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Heparin Dose, Transfusion Rates, and Intraoperative Graft Patency in Minimally Invasive Direct Coronary Artery Bypass

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ABSTRACT

Background: Many investigators have demonstrated the short-term and midterm efficacy of minimally invasive direct coronary artery bypass (MIDCAB). However, the influence of heparin dosing during MIDCAB on postoperative and immediate graft patency is less well defined. This report outlines our experience with MIDCAB employing a variety of heparinization protocols.

Methods: The traditional MIDCAB approach was used in 152 patients who underwent single-vessel off-pump coronary artery bypass. Before the left internal mammary artery was divided, a 150-U/kg bolus of heparin sodium was given to 76 patients (group 1), and 300 U/kg was given to another 76 patients (group 2). Additional heparin was given during the procedures to maintain an activated clotting times of greater than 300 seconds for group 1 and greater than 400 seconds for group 2.

Results: On average, patients in group 1 required more boluses of heparin during treatment than patients in group 2. A larger standard deviation from the mean was observed for the activated clotting time in group 1 at any time during treatment than for patients in group 2. The number of revised grafts was smaller in group 2 (1/76, 1.3%) than in group 1 (4/76, 5.2%). All of these revisions revealed thrombus at the site of anastomosis. In addition, noncoronary thrombotic complications were seen in 5 patients in group 1, and none were seen in group 2.

Conclusion: Coronary artery surgery without cardiopulmonary bypass does not trigger the systemic inflammatory response, but surgical tissue trauma remains a constant. The preserved hemostasis theoretically may lead to a procoagulant state. This study demonstrates that insufficient anticoagulation therapy can lead to intracoronary thrombosis following MIDCAB as well as increased noncoronary thrombotic complications.

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INTRODUCTION

Coronary artery bypass grafting (CABG) without cardiopulmonary bypass (CPB) has been popularized as an alternative to conventional myocardial revascularization in the treatment of coronary artery disease [Mack 2001]. Long-term studies of off-pump CABG (OPCAB) are pending; short-term and midterm efficacy of both minimally invasive direct coronary artery bypass (MIDCAB) and OPCAB have been demonstrated by many investigators [Calafiore 2001, Mack 1999, Karamanoukian 2001, Stamou 2001]. Technical refinements have improved hemodynamics, target vessel exposure, and mechanical epicardial stabilization, enabling both MIDCAB and OPCAB to be performed by the vast majority of cardiac surgeons. Despite these enabling technologies, hemorrhagic complications and the need for allogeneic transfusions are still major problems after MIDCAB and OPCAB [Bergsland 1999, Bergsland 2000]. Investigators have demonstrated not only reduced bleeding following MIDCAB and OPCAB but also reduced requirements in the postoperative period for transfusions of packed red blood cells, fresh frozen plasma, and platelet-rich plasma [Nader 1999, Lancey 2000, Puskas 1999]. However, the influence of heparin dosing during MIDCAB and OPCAB on postoperative bleeding and immediate graft patency is less well defined [D'Ancona 2001a]. The present report outlines our experience with MIDCAB employing two different anticoagulation regimes.

MATERIALS AND METHODS

From May 1999 to July 2001, 152 patients underwent single-vessel OPCAB using the traditional MIDCAB approach as described by Calafiore and colleagues. All patients requiring MIDCAB during this period were included in this series except patients who underwent a redo procedure and patients who were taking platelet glycoprotein IIb/IIIa inhibitors or clopidogrel at the time of the operation. This series also excluded 53 patients who underwent single-vessel OPCAB via the endoscopic atraumatic coronary artery bypass procedure, which used the AESOP robotic system (Computer Motion, Goleta, CA, USA) to harvest the left internal mammary artery (LIMA) via minimal access techniques [Vassiliades 2000]. The clinical characteristics of the MIDCAB

Table 1. Patient Demographics

	Group 1 (n = 76)	Group 2 (n = 76)
Age, y	64 ± 10	68 ± 10
Urgent	44%	48%
Left ventricular ejection fraction	51% ± 6%	48% ± 5%
Risk factors, n*	30 (40%)	34 (45%)

*Risk factors assessed include previous stroke, hypertension, previous myocardial infarction, and congestive heart failure.

patients are summarized in Table 1. A standard MIDCAB incision (8 cm) was used in these 152 patients. Three patients (3/152, 2%) required rib resection to enable complete harvesting of the LIMA. Before the left internal mammary artery was divided, a 150-U/kg bolus of heparin sodium was given to 76 patients (group 1), and 300 U/kg was given to another 76 patients (group 2), with the patients assigned at random to groups by medical record number. Additional heparin was given during the procedure to maintain an activated clotting time (ACT) greater than 300 seconds for group 1 or greater than 400 seconds for group 2. A mechanical stabilizer (CardioThoracic Systems, Cupertino, CA, USA) was used for stabilization of the left anterior descending coronary artery target. A humidified, sterile, carbon dioxide blower was used to clear the surgical field of blood from the arteriotomy (Medtronic DLP, Grand Rapids, MI, USA). The coronary target was occluded proximally with a pledgetted 4-0 polypropylene (Prolene) snare in all cases unless the native left anterior descending coronary was occluded proximally. All targets were shunted locally via intracoronary shunts (CardioThoracic Systems) during creation of the anastomosis. Intraoperative graft patency was verified in all cases with the transit time flow measurement technique and the Medi-Stim Butterfly Flowmeter (Model BF2004; Medi-Stim AS, Oslo, Norway), as described by D'Ancona and colleagues [D'Ancona 2001b]. All shed blood was recycled with a Cell Saver (Continuous AutoTransfusion System; Fresenius, Schweinfurt, Germany). Systemic heparinization was reversed completely with protamine in all patients. All patients were administered aspirin before surgery and in the intensive care unit the day following surgery.

RESULTS

There was no operative or 30-day mortality in this series of MIDCAB patients. Postoperative myocardial infarctions as assessed by cardiac enzyme levels (creatine phosphokinase and troponin) or electrocardiogram occurred in 2 patients, and none were transmural. One myocardial infarction occurred in group 1, and another occurred in group 2. Overall, there were no neurologic complications in these patients. The average length of stay in the intensive care unit was 24 hours for group 1 and 26 hours for group 2, and the total postoperative length of stay was 3.8 days for group 1 and 4.3 days for group 2 (Table 2). There were no differences in age, sex, or elective/urgent status between the groups. Preoperative risk factors (stroke, hypertension, previous myocardial infarction, diabetes, and congestive heart failure) were identical in the two groups (Table 1).

Following harvest of the LIMA, group 1 patients received 150 U/kg of heparin as a bolus, and group 2 patients received 300 U/kg of heparin as a bolus. Group 1 patients received both a smaller bolus of heparin and a smaller total heparin dose (28,000 U) to maintain ACT levels above 300 seconds during the procedure. This value is lower than the total heparin dose (32,000 U, bolus and maintenance) required to maintain the ACT above 400 seconds for group 2 patients during the MIDCAB procedure. On average, patients in group 1 required more boluses of heparin (5000 units) during the procedure than patients in group 2 (2.8 versus 1.5; $P < .05$).

A larger standard deviation from the mean value for ACT was observed for patients in group 1 at any time during the procedure than for patients in group 2 (95 seconds versus 55 seconds). Thus, the ACT was more variable in group 1 than in group 2 at any time during the MIDCAB procedure. This observation remained true at the end of the procedure before reversal with protamine, and therefore the mean dose of protamine required to reverse the heparin therapy and to obtain the baseline values of ACT at the end of grafting was slightly higher (1.3 times) for patients in group 1 than for patients in group 2.

The number of revised grafts was smaller in group 2 (1/76, 1.3%) than in group 1 (4/76, 5.2%; $P < .05$). All of these revisions revealed thrombus at the site of anastomosis without any other technical problems (eg, dissection, "back-walling," conduit failure, and so on).

The mean volume of shed blood harvested by the Cell Saver was 800 mL for group 1 and 650 mL for group 2. Blood transfusion was required for 34% of the patients in group 1 and 28% of the patients in group 2. On average, patients in group 1 who required transfusion received 1.4 units of packed red blood cells (range, 1-3 units), and patients in group 2 who required transfusion received 1.2 units of packed red blood cells (range, 1-2 units) (Table 2). There were no differences in the frequencies of transfusions of fresh frozen plasma or platelets between the groups, because the frequencies of transfusions for these products were very small (less than 5%).

Nine patients (6%) developed postoperative complications (Table 3) within the first 30 days of surgery. These complications included respiratory insufficiency (5 patients), renal insufficiency (1 patient), superficial wound infection (2 patients),

Table 2. Postoperative Data

	Group 1 (n = 76)	Group 2 (n = 76)
Extubation (<4 h)	68%	64%
Intensive care unit stay, h	24	26
Transfusion, n	26 (34%)	21 (28%)
Packed red blood cells, units	1.4	1.2
Hospitalization, d	3.8 ± 1	4.3 ± 1
Observed mortality	0%	0%
Expected mortality	2.4%	2.8%

Table 3. Postoperative Complications

	Group 1 (n = 76), n	Group 2 (n = 76), n
Mortality	0 (0%)	0 (0%)
Respiratory insufficiency	3 (3.9%)	2 (1.6%)
Renal insufficiency	1 (1.3%)	0 (0%)
Wound infection	1 (1.3%)	1 (1.3%)
Bleeding with reexploration	1 (1.3%)	0 (0%)
Myocardial infarction	1 (1.3%)	1 (1.3%)
Neurologic complications	0 (0%)	0 (1.3%)
Noncoronary thrombosis	5 (6.6%)	0 (0%)

bleeding requiring reexploration (1 patient), nontransmural myocardial infarction (2 patients), and noncoronary thrombotic complications (5 patients). Table 4 shows that respiratory insufficiency was due to atelectasis (3 patients), pulmonary embolism (1 patient), and pneumonia (1 patient). Of the entire study group, 3 patients (3/152, 2%) were readmitted during the first 30 days after discharge. Two patients (group 1) had deep vein thrombosis requiring anticoagulation therapy, and 1 patient experienced a pulmonary embolism. Noncoronary thrombotic complications were seen in 5 patients in group 1, and none were seen in group 2 (Table 5). Postoperative atrial fibrillation rates were nearly identical in the two groups (15% for group 1 and 18% for group 2).

COMMENT

Surgical coronary revascularization using CPB remains an important determinant of morbidity, which includes bleeding, thromboembolism, and temporary or permanent organ dysfunction [Butler 1993, Edmunds 1998, Ohata 1997]. Avoidance of CPB has recently emerged as an effective strategy to further reduce the complications encountered during single-vessel CABG, especially in patients with major preoperative risk factors who may benefit to a greater extent [Contini 2001]. Significant improvements in technology and technique have rendered it possible to perform MIDCAB in a large proportion of the patients with single-vessel disease requiring surgical revascularization and have resulted in excellent angiographic patency rates [Puskas 1999]. Although postoperative bleeding following OPCAB and MIDCAB is reduced compared with CABG using CPB, questions and concerns have arisen about the need, type, and amount of antiplatelet therapy before and after OPCAB and about the amount of heparinization required to perform these procedures safely [D'Ancona 2001a]. A recent study performed by our group has shown that the practice pattern of cardiac surgeons with regard to the use of both antiplatelet therapy and heparinization for MIDCAB and OPCAB is highly variable [D'Ancona 2001a]. Unlike conventional surgery on CPB, OPCAB surgery does not trigger the systemic inflammatory response; however, surgical tissue trauma remains a constant between the two techniques. The preserved hemostasis theoretically achieved by using the MIDCAB or OPCAB technique may lead to a procoagulant state, as has been reported

Table 4. Respiratory Insufficiency

	Group 1, n	Group 2, n
Total	3	2
Atelectasis	2	1
Pulmonary embolism	1	0
Pneumonia	0	1

for major general surgery. On the contrary, whenever hemostasis is impaired, as occurs during CABG with CPB, the chances of microvascular thrombosis are reduced. As a consequence, it is reasonable to conclude that the risk of anastomotic thrombosis unrelated to technical mistakes should be greater in MIDCAB and OPCAB patients. In our experience, anastomotic thrombosis has been diagnosed more frequently during MIDCAB/OPCAB than during CABG using CPB [D'Ancona 2001b]. The current study demonstrates this fact and provides further support for the practice of maintaining high ACT levels (exceeding 400 seconds) during MIDCAB. Higher ACT levels were achieved in group 2 patients, and the number of revised grafts was smaller (1/76, 1.3%) than in group 1 (4/76, 5.2%). All of these revisions revealed thrombus at the site of anastomosis without other technical problems (eg, dissection, back-walling, conduit failure, and so forth). The higher dose of protamine required to reverse the heparin effect in group 1 cannot alone account for the 4-fold increase in graft thrombus formation compared with patients in group 2.

Intraoperative graft flow measurements are very useful in diagnosing anastomotic thrombosis following CABG. Surgeons who do not use any method of graft patency verification may not be aware of the actual graft patency rates at the end of the MIDCAB procedure [D'Ancona 2000]. The current study demonstrates that insufficient anticoagulation therapy can lead to increased intracoronary thrombosis following MIDCAB. Mariani and colleagues [Mariani 1999] have reported intracoronary thrombosis and pulmonary embolism in OPCAB. They tested the procoagulant activity in a series of patients undergoing OPCAB. Prothrombin F1+2, factor VII, and fibrinolysis degradation products were sampled to test inherent coagulation activity. Procoagulant activity as represented by prothrombin F1+2 levels increased significantly 24 hours after surgery. A depletion of the coagulation factors in the extrinsic pathway was indicated by a significant decrease in factor VII levels 24 hours after surgery. Fibrinolysis was also activated, as indicated by an increase in

Table 5. Noncoronary Thrombotic Complications*

	Group 1, n	Group 2, n
Iliofemoral DVT	2 (2.6%)	0 (0%)
Pulmonary embolism	1 (1.3%)	0 (0%)
Upper extremity DVT	2 (2.6%)	0 (0%)

*DVT indicates deep vein thrombosis.

the level of degradation products at postoperative day 1. Our current study leads one to believe that a procoagulant effect in MIDCAB can be reduced intraoperatively by maintaining higher ACT levels. It is surmised that the further procoagulant activity of MIDCAB and OPCAB at 24 hours following surgery, as described by Mariani and colleagues, may be attenuated by an aggressive anticoagulation protocol during surgical coronary revascularization without CPB.

Pulmonary embolism may have been underdiagnosed in our patients, and we were able to confirm pulmonary embolism for only 1 patient in this series of 152 patients who underwent MIDCAB. This embolism occurred in a female patient with a previous history of deep vein thrombosis who was given a bolus with full-dose heparin (group 2). Two patients in group 1 had femoral deep vein thrombosis and were readmitted within 30 days of discharge, and 2 other patients in group 1 had upper extremity deep vein thrombosis that was treated with outpatient anticoagulation therapy. These observations are further corroborative evidence to suggest that proper anticoagulation therapy may be beneficial in attenuating the procoagulant state associated with coronary revascularization without CPB. This study supports the basic science work presented by Mariani and colleagues [Mariani 1999].

Despite the smaller dose in the heparin bolus and the smaller total heparin dose used during MIDCAB in group 1, patients in this group shed more blood than the patients in group 2 whose anticoagulation therapy consisted of a full heparin dose (800 mL versus 650 mL). The higher rate of bleeding resulted in a higher frequency of transfusions in group 1 patients. As this study has demonstrated, a larger bolus of heparin during the harvesting of the LIMA conduit enables a higher baseline ACT (exceeding 400 seconds) and reduces the need for excessive bolus administrations of heparin. Also, this practice avoids a larger standard deviation from a mean value for a therapeutic ACT. Such swings in ACT values may create a prothrombotic state and may explain in part the increased frequency of graft thrombosis following MIDCAB and the larger amounts of blood shed despite a smaller total dose of heparin for a given MIDCAB procedure. ACT levels were more variable in group 1 than in group 2 at any time during the MIDCAB procedure. This observation remained true at the end of the procedure, ie, before reversal with protamine. Thus, the mean dose of protamine required to reverse heparin therapy and to obtain baseline values of ACT at the end of grafting was slightly higher in group 1 patients than in the patients of group 2. Protamine dosing at the termination of the MIDCAB procedure may also be another important factor in the rates of graft thrombosis and transfusion needs following MIDCAB. A larger study investigating this variable in beating heart coronary artery surgery is in progress.

The improved intraoperative patency rates documented by transit time flow measurements and reduced transfusion rates in MIDCAB cases treated with the full heparinization protocols presented here are encouraging. These data are clear evidence that careful surgical technique, enabling stabilization technologies, and meticulous blood recovery techniques using Cell Saver permit reproducible and precise construction of coronary bypass anastomoses on the beating heart. However, only a large, prospective, randomized longitudinal comparison of graft patency using angiographic techniques after MIDCAB and OPCAB procedures can validate the safety, efficacy, and superiority of full-dose heparinization during beating heart coronary artery bypass surgery.

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REVIEW AND COMMENTARY

1. Editorial Board Member SO155 writes:

It is not clear why nonthrombotic complications are greater in group 1. Does this explain the other complications? Are they related?

Authors' Response by Harry W. Donias, MD:

Given the paucity of scientific data regarding the prothrombotic state in OPCAB, we attribute the noncoronary thrombotic complications to be further corroborative evidence to suggest that proper anticoagulation may attenuate the procoagulant state that may be seen in coronary revascularization without cardiopulmonary bypass.

2. Editorial Board Member SG14 writes:

In the "Comment" section, the authors claim that a higher transfusion rate occurred in group 1 patients without any indication of P value in Table 2. Was there a statistical significance? Also in the "Comment" section, the authors realize that "swings" in ACT values occur more often in group 1, where the problem also should be expected. I would change the argument from the point of view that less heparin leads to bypass occlusion to the point that if swings on ACT values occur, more graft occlusions occur.

Authors' Response by Harry W. Donias, MD:

After reviewing the editorial analysis, we agreed that the current study lacked sufficient power to achieve statistical significance, however it did seem that a higher rate of transfusions occurred in group 1 patients receiving 150 U/kg of heparin. We agree that the swings in ACT is the most plausible explanation for the greater number of graft occlusions seen in group 1; however, we did not want to speculate that this is the only reason for the increased graft occlusion, given the small number of subjects.

As we mentioned in the "Comment" section, we are currently conducting a larger study to investigate the effect of protamine reversal and ACT swings on graft patency in beating heart coronary surgery. We hope that this study will add more power to our results.