



Coronary Switch: Total Reversal of Coronary Circulation in Acute Canine Model

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Abstract

Background: Till date there is no optimal coronary revascularisation technique for diffuse coronary artery disease. This study was conducted to proof the concept of total coronary venous retro perfusion, for end-stage coronary artery disease patients. The coronary venous circulation is arterialisised while the coronary arteries drain the heart to the right atrium "Coronary Switch".

Methods: Sixteen adult Mongrel dogs were used. After preparation for bypass, the heart was instrumented with minor axis son micrometric crystals, carotid and left ventricular Millar catheters. Colored microspheres were used for Regional Myocardial Blood Flow "RMBF" measurements. After aortic cross clamping and cardioplegia, the coronary sinus ostium was closed, and then a 3 mm Gore-Tex tube was anastomosed to the coronary sinus and its top-end to the aorta. A similar tube was sequentially anastomosed between the three coronary arteries and ended in the right atrium. Coronary switch was established by occluding the coronary arteries proximal to the anastomoses.

Results: The mean left ventricular function was 85,820.1 dyn. Cm² "Preoperative" versus 87,984.2 "Postoperative" (p=NS). The RMBF was 1.38 ± 1.1 ml/min/gm "Preop" versus 1.44 ± 0.98 in combined "ante/retro flow" and 1.58 ± 0.29, 1.28 ± 0.19, and 1.45 ± 0.35 at 60, 120, 180 minutes after "Coronary Switch" (p=NS).

Conclusion: Primary results support "Coronary Switch" as an alternative therapeutic modality for end-stage coronary artery disease. Survival studies and long-term follow-up are needed.

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Introduction

Although the initial attempts to treat myocardial ischemia were directed towards the coronary venous system, which is free from atherosclerotic disease, most of the coronary interventions for augmenting blood flow to the ischemic myocardium are directed towards the coronary arterial system where unstable atherosclerotic lesions are found [1-4]. The coronary veins and venous microcirculation considerably outnumber the coronary arterial system; therefore, most of the myocardium can be reached by a perfusate if applied via the coronary sinus [5]. Research findings suggested that the access to and protection of areas supplied by stenotic or occluded coronary arteries is much better with retrograde delivery than with antegrade infusion [6,7]. In 1948, Beck et al. [8] reported the method of a systemic artery coronary sinus anastomosis (Beck II procedure), which included partial occlusion of the coronary sinus toward the right atrium done at a second operation. The mortality was high (29%), and the procedure was eventually abandoned. Arealis and colleagues [9] were the first to demonstrate experimentally the potential immediate beneficial effects of myocardial perfusion by anastomosing the Internal Mammary Artery (IMA) to a ligated coronary vein and few clinical short-term successes were obtained, but soon the procedure lost favour as a result of alternative arterial revascularisation techniques such as sequential grafting, coronary artery patching techniques, and extensive coronary endarterectomy [10,11,12]. The Selective Retrograde Coronary Venous Bypass (SRCVB) technique was investigated and performed clinically for patients with extensive and diffuse CAD by a number of investigators [9-17] and the results of the last extensive research by Hockberg et al. [18] were encouraging, although no significant long term conclusion could be made. This group of patients with extensive diffuse CAD represents 12% 15% of possible candidates for coronary revascularisation [13] and it may be reasonable to offer this alternative technique of coronary venous retro perfusion to the desperate patient (not amenable to endarterectomy or transplantation) or to patient in whom multiple conventional coronary artery bypass procedures have failed. We are introducing a new surgical technique of coronary

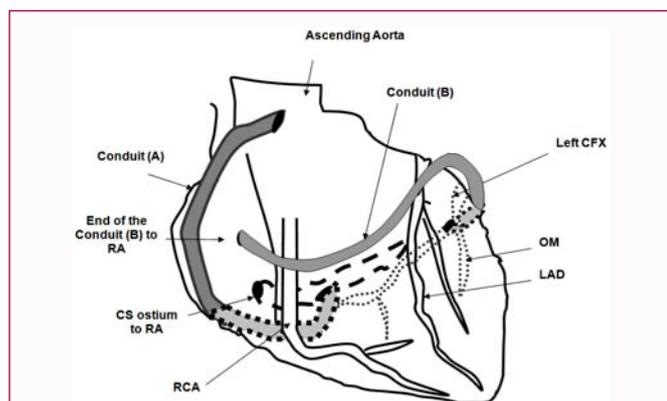


Figure 1: Diagrammatic representation of the Coronary Switch Procedure. Conduit-A: Conduit taking arterial blood from the aorta to the coronary sinus; Conduit-B: Conduit taking venous blood from the occluded coronary arteries to the right atrium; RA: Right Atrium; Lt. CFX: Left Circumflex Coronary Artery; OM: Obtuse Marginal branch of CFX; LAD: Left Anterior Descending Coronary Artery; CS: Coronary Sinus

retro perfusion, whereby the whole coronary venous circulation is arterIALIZED and the coronary arteries are redirected to drain the venous blood to the right atrium “coronary switch”. This research work may answer the following: (1) If the “Coronary Switch” can protect the heart against acute multiple ischemia? (2) If there is an adequate RMBF in the switched heart? (3) If there is a change in myocardial function after the switch?

Material and Methods

Preparation

Animals were treated in accordance with the Guide to the Care and Use of Laboratory Animals published by the US National Institute of Health (NIH publication 85-23, revised 1985). The Institutional Animal Care and Use Committee (IACUC) of the Medical College of Virginia, Virginia Commonwealth University, USA; approved the experimental protocol.

Sixteen adult Mongrel dogs (mean weight 22.5 Kg) were used for eight experiments (n=8). Animals were anesthetized, ventilated with Harvard respirator. Right femoral arterial and venous lines were inserted, as well as ECG leads. Right carotid micro monometer-tipped catheter (Millar, Houston, Texas) was inserted. The chest was opened through a median sternotomy, and a pericardial cradle was created. Another LV Millar catheter was introduced into the LV cavity. LV dimension data were obtained with pulse transit son micrometry (Triton Technology, San Diego, CA). One pair of 2.5 mm diameter LTZ-piezoelectric hemispheric crystals was sewn onto the anterior and posterior myocardial wall along the minor axis of the left ventricle. The epicardial diameter of the left ventricle ranged from 40 mm to 66 mm. Analog data were digitized at 200 Hz and stored on the hard disk of a personal computer.

The surgical technique

Following instrumentation, full heparinization (12,000–15,000 IU Heparin, ACT >500 Sec.), arterial cannulation through the left common carotid artery and venous cannulation through the RA were achieved. Once CPB was established, the aorta cross-clamped and cardioplegia solution was delivered in the aortic root. The heart was retracted cephalade to expose the CS. The CS ostium was closed with 5/0-proline suture just at the junction with the right atrium making sure that none of the CS tributaries were occluded. An end to side

anastomosis was fashioned between the CS and a 3 mm Gore-Tex tube graft using a continuous 7/0 proline suture. A similar Gore-Tex tube graft was anastomosed end to side with the proximal left CFX coronary artery, proximal LAD and RCA (Figure 1). The top-end of the first conduit to the CS was anastomosed to the aorta, while the second conduit from the coronary arteries was anastomosed to the RA and intermittently occluded to prevent steal phenomenon.

After weaning off CPB, alternating antegrade/retrograde flow was allowed for 30 min, and then complete occlusion of the three coronary arteries proximal to the anastomoses was done gradually with opening the conduit to the RA, allowing complete switch of coronary circulation to be established (when total occlusion of coronary arteries is done using adjustable snares). All hearts were monitored for three and half hours off pump after full established switch procedure; then arrested with an intracardiac injection of 80 meq KCl and harvested.

Blood flow determination

Using an established technique [19], RMBF was determined using IMT's NuFlow™ Colored Microspheres “CM” (Interactive Medical Technologies, Ltd., Los Angeles, CA). Two and a half million Microspheres were diluted in 20 ml of normal saline solution, sonicated for 10 min and thoroughly dispersed by vortex mixing for two minutes prior to injection through a catheter into the LA over 20 sec. Arterial reference blood samples were obtained by Harvard withdrawal pump from the femoral artery catheter (starting 10 sec. before injection at a constant rate of 10 ml/min for 90 seconds). RMBF measurement was repeated five times during each experiment starting before the procedure as a control, off CPB with alternating Ante/Retro flow and then 60-120-180 mins after the full switch procedure (retrograde flow only). Corrected counts obtained for each heart sample were multiplied by the known reference withdrawal rate and divided by the corrected reference blood sample counts to determine sample flow expressed as ml/min/gm of tissue.

Histologic staining

Vital staining of the heart was used to demonstrate areas of myocardial infarction “necrosis”. The territories of the three major coronary arteries were identified and labelled. Fifteen sections were taken from the base to the apex at 5-mm intervals and incubated for 30 min at 37°C, in freshly prepared Triphenyltetrazolium Chloride (TTC, 1%) (Sigma Chemical Co, St. Louis, MO), and then fixed with formaldehyde (10% in phosphate buffer) [20]. Normal healthy myocardial tissues containing dehydrogenase enzyme are stained brick red by TTC, but areas of infarction “necrosis” depleted of these enzymes are not stained and appear as white or pale yellow [21]. Following vital staining, slices were examined for infarcted areas, and then specimens (mean weight 3-4 grams) from the three layers of the heart muscle (endomyocardium, myocardium, and epimyocardium) were collected from each of the three major coronary artery territories “LAD, CFX, and RCA” (Figure 2). The specimens were placed, each in a separate tube, labelled, and sent with the reference blood for Spectrophotometric analysis and RMBF measurement.

Measurements

Hemodynamic measurements were performed at base line “Control” before the CPB, after off CPB with alternating ante/retro flow, then 60 min, 120 min, and 180 min after the fully established switch procedure. Heart performance was measured from the slope of the relationship between Stroke-Work and End-Diastolic Length

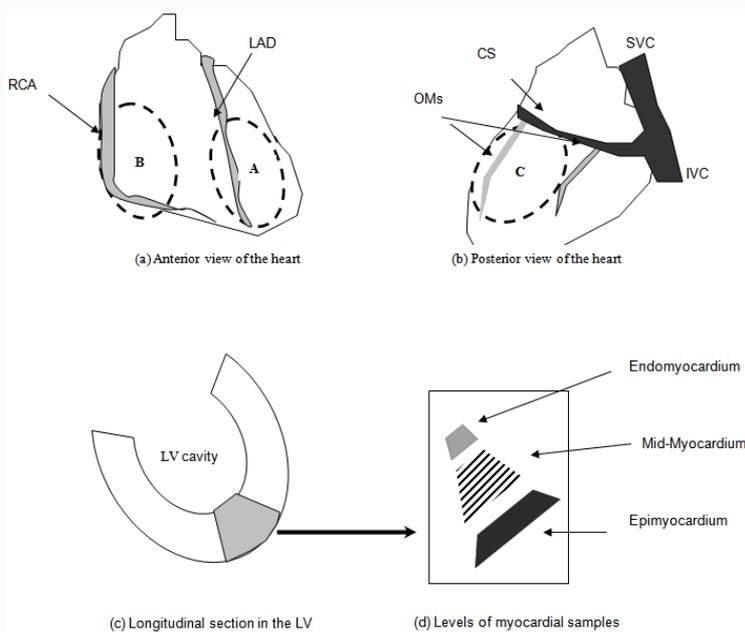


Figure 2: Diagrammatic illustration of myocardial sample sites. Circles A, B, C: Represents the Biopsy Site of the Corresponding Coronary Artery; LAD: Left Anterior Descending Coronary Artery territory; CFX: Left Circumflex Coronary Artery; RCA: Right Coronary Artery; CS: Coronary Sinus; IVC: Inferior Vena Cava; SVC: Superior Vena Cava

(SW/EDL). The slope of this linear relationship is a sensitive index of contractility, independent of load within the physiological range. This method is more accurate than hemodynamic and load-dependent indices of contractility such as LV arterial pressure and positive and negative dp/dt values [22]. The arterial graft flow to the CS was monitored as well as the Coronary Sinus Pressure (CSP). Any ECG changes suggestive of ischemia as well as arrhythmias were recorded. Infarcted areas were detected by vital staining. RMBF measurements were recorded as mentioned above at five different stages of the experiment. The RMBF for each Myocardial layer (endomyocardium, myocardium, and epimyocardium) was calculated as the average of all samples of the same layer in all territories. While RMBF in any coronary artery territory, was calculated as the average of all samples from all layers of the same territory (LAD, CFX, and RCA).

Statistical analysis

Statistical analysis was performed using the SPSS software (SPSSR 7.5 for windows). All results are reported as Mean ± Standard Deviation. Analysis of Variance “ANOVA” (F test) was used for comparison of more than two groups. Significance was assigned at p less than 0.05. Post-Hoc multiple comparison test would be used if p value was significant.

Results

Coronary sinus pressure and flow

The average coronary sinus pressure was 25 ± 4.6 mmHg corresponding to an average arterial graft flow of 100 ± 14.6 ml/min provided by a 3 mm Gore-Tex tube graft to the coronary sinus.

Left ventricular function

The slope of the relationship between stroke work and end diastolic length (SW/EDL slope) (Table 1) was used to assess the LVF. The average slope before the procedure “control” was 85,828.3 ± 4235 Dyn.Cm2 compared with 87,165.1 ± 3215, 91,564.4 ± 6235, 87,724.3 ± 8652, and 85,484.5 ± 4352 Dyn.Cm² at the stage of ante/retro flow,

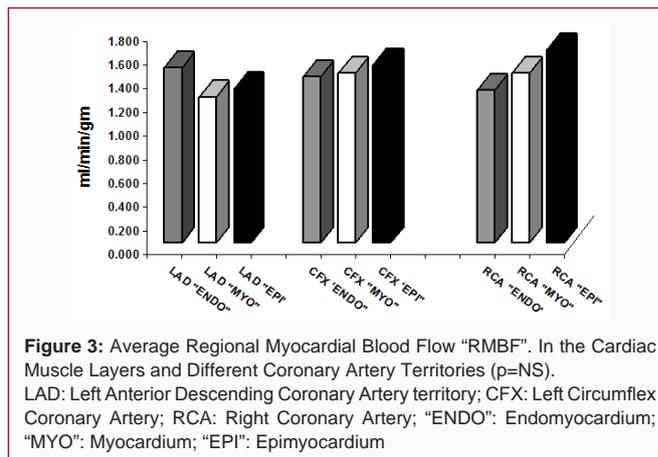
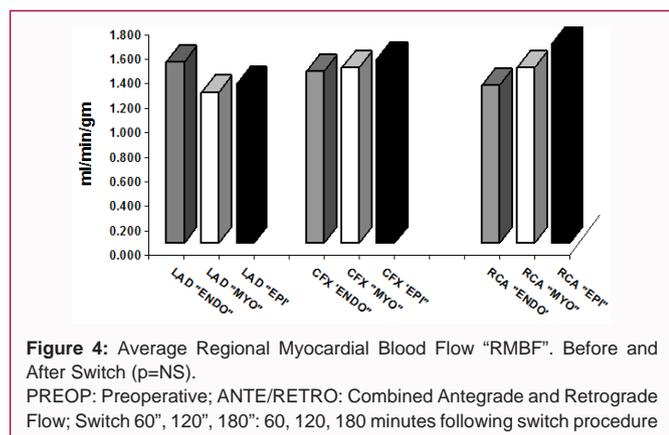


Figure 3: Average Regional Myocardial Blood Flow “RMBF”. In the Cardiac Muscle Layers and Different Coronary Artery Territories (p=NS). LAD: Left Anterior Descending Coronary Artery territory; CFX: Left Circumflex Coronary Artery; RCA: Right Coronary Artery; “ENDO”: Endomyocardium; “MYO”: Myocardium; “EPI”: Epimyocardium

and 60 mint, 120 mint, and 180 minutes after the switch procedure. There was no significant statistical difference between the systolic function before and after the switch procedure.

Regional myocardial blood flow “RMBF”

Regional myocardial blood flow “RMBF” was measured in the endomyocardial, myocardial, and epimyocardial layers of the heart muscle in the LAD, CFX, and RCA territories expressed as ml/min./gm of tissue (Table 2 and 3, Figure 3 and 4). The average RMBF before surgery “control” in the endomyocardial layer was 1.329 ± 0.38 compared with 1.38 ± 0.23 in ante/retrograde flow, and 1.467 ± 0.34, 1.303 ± 0.12, 1.433 ± 0.25 at 60, 120, and 180 mins after the switch. There was no significant statistical difference between the RMBF in the endomyocardial layer before and after the switch. In the myocardial layer, the average RMBF before surgery “control” was 1.337 ± 0.36 compared with 1.276 ± 0.34, 1.57 ± 0.34, 1.39 ± 0.23, and 1.51 ± 0.56 at similar stages of the procedure with no significant statistical difference. In the epimyocardial layer, the average RMBF before surgery “control” was 1.44 ± 0.18 compared with 1.66 ±



0.41, 1.71 ± 0.11 , 1.15 ± 0.22 , and 1.42 ± 0.31 at similar stages of the procedure with no significant statistical difference as well. In general, the average RMBF in the endomyocardium was relatively lower compared with the RMBF in the myocardium and epicardium respectively, though statistically insignificant. Also comparing RMBF of the three coronary artery territories (LAD, CFX, and RCA) at the different stages of the experiment did not show a significant statistical difference.

Myocardial infarction (Necrosis)

Using TTC vital staining, there were no detectable areas of myocardial infarction "necrosis" following the switch procedure.

Table 1: Left Ventricular Systolic Function Before, During, and After Coronary Switch.

Parameter	Preoperative	Ante/Retrograde	CORONARY SWITCH			F
			60'	120'	180'	
SW/EDL Slopes Dyn.Cm ² .X10 ⁻³	85.83 ± 4.5	87.17 ± 3.2	91.56 ± 6.2	87.72 ± 8.7	85.48 ± 4.4	NS
X-Axis Intercept	56.17 ± 3.5	57.13 ± 4.6	56.5 ± 3.6	60.8 ± 6.5	58.16 ± 5.4	NS
r	0.93	0.9733	0.962	0.92	0.9518	NS
Number of Beats	15	18	16	19	18	NS

SW/EDL slope: Left Ventricular Systolic work/ End Diastolic Length Slope in Dyn.Cm².X10⁻³, X int: Intercept, r: correlation coefficient, N: number of beats per each systolic function record, NS statistically insignificant. Results are presented as Mean ± SD (n=8).

Table 2: Transmural Regional Myocardial Blood Flow. Average RMBF measurements (ml/mint/gm wet weight) in the three layers of myocardial muscle in the three coronary artery territories.

	Preoperative	Ante/Retro grade	CORONARY SWITCH			F Probability
			60'	120'	180'	
LAD						
End	1.09 ± 0.39	1.64 ± 0.48	1.54 ± 0.6	1.61 ± 0.7	1.50 ± 1.1	NS
Mid	1.11 ± 0.6	1.39 ± 0.68	1.43 ± 0.8	1.26 ± 0.9	1.32 ± 0.7	NS
Epi	1.34 ± 0.72	1.89 ± 0.84	1.29 ± 0.63	1.3 ± 0.65	1.41 ± 0.8	NS
CFX						
End	1.32 ± 0.6	1.41 ± 0.7	1.26 ± 0.81	1.27 ± 0.9	1.73 ± 0.9	NS
Mid	1.23 ± 0.8	1.51 ± 0.6	1.72 ± 0.85	1.1 ± 0.75	1.69 ± 0.6	NS
Epi	1.26 ± 0.9	1.56 ± 1.3	1.92 ± 1.21	1.3 ± 0.91	1.02 ± 0.6	NS
RCA						
End	1.59 ± 0.6	1.1 ± 0.43	1.6 ± 0.32	1.03 ± 0.6	1.1 ± 0.62	NS
Mid	1.7 ± 0.45	1.4 ± 0.42	1.6 ± 0.85	0.93 ± 0.3	1.94 ± 0.6	NS
Epi	1.72 ± 1.2	1.55 ± 1.01	1.95 ± 1.4	1.35 ± 0.7	1.6 ± 0.62	NS

RMBF measurements are expressed as ml/mint/gm wet weight in the three layers of myocardial muscle in the three coronary artery territories. Results are presented as Mean ± SD (n=8).

Post-bypass events

All animals were weaned off CPB easily. No inotropic support was used. Ischemic ST segment elevation was noticed in the first 30 min to 45 min after the switch in 4 experiments (50%). The average ST segment elevation was 1.9 0.92 mm. These ST changes disappeared spontaneously one hour after the switch procedure.

Premature Ventricular Contractions (PVC's) and short runs of ventricular tachycardia were reported as well in four experiments (50%) and were easily terminated with 25-50 mgm, intravenous Lidocain bolus. The ventricular arrhythmias were usually detected immediately after the switch procedure and disappeared within one hour.

Discussion

The rationale of this study was to provide a proof of concept of retrograde coronary perfusion as a therapeutic modality for diffuse CAD not amenable for CABG or PCI. Coronary Switch technique introduces the idea of global revascularisation, by total coronary venous retro perfusion (arterialization) in the presence of acute ischemia involving the three major coronary arteries, a situation similar to multiple coronary artery disease. This technique avoids the use of external pumps or timing devices [20].

Unlike the pig heart, the canine model has relatively significant coronary collaterals that mimic chronic ischemic hearts, which developed collaterals. Gore-Tex tube grafts of 3 mm calibre were used to provide a standard flow not exceeding 100 ml/min to the CS. This flow was recommended by some investigators [11-13]

Table 3: N Average RMBF measurements in the three layers of myocardial muscle.

Myocardial muscle layer	Preoperative	Ante/Retrograde	CORONARY SWITCH			F Probability
			60"	120"	180"	
Endomyocardium	1.329 ± 0.38	1.38 ± 0.23	1.467 ± 0.34	1.303 ± 0.12	1.433 ± 0.25	NS
Mid-Myocardium	1.337 ± 0.36	1.276 ± 0.34	1.57 ± 0.34	1.39 ± 0.23	1.51 ± 0.56	NS
Epimyocardium	1.44 ± 0.18	1.66 ± 0.41	1.71 ± 0.11	1.15 ± 0.22	1.42 ± 0.31	NS

RMBF measurements are expressed as ml/mint/gm wet weight in the three layers of myocardial muscle in the three coronary artery territories. Results are presented as Mean ± SD (n=8).

to provide an effective perfusion and avoid high CS pressure. The second conduit draining the coronary venous effluent from the occluded coronary arteries to the right atrium aimed at establishing a normal physiological circulation, therefore preventing myocardial congestion, edema, hemorrhages and late stiffness reported by some investigators [23].

Although the mortality was high with Beck's procedure [3,4,9], Bakst and Bailey [23] demonstrated that retrograde perfusion of the myocardium did occur, myocardial oxygen extraction during retrograde perfusion was measurable, and increased intercoronary collateral flow was present. They also demonstrated obliterative changes in the coronary veins within few weeks of the operation, which could be attributed to the absence of the normal venous drainage of the heart, or longstanding combined antegrade/retrograde flow, a technique that was avoided in the switch procedure.

From the research of Hockberg and colleagues [17,18], effective perfusion of all layers of the myocardium was well demonstrated. They concluded that encouraging long term patency data in animals (3 to 5 months) suggested that possible judicious use of this bypass method might be of value in selected patients with diffuse atherosclerosis or a previously failed coronary artery bypass. The primary data of the switch procedure proves clearly, as well the effectiveness of retrograde perfusion to all layers of the myocardium in different territories supplied with occluded coronary arteries.

Some factors that reduce the efficiency of retrograde coronary sinus perfusion are eliminated by the switch technique, such as exclusion of some tributaries of CS by a retrograde balloon, concomitant antegrade flow, and the absence of free coronary venous blood drainage. Therefore, RMBF measurements in the endocardium, myocardium, and epicardium of both antegrade "control" and retrograde perfusion "Coronary Switch" is comparable in this study.

The presence of transient ischemic ST segment changes as well as ventricular arrhythmias in switched hearts could be explained by a degree of perfusion mismatch or initially low retrograde perfusion. The absence of myocardial infarction, in addition to the preserved LV function after the switch procedure proves the efficiency of RMBF provided by this technique. Recently, Martin et al. [20] proved that LV-powered coronary sinus retroinfusion "LVCSR" reduces infarct size in acutely ischemic pigs, which was enhanced by pressure controlled sinus occlusion "PCSO" with failure to improve RMBF and myocardial function. Postischemic myocardial stunning was likely responsible.

Mechanisms of salvaging ischemic myocardium by CS retroinfusion remain to be defined. However, enhanced washout of toxic reactive oxygen metabolites, diminished granulocyte trapping, cellular and interstitial edema, plugging of the microcirculation, and actual delivery of blood substrate to the ischemic myocardium beyond an acute coronary artery occlusion have all been suggested

[5,20].

Limitations

The long-term efficacy of this retro perfusion technique in a chronic ischemic model was not investigated in this study. In summary, the primary results of coronary switch technique, demonstrated that there is an immediate protection resulting from the "Coronary Switch" in the presence of multiple acute coronary artery occlusions, an effective perfusion of all layers of the myocardium in different coronary artery territories, and preserved LV function after the procedure. Developing a chronic ischemic model, similar to chronic diffuse coronary artery disease and applying the switch procedure in a survival study is warranted.

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