The Heart Surgery Forum #2005-1104
9 (2), 2006 [Epub February 2006]
doi:10.1532/HSF98.20051104

Online address: http://cardenjennings.metapress.com/link.asp?id=112496

Direct Left Ventricle to Great Cardiac Vein Retroperfusion: A Novel Alternative to Myocardial Revascularization

Geng-Hua Yi, MD,[1] Kun-Lun He, MD, PhD,[4] Nicholas C. Dang, MD,[2] Myung Jae Lee, BS,[1] Patrick Cahalan, BS,[3] Aftab R. Kherani, MD,[2] Anguo Gu, MD,[1] Daniel Burkhoff, MD, PhD,[1] Jie Wang, MD, PhD[1]

[1]Department of Medicine, Division of Circulatory Physiology and [2]Department of Surgery, Columbia University, College of Physicians and Surgeons, New York, New York, USA; [3]Percardia, Inc., Merrimack, New Hampshire, USA; [4]Department of Cardiac-Nephrology, Chinese PLA General Hospital, Beijing, P.R. China

ABSTRACT

Background. As the number of patients with diffuse coronary artery disease continues to grow, there is renewed interest in alternative methods of perfusing the ischemic myocardium. We tested the feasibility of myocardial retroperfusion via a direct left ventricle-to-great cardiac vein (LV-GCV) conduit to support regional contractility in this setting.

Methods. LV-GCV flow was established using an extracorporeal circuit in 5 dogs. Left ventricle (LV) pressure, aortic pressure, regional myocardial segment length, and circuit blood flow were measured prior to left anterior descending coronary artery (LAD) ligation, following LAD ligation, and after LV-GCV circuit placement. To eliminate backward flow during diastole, an in-line flow regulator was placed. Regional myocardial function was quantified by pressure-segment length loop area divided by end-diastolic segment length (PSLA/EDSL).

Results. LAD ligation reduced PSLA/EDSL from 10.0 ± 1.2 mm Hg × mm to 1.6 ± 0.3 mm Hg × mm ($P < .05$). With LV-GCV retroperfusion, mean peak systolic flow was +152 ± 14 mL/min, mean peak diastolic flow was –39 ± 11 mL/min, and net mean flow was +36 ± 13 mL/min. Regional function recovered to ~39% of baseline (3.9 ± 0.4 mm Hg × mm, $P < .05$). Upon elimination of backflow, mean flow increased to +41 ± 12 mL/min and regional function recovered even further to ~47% of baseline (4.6 ± 0.7 mm Hg × mm, $P < .05$).

Conclusions. A LV-GCV circuit can significantly restore regional function to the acutely ischemic myocardium. An in-line valve that eliminates backward diastolic flow improves regional function even further. This approach may provide an effective therapy for diffuse coronary disease not amenable to traditional revascularization strategies.

Received October 29, 2005; accepted November 19, 2005.

The two authors, Geng-Hua Yi and Kun-Lun He, contribute equally to this work.

Address correspondence and reprint requests to: Kun-Lun He, MD, PhD, Department of Cardio-Nephrology, Chinese PLA General Hospital, 28 Fuxing Road, Beijing 100853, China; 8610-68152720; fax: 8610-68181689 (e-mail: hekunlun2002@yahoo.com).

INTRODUCTION

As medical therapy for heart disease improves and elderly patients live longer, the number of patients with diffuse coronary artery disease is growing. Oftentimes, such extensive coronary disease is not amenable to treatment with bypass surgery or percutaneous coronary intervention. As a result, there has been renewed interest in novel techniques of nourishing the chronically ischemic myocardium. One such technique employs the concept of coronary venous retroperfusion [Gerber 2000; Keelan 2000]. Retroperfusion directly from the left ventricle (LV) to the coronary sinus has been proposed, and conduits establishing this connection could be set in place either surgically or percutaneously with specially designed catheters and shunts.

Although LV-driven coronary sinus retroperfusion has been shown to reduce infarct size following acute left anterior descending coronary artery (LAD) ligation [Martin 2000], the degree to which retroperfusion can nourish and maintain contractile function in an acute ischemic setting remains undetermined. The purposes of this study are to determine (1) the degree to which myocardial function is restored following application of a direct LV-to-great cardiac vein (GCV) conduit with resultant myocardial retroperfusion and (2) whether eliminating backflow during diastole translates into additional restoration of contractile function.

MATERIALS AND METHODS

Studies were performed in compliance with the "Guide for the Care and Use of Laboratory Animals" by the Institute of Laboratory Animal Resources, National Research Council (Washington, DC, USA), 1996. This study was approved by the Institutional Animal Care and Use Committee of Columbia University, New York, NY, USA. The study was supported by the manufacturer of the LV-GCV circuit device, Percardia (Merrimack, NH, USA), which otherwise took no role in the design or control of the study or the collection and interpretation of these data.

Five adult mongrel dogs weighing 26 kg to 28 kg were used in this study. Aspirin (325 mg oral) was administered daily for 3 days prior to surgery. The animals were induced with thiopental (5-7 mg/kg intravenous) and maintained on

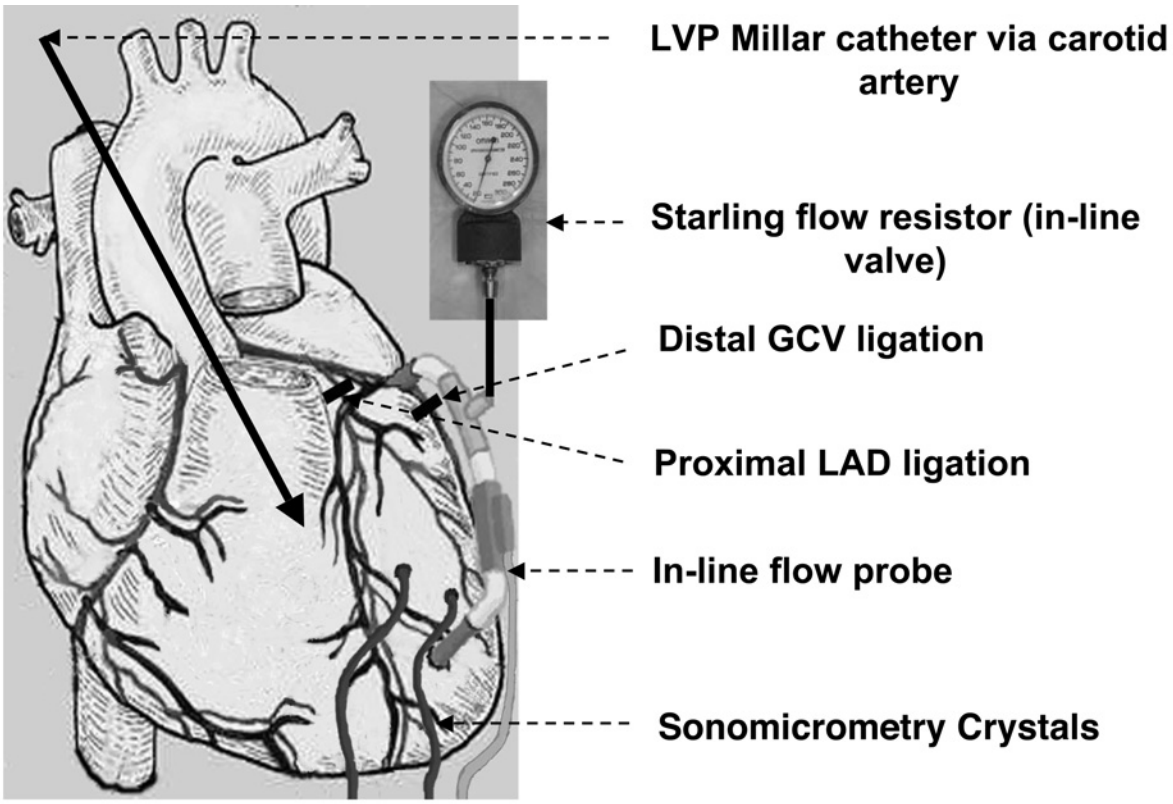

Figure 1. Surgical set-up of the left ventricle-to-great cardiac vein (GCV) retroperfusion circuit. LVP indicates left ventricle pressure; LAD, left anterior descending coronary artery.

1.5% to 2.0% inhaled isoflurane. Catheter tip transducers (Millar Instruments, Houston, TX, USA) were inserted into the LV and descending aorta through the right and left carotid arteries, respectively, to measure LV pressure (LVP) and aortic pressure. A 10- to 15-cm left thoracotomy was performed via the fifth intercostal space and the pericardium was opened. An ultrasonic flow probe (Transonic Systems, Ithaca, NY, USA) was placed on the ascending aorta to measure cardiac output. A pair of sonomicrometry crystals was placed mid-myocardium into the region to be supplied by the LV-GCV circuit and connected to a sonomicrometry system (Sonometrics, London, Ontario, Canada) to monitor segment length shortening. All data were recorded by a digital sonomicrometry system (frequency ~200 Hz).

After the animals were heparinized with 8000 U intravenous, an extracorporeal circuit was established to create a shunt between the LV and the great cardiac vein. A perfusion cannula (internal diameter: ~2.5 mm) was introduced into the GCV following venotomy and was connected to a cannula (internal diameter: ~2.5 mm) inserted across the LV free wall with PVC tubing. An in-line flow probe (Transonic Systems; diameter: 2.5 mm) and a Starling flow resistor were also placed within the LV-GCV circuit (Figure 1). The Starling flow resistor features a thin-walled, collapsible, polyurethane inner tube (internal diameter: 2 mm) inside an airtight polycarbonate T-tube that can be adjusted to a desired compression pressure ($P_{starling}$). When the pressure inside the lumen falls below $P_{starling}$, the lumen collapses, causing the resistor to act as a valve. The GCV segment proximal to the connection of the circuit was ligated to prevent shunting from the LV to the coronary sinus.

Experimental Protocol

Electrocardiographic data, LVP, and regional segment lengths were measured prior to and following LAD ligation. After all baseline measurements were made, the circuit was activated, establishing communication between the LV and the GCV. $P_{starling}$ was initially set to 0 mm Hg, and then to 70% to 80% of LVP. At each level of $P_{starling}$, physiologic measurements were taken after at least 2 minutes of stable hemodynamic conditions were maintained. All hemodynamic signals were recorded by the sonomicrometry system that digitized pressure and flow and measured the distance between the pair of crystals every 10 ms for off-line analysis.

Regional Myocardial Contractility and Perfusion

Pressure-segment length loop area (PSLA) divided by end-diastolic segment length (EDSL) was used as an index of regional myocardial contractile function [Suehiro 2001]. Regional myocardial perfusion was measured with the use of colored microspheres as described by Kowallik et al [1991] under 3 conditions—baseline, following LAD ligation, and following circuit implantation and LV-GCV retroperfusion. At the end of the experiments, the animals were sacrificed and their hearts explanted. Two transverse segments of myocardium from the LV anterior wall under distribution of

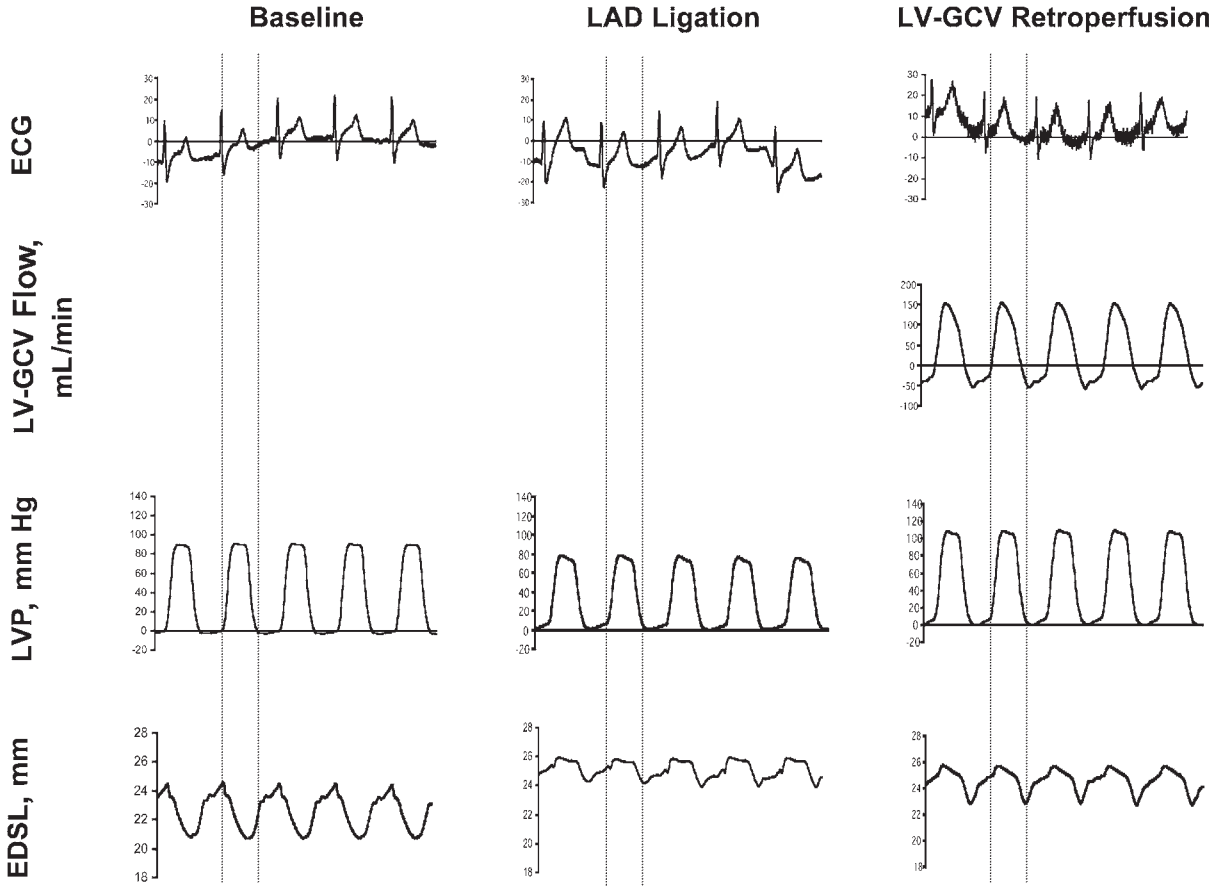

Figure 2. Hemodynamic tracings at baseline, following left anterior descending coronary artery (LAD) ligation, and after left ventricle-to-great cardiac vein (LV-GCV) retroperfusion. ECG indicates electrocardiograph; LVP, left ventricle pressure; EDSL, end-diastolic segment length.

the LV-GCV circuit were defined as the ischemic zone and used to determine regional myocardial blood flow. The posterior LV wall was defined as the nonischemic zone.

All data are presented as mean ± standard deviation. Statistical comparisons were performed by 1-way ANOVA tests. For all analyses, a P value < .05 was considered statistically significant.

RESULTS

Impact of GCV Retroperfusion on Hemodynamics

Hemodynamic parameters were measured prior to LAD ligation, following LAD ligation, and after device implantation, as shown in Figure 2. Electrocardiographic data, LV-GCV blood flow, LV systolic pressure, and myocardial regional segment length are shown.

After LAD ligation, LV systolic pressure and regional contractile function significantly decreased, as manifested by regional dyskinesis. Once retroperfusion was established between the LV and GCV, a large amplitude GCV flow pulse was observed during systole with backward flow to the LV during diastole. LV systolic pressure was completely restored to baseline and regional myocardial function was partially restored. Systemic hemodynamic changes for all subjects are summarized in Table 1.

Characteristics of LV-GCV Retroperfusion Blood Flow Patterns

Under normal, baseline conditions, peak epicardial coronary blood flow occurred during diastole and there was continued positive flow during systole without incidence of back flow. Conversely, following LV-GCV circuit activation, blood flow via the circuit was characterized by peak forward flow during systole and back flow during diastole. With a patent LAD, there were large positive and negative peak flows in the circuit. LAD ligation caused reductions in these peaks with an increased mean net retroperfusion flow. Application of the Starling resistor decreased these peaks even further, but also further increased mean net retroperfusion flow (Figure 3).

Regional Myocardial Contractility

Figure 4 shows typical LVP-segment loops from 1 experiment. The gray loop at the far left represents regional function at baseline. After LAD ligation, the pressure-segment loop is shifted to the right (black loop) and its normal configuration is lost, indicating regional dyskinesis. With LV-GCV retroperfusion to the ischemic myocardium, regional myocardial function is partially restored, as shown by

Table 1. Hemodynamic Measurements at Baseline, Following LAD Ligation, after LV-GCV Retroperfusion, and after LV-GCV Retroperfusion + Starling Resistor*

	Baseline	LAD Ligation	LV-GCV Retroperfusion	LV-GCV Retroperfusion + Resistor
LVP, mmHg	96.7 ± 4.1	82.3 ± 3.4†	91.7 ± 5.3‡	96.7 ± 7.2‡
LV dP/dt, mmHg/s	1705 ± 256	1387 ± 224†	1598 ± 223‡	1845 ± 278‡
Mean CO, L/min	2.55 ± 0.28	2.17 ± 0.23†	2.61 ± 0.18‡	2.85 ± 0.29‡
PSLA/EDSL, mmHg × mm	10.04 ± 1.15	1.61 ± 0.27†	3.87 ± 0.35†‡	4.61 ± 0.70†‡

*All values are mean ± standard error of mean. LAD indicates left anterior descending (coronary artery); LV-GCV, left ventricle-to-great cardiac vein; LVP, left ventricular pressure; CO, cardiac output; PSLA/EDSL, pressure-segment length loop area/end-diastolic segment length.

†$P < .05$ versus baseline.

‡$P < .05$ versus LAD ligation.

enlargement of the pressure-segment loop (shaded gray loop). Application of the Starling resistor enlarged the pressure-segment loop even further (thin gray loop).

Alterations in regional myocardial function are summarized in Figure 5. Following LAD ligation, regional myocardial function was significantly blunted. With support of retroperfusion via the LV-GCV circuit, regional myocardial function recovered to approximately 39% of baseline. Once backflow in the circuit was eliminated through the use of a Starling resistor, regional myocardial function recovered even further to approximately 47% of baseline.

Regional Myocardial Blood Flow

Regional myocardial blood flow in the ischemic zone decreased dramatically after LAD ligation, from 1.17 ± 0.32 mL/min per gram to 0.14 ± 0.03 mL/min per gram of tissue ($P < .05$, Figure 6A), but was not improved upon establishment of the LV-GCV retroperfusion circuit (0.07 ± 0.01 mL/min per gram of tissue; P = NS). In the nonischemic zone, regional myocardial blood flow was not significantly different at baseline, post-LAD ligation, and after LV-GCV retroperfusion (Figure 6B).

DISCUSSION

The concept of retroperfusing the venous system with arterial blood has been studied extensively in the past. The use of the GCV as a target vessel for retroperfusion was investigated by Chang et al, who demonstrated staining of the acutely ischemic myocardium by injection of monastral blue dye into the GCV, indicating efficiency of this mode of perfusion [Chang 1987]. Farcot et al examined coronary

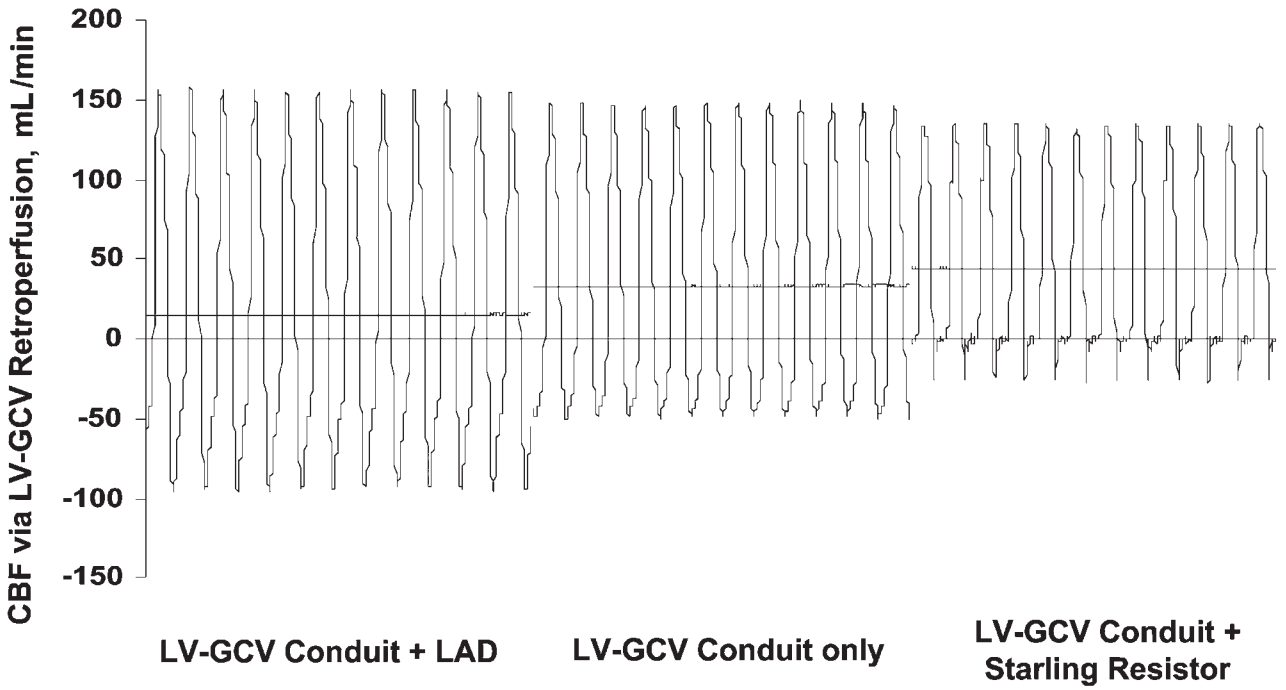

Figure 3. Changes in left ventricle-to-great cardiac vein (LV-GCV) retroperfusion coronary blood flow (CBF) patterns with in-line Starling resistor. LAD indicates left anterior descending artery.

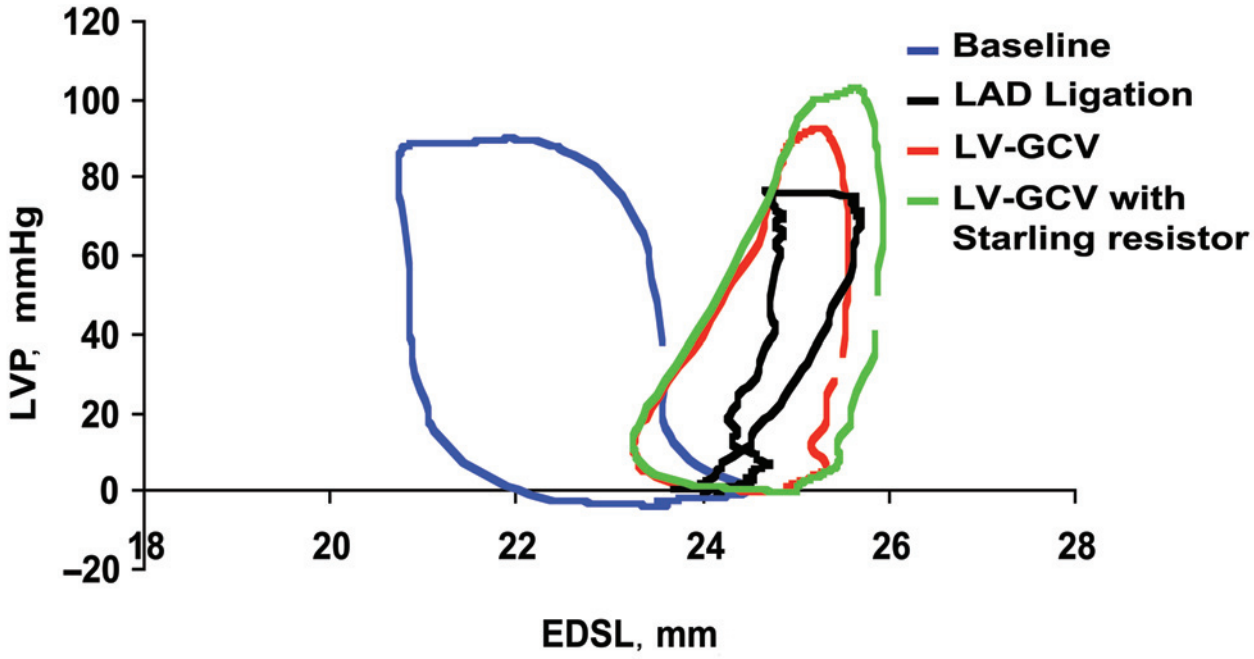

Figure 4. Left ventricular pressure (LVP)-segment length loops at baseline, following left anterior descending coronary artery (LAD) ligation, after left ventricle-to-great cardiac vein (LV-GCV) retroperfusion, and after LV-GCV retroperfusion + Starling resistor. EDSL indicates end-diastolic segment length.

sinus-based retroperfusion in the setting of acute coronary occlusion [Farcot 1983] and showed improvements in both regional perfusion and myocardial function in ischemic portions of the myocardium. In a similar report, the application of a retroperfusion circuit to ischemic myocardium restored mean blood flow to approximately 50% of control levels [Berdeaux 1981]. However, because the aorta was used as the source for retroperfusion in these studies, technical aspects of the procedure limited translation to clinical practice, particularly in regards to the potential for percutaneous and

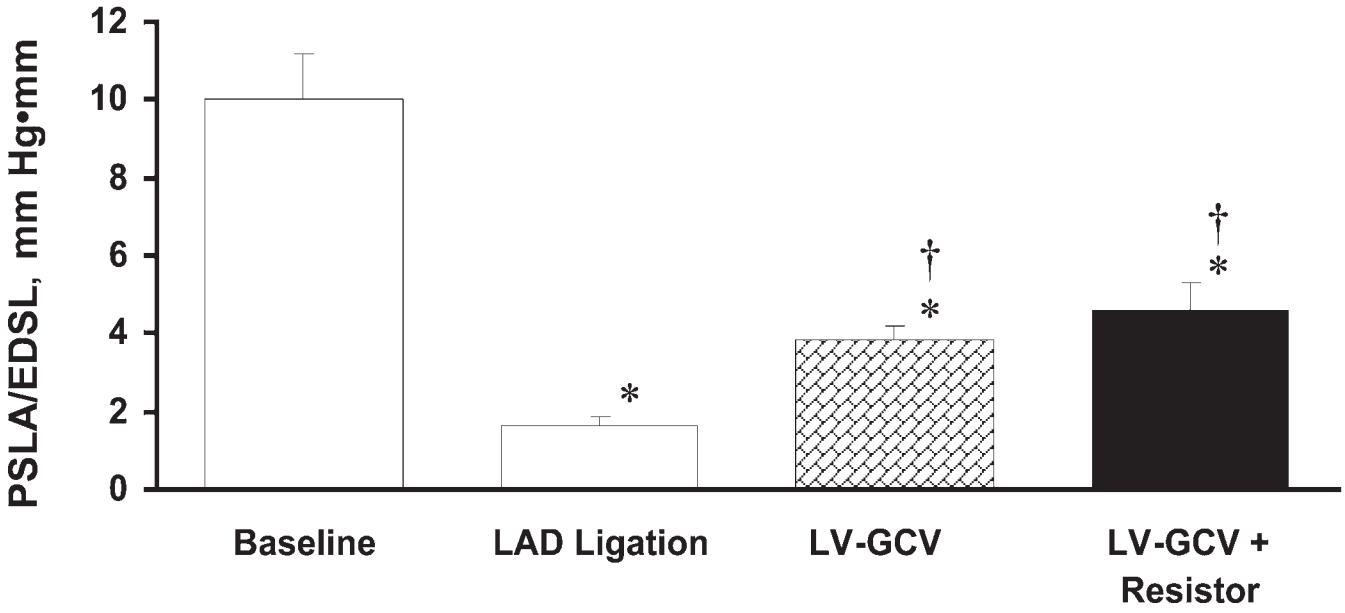

Figure 5. Regional myocardial function at baseline, following left anterior descending coronary artery (LAD) ligation, after left ventricle-to-great cardiac vein (LV-GCV) retroperfusion, and after LV-GCV retroperfusion + Starling resistor. All values are mean ± standard deviation; *P < .05 versus baseline; †P < .05 versus LAD ligation. PSLA indicates pressure-segment length loop area; EDSL, end-diastolic segment length.

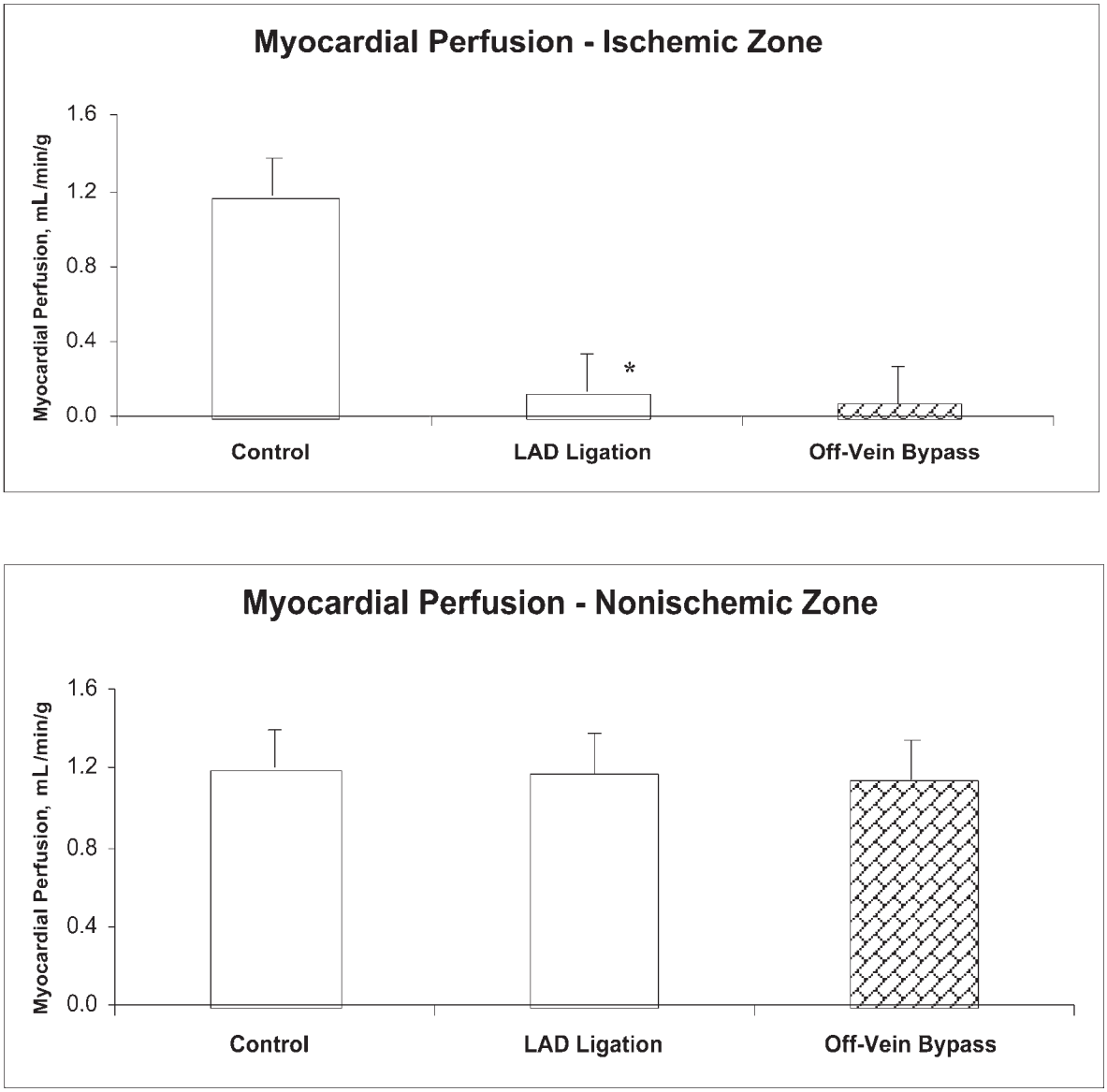

Figure 6. Regional myocardial blood flow at baseline, following left anterior descending coronary artery (LAD) ligation, and after left ventricle-to-great cardiac vein retroperfusion (off-vein bypass) in ischemic zone (A) and nonischemic zone (B). All values are mean ± standard deviation; *P < .05 versus control.

catheter-based approaches. The LV was in fact used as a source for retroperfusion in a study by Martin et al, but reduction of infarct size was their primary endpoint, and myocardial function was not found to be improved [Martin 2000]. The present study evolved not only as a culmination of these previous efforts to validate the principle of coronary retroperfusion, but also as a means to investigate the potential for percutaneous establishment of a direct LV-GCV conduit. Nonetheless, prior to the development of such a minimally invasive approach, the physiology underlying this approach needs to first be addressed.

Changes in coronary blood flow patterns were of primary concern with LV-GCV retroperfusion because coronary blood flow is dictated by relative resistance pressures within the overall circuit (Table 2). These resistances included proximal LAD ligation, distal GCV ligation, the LV-GCV conduit itself, and the in-line Starling resistor. With establishment of the LV-GCV circuit, peak forward flow occurred during systole and back flow occurred during diastole. Although this flow pattern is the reverse of what occurs under physiologic conditions via the epicardial coronary vessels, it was still capable of providing sufficient blood supply to sustain adequate myocardial function. We further demonstrated that LAD ligation decreased upstream antegrade blood flow, thereby augmenting net mean retrograde flow, and while the in-line Starling resistor blunted both forward and backward flow peaks within the LV-GCV conduit, back flow was selectively eliminated, leading to even greater augmentation of net mean

Table 2. Coronary Blood Flow Characteristics by LV-GCV Retroperfusion with In-Line Starling Resistor*

	LV-GCV Retroperfusion	LV-GCV Retroperfusion + Resistor
Forward LV-GCV flow, mL/min	+152.0 ± 14.4	+139.1 ± 24.5
Backward LV-GCV flow, mL/min	−39.2 ± 10.8	−33.3 ± 17.1
Mean LV-GCV flow, mL/min	+35.9 ± 12.7	+41.3 ± 12.1

*All values are mean ± standard deviation. LV-GCV indicates left ventricle-to-great cardiac vein.

retroperfusion.

Although clear differences in coronary blood flow patterns were demonstrated, the more critical issue was whether such changes in blood flow would translate into any meaningful functional benefit. Several previous studies had examined this question using various approaches. O'Byrne et al used positron emission tomography in dogs to demonstrate that coronary sinus retroperfusion with arterial sourcing could deliver oxygenated blood to regions of myocardium at risk for ischemia. With this approach, they achieved a 70% infarct reduction in treatment dogs compared to controls [O'Byrne 1991]. This concept was modified for use in humans and the initial experience with retroperfusion in patients with unstable angina undergoing high-risk angioplasty was favorable [Costantini 1991]. Those who underwent retroperfusion-supported balloon inflation experienced significantly less regional wall motion changes during angioplasty than those who did not receive retroperfusion support.

Retroperfusion strategies have also found clinical utility in the prevention of further myocardial damage during myocardial ischemia [Kar 1991; Lazar 1991; Martin 2000]. However, no improvements in regional myocardial function and hemodynamics were shown. Therefore, these reports touted the concept of myocardial salvage as the primary advantage of retroperfusion strategies. In distinction from these previous investigations, the present study demonstrates that retroperfusion via ventricular sourcing not only significantly improved regional myocardial function, as represented by PSLA/EDSL, but also restored deteriorated systemic hemodynamics due to myocardial ischemia. The degree of functional improvement appeared to be directly related to the net mean retroperfusion flow, with initial improvement manifest at the time of LV-GCV circuit activation and even further improvement upon Starling resistor application and elimination of back flow. This correlation suggests that coronary venous retroperfusion is a valid approach to revascularizing the capillary bed of ischemic myocardium, and is capable of restoring myocardial contractility to upwards of 47% of baseline function.

Although coronary venous retroperfusion seems to have unique advantages, its clinical applicability ultimately rests on the ease and efficiency with which it can be performed. Accordingly, percutaneous catheter-based technologies already exist that are capable of performing in situ coronary venous arterialization [Oesterle 2001]. The advancement of these technologies may stimulate greater interest in performing these procedures in patients who might have contraindications to open-chest surgery or traditional arterial revascularization.

A particular concern raised in previous retroperfusion studies is the potential for hemorrhagic infarction resulting from hyperperfusion of the myocardial tissue. This becomes an issue when venous outflow is occluded, leading to systemic artery-to-coronary vein shunting. The risk of hyperperfusion is significantly reduced if venous outflow is only partially occluded [Meerbaum 1986]. The LV-GCV retroperfusion conduit in the present study may therefore have an advantage over previous retroperfusion circuits in this regard. While the LV-GCV conduit provides blood from the ventricle source to the myocardium during the systolic phase, there is significant back flow through the coronary venous system to the LV during the diastolic phase, such that intramyocardial pressure is reduced. The LV-GCV conduit therefore serves as a regulator or relief valve between the LV and coronary vein. The back flow of blood into the LV during diastole reduces pressure within the myocardium, effectively decreasing the risk of hyperperfusion. However, this decreased risk offsets the functional myocardial improvements attained by the very elimination of that back flow, hence a fine balance is necessary to optimize both scenarios. The ability to regulate back flow between the ventricular source and the target coronary vein would be essential in this regard.

Study Limitations

This was a small experiment involving 5 animals, and a larger number of animals would need to be studied to validate our findings and permit application to a clinical setting.

In this study, regional myocardial blood flow was assessed with the colored microsphere technique, and although regional blood flow decreased significantly upon LAD ligation, it did not recover to any significant extent with activation of the LV-GCV circuit. These findings are curious in light of the fact that blood flow is clearly augmented via a direct channel from the LV. However, this observation may be related to technical issues with the microsphere technique, as outlined by Martin et al [2000]. In fact, the microsphere technique underestimates coronary sinus retroperfusate delivery, and approximately 10% of microspheres delivered by retrograde perfusion are known to escape through venovenous and thebesian channels [Berdeaux 1981], and antegrade flow dislodges microspheres injected through the coronary sinus. This underestimation of blood flow could potentially result in a lack of concordance with regional myocardial contractility. Therefore, the microsphere technique may not be the optimal approach to evaluate regional myocardial blood flow under conditions of retroperfusion and refined techniques to more accurately assess flow are warranted for future related studies.

CONCLUSIONS

A LV-GCV retroperfusion conduit can partially restore regional myocardial function of the acutely ischemic myocardium, resulting in significantly improved systemic hemodynamics. An in-line resistor valve further improves flow

and function. This unique approach may provide an effective therapy for diffuse coronary artery disease not amenable to traditional revascularization strategies.

REFERENCES

Berdeaux A, Farcot JC, Bourdarias JP, Barry M, Bardet J, Giudicelli JF. 1981. Effects of diastolic synchronized retroperfusion on regional coronary blood flow in experimental myocardial ischemia. Am J Cardiol 47:1033-40.

Chang BL, Drury JK, Meerbaum S, Fishbein MC, Whiting JS, Corday E. 1987. Enhanced myocardial washout and retrograde blood delivery with synchronized retroperfusion during acute myocardial ischemia. J Am Coll Cardiol 9:1091-8.

Costantini C, Sampaolesi A, Serra CM, et al. 1991. Coronary venous retroperfusion support during high risk angioplasty in patients with unstable angina: preliminary experience. J Am Coll Cardiol 18:283-92.

Farcot JC, Berdeaux A, Giudicelli JF, Vilaine JP, Bourdarias JP. 1983. Diastolic synchronized retroperfusion versus reperfusion: effects on regional left ventricular function and myocardial blood flow during acute coronary occlusion in dogs. Am J Cardiol 51:1414-21.

Gerber TC, Kantor B, Keelan PC, Hayes DL, Schwartz RS, Holmes DR. 2000. The coronary venous system: an alternate portal to the myocardium for diagnostic and therapeutic procedures in invasive cardiology. Curr Interv Cardiol Rep 2:27-37.

Kar S, Drury JK, Hajduczki I, et al. 1991. Synchronized coronary venous retroperfusion for support and salvage of ischemic myocardium during elective and failed angioplasty. J Am Coll Cardiol 18:271-82.

Keelan PC, Kantor B, Gerber TC, Holmes DR, Schwartz RS. 2000. Bypass without the surgeon: the coronary veins as arterial conduits. Curr Interv Cardiol Rep 2:11-9.

Kowallik P, Schulz R, Guth BD, et al. 1991. Measurement of regional myocardial blood flow with multiple colored microspheres. Circulation 83:974-82.

Lazar HL, Treanor P, Rivers S, Bernard S, Shemin RJ. 1995. Combining percutaneous bypass with coronary retroperfusion limits myocardial necrosis. Ann Thorac Surg 59:373-8.

Martin JS, Byrne JG, Ghez OY, et al. 2000. LV-powered coronary sinus retroperfusion reduces infarct size in acutely ischemic pigs. Ann Thorac Surg 69:84-9.

Meerbaum S. 1986. Coronary venous retroperfusion delivery of treatment to ischemic myocardium. Herz 11:41-54.

O'Byrne GT, Nienaber CA, Miyazaki A, et al. 1991. Positron emission tomography demonstrates that coronary sinus retroperfusion can restore regional myocardial perfusion and preserve metabolism. J Am Coll Cardiol 18:257-70.

Oesterle SN, Reifart N, Hauptmann E, Hayase M, Yeung AC. 2001. Percutaneous in situ coronary venous arterialization: report of the first human catheter-based coronary artery bypass. Circulation 103:2539-43.

Suehiro K, Shimizu J, Yi GH, et al. 2001. Direct coronary artery perfusion from the left ventricle [published correction appears in J Thorac Cardiovasc Surg 2001;121:1063]. J Thorac Cardiovasc Surg 121:307-15.