The Heart Surgery Forum #2003-07182
6 (3), 2003

Online address: www.hsforum.com/vol6/issue3/2003-07182.html

Myocardial Contractile Performance, Preload Recruitable Stroke Work Relationships, and Histomorphometric Changes Following Off-Pump and On-Pump Coronary Bypass Grafting of the Left Internal Thoracic Artery to the Left Anterior Descending Artery

Dr. Bittner

(#2003-07182 . . . February 14, 2003)

Hartmuth B. Bittner, Peter V. Ching

University of Minnesota, Division of Cardiovascular and Thoracic Surgery, Minneapolis, Minnesota, USA

ABSTRACT

Background: It has been shown that coronary artery bypass grafting without cardiopulmonary bypass (off-pump or OPCABG) preserves better cerebrocognitive, pulmonary, hepatorenal, and blood cell functions compared with on-pump surgery because of an attenuated inflammatory response. The degrees of ischemia/reperfusion injury, myocardial protection, and quantitative changes in myocardial contractile performance following OPCABG have not been well documented.

Methods: A canine myocardial ischemic injury model (60-minute occlusion of the left anterior descending artery [LAD]; n = 30, 27-35 kg body weight) was used to quantitatively assess postoperative regional left ventricular function (sonomicrometry, micromanometry, preload recruitable stroke work [PRSW]). The left internal thoracic artery (LITA) was anastomosed to the distal LAD in off-pump and on-pump CABG with antegrade/retrograde cold blood cardioplegic arrest (cardiopulmonary bypass time, 58 ± 2 minutes; cross-clamp time, 28 ± 3 minutes). Anastomosis patency and endothelial changes at the anastomoses were analyzed with light microscopy and histopathologic techniques.

Results: LAD occlusion resulted in ischemia/infarction (creatine kinase–MB levels on-pump and off-pump versus the baselines were, respectively, 17.5 ± 1.4 mg/L versus 1.5 ± 0.3 mg/L [$P < .05$ by analysis of variance and t test] and 19.5 ± 1.8 mg/L versus 2.1 ± 0.4 mg/L [$P < .05$]) and a significant decrease in regional myocardial function in both groups (50% decrease of PRSW). Revascularization led to reestablishment of myocardial function to baseline (on-pump and off-pump PRSW were, respectively, 57-196 $\times 10^3$ erg · cm^{-2} [mean, 127 $\times 10^3 \pm 25 \times 10^3$ erg · cm^{-2}] and 81-98 $\times 10^3$ erg · cm^{-2} [mean, 90 $\times 10^3 \pm 15 \times 10^3$ erg · cm^{-2}]). All anastomoses were widely patent in all animals 14 days after surgery. There was a significantly increased intimal thickening at the 8-0 monofilament suture line in the off-pump LITA-to-LAD anastomoses.

Conclusions: Compared with most commonly applied myocardial preservation techniques (cardiopulmonary bypass, hypothermic blood cardioplegic arrest), OPCABG provides at least equal myocardial protection, because there were no significant quantitative differences between off-pump and on-pump CABG in myocardial contractile performance following LITA-to-LAD revascularization. The more prominent intimal thickening observed in OPCABG procedures is worrisome and deserves further investigation.

INTRODUCTION

Recent years have witnessed a renaissance of interest in the techniques of coronary artery bypass grafting (CABG) on the beating heart, or off-pump coronary revascularization (OPCABG) without cardiopulmonary bypass (CPB). Technological innovation has led to the promise of technical quality equivalent to on-pump techniques with added benefits ranging from faster recovery times to decreased morbidity to lowered costs. The allure of OPCABG lies in the avoidance of CPB and its associated inflammatory response syndrome. During and after extracorporeal circulation, several abnormalities develop, including a diffuse capillary fluid leak with increased fluid requirements, acute lung injury requiring mechanical ventilation, acute renal insufficiency, a decrease in hepatic synthetic capacity, and disturbances in coagulation [Bone 1996, Kirklin 1991, Butler 1993]. In addition to the systemic effects of CPB, the heart may be ischemic preoperatively and is always made ischemic during the aortic cross-clamp period in traditional cardiac surgery when cardioplegic arrest is used in addition to CPB. When the myocardium is subsequently reperfused with blood, it is often markedly impaired by what is now recognized as a distinct pathologic

Presented at the Fifth Annual Meeting of the International Society for Minimally Invasive Cardiac Surgery, New York, New York, USA, June 20-23, 2002.

Submitted January 9, 2003; accepted February 14, 2003.

Address correspondence and reprint requests to: Hartmuth B. Bittner, MD, University of Minnesota, Division of Cardiovascular and Thoracic Surgery, Department of Surgery, Box 207, 420 Delaware St, Minneapolis, MN 55455, USA; 1-612-626-5839; fax: 1-612-625-1683 (e-mail: Heartbeatgermany @aol.com).

process, referred to as ischemia/reperfusion injury [Zughaib 1993]. This process can result in the prolonged need for pharmacologic or mechanical circulatory support despite the use of cardioprotective techniques including cardioplegia and hypothermia.

This study was designed to quantify the differences in cardiopulmonary function and inflammatory reactions for two surgical coronary revascularization methods, on-pump and off-pump CABG, in a large-animal preparation of acute myocardial ischemia and coronary syndrome.

MATERIALS AND METHODS

A canine myocardial ischemic injury model (n = 30; 27-35 kg ± 0.3 kg) was used, and the animals were divided into two groups. Acute myocardial ischemia and acute coronary syndrome were established by permanently ligating the left anterior descending artery (LAD) distal to the origin of the first diagonal branch. Reperfusion of the ischemic myocardium was performed by means of surgical revascularization via anastomosis of the left internal thoracic artery (LITA) to the distal LAD. The animals underwent either on-pump (group 1) or off-pump (group 2) CABG.

This protocol was conducted in accordance with the University of Minnesota Experimental Surgical Services Laboratory standard operating procedures, which are in compliance with regulations in US Food and Drug Administration publication 21 CFR Part 58 [FDA 2002]. The University of Minnesota complies with the Animal Welfare Act and subsequent amendments. The University of Minnesota adheres to the principles stated in the Guide for the Care and Use of Laboratory Animals [NAS 1996]. The University of Minnesota maintains a formal Institutional Animal Care and Use Committee that meets periodically to review current and ongoing studies at the university's laboratories. The committee makeup and operation are in accordance with the recommendations of the National Institutes of Health (Office for Protection from Research Risks) and the US Department of Agriculture (Animal and Plant Health Inspection Service).

Instrumentation and Surgical Technique

The animals were placed on the operating table in the supine position. Mechanical ventilation (12 breaths per minute) was initiated with 100% oxygen set at 15 mL/kg, the fraction of inspired oxygen at 100%, the positive end-expiratory pressure at 3 cm water, and the rate-controlled ventilation mode adjusted to maintain an arterial partial carbon dioxide pressure between 30 mm Hg and 40 mm Hg. Arterial pH, partial oxygen and carbon dioxide pressures, oxygen saturation, hematocrit, and potassium levels were measured at 30-minute intervals, as well as 15 minutes after any changes in ventilator settings were made or any medications were administered. An esophageal temperature probe was placed, and the body temperature of the animal was maintained between 36°C and 37°C before and after bypass by application of heating pads, blankets, and heated, humidified inspiration gas. Electrocardiographic monitoring was performed with 3 standard limb electrodes. The animal's chest and bilateral groin areas were scrubbed for 5 to 10 minutes with povidone-iodine (Betadine) scrub. After the intravenous administration of 5 mL pancuronium bromide, a standard median sternotomy was performed. A Favaloro sternum retractor was inserted to dissect the LITA for use as a bypass graft to the LAD. The right femoral artery was dissected out to expose approximately 4 to 5 cm of artery, which served as the arterial return site for CPB experiments. A chest retractor was placed in the chest space and opened to expose the organs and vessels of the mediastinum. A pericardiotomy was performed ventral to the phrenic nerve. Traction with 5 2-0 Ethibond sutures (Ethicon, Somerville, NJ, USA) tied to the margins of the pericardiotomy formed a pericardial cradle for the heart. A transonic flow meter (T208X; Transonic Systems, Ithaca, NY, USA) was placed around the ascending aorta to measure blood flow from the ascending aorta. Ultrasonic dimension transducers (1.5 mm outer diameter, no. 1-1015-5A; Vernitron, Bedford, OH, USA) were positioned 10 to 15 mm apart across the anteroposterior minor axis of the left ventricle in a distal LAD-perfusing myocardial zone to measure the left ventricular myocardial segment length. A Millar pressure transducer (MPC-500; Millar Instruments, Houston, TX, USA) was placed through the apex into the left ventricle for continuous recording of left ventricular pressures, including end-diastolic ventricular pressures. Data were acquired and processed with the WinDaq and Codas software packages (DATAQ Instruments, Akron, OH, USA) on a personal computer. A coronary sinus catheter was inserted for sampling coronary sinus blood as well as for administering retrograde cardioplegic solution. All animals were anticoagulated with 250 U/kg heparin administered intravenously.

Perfusion Protocol

A no. 16 Bardic cannula was inserted and secured in the femoral artery, and a no. 20-22 Bardic 2-stage cannula was inserted and secured in the right atrium in preparation for CPB. Cooling of the animal began when adequate venous return had been established to the CPB reservoir and was stopped when 28°C had been reached. Once the animal was stabilized on CPB, the ascending aorta was cross-clamped proximal to the brachiocephalic branch, and the heart was arrested antegradely and retrogradely with cold blood cardioplegia. A lateral arteriotomy (1.5 mm) was performed on the coronary artery, and the bypass graft was anastomosed end to side to the margins of this incision with 8-0 monofilament suture. The cross-clamp was then removed from the aorta to reestablish blood flow, and systemic warming was initiated. Protamine was administered at an approximate ratio of 1 mL protamine to 1 mL heparin.

Off-pump and on-pump beating heart coronary bypass surgeries were performed in a similar fashion. However, off-pump CABG was performed with the use of a clinically used retractor (OPCAB retractor; Genzyme, Cambridge, MA, USA), a heart stabilizer (Cohn Cardiac Stabilizer and Retractotape; Genzyme), a carbon dioxide blower and NaCl mister (ClearView Misted Blower; Medtronic, Minneapolis, MN, USA), and proximal coronary artery occluders (Retractotape) to keep the bypass target vessel bloodless and motionless.

Ischemia/Reperfusion

Following 30 minutes of permanent proximal LAD ligation (all animals), LITA-to-LAD revascularization was commenced either on-pump (global cardioplegic arrest for 30 minutes and a total CPB time of 60 minutes) or off-pump. The effective ischemia time (the period from LAD ligation until perfusion through the LITA bypass graft) was identical in all animals (60 minutes) and was independent of the surgical technique used.

Termination of the Experiment

After the study was completed, the animals were allowed to recover and were returned to the animal care facility. After 8 to 14 days, the animals were sacrificed, the hearts were excised, and the myocardia were examined for bypass graft patency and ischemic changes by histopathologic means (hematoxylin-eosin staining or azan staining, high-power micrometric evaluation, and light microscopy).

Data Acquisition and Analysis of Left Ventricular Function

Functional data were collected at baseline (after instrumentation of the heart and before coronary artery occlusion) and after 15 minutes of LAD occlusion. In the on-pump group, data were collected immediately and 45 minutes after CABG and termination of CPB. Off-pump data were collected on completion of the distal anastomosis and after 45 minutes of reperfusion. At each data point, 3 files of data were recorded during steady-state conditions and during rapid vena cava occlusion to obtain data over a range of cardiac preload. These data were acquired with the ventilator intermittently disconnected during the acquisition of each file. Functional and hemodynamic data were digitized online, collected, and stored on a microprocessor for computerized analysis according to the quantification method of regional myocardial dysfunction after acute ischemic injury, as has been described previously [Owen 1993]. Briefly, the cardiac cycle is defined automatically with *dP/dt*. Diastole begins with the first zero crossing of *dP/dt* after the negative *dP/dt* peak and ends 40 milliseconds before the positive *dP/dt* peak. A segmental stroke work analog (*SW*) was calculated as the integral of the left ventricular transmural pressure (*P*) and myocardial segment length (*L*) over the entire cardiac cycle:

$$SW = \int P \cdot dL.$$

For each vena caval occlusion, linear regressions were performed on data from 5 beats before the onset of vena caval occlusion to the achievement of a steady state at the end of vena caval occlusion. Linear regressions of the relationship between *SW* and end-diastolic length (*EDL*) were fitted to the equation,

$$SW = M_{SW} (EDL - L_W),$$

where L_W and M_{SW} are the intercept on the x-axis and the slope, respectively. The relationship of segmental *SW* and *EDL* is termed the preload recruitable work relationship (PRSW), which represents a load-independent index of left ventricular function and contractility. With the PRSW relationship of the second equation, preload recruitable stroke work area (PRWA) can be defined as the area under the regression line of *SW* versus *EDL*.

Blood Sampling

Arterial and coronary sinus blood samples were drawn after the administration of heparin and surgical instrumentation (baseline) and 12 hours and 24 hours after reperfusion (following termination of CPB or completion of the distal anastomosis in off-pump coronary artery surgery). Creatine kinase–MB (CK-MB) levels were measured by a standard commercially available immunoassay prepared according to the manufacturer's instructions (AxSYM Immunoassay Analyzer; Abbott Laboratories, Abbott Park, IL, USA).

Arterial blood gases were drawn throughout the case, and arterial pH, partial oxygen and carbon dioxide pressures, oxygen saturation, hematocrit, and potassium levels were measured (Gem Stat; Mallinckrodt Sensor Systems, Ann Arbor, MI, USA) at 30-minute intervals, as well as 15 minutes after any ventilator setting changes were made or any medications were administered. Blood samples were drawn from an external iliac artery pressure catheter (Gould Electronics, Oxnard, CA, USA).

Statistical Analysis

Data were acquired before and at intervals after myocardial ischemia and coronary revascularization. The variables of interest were grouped and reported as means, and analyses of variance were performed. Follow-up paired Student *t* tests were used to compare baseline values with data after revascularization. Each animal served as its own control. Linear regressions were performed on left ventricular functional assessments, and slopes were grouped into time points. The slope means were evaluated with *t* tests for significant differences between on-pump and off-pump groups. A difference was considered statistically significant for *P* less than .05.

RESULTS

The permanent proximal LAD ligation led to marked myocardial ischemia, and significant myocardial injury was incurred in all animals (CK-MB levels on-pump and off-pump versus the baselines were, respectively, 17.5 ± 1.4 μg/L versus 1.5 ± 0.3 μg/L [$P < .05$] and 19.5 ± 1.8 μg/L versus 2.1 ± 0.4 μg/L [$P < .05$]). The effective ischemia time or the interval from LAD ligation until unclamping of the LITA pedicle and reperfusion ranged between 50 and 55 minutes. Revascularization led to reestablishment of myocardial function to baseline (on-pump and off-pump PRSW were, respectively, 57-196 $\times 10^3$ erg · cm^{-2} [mean, 127 $\times 10^3 \pm 25 \times 10^3$ erg · cm^{-2}] and 81-98 $\times 10^3$ erg · cm^{-2} [mean, 90 $\times 10^3 \pm 15 \times 10^3$ erg · cm^{-2}]). Figure 1 is a representative example of left ventricular segmental stroke work analysis at baseline, at ischemia (15 minutes), and after reperfusion (45 minutes) during the experiment. The general trend of collapsing left ventricular pressure-volume loops associated with ischemia is well demonstrated (Figure 1). The initial ischemic measurements show a negative association between increasing segment length and the segment

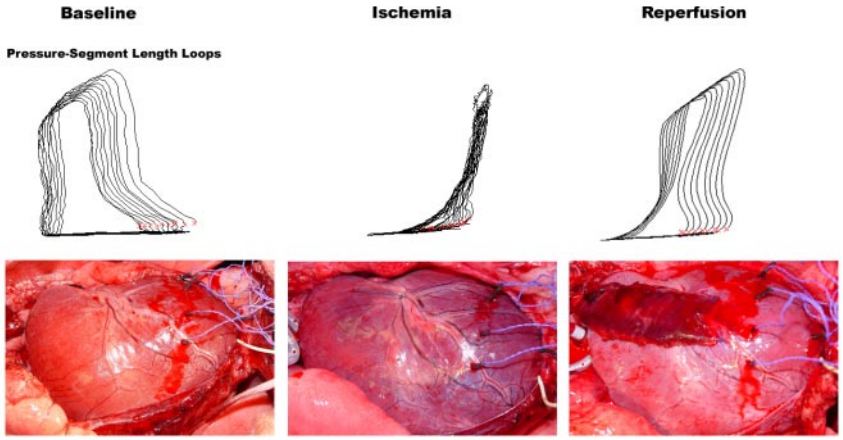

Figure 1. A representative example of data acquisition during a single study. Measurements are obtained at baseline, at ischemia (proximal permanent left anterior descending artery [LAD] ligation), and after 45 minutes of reperfusion (through the left internal thoracic artery–to-LAD bypass). Note collapse of pressure-area loop associated with ischemia and reconstitution following reperfusion.

work performed due to paradoxical dyskinetic motion of the ischemic area. Figure 2 is a representative graph of a PRWA calculation for one animal. Contraction generates a bulging of the ischemic area, so segmental work in the affected area is negative as measured. Once reperfusion is established, recovery of myocardial function progresses back toward the baseline as time proceeds (Figure 2).

All subjects demonstrated a significant decrease in regional PRWA with ischemia. On-pump PRWA decreased to 46% ± 4% of baseline, and off-pump PRWA decreased to 23% ± 18% of baseline. Reperfusion returned the PRWA to baseline (Figure 3).

Analysis of the arterial blood gas data collected before and after the operations revealed a significant decrease in the A-a gradient in the off-pump group. The mean difference in the partial pressure of oxygen before and after surgery was 309 ± 49 mm Hg in the on-pump group, compared with 72 ± 79 mm Hg in the off-pump group ($P < .05$).

Histopathology

Vertical, thin tissue slices of the LITA-to-LAD anastomosis taken 10 to 14 days following surgery allowed a high-power evaluation of intimal thickening at the hood, the floor, and the 8-0 monofilament suture line of the anastomosis. Significant differences in thickness were found only at the suture line: off-pump, 224 ± 208 μm; on-pump, 114 ± 59 μm (Figure 4). All animals had small areas of myocardial tissue necrosis in the LAD territory.

Complications

Two animals in the on-pump group developed low cardiac output syndrome. These animals suffered severe right ventricular distension and acute right ventricular failure immediately after protamine administration. Three additional animals in the on-pump group required blood transfusions because of low hematocrit levels. One animal in the off-pump group required frequent cardioversion shocks because of reperfusion-induced malignant ventricular arrhythmias. These animals were excluded from the analysis of the functional data.

DISCUSSION

Beating heart CABG has recently been rediscovered, refined, and popularized in an effort to avoid the inflammatory response associated with CPB. Recent reports have documented a decreased incidence of multiorgan dysfunction and complications in off-pump CABG compared with CABG on CPB [Ascione 2000, Edmunds 1998], leading to improved outcomes and lower costs with OPCABG [Puskas 1998]. The functional benefits for the heart and the myocardium have not been well defined, and concerns for myocardial protection during OPCABG have risen. The brief periods of ischemia necessary to visualize the target vessels during the construction of the distal anastomosis may produce some degree of myocardial injury [Bufkin 1998]. One of the most formidable aspects of coronary revascularization is optimal myocardial protection, which translates into decreased morbidity and

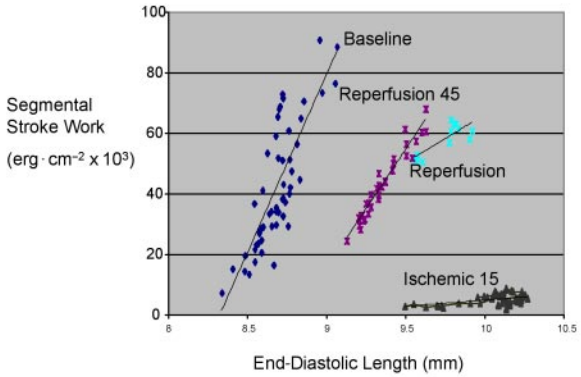

Figure 2. A representative example of left ventricular segmental stroke work analysis at baseline, at ischemia (15 minutes), at reperfusion, and after reperfusion for 45 minutes during an experiment.

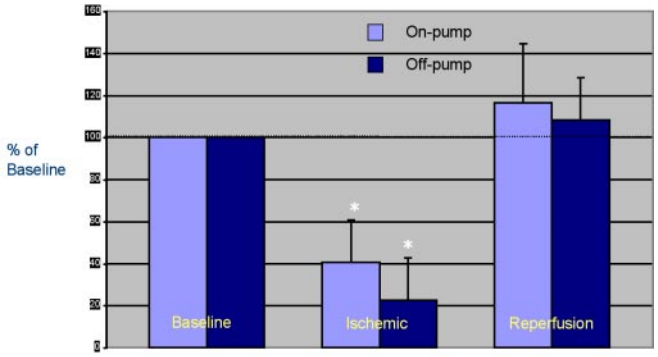

Figure 3. Preload recruitable stroke work area (PRWA) as a percentage of baseline values for on-pump procedures (57-196 $\times$ 10^3 erg $\cdot$ cm^{-2}; mean, 127 $\times$ 10^3 $\pm$ 25 $\times$ 10^3 erg $\cdot$ cm^{-2}) and for off-pump procedures (81-98 $\times$ 10^3 erg $\cdot$ cm^{-2}; mean, 90 $\times$ 10^3 $\pm$ 15 $\times$ 10^3 erg $\cdot$ cm^{-2}). Note the significant drop in PRWA associated with ischemia and the recovery in PRWA on reperfusion.

mortality in the clinical setting. Optimal myocardial protection during complex coronary revascularization procedures has been well established over the past 10 years, and the protective role of hypothermic blood cardioplegia delivered antegradely and retrogradely is well documented [Franke 2001]. However, recent reports have demonstrated that OPCABG may preserve myocardial function to a higher degree than on-pump CABG. Comparisons of myocardial injury markers such as CK-MB, myoglobin, and troponin indicated significantly lower levels of these markers in off-pump beating heart coronary revascularization procedures compared with traditional on-pump CABG with cardioplegic arrest [Bouchard 1998, Penttila 2001]. It is known that CPB triggers the inflammatory response that is reflected in adhesion molecule and cytokine activation [Struber 1999, Wan 1999]. Neutrophil activation with increased cell surface expression of adhesion molecules, such as the integrin complex CD11b/CD18, has been well documented with CPB [Ilton 1999, Galinanes 1996] and may cause neutrophil migration into the myocardium, resulting in myocardial depression.

In toto, it is hypothesized that the attenuated inflammatory response syndrome in off-pump CABG compared with on-pump CABG may lead to decreased myocardial injury and better preservation of cardiac function following coronary revascularization. However, the real answer to the question of which technique better preserves myocardial function is not yet known. Clinical results have been limited because of the selected patient populations, the low numbers of patients studied, and measurement techniques used that describe hemodynamic parameters rather than qualitative measurements. This report describes the quantitative analysis of myocardial function after off-pump and on-pump CABG. In a large-animal preparation simulating the clinical scenario of an acute coronary syndrome treated with immediate surgical revascularization and reperfusion, the preload recruitable stroke work analysis was applied to objectively measure myocardial function after revascularization. The analysis of the data described in this report revealed that there were no significant differences between these two surgical revascularization methods. The degrees of myocardial injury after coronary bypass–supported coronary revascularization and after off-pump beating heart CABG were similar. There were no significant differences in the levels of the cardiac injury markers (CK-MB). The amounts of myocardial necrosis in the region of the LAD were identical in the two groups as evaluated by CK-MB levels and by necropsy 8 to 14 days after bypass grafting. In both groups, all anastomoses of the LITA to the distal LAD were widely patent, and there was no difference in the effective ischemic time between groups (the time from the ligation of the proximal LAD until release of the clamp from the bypass graft pedicle).

The measurements and the techniques are sensitive enough to assess the changes in segment length after ischemia. The well-described phenomenon of a collapsed segment pressure loop after ischemia and its reconstitution with reperfusion was consistently observed in this study. The reason why functional changes were minimal in the on-pump procedures is likely related to the application of optimal myocardial protection. Myocardial protection consisted of antegrade and retrograde cold blood cardioplegia. This protection, in combination with the relatively short global ischemia and cardiac arrest with CPB times, may have preserved left ventricular regional function in the on-pump animals.

The finding of significantly thicker intima formation at the suture line in the OPCABG animals compared with the

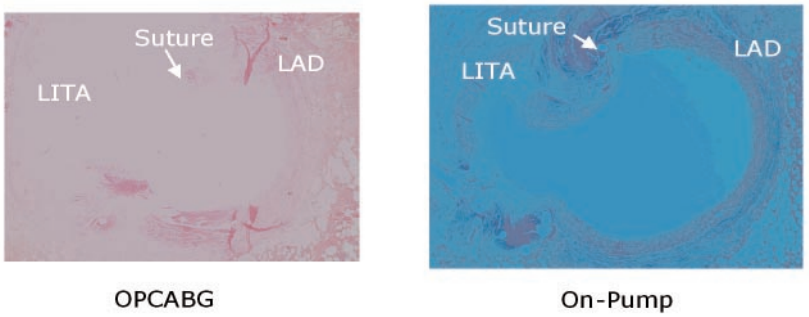

Figure 4. Histopathology of the bypass anastomosis of the left internal thoracic artery (LITA) to the left anterior descending artery (LAD). Hematoxylin-eosin (off-pump coronary artery bypass graft [OPCABG]) and azan (on-pump) staining as a representative example of intimal thickening at the 8-0 monofilament suture line.

on-pump group is worrisome. It cannot be explained by the mechanical input of the carbon dioxide blower/NaCl mister, because no differences were seen at the floor of the anastomosis. Suture materials and technique were identical in the off-pump and on-pump coronary surgeries. Although the significance of this observation is unclear, a future investigation of adhesion molecule activation at the anastomosis is indicated.

Overall, the results of the myocardial functional analysis should be emphasized, because it is a reliable model that allows comparisons of the two surgical coronary revascularization techniques. The model itself is stable and standardized, and this conclusion is supported by the high number of successful chronic studies.

As has been found in clinical investigations, pulmonary function and oxygenation was demonstrated to be better preserved in the animals in the off-pump group. The decrease in postoperative oxygenation was significantly more severe than in the on-pump group. The results of this basic science study may argue against the current efforts to establish a minimally invasive, totally endoscopic, robotically supported off-pump beating heart coronary artery bypass procedure. To date, minimally invasive surgeries have been performed with CPB support on the arrested heart of highly selected patients. One criticism leveled at such efforts was the use of CPB, because it may negate the advantages of minimally invasive surgery. The results of this study suggest that this may not be a serious criticism for single-vessel bypass grafting and short bypass time–related revascularization procedures. A short period of cardiac arrest and CPB does not significantly impair myocardial function, and a totally endoscopic bypass procedure may be done safely on the motionless heart without adverse sequelae.

REFERENCES

Ascione R, Lloyd CT, Underwood MJ, Lotto AA, Pitsis AA, Angelini GD. 2000. Inflammatory response after coronary revascularization with or without cardiopulmonary bypass. Ann Thorac Surg 69:1198-204.

Bone RC. 1996. Toward a theory regarding the pathogenesis of the systemic inflammatory response syndrome: what we do and do not know about cytokine regulation. Crit Care Med 24:163-72.

Bouchard D, Cartier R. 1998. Off-pump revascularization of multivessel coronary artery disease has a decreased myocardial infarction rate. Eur J Cardiothorac Surg 14(suppl 1):S20-4.

Bufkin BL, Shearer ST, Vinten-Johansen J, et al. 1998. Preconditioning during simulated MIDCABG attenuates blood flow defects and neutrophil accumulation. Ann Thorac Surg 66:726-31.

Butler J, Rocker GM, Westaby S. 1993. Inflammatory response to cardiopulmonary bypass. Ann Thorac Surg 55:552-9.

Edmunds LH Jr. 1998. Inflammatory response to cardiopulmonary bypass. Ann Thorac Surg 66:S12-6.

[FDA] US Food and Drug Administration. 2002. Good laboratory practice for nonclinical laboratory studies. Rockville, Md: US Food and Drug Administration. Publication 21 CFR Part 58.

Franke U, Wahlers T, Cohnert TU, et al. 2001. Retrograde versus antegrade crystalloid cardioplegia in coronary surgery: value of troponin-I measurement. Ann Thorac Surg 71:249-53.

Galinanes M, Watson C, Trivedi U, Chambers DJ, Young CP, Venn GE. 1996. Differential patterns of neutrophil adhesion molecules during cardiopulmonary bypass in humans. Circulation 94:II364-9.

Ilton MK, Langton PE, Taylor ML, et al. 1999. Differential expression of neutrophil adhesion molecules during coronary artery surgery with cardiopulmonary bypass. J Thorac Cardiovasc Surg 118:930-7.

Kirklin JK. 1991. Prospects for understanding and eliminating the deleterious effects of cardiopulmonary bypass. Ann Thorac Surg 51:529-31.

[NAS] National Academy of Sciences. 1996. Guide for the care and use of laboratory animals. Washington, DC: National Academy Press.

Owen CH, Zipprich DA, Sabiston DC, Smith PK, Glower DD. 1993. Regional geometry and function during myocardial ischemia and recovery. J Surg Res 54:545-57.

Penttila HJ, Lepojarvi MV, Kiviluoma KT, Kaukoranta PK, Hassinen IE, Peuhkurinen KJ. 2001. Myocardial preservation during coronary surgery with and without cardiopulmonary bypass. Ann Thorac Surg 71:565-71.

Puskas JD, Wright CE, Ronson RS, Brown WM, Gott JP, Guyton RA. 1998. Off-pump multivessel coronary bypass via sternotomy is safe and effective. Ann Thorac Surg 66:1068-72.

Struber M, Cremer JT, Gohrbandt B, et al. 1999. Human cytokine responses to coronary artery bypass grafting with and without cardiopulmonary bypass. Ann Thorac Surg 68:1330-5.

Wan S, Izzat MB, Lee TW, Wan IY, Tang NL, Yim AP. 1999. Avoiding cardiopulmonary bypass in multivessel CABG reduces cytokine response and myocardial injury. Ann Thorac Surg 68:52-6.

Zughaib ME, McCay PB, Jeroudi MO. 1993. Moderate ischemic injury and myocardial stunning. In: Piper HM, Preusse CJ, editors. Ischemia-reperfusion in cardiac surgery. Dordrecht, Netherlands: Kluwer. p 3-40.

REVIEW AND COMMENTARY

1. Editorial Board Member NS55 writes:

It is noted that the cross-clamp time is 28 minutes in on-pump patients and that the time to the LITA unclamping time was 20 to 25 minutes for all patients after the initiation of anastomoses. In our practice, the total vessel occlusion time for anastomoses on the beating heart averages 5 to 8 minutes. The relatively long anastomotic times recorded make one wonder if the anastomoses were performed by inexperienced laboratory personnel or by experienced off-pump surgeons. Long anastomotic times by inexperienced technicians may certainly be associated with more intimal trauma, especially in the more demanding off-pump anastomoses, and this alone may account for the increased intimal scaring in the off-pump group.

The conclusions state, "A short period of . . . cardiopulmonary bypass does not significantly impair myocardial function. . . ." Certainly short ischemic times are better than long ischemic times, but I am unaware of any literature confirming that the intensity of the inflammatory response to CPB is correlated to the time on bypass.

Authors' Response by Hartmuth B. Bittner, MD:

Overall, the myocardial ischemia periods were comparable. The cross-clamp time was 30 minutes in on-pump experiments, and 30 minutes of ischemia time occurred in off-pump

coronary revascularization experiments (the time from permanent proximal LAD occlusion and LITA pedicle unclamping following the construction of the LITA-LAD anastomosis). As stated in the "Materials and Methods" section, the ischemia times do not reflect the time required for constructing the anastomosis. The anastomosis construction required approximately 8 to 10 minutes and was performed by an experienced research fellow in the on-pump cases and by faculty in the off-pump cases.

I agree that there is only a vague literature describing a correlation between the severity of the systemic inflammatory response syndrome and the time on bypass, if, for example, only cytokine plasma concentrations, tumor necrosis factor α, or neutrophil activation markers are used for assessment. However, Dr. J. Kirklin has investigated extensively the deleterious effects of long CPB times on multiorgan dysfunction, and the outcomes have been published in textbooks and cardiac surgery journals. A higher incidence of the post-pump–associated vasoplegic syndrome has been reported and experienced with very long CPB runs (eg, resternotomy for assist device explantation and heart transplantation). Intravenously administered vasopressin and alpha-stimulating pressors are required following long CPB-supported operations.