the physiological effects of CVBG and are all methods that are applicable in a clinical setting.

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