

Acute coronary syndromes without persistent st-segment elevation: advances in surgical revascularization

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Abstract. Coronary artery bypass grafting (CABG) still plays a fundamental role in the management of acute coronary syndromes. The aim of this study is to report the experience of our center in the treatment of patients with acute coronary syndromes without persistent ST elevation urgently operated on with CABG, and to discuss surgical problems related. Two-hundred and six patients were urgently operated on for CABG for acute coronary syndromes without persistent ST-segment elevation from January 2001 to February 2003. The majority of them had three vessel coronary disease (72%) and left main stem disease occurred in 20% of the patients. Mean LVEF (left ventricular ejection fraction) was $54\pm 12\%$ whereas 9% of the patients had a $LVEF < 40\%$. Twenty-one patients (10%) received glycoprotein IIb/IIIa receptor inhibitors and 35 (17%) received intravenous heparin therapy before surgery. Mean interval time between the onset of symptoms and surgery was 16 ± 10 days (range 4-50). In-hospital mortality was 2% (4 patients). Perioperative AMI (acute myocardial infarction) occurred in 4% (8 patients) and a transient low cardiac output syndrome in 27 patients (13%). Bleeding requiring surgery occurred in 1% of the patients. Transient respiratory insufficiency was present in 12 patients (6%) and acute renal failure in 8 patients (4%). Mean I.C.U. time was 2.4 days (1-17). Urgent CABG for acute coronary syndromes shows a low risk for in-hospital mortality and morbidity. In acute patients arterial grafts are not detrimental for the outcome, but are recommended in the absence of contraindications to improve long-term results. In spite of recent developments in cardioplegic cardiac arrest, optimal myocardial protection against perioperative myocardial infarction still remains a challenge.

Key words: coronary disease, bypass, surgery.

Introduction

The syndrome of unstable angina and myocardial infarction without ST-segment elevation accounts for approximately 1.4 million annual hospital admissions in the USA and for 2.5 million worldwide (1).

The initial treatment is traditionally based on medical stabilization through the use of antianginal and antithrombotic drugs, such as aspirin or unfractionated or low-molecular-weight heparin. Nevertheless, the optimal strategy for the treatment of these patients is

still a matter of debate, in part because the pathophysiology of acute coronary syndromes has been clarified only in recent years (2) and in part because major advances have occurred in this field. Respectively, inhibitors of platelet glycoprotein IIb/IIIa were found to reduce the risk of death, myocardial infarction and recurrence of angina in this setting, especially when PTCA (percutaneous transluminal coronary angioplasty) was performed (3, 4), and intracoronary stents were found to improve angiographic and clinical results reducing the rate of restenosis (5, 6).

Some clinicians favour a more conservative strategy, with initial medical stabilization followed by cardiac catheterization only if the patient shows high-risk features (recurrent myocardial ischemia or congestive heart failure) or severe myocardial ischemia during noninvasive testing.

CABG still plays a fundamental role in the management of acute coronary syndromes, depending on the extent and on angiographic characteristics of the lesions identified by coronary angiography even if it is still now burdened with mortality and morbidity. In fact it is known that mortality rates, reported from the literature, range from 2 to 31.7% in urgency/emergency CABG (7-10) and that preoperative depressed ejection fraction, cardiogenic shock, prolonged aortic cross clamp time and nonuse of blood cardioplegia have been identified as risk factors for hospital mortality (7).

The aim of this paper is to examine perioperative mortality and morbidity in the treatment of our groups of patients urgently operated on with CABG, to review the actual indications for surgery in this setting of unstable angina and myocardial infarction without ST-segment elevation, and to discuss the recent improvements in the operative management of this kind of patients.

Materials and methods

Two-hundred and six patients were urgently operated on with CABG for acute coronary syndromes without persistent ST-segment elevation from January 2001 to February 2003. Mean age was 68±8 years. Patients with stable angina were excluded from the study. The majority were males (76%). Preoperative risk factors were: diabetes in 33 patients (18%), hypertension in 115 patients (56%), COPD (chronic obstructive pulmonary disease) in 43 (21%), chronic renal failure in 4 (2%) (Table 1).

The cardiovascular preoperative data are listed as follows. Forty-three patients (21%) experienced a previous transmural myocardial infarction. Eighteen patients (9%) were in NYHA functional class IV. Hemodynamically significant functional ischemic mitral regurgitation was present in 12 patients (6%). Only 2 patients had RE-DO (1%). EUROScore resulted >6 in 72 patients (36%). The majority (148 patients) had three-

Table 1. Preoperative data

Variable	N°	%
Patients number	206	
Mean age	68±8	
Males	156	76
Diabetes	33	18
Hypertension	115	56
COPD	43	21
Chronic renal failure	4	2

COPD: chronic obstructive pulmonary disease

Table 2. Preoperative cardiovascular characteristics

Variable	N°	%
Transmural AMI	43	21
NYHA 4	18	9
MI 3+/4+	12	6
EUROScore > 6	72	36
Three vessels disease	148	72
Left Main disease	41	20
Mean LVEF		54±12
LVEF <40%	18	9
Glycoprotein IIb-IIIa inhibitors therapy	21	10
Mean Time symptoms-surgery	16±10 days (4-50)	

AMI: acute myocardial infarction

MI: mitral insufficiency

LVEF: left ventricular ejection fraction

vessel coronary disease (72%) and left main stem disease occurred in 20% of the patients. Mean LVEF was 54±12% whereas 9% of the patients had a LVEF<40%. Twenty-one patients (10%) received glycoprotein IIb/IIIa receptor inhibitors and 35 (17%) received intravenous heparin therapy before surgery. Mean interval time between the onset of symptoms and surgery was 16±10 days (range 4-50) (Table 2).

Results

LIMA (left internal mammary artery) was used in 194 patients (94%) and radial artery in 31 patients (15%). Total arterial myocardial revascularization was performed in 25 patients (12%). Mean number of anastomoses was 2,6 (range 1-4). Four patients required concomitant mitral valve annuloplasty for severe valve regurgitation. Mean cardiopulmonary bypass time was 114 ± 32 min and mean aortic cross-clamping time was 53 ± 20 min. Antegrade warm blood intermittent cardioplegia was delivered in all patients undergoing on-pump surgery, whereas off-pump CABG was performed in 7% of the patients.

In-hospital mortality was 2% (4 patients), due to MOF (multi organ failure) in 2 patients, severe perioperative AMI in 1 patient and ventricular fibrillation in 1 patient. Perioperative AMI occurred in 4% (8 patients) and a transient low cardiac output syndrome occurred in 27 patients (13%). IABP (intra aortic balloon pump) was necessary in 6 patients (3%) and LVAD (left ventricular assist device) in 1 patient because of difficult weaning from extracorporeal circulation. Bleeding requiring surgery occurred in 1% of the patients. Prolonged mechanical ventilatory support due to transient respiratory insufficiency was necessary in 12 patients (6%) and acute renal failure occurred in 8 patients (4%). Mean I.C.U. time was 2.4 days (1-17) (Table 3).

All the survivors were discharged without symptoms after a mean time of 5,9 days (range 3-17 days).

Discussion

Early invasive strategy, with cardiac catheterization during the first 24 to 48 hours from the onset of symptoms allows identification of patients with high-risk coronary anatomy such as those who experienced unstable angina and myocardial infarction without ST-segment elevation, as in the series of patients we analysed. Recently, two large-scale randomized clinical trials (the Fragmin and Fast Revascularization during Instability in Coronary Artery Disease (FRISC) II (11) and the Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy (TACTICS) (12), have demonstrated

that advances in percutaneous coronary intervention and combined medical therapy have tipped the balance in favour of an early invasive strategy.

From these data it appears that a modern invasive strategy, preceded by antischemic and antithrombotic therapy in this setting of high-risk patients reduces death, myocardial infarction, symptoms and readmissions as compared with a conservative strategy, mainly in the setting of unstable angina and myocardial infarction without ST-segment elevation

CABG still plays a fundamental role in invasive myocardial revascularization for acute coronary syndromes depending on the extent and on angiographic characteristics of the lesions identified by coronary angiography. In contrast with the EuroHeart Survey that showed a very low current rate of CABG, accounting for 5.4% of the patients suffering from acute coronary syndromes (13), in the FRISC II (11) and TACTICS (12) trials, 35.2% and 20% of

Table 3. Operative data and results

Variable	N°	%
LIMA graft	194	94
Radial Artery Graft	31	15
RIMA	20	10
Total Arterial Revascularization	25	12
Mitral Valve Annuloplasty	4	2
Mean ECC time	114±32	
Mean Aortic cross clamping time	53±20	
Off Pump CABG	14	7
In hospital mortality	4	2
Preoperative AMI	8	4
Low cardiac output syndrome	27	13
Bleeding requiring surgery	2	1
Mean ICU time	2.4 days (1-17)	

LIMA: left internal mammary artery

RIMA: right internal mammary artery

ECC: extra corporeal circulation

CABG: coronary artery bypass grafting

AMI: acute myocardial infarction

ICU: intensive care unit

the patients enrolled in the invasive arm, respectively, had CABG. In FRISC II, the postoperative 30-days mortality rate of the surgically treated patients was 2% and 3.6% in TACTICS, although the majority of these surgical procedures were performed in patients with left main or multivessel disease and early infarction (<7 days). Similar anatomic data from TIMI IIIB (14) and FRISC II (11) trials show that from 30 to 38% of the patients with unstable coronary syndromes have single-vessel disease and from 44 to 59% have multivessel disease. The incidence of left main narrowing varies from 4 to 8%.

The American College of Cardiology-American Heart Association Practice Guidelines for unstable angina and non-ST segment elevation myocardial infarction (like all the patients we included in the study) (NSTEMI) management now recommend that patients with acute coronary syndromes be managed with an early invasive strategy in the presence of high-risk features (elevated cardiac troponin, new ST-segment depression, decreased left ventricular function and prior coronary artery bypass grafting) (1). The Task Force on the Management of Acute Coronary Syndromes of the European Society of Cardiology has recently summarized respective indications for percutaneous coronary intervention or surgery (15). Based on these indications, patients with single vessel disease should be treated with percutaneous coronary intervention with stent implantation and combined treatment with GIIb/IIIa inhibitors. In these patients CABG should only be considered in case of unsuitable anatomy (extreme tortuosity of the vessel, angulation) precluding safe percutaneous intervention. On the other hand, patients with left main or three-vessel disease, eventually associated with left ventricular dysfunction, are usually managed with CABG. In these specific clinical settings, the surgical procedure shows a prolonged survival, an improvement in the quality of life and a reduction in hospital readmission due to a decreased need for a new intervention if compared to PTCA (16-18). In patients with two-vessel disease (or three vessel disease with lesions suitable for PTCA and stenting) the indications for CABG or PTCA have to be evaluated on an individual patient basis. In many patients with multivessel disease, some of the lesions cannot be appropriately managed with a percu-

taneous intervention, and therefore surgery will obviously be the best choice (16-19). In other patients with multivessel disease who present anatomic and clinical high-risk factors for traditional surgery and in which a total revascularization is not achievable by PTCA, a combined approach based on off-pump coronary surgery completed by PTCA on the vessels of the posterior left ventricular wall has to be considered.

There is uncertainty regarding the appropriate intervention (CABG or PTCA) required for unstable angina treatment since interventional cardiology is a continuously and rapidly evolving field as surgical techniques also continue to improve. The current state of current practice has been presented in the Arterial Revascularization Therapies Study (ARTS) trial, in which the clinical outcomes, costs, and cost-effectiveness of treatment of patients with multivessel disease and unstable angina were compared with those of patients with stable angina (20). Both groups of patients were randomized to either PTCA with stent implantation or CABG using arterial grafts. The percentage of unstable patients was around 36% in each group: the treatment was successful in 97% in the stent group and 96% in the surgical one. The composite adverse event rate (death, MI, stroke, and need for revascularization) at 30 days was 8.7% in the stent group and 6.8% in the surgical group ($P=ns$). Even if at 1 year follow-up there was no difference in the rates of death, myocardial infarction and cerebrovascular events, at 2-year follow-up there was a difference (20.5% vs 15.2%) due to the need of subsequent revascularization in the stented group. Further randomized trials comparing the outcome of new generation stents implantation versus CABG in the management of patients with multivessel coronary disease need to be addressed.

Perioperative bleeding

It is important to consider the risk of bleeding complications in patients who underwent surgery and who were initially treated with aggressive antiplatelet treatment. The Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrelin Therapy (PURSUIT) trial (28) was a large, randomized, double blinded, placebo-controlled trial with eptifibatid in patients suffering from acute coronary

syndromes. In this study a total of 78 patients underwent immediate CABG within 2 hours after drug (or placebo) interruption: major bleeding was not different between the groups, occurring in 64% of the patients receiving the placebo and 63% of the patients receiving eptifibatide. The rate of blood transfusion was similar in both groups (57% vs 59%). In the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial (29), 1822 out of the 6259 patients of the clopidogrel group underwent CABG. Overall, there was no significant excess of major bleeding episodes after CABG (1.3% vs 1.1%) but in the 912 patients who stopped clopidogrel within 5 days before surgery, the rate of major bleeding was higher than in the clopidogrel group (9.6% vs 6.3%, $P=0.06$). These data show that pre-treatment with aggressive anti-platelet drugs should only be considered as a relative contraindication to surgery in the management of acute coronary syndromes. In fact bleeding requiring surgery occurred in 1% of the patients in our groups. Specific surgical measures to minimize bleeding include platelet transfusion (frequently large amounts), reduction of heparin dosing, delay of operative intervention (when appropriate) and the use of a hemoconcentrator during cardiopulmonary bypass.

Arterial conduits in urgent CABG

The demographics of patients undergoing CABG have changed over time: in a recent study Abramov et al. from the University of Toronto have analysed the improvements in surgical mortality and morbidity to evaluate trends in results of coronary artery surgery (21). From this study it appears that there has been a trend toward operating on older patients with more comorbidities. Even if hospital mortality has been stable, the risks of mortality and morbidity have been in a constant decline. It was associated with an increased use of left internal mammary artery grafts, multiple arterial conduits, and warm blood cardioplegia during the later years of the study. Almost 90% of the acute patients in our experience received a LIMA graft to the left anterior descending artery. Although it has been suggested that in the acute situation arterial grafts (LIMA, radial artery) may be avoided because of spastic reactions, in our experience

we have not encountered hemodynamic problems related to spasm of these conduits or to hypoperfusion syndrome in acute patients. Because of the absence of problems and in consideration of the well-known superior long-term patency rate of LIMA and radial artery grafts versus saphenous grafts, we believe that they should indeed be used, whenever suitable anatomic and angiographic conditions are present.

Off-pump surgery

The ideal indication for off-pump coronary artery bypass grafting has yet to be defined. Recent papers suggest that revascularization can be performed off-pump in the setting of acute coronary syndromes, although the presently published number of patients are small and non randomized trials have assessed the midterm effects of off-pump surgery in high-risk patients (22). The operative mortality rate in recent studies ranges from 0 to 12% (23-26). Recently, Angelini et al. analyzed short-term morbidity comparing off-pump with usual on-pump coronary artery surgery in 2 randomized trials (27). In the Beating Heart Against Cardioplegic Arrest Study (BHACAS) 1, the authors excluded patients with myocardial infarction in the past month or requiring grafting of the circumflex artery distal to the first obtuse marginal branch. In BHACAS 2, they included such patients. Primary end-points were all-cause mortality and cardiac-related events at mid-term follow-up. Unstable angina was present in 35% of the patients included in the off-pump arm of BHACAS 1 and in 48% of the patients included in the off-pump of BHACAS 2. The overall results of patients, stable and unstable, of the BHACAS 2 study confirmed that in-hospital morbidity was lower in patients who had off-pump surgery and that these procedures did not compromise midterm outcome, even if these studies did not show specific results about the off-pump treatment of the acute coronary syndromes. Our strategy is to perform these procedures only in selected patients with a suitable coronary anatomy (excluding patients requiring grafting of the circumflex artery distal to the first obtuse marginal branch) or with severe contraindications to traditional surgery, such as the evidence of a porcelain aorta or severe COPD. In our series we selected 14

patient with these characteristics. In the future, this approach may become feasible in certain subgroups of patients who require immediate revascularization in the presence of contraindications for extracorporeal circulation even if the results of off-pump surgery need to be compared to those of multivessel PTCA as a management strategy for coronary artery disease.

Myocardial protection

Although cold crystalloid cardioplegia is associated with an excellent clinical outcome in elective surgery, blood cardioplegia techniques seem to offer superior cardioprotection in high risk situations, such as advanced left ventricular dysfunction, acute myocardial ischemia, heart transplantation and hypertrophied myocardium. Myocardial oxygen consumption, lactate release, acid release, early postoperative left ventricular function are well preserved after tepid cardioplegia suggesting that this kind of myocardial protection seems effective in reducing metabolic demands and allows immediate recovery of the cardiac function. Moreover, tepid protection provides better results than those obtained with cold protection, with a decrease in ventricular rhythm disorders, a reduced need for post ischemic DC (direct current) shock and less blood loss.

In 1994 the Warm Heart Trial reported the results of a prospective randomized trial involving 1732 patients undergoing coronary artery bypass grafting, randomized to either normothermic or hypothermic cardioplegic solutions. Patients in the normothermic group experienced a lower incidence of postoperative low cardiac output syndrome, even if no differences in mortality or myocardial infarction were found between the groups. Fremes et al. reviewed the late results of trial patients from 1 of the 3 centers participating in the Warm Heart Trial (30): urgent CABG accounted for 23% of the procedures in the warm cardioplegia group and 23,7% in the cold cardioplegia group. The Authors showed that early incidence of myocardial infarction detected by significant myocardial enzyme release was lower in the warm cardioplegia group and that late survival (including perioperative deaths) at 72 months was nonsignificantly greater in the warm cardioplegia pa-

tients than in the cold cardioplegia patients. Even if we used warm blood cardioplegia in all patients who underwent on-pump surgery, we found that surgical procedures were not free of mortality and morbidity. In fact in-hospital mortality occurred in 4 patients (2%), perioperative AMI occurred in 8 patients (4%) and a transient low cardiac output syndrome in 27 patients (13%). These data confirmed that intraoperative myocardial protection still remains suboptimal in this setting of high-risk patients.

Glucose-insulin-potassium solutions are commonly used to treat myocardial ischemia in a variety of medical and surgical situations. Despite encouraging results obtained by smaller non randomized studies or by randomized trials in elective coronary artery surgery, the recent Insulin Cardioplegia Trial failed to demonstrate a significant benefit of insulin-cardioplegic solution in the setting of high-risk patients (such as unstable angina) undergoing isolated myocardial revascularization (31).

Other therapeutic options in the management of acute coronary syndromes are based on a direct cell protection to counteract the events leading to myocardial infarction and death. The transmembrane sodium/hydrogen exchanger maintains myocardial cell pH integrity during myocardial ischemia but paradoxically may precipitate cell necrosis. The development of cariporide, a potent and specific inhibitor of the sodium-hydrogen exchanger, prompted investigations on the effectiveness of this drug in the prevention of myocardial cell necrosis. Even if pilot studies in humans have been promising, the first large-scale trial assessing the potential protective effect of sodium-hydrogen exchanger inhibition in humans is the GUARDIAN trial (GUARD During Ischemia Against Necrosis) (32). This trial enrolled 11590 patients with unstable angina or non ST elevation myocardial infarction or undergoing high-risk percutaneous or surgical revascularization, but failed to show an overall clinical benefit of cariporide over placebo on the primary end point of death or myocardial infarction. Nevertheless, the stated highest dose of cariporide was associated with a significant reduction of risk, limited only to patients undergoing bypass surgery, with no effect on mortality. As a consequence of these findings, the multinational, double blinded, randomized, placebo-controlled sodium/hydrogen Exchange Inhibition to Prevent Coronary Events in Acute Cardiac Conditions (EXPEDI-

TION) Trial started in 2000. The purpose of this study was to test the hypothesis that the sodium hydrogen exchange inhibitor cariporide reduces all-cause mortality and nonfatal myocardial infarction after CABG surgery performed in high-risk patients (urgent or repeated CABG, multivessel disease, comorbidities). Other clinical end-points are the rate of newly developed ventricular dysfunction, major arrhythmia, need for inotropic support or mechanical ventricular devices. To date no definitive results of this trial have been published yet.

Conclusions

Our experience showed that urgent CABG for acute coronary syndromes shows a low risk for in-hospital mortality and morbidity. The use of arterial grafts is not detrimental in acute patients and is recommended in the absence of contraindications to improve long-term results. At present warm blood cardioplegia offers the best myocardial protection in these unstable patients. Off-pump surgery is a relatively low-risk procedure for patients with an acute coronary syndrome, even if ideal indications for urgent off-pump coronary artery bypass grafting have to be completely defined. Pre-operative treatment with glycoprotein IIb/IIIa receptor inhibitors is not a significant risk factor for important postoperative bleeding requiring surgery. However, in spite of recent developments in cardioplegic cardiac arrest, the optimal myocardial protection against perioperative myocardial infarction still remains a challenge. We performed warm cardioplegia in all the patients included in this series. Moreover, other therapeutic options have to be evaluated in order to improve cardioplegic solutions and perioperative pharmacological management of these high-risk patients.

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