

Optimizing Off-Pump Coronary Artery Bypass Graft: Technical and Metabolic Aspects

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ABSTRACT

Purpose: Our purpose was to determine if complete revascularization could be successfully performed off bypass in the majority of coronary artery bypass graft (CABG) patients.

Methods: Using a metabolic protocol and the Medtronic Octopus stabilizer device (Medtronic, Inc., Minneapolis, MN), 285 consecutive patients between July 1, 1997 and July 31, 1999 were successfully revascularized off pump via median sternotomy. A relative contraindication for off bypass CABG was cardiogenic shock. The metabolic protocol was designed to enhance systolic and diastolic cardiac function during surgery.

Results: Of 298 patients on whom we attempted off-pump revascularizations, 96% (285/298) were successful. The mean number of grafts per case was 3.3. The mean age of patients was 69.5 years, and 38% (109/285) were 75 years of age or older. Perioperative myocardial infarction (MI) occurred in two patients (0.7%) and operative mortality was 2.8% (8/285). Average Parsonnet score was 4.8. Cost savings were realized through minimal blood product utilization (average 1.5 units per case) and decreased cardiopulmonary bypass supplies.

Conclusion: Complete revascularization can be performed off bypass in the majority of CABG patients. The concomitant use of the Octopus off-bypass technique with aggressive metabolic support ensures manual manipulation of a beating heart and results in a low incidence of postoperative complications and significant cost savings.

INTRODUCTION

Coronary artery bypass has long been established as the procedure of choice for multi-vessel coronary artery disease. The use of cardiopulmonary bypass (CPB) results in known metabolic and inflammatory derangements contributing to perioperative and postoperative complications [Hill 1998]. These include cerebrovascular accident (CVA), neurocognitive disorders, kidney failure, bleeding, and a generalized systemic inflammatory response. Procedures done with off-pump bypass (OPB) are not associated with these derangements and are slowly gaining acceptance.

All patients with angiographically documented coronary artery disease are known to exhibit moderate to severe insulin resistance [Bressler 1996]. This is characterized by hypokalemia, hypomagnesemia, hyperuricemia, hyperlipidemia, endothelial dysfunction, and increased intracellular calcium levels. A study by Furnary et al. focused on substernal wound infection rates postoperatively and showed benefit from insulin infusion and glucose normalization [Furnary 1999]. From 1991 to 1997, metabolic protocols were established at our hospital to improve outcomes initially in the diabetic patient [Marcus 1990, 1998, 1999]. We extended this protocol to all patients undergoing off-pump coronary artery bypass (OPCAB) because we were not able to ascertain which patients would tolerate manual manipulation of the heart by simply measuring ejection fraction. The use of milrinone and levophed provided additional support for the ventricle, thus allowing us to perform the surgery.

The correction of these metabolic disorders preoperatively and intraoperatively improved both systolic and diastolic function in all patients. The implementation allowed us to successfully perform beating heart surgery on 96% of our patients since July 1997. The added benefit, not anticipated at the time, has been the decrease in major morbidity and mortality, decrease in blood usage, and reduction in cost.

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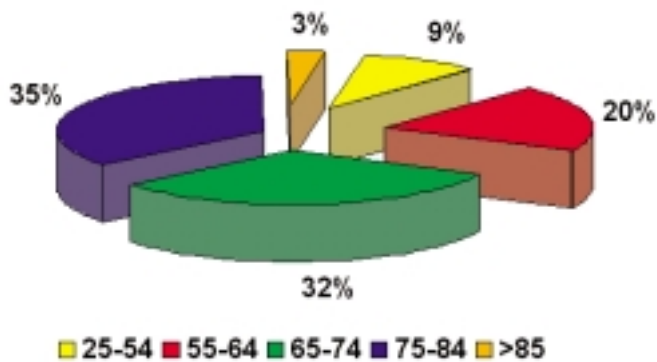


Figure 1. Age breakdown: Nearly 40% of off-pump patients were greater than 75 years of age. Source: Cardiac Surgery Outcomes Data, July 1997–July 1999, Saddleback Memorial Medical Center, Laguna Hills, CA.

PATIENTS AND METHODS

From July 1997 through July 1999, 285 patients successfully underwent OPB using the Medtronic Octopus (Medtronic, Inc., Minneapolis, MN) stabilizer device. This group of patients included both first-time open heart surgeries and redo surgeries, and comprised 96% of all patients undergoing CABG. Thirteen patients did not tolerate the procedure and were placed on bypass, with good results. Patients were stratified according to the Parsonnet scoring system [Parsonnet 1989]. The expected 30-day mortality was 4.8%; the observed mortality was 2.8%. The unique characteristic of this study patient population is age. Sixteen percent were greater than age 80, with 38% being over the age of 75 years (see Figure 1, ●). Thirty-eight percent had an ejection fraction less than or equal to 50% (see Figure 2, ●). Eighty percent of the patients received three or more grafts. Other significant co-morbidities are listed in Table 1 (●).

TECHNIQUE

Surgical Procedures

The patient arrives in a warmed operating suite. Anesthesia is induced using narcotics and pancuronium. A pul-

monary artery catheter is used in all patients to monitor left-sided pressures as well as cardiac output. We are comfortable in the knowledge that the perfusionist is present in the suite to place the patient on CPB if necessary.

At the start of the incision, milrinone is used at a rate of 0.5 mcg/kg/min. We are looking for an increase in cardiac output of 25-50% and a reduction in pulmonary artery pressure of 20-30% to allow for cardiac manipulation. One of the main effects of milrinone is the reduction of end diastolic pressure and reduction of vascular resistance. Once the sternotomy is complete, the left internal mammary artery (LAD) is dissected free from the chest wall. Alternate conduits are harvested at the same time, and at the completion of the mammary dissection, a full dose of heparin is administered. Levophed (Norepinephrine) is also given at a rate of 1 mcg/min. at this time to counteract the vasodilation induced by milrinone, and to stabilize the intracellular Na-K ATPase pump.

The pericardium is opened and retracted anteriorly with sutures placed above the left phrenic nerve. A warm, moist lap pad is placed beneath the apex of the heart to displace it anteriorly and to the right for additional support. The Medtronic Octopus device is brought onto the field. The device has two asymmetrical arms lined with suction domes. The arms are malleable to allow the domes to conform to the topology of the heart. Suction is set at -400 mmHg to affix the target site. The left anterior descending artery is then stabilized. The vessel is unroofed in the mid-portion after stabilization and the epicardium is incised on either side of the artery. A bulldog clamp is placed across the artery and a 6-7 mm arteriotomy is made distal to the clamp. The mammary artery is sewn in place using 7.0 suture and the field is kept clear of blood with a misted blower. No shunts are used on the left-sided vessels of the heart.

The order of grafting of the vessels is as follows: The mammary to the left anterior descending, followed by the diagonal, ramus, marginal, circumflex, posterior left ventricular branch of the right coronary, posterior descending artery, and the proximal right. If the right coronary artery is grafted proximal to the crux of the heart, a shunt is used to perfuse the artery distally. This artery seems to be the only one requiring shunting because of heart block or other arrhythmias. The proximal anastomoses are completed under a partial occlusion clamp. All air is evacuated

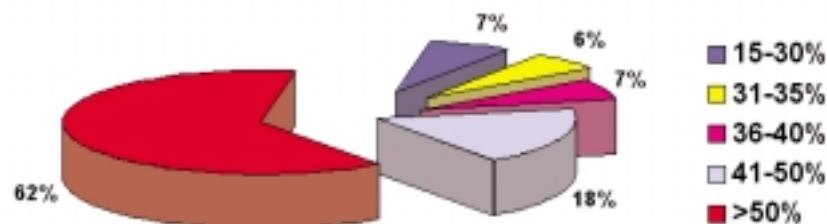


Figure 2. Ejection fraction breakdown, off-pump patients: 38% of patients had ejection fraction of 50% or less. Source: Cardiac Surgery Outcomes Data, July 1997–July 1999, Saddleback Memorial Medical Center, Laguna Hills, CA.

Table 1. Baseline Characteristics of Off-Pump Patients

n	285
Male/Female	74.0%/26.0%
Mean Age (y)	69.3 (± 10.2)
Median Age (y)	71.0 (± 10.2)
Parsonnet 96 Risk Stratification (%)	
Low	43.2%
Moderate	24.7%
High or Very High	32.1%
Number of Vessels (#)	Mean of 3.4 grafts per patient
1/2/3/4/5/6	2/17/36/37/7/1
Ejection Fraction (%)	56.6 % (± 14.4 %)
Risk Factors	
Preoperative Atrial Fibrillation	7.4%
Preoperative CVA	7.4%
Renal Failure	2.1%
Peripheral Vascular Disease	20.0%
Hypertension	65.0%
Diabetes	37.8%
Hypertriglyceridemia	27.6%

Source: Cardiac Surgery Outcomes Data, July 1997–July 1999, Saddleback Memorial Medical Center, Laguna Hills, CA.

from the aorta and grafts, then the clamp is released. Protamine is administered to reverse the heparin at the completion of the proximal anastomoses, and closure commences when hemostasis is satisfactory.

We have concluded that it is no longer necessary to clamp, observe, and reclamp the coronary artery to determine patient response to ischemia. The combination of drugs impacting the metabolic aspects of bypass surgery expedites the procedure by eliminating multiple steps. In OPB, one is not afforded the luxury of time during the distal anastomosis as with pump support. Eight minutes per graft is the crucial time limitation.

Metabolic Protocols

In order to optimize the patient metabolic profile, reduce oxidative damage, and improve cellular oxygen delivery, multiple pharmaceutical approaches are utilized. To minimize the development or advancement of nephropathy, patients are immediately given Allopurinol after heart catheterization. The combination of contrast dye and increased uric acid production is particularly damaging to the proximal tubules of the kidney [Objalo 1992]. It is clinically significant that none of our patients required hemodialysis postoperatively although 3.5% of the patient population had a creatinine greater than 2.0 preoperatively. The additional benefit of Allopurinol is that, like all the other metabolic interventions used, it acts as an antioxidant and free radical scavenger during times of ischemia [Simko 1996].

Insulin infusion begins the evening before surgery if the patient is an inpatient or two hours before if the patient is a morning admission. The infusion continues

through surgery and into the postoperative period to maintain blood glucose below 200 mg/dl. Levels and drips are checked every one to two hours as clinically appropriate. Twenty-four hours postoperatively, the insulin drip is changed to subcutaneous insulin delivery with target levels for fasting and pre-meal blood sugar greater than 70 and less than 110, and one-hour post-prandial blood sugar of less than 180.

The benefits of insulin infusion cannot be underestimated. Insulin stimulates the production of nitric oxide by the endothelium, by activating nitric oxide synthetase resulting in peripheral vasodilation [Baron 1996]. These patients, as a result of their insulin resistance, are limited in their ability to make and store glycogen in the liver and the skeletal muscle resulting in protein and fat breakdown products being used as a source of energy rather than glucose. Glucose uptake by tissue, stimulated by insulin infusion, is accompanied by increased oxygen uptake by cellular tissue. Under the conditions of operative stress, the conversion of glucose to pyruvate remains intact through the glycolytic pathway. However, the patient converts pyruvate to lactate in the absence of adequate insulin, which then produces a free hydrogen ion. This results in the development of metabolic acidosis, decreasing oxygen delivery to the tissue as well as adversely affecting cellular function. Insulin resistant patients produce adequate levels of methyl malonyl CoA in the liver. Therefore, these patients do not become ketotic, although they can become hyperosmolar. The maintenance of blood sugar below 200 mg/dl is essential for the proper function of the macrophage, which minimizes infection.

Patients with insulin resistance are more likely to have depleted magnesium stores, and the administration of large amounts of fluids can further cause depletion of this critical intracellular ion [Resnick 1990, 1992]. In order to correct magnesium delivery, magnesium sulfate (5 Gms) is administered intravenously preoperatively over three hours. The target level is at least 2 mEq./L. As a result of our work, we have discovered that 90% of the patients require the additional administration of five Gms magnesium postoperatively to ensure the target level of magnesium. Magnesium is involved in every aspect of production, utilization, and degradation of adenosine triphosphate (ATP) in the cell. Additionally, magnesium is involved in scar tissue formation and insulin sensitivity. Clearly, the less magnesium available, the less the energy production of the cell.

Additional benefits of magnesium therapy are as follows: Magnesium stimulates the endothelium to produce prostacyclin (a profound vasodilator) and is a co-factor in many enzymatic reactions. It helps stabilize the cell membrane during ischemia as well as the mitochondria and is essential for the function of the Na-K ATPase pump. Magnesium physiologically acts as a calcium channel blocker and therefore blocks neuromuscular transmission. Magnesium deficiency is known to be associated with an increase in arrhythmias, symptoms of cardiac insufficiency, and sudden death.

The use of milrinone and levophed in combination enhances cardiac output in off-pump CABG. The milrinone infusion is initiated at the time of the sternotomy incision at a rate of 0.5 mcg/kg/min. to increase the cardiac output by 25-50% over the baseline. Milrinone affects both systolic and diastolic functions of the heart [Benotti 1985]. Milrinone is approximately ten-fold more potent and has a shorter half-life than amrinone with less risk of thrombocytopenia.

These patients often present with poorly compliant ventricles resulting in reduced stroke volume at any given blood pressure. When the left ventricular compliance decreases, a small amount of volume may lead to a significant rise in the left ventricular pressures. Moreover, when manipulating the heart during off-pump CABG, the requisite distortions in the left ventricle may exacerbate these problems. Milrinone is a PDE-III inhibitor, which increases cyclic adenosine monophosphate (AMP) within the cell. The calcium flux is then increased within the cell, resulting in net inotropic action.

Sympathomimetic agents, such as levophed, stimulate alpha and beta receptors as well as increase nitric oxide production [Cohen 1997, Musters 1997]. Beta receptor stimulation increases intracellular cyclic AMP. The difference between PDE inhibitors and beta agonists is that the former do not involve a receptor but primarily work intracellularly.

PDE-III inhibitors suppress PDE-III enzymes in cardiac muscle, leading to an increase in cyclic AMP allowing more calcium to enter the myocardial cell via the voltage dependent calcium channel. This results in a large quantity of calcium being released from the sarcoplasmic reticulum, increasing contractility. Milrinone also increases cyclic AMP in vascular smooth muscle by preventing the breakdown of cyclic nucleotides, which then produces vasodilation. This is accomplished by the rapid uptake of calcium via the sarcoplasmic reticulum. The overall hemodynamic effects are striking. There is no increase in the heart rate, but there is a reduction in the end diastolic pressure. Contractility of the heart increases and systemic vascular resistance decreases. Since beta receptors are not involved in this process, patients who are hypertensive and prone to beta agonist fatigue are not affected. One of the most important effects of milrinone is its lusitropic action, which reduces diastolic wall tension and allows easier manipulation of the heart during CABG. In our experience, milrinone and levophed act in a complementary fashion by stimulating different receptors, thus facilitating off-pump CABG. The use of levophed counteracts the vasodilation effect of milrinone and also acts as an inotrope. Animal studies show that levophed acts as a chemical preconditioner reducing the effects of ischemia by 40%.

Postoperatively, the metabolic protocols are maintained for the next 24 hours. The inotropes are weaned dependent upon the cardiac index stabilizing above 2.1 L/min. Guidelines call for extubation attempts to begin within six hours of completion of surgery. Fifty-four percent of the patients are extubated within six hours.

Table 2. Baseline Characteristics of Off-Pump Patients

n	80
Male/Female	75%/25%
Mean Age (y)	75.9 (±8.05)
Median Age (y)	77 (±8.05)
Parsonnet Risk Stratification (%)	
Low	31%
Moderate	35%
High or Very High	34%
Number of Vessels (#)	Mean of 3.4 grafts per patient
1/2/3/4/5/6/8	1/1/32/48/12/5/1
Ejection Fraction (%)	54% (±14%)
Risk Factors	
Preoperative Atrial Fibrillation	14.1%
Preoperative CVA	10.0%
Renal Failure	2.5%
Peripheral Vascular Disease	26.2%
Hypertension	62.0%
Diabetes	25.0%
Hypertriglyceridemia	n/a

Source: Cardiac Surgery Outcomes Data, July 1997–July 1999, Saddleback Memorial Medical Center, Laguna Hills, CA.

RESULTS

Of the 298 off-pump revascularizations attempted, 285 were successfully completed. Six of the thirteen patients were redo operations, and the other seven did not tolerate the procedure in spite of the protocols. For these patients, we were unable to manipulate the heart and maintain cardiac output and blood pressure, and converted to on-pump with good results. Patients in cardiogenic shock were not attempted off-pump and are not included in this analysis or in the tables of comparison with on-pump patients.

Postoperative mortality was 2.8% as compared to an expected mortality of 4.8% in this high-risk group. Complications included one Q-wave myocardial infarction, and one perioperative CVA, an incidence of 0.3% for each event. Evaluation of the CVA event identified that the suspected origin of the embolism was a clot in the left ventricle. There was no incidence of renal failure requiring dialysis.

The rate of new onset atrial fibrillation was 24%. Of the 67 patients who experienced atrial fibrillation, three expired from a cerebral embolus related to their atrial fibrillation. As a result of this finding, atrial fibrillation is considered a lethal arrhythmia in the immediate postoperative period, and our group aggressively treats this as a risk for increased mortality. Treatment is aggressive and immediate. Diltiazem 0.25mg/kg over ten minutes is given and then 30mg PO. Pronestyl (15 mg/kg over 60 minutes) is administered followed by 2 mg/min. intravenously. If conversion does not occur, then discontinue cardioversion is used. The various protocols designed to treat this complication arose from the collaborative and individual efforts of participating cardiologists.

During preoperative evaluation, patients with ejection fractions of less than 35% have an intra-aortic pump insert-

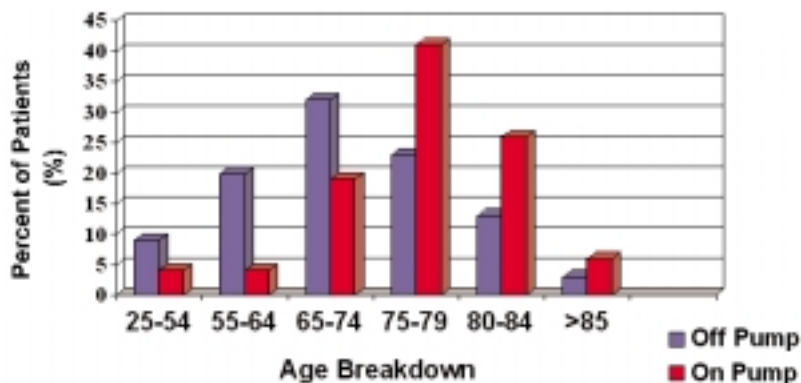


Figure 3. Off- and on-pump patients: Age distribution. Source: Cardiac Surgery Outcomes Data, July 1997–July 1999, Saddleback Memorial Medical Center, Laguna Hills, CA.

ed prior to surgery. During this series, one intraoperative balloon pump was required in a patient whose ejection fraction was 50% due to a severe protamine reaction. Two patients required reoperation for an incidence of 0.7% and four patients required catheter intervention for an incidence of 1.3%. The occluded grafts in those patients who were reoperated on were not a result of technical difficulties with the anastomoses, but rather the result of a hypercoagulable state after beating heart surgery.

There were a total of eight deaths in this group. Two patients expired due to a saddle embolus early in our series, prompting us to switch from half dose heparin to full dose. To date, we have not experienced another incident of saddle embolus. Two patients died as a result of sepsis, one 89-year-old male from necrotizing colitis, and a 77-year-old male with an ejection fraction of 15% as a result of pneumonia. Surprisingly, his cardiac function remained good. Three patients experienced sternal infection, a rate of 1%. All three patients had Gram negative organisms (two *Enterobacter* and one *E.coli.*), and two of these patients were insulin dependent diabetics.

We retrospectively evaluated the baseline characteristics of 80 on-pump patients from July 1996 to July 1999. The baseline characteristics of this group are listed in Table 2

(©). The mean age of the off-pump patient population was 69.3 years (38% greater than 75 years of age) compared to 75.9 years for the on-pump patients (see Figure 3, ©). The mean age of the off-pump group reflects the change in the marketplace, health insurance, and practice patterns of the cardiologists.

Overall cost differences were significant when comparing the on- and off-pump populations. The overall complications were reduced by 73% in the off-pump group. Average cost savings of blood product utilization were approximately \$418. Perfusion costs (equipment, medications, perfusion fee) were reduced between \$2,120 and \$2,400, and length of stay was reduced by 0.6 days (see Figures 4-7, ©). A decrease in stroke and renal failure resulted in additional savings not included in this study.

DISCUSSION

CPB stimulates multiple facets of the systemic inflammatory response and results in adverse outcomes [Park 1999]. Cytokines such as interleukin 1, 6, 8, and 10, tumor necrosis factor, complement, and leukocytes are all stimulated. A significant development during the last ten years is

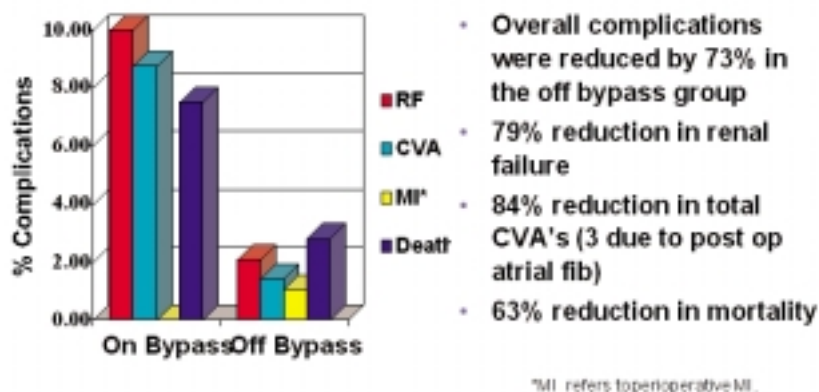


Figure 4. Off-Bypass Outcomes Study: Post-op complications and mortality. Source: Cardiac Surgery Outcomes Data, July 1996–July 1999, Saddleback Memorial Medical Center, Laguna Hills, CA.

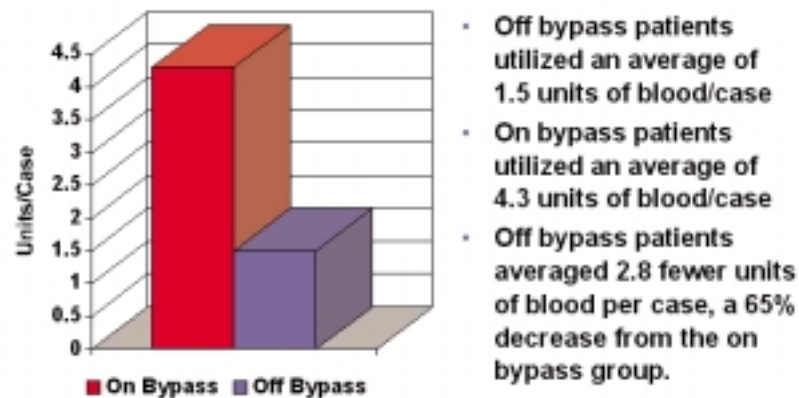


Figure 5. Off-Bypass Outcomes Study: Overall blood product utilization (average units per case). Source: 1996–1999 Cardiac Surgery Outcomes Data, Saddleback Memorial Medical Center, Laguna Hills, CA.

the recognition of the endothelium as an active participant with the above compounds. We only now understand the impact of these compounds on adverse outcomes postoperatively. Disruption of the endothelium affects changes in the basement membrane of the vessel wall, resulting in the proliferation of smooth muscle growth and fibroblasts. A review of patient characteristics prior to surgery showed diabetes to be a greater risk in developing coronary artery disease requiring surgical intervention than that of hypertension or hyperlipidemia. The administration of insulin to produce nitric oxide by the endothelium, and the production of prostacyclin by the administration of magnesium, helps maintain endothelial homeostasis. In fact, since all of our patients either presented with hypertension, hyperlipidemia, or diabetes, with the incidence increasing with age, our objective has been to address these issues under the acute phase of surgical stress. It has been our experience that metabolic protocols are extremely beneficial.

Use of CPB results in the production of potent vasoconstrictors, such as thromboxane and angiotension2, impacting the final patient outcome. The off-pump technique eliminates the widespread activation of the coagulation

cascade, including the consumption of clotting factors and degranulation of platelets. CPB results in the rapid rise of tissue plasminogen activator (TPA), which to our knowledge is not present in the off-pump technique. Conversely, the clotting mechanism in off-pump patients is not distorted and may result in early graft closure. These patients have shown an increase in procoagulant activity in the first 24 hours as reported by Mariani et al. [Mariani 1999]. We administer a full dose of heparin at the end of the dissection of the mammary artery and maintain an average clotting time (ACT) of greater than 350 seconds. (Our early graft closures, like theirs, were not on the basis of technical factors but rather due to clotting of the grafts.) Angiographic studies of our early patients with graft closures showed patent coronary arteries at the site of anastomoses, ruling out surgically inadequate anastomoses. Presumptively, these graft closures were due to clotting of the graft, hyperplasia, or associated disorders of smooth muscle in these high risk patients. Attempts to address this problem are currently under evaluation and study.

To prevent endothelial dysfunction, the use of Pravastatin (Pravachol) is beneficial. Pravastatin improves endo-

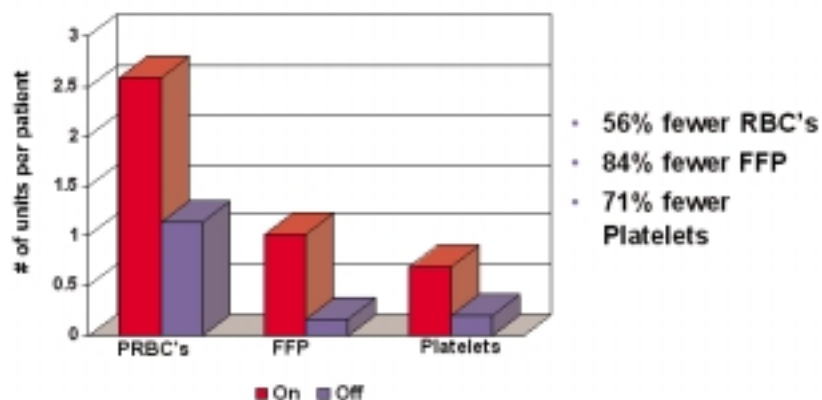


Figure 6. Off-Bypass Outcomes Study: Overall blood product utilization. Source: 1996–1999 Cardiac Surgery Outcomes Data, Saddleback Memorial Medical Center, Laguna Hills, CA.

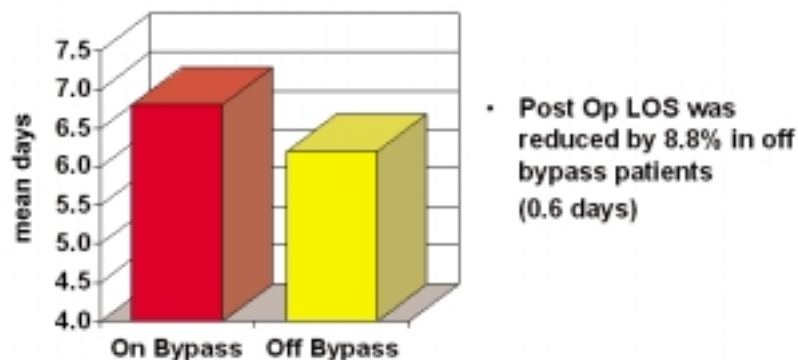


Figure 7. Off-Bypass Outcomes Study: Post-op length of stay. Source: 1996–1999 Cardiac Surgery Outcomes Data, Saddleback Memorial Medical Center, Laguna Hills, CA.

thelial function, stabilizes atherosclerotic plaques, and prevents the oxidation of very low-density lipoproteins and their migration into the basement membrane of the vascular wall [Shepherd 1995]. We believe that this may be useful in maintaining the long-term patency of grafts.

Neurocognitive complications associated with cardiopulmonary bypass can range from minor dysfunction to major disability. Generalized atherosclerosis in the elderly patient is a direct contributor to the microembolic phenomenon, and most likely originates in the great vessels or the aorta. Taylor et al. reported a series of patients who underwent CPB and noticed that all patients sustained microemboli [Taylor 1999]. This conclusion was obtained by diagnostic doppler sonography of the middle cerebral artery at all stages of the operative procedure. Of interest, they reported that the incidence of emboli was higher during the administration of drugs during the pump run, as opposed to the actual surgical manipulation. It is speculated that micro-air bubbles are not eliminated even with in-line arterial filters and may contribute to some of the neurologic sequelae. The advantages of off-pump bypass are the elimination of the aortic cannulation site and its removal, the cross-clamp and its removal, and elimination of CPB itself.

Our series of 285 patients indicates that the application of a partial occlusion clamp to the ascending aorta to perform the proximal anastomosis does not result in neurologic compromise. The one intraoperative stroke occurred in a patient with unstable angina who had sustained a myocardial infarction three weeks prior to surgery with a known clot in the left ventricle. This patient had no residual symptoms postoperatively. One possible explanation for the occurrence of stroke with the use of cardiopulmonary bypass in patients with cerebrovascular disease may be the reduced blood flow to the brain resulting from generalized inadequate blood flow or lowered mean arterial blood pressure. Maintaining pulsatile blood flow in the off-pump procedure supports normal homeostatic vascular function. Therefore, we conclude that the off-pump procedure is a distinct advantage to the neurological well-being of the patient. This is manifested in the appearance and alertness of the patient in the immediate postoperative period.

The long-term follow-up is being done by our team of cardiologists, who have played an active role in assessing the pros and cons of off-pump bypass. At present they are recommending that all patients who are able to tolerate the procedure be done off-pump.

SUMMARY

The approach to the patients in this series has been an evolving process during the last 10 years. We began by developing an understanding of the deranged physiology of these patients and developing therapeutic interventions aimed at correcting these abnormalities. We progressed to using continuous tepid retrograde cardioplegia for all of our patients undergoing CABG on pump. The next natural progression was off-pump CABG. This series is unique because all patients during the last two and one-half years were attempted off pump unless they arrived from the catheterization suite in cardiogenic shock. The success rate was 96%. Additionally, the demographics demonstrate an elderly population having a mean age of 69.5 years. The reduction of equipment has led to substantial cost savings and may in fact be less expensive than multi-vessel stent placement. The short-term results show that off-pump bypass is durable and more complete than multi-vessel stent placement and results in fewer subsequent interventions. Off-pump bypass is technically demanding of the surgeon, but as more groups master the procedure, new and better ways will evolve to make it less stressful.

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