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Safe Introduction and Quality Control of New Methods in Coronary Surgery

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Original paper
SUMMARY
Introduction: The first part of the paper analyses off pump coronary bypass surgery (OPCAB), which is compared with traditional on-pump procedures (ONCAB). Furthermore ,the paper evaluates the use of a new automatic device for performance of the proximal anastomosis and finally the effect of intracoronary shunt on myocardial ischemia during OPCAB. **The main goal** of the paper is to demonstrate the importance of careful clinical studies during introduction of the new techniques in cardiac surgery. **Methods:** Statistical analysis was performed on a large clinical database from Buffalo, NY, USA comparing OPCAB and ONCAB. Subsequently, a sequential controlled clinical study compared patients operated with a new automatic connector device to patients operated with classic suture technique. Finally a randomized study was performed to evaluate the effect of the use of an intracoronary shunt during construction of distal anastomosis. **Results:** The studies from Buffalo demonstrated reduced complications rates in high risk patients when OPCAB techniques were used. The use of connector devices in saphenous venous anastomosis was clearly inferior to standard technique. Intracoronary shunt was found to be beneficial by preventing ischemia. **Discussion:** Numerous studies have studied the results of OPCAB vs ONCAB and although results are variable it seems that OPCAB is advantageous in high risk patients, while in low risk patients there are much less if any benefit. The results of the studies of connector devices caused the product to be taken off the market. The value of shunt in OPCAB was clearly demonstrated by the randomized studies. **Conclusion:** The investigations presented in this paper clearly demonstrates the importance of well-designed studies when new surgical methods are introduced. In the present period of rapid technological development, carefully controlled, un-biased clinical trials are crucial to preserve patient safety and avoid unjustified societal cost.
Key words:Coronary surgery, quality control of new methods.

1. INTRODUCTION

Few "new" procedures, at least within the cardiac surgical community, have been as controversial at introduction as OPCAB. Although the procedure was not really new (1) and had been used for many years in certain parts of the world, the emotions of cardiac surgeons got charged whenever OPCAB was discussed, as the procedure gained popularity in the early 1990s. There are probably many reasons for this.

Standard coronary artery bypass operation had become one of the most commonly performed surgical procedures in the developed world. Outcome studies had shown the value of bypass surgery for improving both quantity and quality of life (2, 3, 4, 5) and many were skeptical to any change of such a successful operation.

A report by the American cardiac surgeon Steven Gundry showed poor graft patency, when bypass surgery was performed on the beating heart (6). OPCAB was technically more demanding than CABG performed with cardiopulmonary bypass (CPB) (ONCAB). Advocates of the "new" procedure, however, felt that OPCAB might offer considerable benefit (7, 8, 9). The operation required less equipment, appeared to be cheaper, and most importantly, the deleterious effects of CPB were eliminated (8).

The French Nobel laureate Alexis Carrell performed experimental coronary bypass 100 years ago as recently pointed out by J. Scott Rankin (1), but clinical application of such a procedure awaited a number of other medical discoveries and inventions (10). Crucial milestones were the development of coronary angiography (11), heparin to prevent clotting of the blood (12) during performance of the vascular anastomosis and to prevent coagulation of blood exposed to the artificial surfaces of the heart lung machine and protamine to reverse the non-coagulative state caused by heparin. The heart lung machine itself was a major invention (13, 14). The first patient to undergo intracardiac repair using a heart lung machine was operated by John Gibbon in 1953 (14). The painstaking work of Clarence Dennis, John H. Gibbon, Clarence Walton Lillehei and others finally produced a reliable device that could pump and oxygenate the blood during cardiac arrest and aortic clamping (14, 15, 16). This invention opened up the field for cardiac repair.

Arteriosclerosis and its complications from the brain, the peripheral vascular system and the heart reached epidemic proportions. The Framingham study did much to clarify risk factors and etiology (17). Myocardial infarction became the most common cause of death

in developed countries and a major cause of death even in developing countries (18). The treatment of the anatomic substrate of arteriosclerosis developed rapidly after the introduction of contrast angiography. Reconstruction of the extra cranial blood vessels, aortic aneurysms, aortoiliac and femoropopliteal obstruction etc. became common and effective (19). The additional challenges from an operation on the coronary arteries on the beating heart were several. The vessels were smaller, they supplied the very muscle which function maintained the circulation, and these 1-3 mm. sized vessels moved in a three-dimensional space at a rate of 60-100 beats pr minute (20). The idea of performing bypass surgery using standard vascular surgical techniques to these small, moving targets was by many considered equilibristic at best (21, 22). When the heart lung machine was used the heart could be fibrillated by hypothermia or electric current (23) or the aorta cross clamped intermittently (24) to reduce the motion of the heart, giving the surgeon better conditions to perform bypass grafts, or cardioplegic solutions could be used to arrest and protect the myocardium. Potassium induced cardiac arrest became the preferential technique since it resulted in a flaccid, nonmoving and almost bloodless heart, creating close to ideal conditions during the anastomostic work (25).

The heart lung machine, the oxygenator and the plastic tubing used for the extracorporeal circuit (26, 27, 28) have been subject to intense research and technical refinements. This fact, combined with the improving surgical experience, better selection of patients and improved monitoring of outcomes, made CABG a safer and better procedure (29) that could be applied to an increasingly more complicated and elderly patient population. The overall value of CABG surgery was documented in large randomized studies that evaluated medical versus surgical therapy (5, 30, 31) and which showed improvement in quality and quantity of life in surgically compared to medically treated patients.

In spite of the improvements, a small fraction of patients died or suffered severe postoperative complications, one of the most serious being damage to the central nervous system. Evaluation of alternative, less invasive treatments was therefore warranted.

Andreas Grüntzigs pioneering work on balloon dilatation of arteriosclerotic vessels (32) offered a new and less invasive approach to coronary artery disease (33). The development of intravascular stents improved the results of percutanous coronary interventions (PCI) especially in the early postprocedural phase (33, 34). CABG surgery continued to offer improving outcomes in spite of worsening risk profiles (35), as documented by governmental agencies (36, 37) and professional associations (35). Longer-term studies demonstrated that CABG offered better intermediate survival and less reinterventions than PCI in patients with three-vessel coronary disease (38), but the invasiveness of the procedures made surgery less attractive for many patients. PCI continued to improve both technologically (34) and in the medical approach to restenosis and thrombosis (39, 40, 41).

The development of a less invasive surgical therapy for coronary artery disease started with the Russian surgeon Vasilii I. Kolessov who based on the experimental work by Demikhov, was among the first to report on a clinical series of CABG (42). He was a prolific clinician and researcher, and reported not only on the elimination of CPB, but also of sternotomy and traditional suture technique (43). Kolessov performed a bypass graft to a coronary vessel using a surgical stapler through a small left anterior thoracotomy without CPB (44) and thereby introduced the concept of modern minimally invasive coronary surgery. His pioneering work was not acknowledged in the USA and Western Europe until much later. In the meantime, groups from Argentina (45) and Brazil (46) reported promising results performing multiple CABG off pump.

The interest for OPCAB in North America was renewed by Federico Benetti (47) who also published promising results from minimally invasive OPCAB (48, 49, 50). The results were confirmed by the Italian surgeon Antonio Calafiore (51), however all these early reports were based on uncontrolled studies.

The introduction of beating heart surgery led to a large number of new innovations in medical technology related to the OPCAB method, such as stabilizers to allow surgery on the beating heart (52, 53), special systems for graft harvesting, a large number of devices for automated anastomosis and shunts to allow surgery on the beating heart without compromising the circulation. These devices facilitated surgery and stimulated centers worldwide to start programs for coronary revascularization on the beating heart.

In this paper we intend to present and analyze some of the early studies performed to assess risk and benefits of OPCAB and certain associated technologies that were developed to make OPCAB easier and safer. I believe that the studies we conducted in Buffalo were important in revitalizing the interest in OPCAB in the USA and Europe. Although the studies had many weaknesses, including the uncontrolled selection to treatment group, the high reliability of the data which was subject to public control, contributed significantly to the knowledge base and inspired others to perform well controlled and randomized studies such as the early in depth study from Oslo (54, 55, 56, 57, 58). Our "OPCAB" group was able to continue studies on other aspects of the procedure in the following years.

1.1. Introduction of new methods in surgery

The approach to the evaluation of surgical methods and techniques is often somewhat different than the evaluation of pharmaceutical interventions. This may partly be due to the way surgery developed as a nonacademic profession, which sprung out from the barber guild.

In principle, however, the effect of new therapy for treatment of a certain condition should be compared to existing treatment in a systematic fashion. Surgical procedures usually consist of numerous steps, the use of various materials etc. Procedures are performed using various approaches and by different individuals, who often modify the procedures according to their own preferences. Therefore a large number of factors may influence the result of a particular surgical procedure. It may take many years before a new procedure may be considered standardized, and even after a procedure is considered standardized new developments of potential major importance may change the results. Before a reasonable degree of standardization is obtained, the performance of controlled studies is of less value. The success of a newly developed procedure has often been evaluated and compared to historic control groups of patients treated with another form of therapy. For example is hepatic resection of metastatic colon cancer considered an established and effective therapy, although it has not been subject to randomized studies (59). Similarly treatment of patients with end-stage heart failure has never been subjected to randomization between heart transplantation and medical therapy (60) due to the dismal results of medical therapy for patients in such condition.

In many situations however, after a new method was established, the procedure or technical modifications of the it were studied and compared to the traditional method using a randomized design (61).

Cardiac surgery was initially developed to correct anatomically well-known abnormalities known to cause death or major disabilities if left uncorrected. New operative treatments were developed, and gradually accepted as results improved. In some situations when alternative methods showed good results, controlled studies were performed. Numerous randomized studies have been performed to determine the optimal method of myocardial protection during surgery (62, 63, 64). Similarly randomized studies have been performed to determine the optimal valve prosthesis to use in aortic valve replacement. Common for such studies has been that the surgical methods, which were compared, have been established and operations performed by experienced surgeons (65, 66). The important issue of the learning curve must be considered when radically different operations are compared (67). This was the case when the treatment was switched from the so-called Senning to the Arterial Switch operation for Transposition of the Great Arteries.

Although it was realized early on that successful CABG effectively relieved angina pectoris (68), major studies were designed to determine whether the procedure prolonged survival and in which patient categories the procedure was most beneficial. Three well-known studies were performed to evaluate the survival benefit of CABG compared to medical treatment (5, 69, 70) in a strict, randomized fashion. Numerous other studies have been performed to compare various modifications of the CABG procedure.

The systematic evaluation of new medical treatment regimen may be divided in distinct phases:

In the first phase a new treatment is evaluated as to whether it is safe and efficacious. In a second phase the method is compared to alternative methods in current use. If outcomes using the new method are acceptable, a controlled randomized study may be performed using well-defined groups of patients. If possible, the evaluating investigators are blinded as to which treatment is administered, making the evaluation less biased.

When we started our studies in the mid 1990's, CABG was already well established. In the USA and Western Europe most coronary operations were performed using CPB and an arrested heart. Our group in Buffalo collaborated with surgeons from Brazil and Argentina, who performed OPCAB regularly, and who had published results indicating that OPCAB could improve results of coronary revascularization (47, 71, 72). Our exposure to this literature and the surgical demonstration of the procedures by the South-American surgeons Buffolo and Benetti made us initiate OPCAB in our center.

Since OPCAB was a modification of an already established method of coronary revascularization, we considered it safe to begin utilizing the technique, and initial results indicated the relative safety of the procedure. A few surgeons in our center utilized the OPCAB procedure, while most surgeons continued to utilize ONCAB. Controlled randomized studies seemed unrealistic at that time, but quality control of results was possible, utilizing the system of outcomes reporting, mandated by New York State. The NY State database recorded risk factors, operative mortality and complications from cardiac surgery, but did not include outcomes beyond 30 days or discharge from the hospital. The goal of our initial studies, therefore, included the study of operative outcomes, comparing OPCAB and ONCAB procedures. In the following years a large number of publications appeared in the surgical literature, describing comparative studies between OPCAB and ONCAB. The majority were single center studies, most of them non-randomized. Not until the ROOBY study was designed within the VA system (73), was a multicenter, partly blinded, randomized study performed which evaluated the OPCAB procedure on a large scale setting, designed to be largely independent of individual surgeon skill.

As surgical procedures mature, modifications of the procedure are common. Important modifications of the OPCAB operation included local stabilization of the operative sites during grafting. This represented a definite improvement, which was almost immediately adopted by surgeons. In our continued work in evaluating the OPCAB procedure, we aimed to assess the value of other technical

modifications of the procedure.

The use of automatic stapling devices, which could replace traditional suturing of coronary anastomosis, was anticipated to revolutionize CABG. Staplers could create anastomosis quickly, in a standardized fashion and relatively independent of surgeons' technical skills. Such device used for creation of proximal vein to aorta anastomosis, was thought to have the potential to reduce the chance of embolization and cerebral stroke. However the device had not been studied in a controlled fashion.

An important aspect of OPCAB is intraoperative prevention and management of myocardial ischemia. During creation of distal coronary anastomosis, coronary flow may be interrupted. However, it is possible to maintain flow by insertion of a temporary plastic shunt during grafting. Both methods have been in use by OPCAB surgeons, but the potential benefit (prevention of ischemia) or adverse effects (vessel damage) had not been thoroughly studied clinically.

2. ETHICAL CONSIDERATIONS

The studies from Buffalo (1, 2) did not require approval from the Ethics Committee, since no patients were identified, and a publicly mandated database was utilized. The study was of retrospective character although the data was collected prospectively as mandated by the state. The surgical procedures utilized in the OPCAB patients were thoroughly evaluated before implementation in the center in Buffalo, both by study tours to centers performing OPCAB and review of literature. The procedures were introduced in our hospitals in cooperation with internationally recognized proctors. The procedures had been utilized extensively in the past and were therefore not considered experimental.

The studies described in papers 3, 4, 5 were prospective controlled studies and required Ethics Committee approvals, which were obtained after submission of appropriate protocols.

3. AIMS OF THE STUDY

General objective

The overall objective of this thesis is to evaluate early results of OPCAB surgery and certain newer technological developments related to this procedure and to discuss the results of these studies as well as limitations of the methodology used in the studies.

The first objective of this study was to evaluate early outcomes and safety of OPCAB by comparing the clinical results of the procedure to outcomes of traditional ONCAB, using a public registry developed and used by New York (NY) State. The value of these and other early registry based studies will be discussed, and outcomes compared to larger and more controlled studies performed later.

The second objective was to evaluate the potential benefit of certain technical modifications introduced in OPCAB operations:

1) The use of an automated proximal connector device to attach saphenous vein-grafts to the ascending aorta.

2) The use of intracoronary shunt during the performance of distal anastomosis with the purpose of preventing intraoperative ischemia.

Specific aims:

1) Investigate the feasibility and safety of the introduction of OPCAB by evaluating and comparing outcomes of the procedure to outcomes of ONCAB using data from a mandatory and publicly available database. (Paper 1 and 2). Critically evaluate the results of these early studies and compare them to later clinical series and randomized controlled studies.

2) Compare clinical and angiographic outcomes in patients having the proximal saphenous vein graft anastomosis performed with a so-called connector device versus traditional suture technique. Compare the amount of micro embolization to the brain measured by Transcranial Doppler in patients operated with the connector and patients operated with traditional technique during performance of the proximal anastomosis. (Paper 3 and 4).

3) Study the development of ischemia of the myocardium perfused by the left anterior descending coronary artery (LAD) during OPCAB surgery. During performance of the anastomosis the LAD was either obstructed by a snare or shunted using an intravascular shunt. A second objective of this study was to study the consequences of the two different methods on anastomotic quality by performing on-table - and midterm-angiographic studies (Paper 5).

4. MATERIAL AND METHODS

4.1. Early clinical material assessed with the New York State Database tool

Buffalo General Hospital, a large University hospital, located in Buffalo, New York, was an important provider of cardiac surgery in the State of New York. Before initiation of our studies CABG was almost exclusively performed as ONCAB. In 1994 OPCAB surgery was introduced in cooperation with pioneers from Chieti, Italy and Sao Paulo, Brazil. Subsequently the OPCAB procedure was adopted by several surgeons, others continued to operate using traditional ONCAB technique. OPCAB was technically more challenging than standard ONCAB surgery, particularly in the beginning when there was little dedicated technology to facilitate the operations. The purpose of the study reported on in Papers 1 and 2, was therefore to evaluate the safety and clinical outcomes of OPCAB surgery compared to standard ONCAB procedures based on the available data in the state registry.

4.2. Clinical material

All patients (n=2001) undergoing CABG at Buffalo General Hospital between January 1, 1995 and August 31, 1996 were included (Paper 1.) Patients undergoing reoperative CABG (n=288) between January 1, 1995 and December 31, 1996 were included in paper 2. Patient referral in

the hospital was made on individual basis from cardiologist to cardiac surgeon, and the individual surgeon decided which method of operation was to be used. There was no obvious change in referral pattern after the introduction of OPCAB. Some of the cardiac surgeons performed most operations as OPCAB while others performed mainly ONCAB. Overall 8.5% of patients where operated using OPCAB in the study period. Of the reoperative cases reported on in paper 2, 36 % of the patients were operated with OPCAB.

4.3. Data collection and statistical analysis

NY State Department of Health has for a number of years administered a mandatory data-collection system for all cardiac surgery procedures (74, 75). The data-collection is compulsory for all providers of cardiac surgery in the state. The mandatory data set includes demographic data, recognized operative risk factors, operative details, postoperative complications and death. Data were collected manually by nurses and physicians, controlled and signed by the operating surgeon and quality controlled by trained data collectors. Complications were defined according to stringent and documentable criteria.

In the studies documented in papers 1 and 2, operations performed using CPB were designated as ONCAB, and operations performed without CPB as OPCAB regardless what may have been the intention at the beginning of the operation. Conversion to another method intra-operatively was not reported in the data system at the time of these studies.

Based on the data entered in the NewYork State database each patient's estimated mortality rate was calculated based on the risk factors of the individual, including the clinical state of urgency at the time of surgery. The average estimated mortality rate of a certain group of patients could then be compared to other groups. Using the estimated mortality rate and the observed mortality rate, the average risk adjusted mortality may be calculated. The risk adjusted mortality rate is used for comparisons between institutions, individual surgeons and different procedures and is considered an important figure in the quality assessment of cardiac surgery providers (74).

In papers 1 and 2 the estimated mortality rate, observed mortality rate and risk adjusted mortality were calculated for the OPCAB and ONCAB patients and compared statistically. Similarly, complication-rates were compared between groups. There was no risk adjustment performed for complications although high estimated mortality rate also predisposes for more frequent complications. Continous data were analyzed using t-test, while categorical data were analyzed by Chi-square test (74).

5. INVESTIGATION OF NEW TOOLS IN OPCAB SURGERY

5.1. Evaluation of the Symmetry aortic connector vs. hand-sewn proximal anastomosis

Introduction: Cerebrovascular accident is a serious and not uncommon complication of coronary surgery. The elimination of CPB may reduce the risk of stroke (76), but strokes still occur. Embolization during clamping and unclamping of the ascending aorta during construction of the aorta to saphenous vein anastomosis has been thought to be responsible for strokes during CABG (77). The concept of the Symmetry ^{R} connector, which made it unnecessary to clamp the aorta, could therefore potentially reduce the chance of embolization. Especially in OPCAB where clamping of the aorta represents the only form of manipulation of the aorta, it was hoped that the use of a connector could reduce embolization rate. Previous uncontrolled studies had been promising (78, 79).

Hypothesis: The hypothesis in this study was that grafts performed with Symmetry^{R} aortic connector would have similar angiographic patency, as hand-sutured grafts, and that embolization to the brain, measured by Transcranial Doppler would be reduced.

Clinical material: Twenty-three patients underwent OPCAB, having the proximal anastomosis performed with the Symmetry^{R} device, while a control group of 23 patients received hand-sewn proximal anastomosis with aorta partially clamped. The study was initially designed as a prospective randomized investigation, but the pilot study raised suspicion of possible problems with the connector anastomosis. The study was therefore redesigned to minimize the number of patients potentially exposed to adverse effects, by including a similar sized control group with the same inclusion criteria as the pilot patients.

Angiographic investigations: At the end of the surgical procedure all bypass grafts were studied with on-table angiography. The angiographic procedure was repeated after three months. On-table and three months graft patencies were recorded.

Transcranial Doppler studies: Thirty-two of the patients who participated in the study underwent monitoring with multifrequency Transcranial Doppler scanning to detect and count the total number of gaseous and solid emboli to the brain.

Statistical analysis: Continuous data were analyzed with T-tests and Mann-Whitney tests while categorical data were analyzed by chi-square. All analysis was performed with SPSS software (SPSS Inc. Chicago, USA).

5.2. Evaluation of the use of intracoronary shunt in OPCAB surgery

Introduction: Maintenance of hemodynamic stability during grafting is essential during OPCAB procedures. Ischemia is the most frequent cause of hemodynamic collapse and subsequent conversion to CPB (80). A randomized study was designed to investigate if intracoronary shunts could prevent ischemia

during grafting of the LAD.

Clinical material: 56 patients scheduled for OPCAB were randomized to a "shunt group" in which the anastomosis between LIMA and LAD was performed with the help of an intra-coronary shunt or to a "no-shunt group" in which the LAD was occluded with a proximal snare until the anastomosis was completed. Postoperatively patients were monitored clinically and with serial ECGs and measurements of biochemical markers of myocardial damage.

Detection of ischemia: Tissue Doppler with strain measurements (81) was utilized to study the occurrence of ischemia in the interventricular septum during LAD grafting. Transesophageal ultrasound (System FiVe^{R} echocardiograph (GE Vingmed Ultrasound, Horten, Norway) was utilized to perform the measurements.

Study of anastomotic quality: Patients underwent coronary angiography on the operating table after completion of the operation and after 3 month.

Statistical analysis: Data were analyzed using Student T-test for continuous data, chi-square for categorical data and logistic regression for further analysis.

6. RESULTS

6.1. Operative outcomes in OPCAB surgery

Preoperative risks: Certain preoperative risk factors were more common in OPCAB than ONCAB in the patients described in paper and 2.

Operative procedures: All ONCAB patients were operated with median sternotomy approach and normothermic or mild hypothermic CPB. In OPCAB patients a more varied surgical approach was utilized: In the patients reported on in paper 1, 54 out of the total 172 patients had a minimally invasive thoracotomy (MIDCAB) performed with a single bypass to LAD, and 2 patients had a lateral thoracotomy approach. In the reoperative cases 16 OPCAB patients had a MIDCAB procedure.

The average number of grafts pr patient was substantially lower in OPCABs reported in paper 1 (1.4 vs 3.39 for ONCAB). This difference was also seen in the reoperations (OPCAB 1.2 and ONCAB 2.7).

Mortality and complications: Although the estimated mortality rate was higher in OPCAB patients, crude mortality was lower, giving identical risk adjusted mortality in the paper 1 material and a lower risk adjusted mortality for OPCAB in reoperations. None of the mortality differences was significant.

Complication rates were non-significantly lower in the OPCAB patients reported in paper 1, the differences were significant when reoperations were reviewed separately. Both cardiovascular and other complications were reduced. This was confirmed in paper 2 where overall freedom from complications in OPCAB was 91.4% vs. 72.1% in ONCAB (p= 0.0001).

6.2. Outcomes of OPCAB surgery performed with new technological tools.

6.2.1. Anastomotic quality and micro-embolization in OPCAB surgery performed with the Symmetry^{R} aortic connector or with hand-sewn technique.

There were no differences in preoperative clinical status or in known risk factors for CABG.

At on-table angiography all LIMA to LAD grafts were patent and the saphenous venous grafts had similar patency independent of whether connector or hand-sewn technique was used.

All LIMA grafts except one were patent on postoperative angiogram. Of 40 saphenous vein grafts in the control group, four were occluded and one stenotic, while out of 32 studied Symmetry grafts, 16 were occluded and 8 were stenotic. The differences between groups were highly significant.

Micro-embolization counts by Transcranial Doppler were higher in patients operated with the connector compared to hand-sewn anastomosis. The number of gaseous emboli was increased significantly in the Symmetry^{R} group, while there was a slight, non-significant increase in the number of solid emboli.

6.2.2. Intraoperative ischemia and anastomotic quality in patients undergoing OPCAB with or without the use of intracoronary shunt.

Most patients with antegrade flow in the LAD on the preoperative angiogram showed evidence of ischemia, when LAD was snared. Patients with total occlusion of the LAD preoperatively and retrograde filling through collaterals, did not develop ischemia. There was a significant difference in the measurements of myocardial strain in the shunted and non-shunted patients. This demonstrated that ischemia was reversed in almost all shunted patients, while the majority of non-shunted patients remained ischemic until the time of reperfusion. None of the patients developed hemodynamic instability or collapse during grafting of the LAD.

Ischemia during grafting had no demonstrable effect on postoperative levels of cardiac enzymes, nor could any clinical adverse effects of the ischemia be demonstrated.

There was a trend towards improved anastomotic quality in the shunt-group at the time of on-table angiogram, but on postoperative angiography findings were similar in both groups. All LIMA to LAD grafts were patent, but fifteen patients had new coronary lesions in the native vessel, proximal to the anastomosis between LIMA and LAD. These new lesions corresponded to the location of the proximal snares, which were applied to occlude the LAD in both treatment groups.

7. DISCUSSION

With the introduction of new medical or surgical treatment alternatives, it is obviously desirable that a new therapeutic regimen is dem-

onstrated to be as good, or better than existing alternatives. As medical care is getting increasingly expensive and complex, it will be even more important to prove a treatments value to improve quality of life at acceptable cost (82). Of the various methods utilized for such comparisons; the controlled, prospective, randomized study represents the "gold standard" although such studies may also be biased (83). Early on, after introduction of a new method, it is often unrealistic to conduct randomized studies, since necessary data to plan a study may be unavailable. Observational studies may reveal more variable results than randomized studies when comparing different types of treatments (84), but in some situations a prospective randomized study may be both difficult and unethical to accomplish (85, 86).

When OPCAB was introduced in Buffalo General Hospital, outcomes were compared to traditional ONCAB using the NY-State registry, which was already well established as a tool for quality assessment of coronary surgery (36, 37). Use of this tool made it possible to compare outcomes of different treatment groups undergoing CABG.

In this early phase of implementation it was important to establish whether the OPCAB procedure was safe and not detrimental to the patients compared the ONCAB technique. Postoperative complications were accounted for up to the time of discharge from the hospital.

With these studies we were able to demonstrate that patients operated with OPCAB, had a non-significantly elevated preoperative risk profile, and a similar risk adjusted mortality compared to ONCAB. Complication rates were lower in OPCAB, although this was only statistically significant for patients undergoing reoperations. We therefore concluded that OPCAB was as safe as ONCAB surgery, and that avoidance of CPB might have a beneficial influence on complication rates. Interestingly an analysis of a dataset from NY State Department of Health which included almost 50,000 patients, did to a large extent confirm the findings of lower complication rates when OPCAB was used (87). In that large patient material studied by the Hannan et al. (87), operative mortality was also significantly lower in patients operated without CPB.

There were numerous limitations to our early study. Assignment to treatment group was not random, but selected by the operating surgeon, thereby certainly introducing the possibility of bias. The NY State database has demonstrated that the individual surgeon is an important risk factor in coronary surgery (88). The surgeon factor was not taken into account in our study and the rate of OPCAB use was very different between surgeons in the institution. It is possible that surgeons with greater technical skill preferentially performed OPCAB surgery. Patients who were converted from OPCAB to ONCAB are known to have unfavorable results (80) and this could bias the study in favor of the OPCAB group since all complications before and after conversion would be registered as ONCAB complications. Similarly conversion from ONCAB to OPCAB could potentially improve the results of ONCAB by removing a patient group with high risk for use of CPB.

The lack of long-term follow up is another serious limitation of these studies. Our studies did not include any postoperative angiographic results demonstrating graft patency. This is an important issue, especially considering results from an earlier US series (6). Combined with the fact that fewer grafts were performed in OPCAB patients, the possibility of earlier return of ischemia or the need for reintervention in OPCAB patients had to be considered a definite possibility. The previously mentioned study from NY State (87) did find increased reintervention rates in OPCAB at three years of observation, although mortality was the same. A study from Emory University with a sample size of more than 12 000 patients demonstrated lower operative mortality and complication rates in OPCAB (89), while 10-year survival was similar in OPCAB and ONCAB patients.

In spite of the limitations, our study was important, being among the first to compare OPCAB and ONCAB using a publicly controlled, mandatory database. Some later studies of the OPCAB procedure did show improvement in operative results, especially in high risk patients (46). A multicenter study confirmed risk reduction for early mortality using OPCAB, especially in reoperations (90).

The Oslo group conducted a study including intraoperative, early postoperative, midterm and long-term results of OPCAB vs. ONCAB. Mortality, morbidity, cognitive status, quality of life as well as graft patency were evaluated in these studies (54, 55). There was no difference in graft patencies after 12 months, and it was concluded that OPCAB and ONCAB gave similar outcomes. Other randomized studies (91) showed benefits of OPCAB both perioperatively and at midterm. Similarly a large meta-analysis (92) demonstrated perioperative benefits of OPCAB on mortality, complication rates and resource use. The Belgian surgeon P. Sergeant demonstrated that in his single hospital series, surgeons with excellent results using ONCAB, could further improve outcomes by re-engineering their services and switch to OPCAB (93). In our own early studies (94, 95) where we found reduced complication-rates in the OPCAB group, patients had a higher risk profile than the ONCAB group. A randomized study in high risk patients has as far as we know not been done to date, although there are other numerous reports indicating that the major benefits of OPCAB are realized in such patients (96).

The ROOBY study conducted within the Veterans Administration hospital-system was conducted after careful evaluation of available data (73), using generally accepted outcome parameters and including enough patients to give adequate power to evaluate critical claims made in smaller single institution studies. Although issues were raised regarding the adequacy of experience in OPCAB surgery by the par-

ticipating surgeons (97) the ROOBY study did not confirm benefits of OPCAB surgery found by us (95) and other investigators. An important finding in the ROOBY study was decreased patency of vein grafts in OPCAB (98). We believe that intraoperative graft patency verification in CABG and especially in OPCAB since more than 3% of the grafts may need revision (99). The use of a reliable method of graft verification such as transit time flowmetry (100) may improve immediate- and thereby long term patency and reduce the need for reintervention. As far as can be told from the published material, graft verification was not routinely required in the ROOBY study (73).

The varying results of the observational and randomized studies remind us of the fact that medical procedures constantly change, as does the population enrolled in various studies. Early investigations of OPCAB were performed without the benefit of stabilizers or other technological innovations (6), which may have compromised results especially in regards to graft patency. Patients included in the randomized studies from our center in Oslo were operated with stabilizers and positioning devices as well as modern methods of graft verification. In this study grafts patency was the similar in OPCAB and ONCAB (54, 55). The fact that these studies did not show any outcomes benefit in contrast to the randomized studies from Bristol, may have been due to patient selection (91).

After demonstrating the apparent safety of OPCAB (54, 55) the Oslo group, which I later became a part of, performed the first randomized studies that showed equal outcomes in OPCAB and ONCAB. Subsequently protocols were developed to investigate other tools, which could potentially improve and facilitate the OPCAB procedure and prevent some of the major complications, which still prevented wider application of the procedure. It was hoped that the Symmetry^{R} device would decrease embolization and stroke rates, since the device made it unnecessary to clamp the aorta during construction of the proximal anastomosis. Although initial results were promising (78, 79), controlled evaluation seemed warranted, since case reports had shown early occlusion within the connector (101). Alerted by these case reports, angiographic controls of patients, who had undergone pilot operations in our centre, were carried out. The angiographic controls raised suspicions, and after having used the device in 23 patients, a sequential group of 23 OPCAB patients served as a control group, having the proximal anastomosis performed with traditional technique. The Symmetry^{R} cases were found to have high occlusion- and stenosis- rates (102) compared to the control group.

Similar to what was found by other investigators the process causing obstruction of the grafts seemed to originate in the connector (103, 104). Other investigators confirmed these findings (105, 106) although a Japanese group showed better patency (107). In contrast to what was the case in our study, some of the Japanese patients received anti-thrombotic therapy in addition to aspirin. Ethnic factors may also have been involved as they are known to influence the tendency for arterial thrombosis (108, 109), and change thrombocyte reactivity and response to aspirin (110). Damage to the endothelium from surgical manipulation of the saphenous vein may also have been an important reason for poor graft patency when Symmetry^{R} was used (111). The device exposes a nitinol metal surface to the bloodstream, this may cause thrombogenicity or intimal hyperplasia (112). The use of a differently constructed connector device by a German group resulted in acceptable graft patency (113). That device did not expose the metal parts of the connector to the bloodstream. Additionally, clopidogrel was given routinely as part of the postoperative regimen in the German study, which may have improved the results (114).

Previous investigations evaluating the amount of cerebral microembolization during CABG using Transcranial Doppler showed reduced number of emboli during OPCAB performed with the Symmetry^{R} connector (115). The use of ONCAB patients as controls in that study was not optimal, since ONCAB by itself results in higher embolic counts than OPCAB (116).

The hypothesis that use of the Symmetry^{R} connector decreased the incidence of embolization (115) could not be substantiated in our study (117). On the contrary, patients operated with the connector had more gaseous emboli and a trend towards more solid emboli than patients with hand-sewn anastomosis. The importance of such emboli during heart surgery has been documented (118). The increased number of gaseous emboli in the Symmetry^{R} group was surprising, but may have been due to a Venturi effect occurring while punching the hole in the aorta before the application of the connector (119).

Prior to our studies of the Symmetry^{R}, the device had been used extensively in USA and Europe. By doing a relatively small study, which included graft angiography both intraoperatively and at intermediate term, we were able to contribute significantly to the subsequent market withdrawal of the device. In this study 46 patients were included, and 23 received the connector. Previous studies had only included intraoperative and early postoperative findings (78, 79). As a result, thousands of patients were operated with the device before the adverse effects of the device were discovered. We believe that our relatively small study demonstrates the value of carefully planned clinical- and if necessary invasive-studies, when new technology is being introduced.

Patients with coronary artery disease, especially those clinically unstable, are prone to develop myocardial ischemia during OPCAB surgery. In unstable patients the practice of occluding native vessels while the anastomosis is constructed, may

cause hemodynamic collapse, necessitating conversion to CPB (120, 121). Insertion of an intracoronary shunt during grafting could potentially prevent intraoperative ischemia, although it had been questioned whether the small internal lumen of the available plastic shunts would have adequate blood flow (122). Our randomized study demonstrated that in most patients with antegrade flow in the LAD, shunting of the LAD prevented ischemia, while most patients operated without shunt became ischemic. Patients who had total occlusion and retrograde filling of the LAD did not develop ischemia since blood was supplied from collaterals. Relief of ischemia in shunted patients was not dependent on shunt-size; however, we did not utilize shunts smaller than 1.5 mm (122). Although no evidence of hemodynamic compromise or leak of cardiac enzymes was seen in the study patients, who had their anastomosis performed without shunt, ischemia is potentially harmful. The short duration of the ischemia, the clinical stability of the patients and absence of risk factors for conversion (120), may have prevented complications in the group of patients included in this study. It has been demonstrated previously (123), and it is also the experience of many surgeons, that a shunt may reverse hemodynamic instability similar to what is seen by interventional cardiologists when opening occluded coronary vessels (123, 124). The use of shunt may therefore be of significant benefit by preventing the need for conversion to ONCAB. Conversion is an important cause of poor outcomes in OPCAB procedures (125).

Endothelial damage and development of coronary lesions have been considered a possible complication of shunt use (126, 127). Occlusive snaring of coronary arteries results in vessel damage in animal models (128) and clinically lower patency rates compared to shunt (129). In our study patency rates were similar or improved when shunts were used. On angiograms performed after three months, obstructive lesions, proximal to the anastomosis, corresponding to the occlusive snare, were seen in 15 vessels distributed between shunt and no-shunt patients. Similar changes were not seen distal to the anastomosis, indicating that use of shunt does not cause permanent damage to arteries, at least at the intermediate term.

There were certain limitations to this study in spite the prospective, randomized design. The number of patients randomized was relatively small, making it difficult to discover differences in patency rates and anastomotic quality. Additionally, shunts were only used routinely during the LAD grafting, which made it less likely to discover changes in biochemical parameters. Such changes could potentially have been demonstrated if all grafts had been performed with or without shunt. Nevertheless, we believe that this study demonstrated that the use of intracoronary shunt is beneficial by preventing ischemia and possibly improving anastomotic quality

8. CONCLUSION

a) Early clinical studies using a large public database indicated the relative safety of the OPCAB procedure and a reduction of complication rates in high-risk patients compared to ONCAB. Although the methodology used in these early studies had significant limitations, a number of larger studies have supported the finding that OPCAB can be performed with at least the same safety as ONCAB surgery. Randomized studies have in general not shown the same benefits as those demonstrated in observational-, registry based, and meta-analytical investigations. Paper 1 and 2 in this thesis demonstrated similar mortality and complication rates when OPCAB surgery was used. High risk and especially reoperative- cases had reduced complication rates compared to ONCAB. High-risk patients are seldom included in randomized studies. As for the applicability of OPCAB to larger, relatively low risk, groups of patients in need of CABG, the ROOBY study has raised significant concerns about whether OPCAB can be recommended as a primary technique for the average surgeon (98). On the contrary, the ROOBY study demonstrated that OPCAB used by cardiac surgeons in a relatively low risk patient is less advantageous than traditional ONCAB. The issue of whether the surgeons of the ROOBY study had enough experience with OPCAB was raised (97), but the authors studied this issue carefully, and did not demonstrate any difference between surgeons with varying amount of OPCAB experience (98). All surgeons participating in the study had performed at least 20 OPCAB procedures. Glance et al. using the material from NY-State Database also found no volume effect on OPCAB results (130). Based on the carefully designed and conducted ROOBY-study we must accept that OPCAB should not be recommended to all surgeons, although it seems evident that certain surgeons are able to obtain superior result using the OPCAB procedure.

b) Use of the proximal connector device, Symmetry^{R}, resulted in unacceptable patency rates, when used to attach saphenous vein grafts to the aorta in OPCAB patients. In contrast to what was expected from the initial hypothesis, the amount of microembolization measured by Transcranial Doppler was increased rather then decreased when the device was used. The research reported on in this study included less than 50 patients, but contributed significantly to the removal of a potentially harmful device from the medical marketplace.

c) Intracoronary shunts prevent ischemia during grafting of the antegradely perfused LAD in OPCAB surgery. Anastomotic quality was equal to or better than when no shunt was utilized. On the basis of this study a strong recommendation could be given for the use of intravascular shunt during construction of coronary anastomosis in OPCAB operations.

Overall we believe that this work has demonstrated the value of using accurate clinical registries in the introduction phase of new surgical methods, prior to the design and

conduct of randomized controlled investigations. Introduction of new tools in established surgical procedures should undergo thorough evaluation under controlled circumstances before being recommended for routine use.

9. FUTURE PROSPECTS

Technological and procedural developments occur at an increasingly rapid rate in surgical practice and compete with traditional methods of therapy. Although new methods may represent significant improvements, some do not and may occasionally result in more expensive and less optimal outcomes. Quality control of new procedures and technological developments is therefore necessary. When new procedures are introduced, an important early requirement is demonstration of safety and efficacy at least comparable to traditional techniques. Therefore, trustworthy, controlled registries are important. By using such registries, failure rates (or advantages) of new methods may be demonstrated early, and data obtained for planning of future randomized studies necessary for the comprehensive evaluation of new procedures. Clinical registries ought to be maintained by public authorities and/or professional organizations rather than by commercial interests.

OPCAB and ONCAB are now used worldwide in patients requiring coronary surgery. The utilization of the procedures varies widely between countries, regions and institutions. In the USA, OPCAB penetration has remained at about 20% of the coronary surgical volume. Japanese surgeons perform 60 % of their revascularizations as OPCAB, while in Scandinavian countries the procedure is used in less than 10% of operations. Reasons for this include the fact that OPCAB is technically more difficult and that the results of standard ONCAB surgery are good.

Although the elimination of CPB makes OPCAB less invasive than ONCAB, the magnitude of the procedure is still significant. Development of new and improved connector devices, improved shunts for the prevention of ischemia and application of endoscopic surgical techniques may further reduce the invasiveness of coronary surgery. Although endovascular stenting of coronary arteries represents a less invasive approach than surgery, subgroups of patients are still best served by surgical revascularization in the foreseeable future.

It is therefore an important goal to reduce invasiveness and complication rates of coronary surgery, while improving long term graft patency and survival. Well-planned and non-biased clinical investigations remain important parts of such development.

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