

Safe introduction and quality control of new methods in coronary surgery

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1. Acknowledgement

Coronary artery disease has been the most common disease process dealt with by cardiac surgeons, constituting about 80 % of their volume of operations. The surgical procedure that became successful and common, rested on the shoulders of the pioneers of cardiac surgery from the 1950s.

I owe my interest in coronary surgery to George Schimert, MD, Thomas Z. Lajos, MD and Joginder Bhayana, MD, whom I trained under while in Buffalo, New York. The chief of the cardiac surgical department in Buffalo General Hospital during the 1990s, Tomas A. Salerno, MD, challenged the routine need for cardiopulmonary bypass (CPB) during coronary bypass surgery (CABG) and brought colleagues to Buffalo to demonstrate new surgical procedures. South-American surgeons Enio Buffalo, MD, PhD and Ricardo Lima, MD, PhD from Brazil and Federico Bennetti, MD from Argentina demonstrated the method of off-pump coronary bypass surgery (OPCAB). From the time in Buffalo I also thank Hratch Karamanukian, MD and Guisepe D'Ancona MD, partners in developing the surgical techniques. Saira Hasnain, PhD, at Buffalo General Hospital maintained data files for cardiac surgery and collected and helped analyze clinical data.

When I joined the Interventional Centre, Dr. Erik Fosse, MD, PhD advised me to pursue a Norwegian PhD. The Interventional Centre had since its inception, been focused on the introduction of new surgical and interventional procedures. Dr. Fosse helped me design the plans for this thesis and was my advisor during the process. Jan L. Svennevig, MD, PhD served as a co-advisor.

The staff at the Interventional Centre and the departments of thoracic surgery, cardiology and radiology at Rikshospitalet was essential for the success of the studies. The Centre, with

which I had become a collaborator while in Buffalo, started a randomized, prospective study of OPCAB in 1999. I joined the group in Oslo two years later, and continued to study the OPCAB procedure. The randomized study, in which I came to Oslo to late to participate, inspired the study of other aspects of the procedure.

Runar Lundblad, MD, PhD, Kjell Arne Rein, MD, PhD, and Per Snorre Lingaas, MD performed the majority of the operations included in Paper 3-5. Per Kristian Hol, MD, PhD, who together with Dr. Fosse had been the coordinators of the randomized OPCAB- study and Rune Andersen, MD, performed the angiograms. Kai Andersen MD, PhD, Thor Edvardsen, MD, PhD and Helge Skulstad, MD, PhD, performed the echocardiographic studies in paper 5. Tor Inge Tønnessen, MD, PhD and Steinar Halvorsen, MD gave expert anesthesia without which OPCAB is not possible. Marianne Berg, Karl Øyri, RN and Bjørn Erik Mørk, PhD were essential in the organization of the clinical studies.

Finally, thanks to my family who gave me support to complete this dissertation.

2. List of papers

Paper 1:

Bergsland J, Hasnain S, Lewin AN, Bhayana J, Lajos TZ, Salerno TA. Coronary artery bypass grafting without cardiopulmonary bypass—An attractive alternative in high-risk patients. *Eur J Cardiothorac Surg* 1997; 11:876-80.

Paper 2:

Bergsland J, Hasnain S, Lajos TZ, Salerno TA. Elimination of cardiopulmonary bypass: a prime goal in reoperative coronary artery bypass surgery. *Eur J Cardiothorac Surg* 1998; 14: 59-62.

Paper 3:

Bergsland J, Hol PK, Lingas PS, Lundblad R, Rein KA, Andersen R, et al. Intraoperative and intermediate-term angiographic results of coronary artery bypass surgery with Symmetry proximal anastomotic device. *J Thorac Cardiovasc Surg* 2004; 128: 718-23.

Paper 4:

Skjelland M, Bergsland J, Lundblad R, Lingas PS, Rein KA, Halvorsen S, et al. Cerebral microembolization during off-pump coronary artery bypass surgery with the Symmetry aortic connector device. *J Thorac Cardiovasc Surg* 2005; 130(6): 1581-5.

Paper 5:

Bergsland J, Lingas PS, Skulstad H, Hol PK, Halvorsen PS, Andersen R, Småstuen M, Lundblad, R, Svennevig J, Andersen, K, Fosse E.

Intra-coronary shunt prevents ischemia in off pump coronary bypass surgery. *Ann Thorac Surg* 2009; 87(1): 54-60

3. Introduction

3.1 Historical background

Few “new” procedures, at least within the cardiac surgical community, have been as controversial at introduction as OPCAB. Although the procedure had been used for years in certain parts of the world (1), many cardiac surgeons were skeptical to OPCAB, as the procedure gained popularity in the 1990s.

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 quantity and quality of life (2-5), and many were reluctant to any change of such a successful operation.

A report from the US showed decreased 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 felt that OPCAB might offer benefits (7-9). The operation required less equipment, appeared to be cheaper, and the deleterious effects of CPB were eliminated (8).

The French Nobel laureate Alexis Carrell performed experimental coronary bypass 100 years ago as pointed out by J. Scott Rankin (1), but clinical application awaited other medical discoveries and inventions (10). Milestones were the development of coronary angiography (11), use of heparin to prevent clotting of the blood (12) during performance of vascular anastomosis and coagulation of blood exposed to the artificial surfaces of the heart lung machine. The heart lung machine was a major invention (13, 14), and in 1953 John Gibbon performed an intracardiac repair using a heart lung machine (14). The work of Clarence Dennis, John H. Gibbon and Clarence Walton Lillehei helped develop a device that could pump and oxygenate blood (14-16).

Arteriosclerosis and its complications from the brain, the peripheral vascular system and the heart reached epidemic proportions. The Framingham study clarified risk factors and etiology (17). Myocardial infarction was a common cause of death in both developed and developing countries (18). Surgical treatment of vascular manifestations of arteriosclerosis developed after the introduction of contrast angiography. Reconstruction of peripheral vascular system became common therapies (19). The challenges from operating on the coronary arteries on the beating heart were several. Vessels were small, supplied the muscle which maintained the circulation, and moved in a three-dimensional space at 60-100 beats per minute (20). Many considered the idea of performing bypass surgery using standard, vascular surgical techniques to these small, moving target as equilibristic (21, 22). When the heart lung machine was used, the heart could be fibrillated by hypothermia or electric current (23) or the aorta clamped intermittently (24) to stop the motion of the heart, giving the surgeon better conditions to perform the bypass grafts. Cardioplegic solutions could be used to arrest and protect the myocardium, and potassium induced cardiac arrest became a common technique since it resulted in a flaccid, nonmoving heart, creating good conditions for the anastomotic work (25).

The heart lung machine, the oxygenator and the plastic tubing used for the extracorporeal circuit (26-28) have been subject to research and technical refinements. Surgical experience, selection of patients and monitoring of outcomes increased the safety of CABG (29). The value of CABG surgery was documented in randomized studies (5, 30, 31). The studies showed improvement in quality and quantity of life in surgically, compared to medically treated patients.

A fraction of patients died or suffered postoperative complications, including damage to the central nervous system. Evaluation of alternative treatments was warranted.

Andreas Grüntzig's work on balloon dilatation of arteriosclerotic vessels (32) resulted in a less invasive treatment of coronary disease (33). The development of intravascular stents improved results of percutaneous coronary interventions (PCI), especially in the early postprocedural phase (33, 34). CABG surgery continued to offer improved outcomes in spite of worsened risk profiles (35), as documented by governmental agencies (36, 37) and professional associations (35). Longer-term studies demonstrated that CABG could offer better intermediate survival and less reinterventions than PCI in patients with three-vessel coronary disease (38), but its invasiveness made surgery less attractive. PCI continued to improve technologically (34) and in the approach to restenosis and thrombosis (39-41). The development of less invasive surgery for coronary disease started with the Russian surgeon Vasilii I. Kolessov, based on the experimental work by Demikhov, was among the first to report a clinical series of CABG (42). Kolessov reported on the elimination of CPB, sternotomy and suture (43) and performed a bypass graft using a stapler through a left anterior thoracotomy without CPB (44). His work was not acknowledged in the USA or Western Europe until later. In the meantime, groups from Argentina (45) and Brazil (46) reported good results using OPCAB.

The interest for OPCAB in North America was renewed by Federico Benetti (47), who published results of minimally invasive OPCAB (48-50). Similar results were documented by Antonio Calafiore (51).

The introduction of beating heart surgery led to innovations of stabilizers to facilitate the suturing (52, 53), devices for automated anastomosis and intravascular shunts to prevent ischemia (54).

This thesis will attempt to use the early clinical studies from Buffalo to demonstrate how OPCAB was introduced clinically in a large US hospital. The results will be discussed in the context of later publications. The thesis will then discuss the introduction of two important

technological modifications of the OPCAB procedure, the use of a stapling device to construct anastomosis between the aorta and saphenous veins and the use of intravascular shunt during grafting of the coronary arteries.

3.2 Introduction of new methods in surgery

The evaluation of surgical methods, techniques and tools follows a different path than pharmaceutical interventions (55). When new drugs are introduced in the US market place, the Federal Drug Administration (FDA) requires rigorous protocols, while medical devices may be approved based on simpler investigations, depending on the danger class they are assigned to (56). In Europe CE-marking is used to indicate approval of medical devices.

Surgical procedures may involve administration of pharmaceuticals, implantation of devices and a number of other steps making the evaluation complex. The learning curve and surgeon skills have impact on outcomes as well as patient selection and perioperative care. It may take years before a procedure is standardized and in the meantime further developments may modify outcomes.

McCulloch et al. described an orderly approach to surgical innovation, dividing it in four phases (57):

1 Idea: In this phase a small number of operations are performed as a proof of concept.

2a Development: In this phase the procedure is developed further and outcomes monitored.

2b Exploration: In this phase more surgeons and procedures are included and outcomes explored through databases and registries.

3 Assessment: In this phase the procedure is evaluated through controlled, preferably randomized investigations.

4 Long-term studies: In this phase late outcomes are compared using surveillance of patients entered in registries or randomized studies.

Although not every surgical procedure can fit into the scheme, it serves as a framework for how surgical innovation and development may be evaluated. Randomized controlled studies represent the gold standard when defined therapies are compared, but may not be possible or ethical if previous studies have shown large benefits or adverse effects of a certain therapy (58). Hepatic resection of metastatic colon cancer is considered highly effective in certain cases, but has not been subject to randomized studies (59). Similarly, patients with end-stage heart failure have not been entered in randomized studies comparing transplantation to medical therapy (60).

Early cardiac surgical procedures were developed to correct conditions causing death or disabilities. Successful outcomes represented great benefits compared to non-operative treatment that controlled studies were unjustified. As alternative methods, devices or surgical techniques were developed, controlled studies became warranted. Numerous randomized studies were performed to determine optimal method of myocardial preservation (61-63). Similarly, randomized studies were carried out to determine the optimal valvular prosthesis (64, 65). The issue of the learning curve was important when difficult operations like the “Senning” was compared to “Arterial switch” for transposition of the great arteries (66).

Although it was known that CABG effectively relieved angina pectoris (67), three randomized studies were designed to determine whether the procedure prolonged survival compared to medical therapy and in which specific patient groups (5, 68, 69).

In the mid 1990’s, CABG was routinely performed using CPB and arrested heart. Results from South America indicated that elimination of CPB improved results of coronary revascularization (47, 70, 71).

Since OPCAB was an established modification of coronary revascularization, it was considered safe to utilize it clinically. At our center in Buffalo, a few surgeons performed

OPCAB while others continued to operate using ONCAB, making it possible to compare the two procedures using NY State database. This could be classified as phase 2a and b in the scheme outlined above (57). The later phases of the evaluation of the OPCAB procedure were continued by the institution in Oslo, with which we already cooperated (72). A multicenter, partly blinded and randomized study, the ROOBY-study, was conducted in the VA system (73), contributing further knowledge to the question of OPCABs role in coronary revascularization.

Surgical procedures are frequently modified by introduction of new innovative technology, designed for patient benefit, making the operation simpler, faster or with fewer complications. Randomized studies demonstrate that stapled lower colonic anastomosis leaked less frequently than hand-sewn (74). Studies of such technical innovations may be simpler than studies comparing complex surgical procedures.

Use of automatic stapling devices to replace suturing of vascular anastomoses was anticipated to revolutionize CABG. Staplers create anastomoses quickly, in a standardized fashion and relatively independent of surgeons' skills. When staplers were used to create anastomoses of saphenous veins to the aorta, the chance of embolization and cerebral stroke could potentially be reduced. Investigations described in paper 3 and 4 were designed to study patency and embolization from anastomoses performed with stapled or hand-sewn aorto-saphenous anastomoses.

Prevention and management of myocardial ischemia is important in OPCAB. If flow in the native vessel is occluded during construction of distal anastomoses, hemodynamic collapse may occur due to ischemia. Flow may be maintained during grafting by insertion of a temporary shunt. Both interruption of flow and insertion of shunt had been in use, and reversal of ischemia demonstrated with shunting in individual cases (54), but the potential benefit of shunt (prevention of ischemia) or adverse effect (vessel damage) had not been

thoroughly evaluated in a prospective, randomized fashion. The study described in Paper 5 was designed to evaluate the potential benefit of shunt.

3.3 Ethical considerations

The studies from Buffalo (Papers 1 and 2) did not require approval from the Ethics Committee, since no patients were identified, and the study used prospectively collected data mandated by the state. The surgical procedures utilized in the OPCAB patients were thoroughly evaluated before implementation, by study tours, proctoring and review of literature. The operations were not considered experimental.

The studies described in papers 3-5 were prospective, controlled studies and required Ethics Committee approvals, which were obtained through submission of detailed protocols.

4. Aims of the thesis

Objectives

The first objective was to evaluate early outcomes and safety of OPCAB of ONCAB, using the public registry developed by New York (NY) State.

The second objective was to evaluate the potential benefit of two technical modifications of OPCAB operations:

Use of an automated proximal connector device to attach saphenous vein-grafts to the ascending aorta.

Use of intracoronary shunt during the performance of distal anastomosis with the purpose of preventing intraoperative ischemia.

Specific objectives:

Investigate the safety of OPCAB by comparing operative outcomes of the procedure to outcomes of ONCAB using data from a mandatory, public database. (Papers 1 and 2). Critically discuss the results of these studies and compare them to clinical series and controlled studies.

Compare clinical and angiographic outcomes in patients having the proximal saphenous vein graft anastomoses performed with connector devices or suture technique. Compare the amount of micro embolization to the brain measured by Transcranial Doppler in patients operated with connector and patients operated with traditional technique. (Papers 3 and 4).

Compare the development of ischemia of the myocardium perfused by the left anterior descending coronary artery (LAD) during OPCAB performed with obstructive snaring or

with intravascular shunt. Study the effects on anastomotic quality by performing on-table- and midterm- angiographic studies (Paper 5).

5. Material and methods

5.1 Early clinical material assessed with the New York State Database tool

Introduction

Buffalo General Hospital, a University hospital, located in Buffalo, New York, was an important provider of cardiac surgery. Before initiation of these studies, CABG was almost exclusively performed as ONCAB. OPCAB surgery was introduced in cooperation with surgeons from Italy and Brazil. The purpose of the study reported on in Papers 1 and 2 was to evaluate safety and clinical outcomes of OPCAB- compared to ONCAB- procedures using data from the state registry.

Hypothesis

The hypothesis of the studies reported on in Papers 1 and 2 was that OPCAB surgery could be performed with similar perioperative mortality and complication rates as ONCAB surgery.

Clinical material

All patients (n=2001) undergoing CABG at Buffalo General Hospital between January 1, 1995 and August 31, 1996 were included in Paper 1. Patients undergoing reoperative CABG (n=288) between January 1, 1995 and December 31, 1996 were included in paper 2. Patient referral was on individual basis, and each surgeon decided method of operation. Some cardiac surgeons performed most operations as OPCAB, while others performed ONCAB. During the study period 8.5% of patients were operated with OPCAB. Of reoperative cases, 36 % of the patients were operated with OPCAB.

Data collection and statistical analysis

NY State Department of Health required mandatory data-collection of all cardiac procedures in the state (75, 76). The data set included demographic data, surgical risk factors, operative

details, complications and death. Nurses and physicians collected data, which was quality controlled by data collectors and subject to random, on-site reviews by NY State Department of Health. Operative mortality was defined as death within 30 days of the operation or before discharge from the hospital. Complications were defined according to stringent and documentable criteria.

Operations performed using CPB were designated as ONCAB, and operations performed without CPB as OPCAB regardless of the intention at the beginning of the operation. Each patient's estimated mortality rate was calculated based on the risk factors of the individual. Using estimated mortality and observed mortality rates, average risk adjusted mortality was calculated. The risk adjusted mortality rate was used to compare institutions, surgeons and procedures and was important in the quality assessment of cardiac surgery providers (75).

Estimated-, observed- and risk adjusted mortalities were calculated for OPCAB and ONCAB and compared statistically. Similarly, complication-rates were compared. There was no risk adjustment for complications, although high estimated mortality rate also predisposed for more frequent complications (75).

Continuous data were analyzed using T-tests, while categorical data were analyzed by chi-square. All analyses were performed with SPSS software (SPSS Inc. Chicago, USA).

5.2 Investigation of new tools in OPCAB surgery

5.2.1 Evaluation of the Symmetry^R aortic connector vs. hand-sewn proximal anastomosis

Introduction

Cerebrovascular accident is a serious complication of coronary surgery. The elimination of CPB may reduce the risk (77). Embolization during manipulation of the ascending aorta has been thought to be a cause of strokes (78). The Symmetry^R connector, which made it unnecessary to clamp the aorta, could potentially reduce the chance of embolization. (79, 80).

Hypothesis

The hypothesis for 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. The study was designed as a prospective randomized investigation, but the pilot study raised suspicion of problems with the connector anastomosis. The study was redesigned to minimize the number of patients exposed to possible adverse effects. Randomization was abandoned and a control group with the same inclusion criteria as the pilot patients was included.

Angiographic investigations

At the end of the surgical procedure bypass grafts were studied with on-table angiography. The angiographic procedures were repeated after three months.

Transcranial Doppler studies

Thirty-two of the participants underwent monitoring with multifrequency Transcranial Doppler scanning to count the 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. Analyses were performed with SPSS software (SPSS Inc. Chicago, USA).

5.2.2 Evaluation of the use of intracoronary shunt in OPCAB surgery*Introduction*

Maintenance of hemodynamic stability is essential during OPCAB. Ischemia is the most frequent cause of hemodynamic collapse and conversion to CPB (81). A randomized study was designed to investigate whether intracoronary shunts could prevent ischemia during grafting of the LAD. Potential damage to the vessel from shunt insertion was investigated by on-table- and postoperative- angiography.

Hypothesis

The hypothesis of the study was that use of intracoronary shunt would prevent ischemia compared to occlusion during grafting of the LAD, and that shunt would not compromise the quality of the anastomosis.

Clinical material

Fiftysix patients were randomized to a “shunt group” in which the anastomosis between LIMA and LAD was performed with an intra-coronary shunt or to a “no-shunt group” in which the LAD was occluded with a proximal snare during grafting.

Detection of ischemia

Tissue Doppler with strain measurements (82) was utilized to detect myocardial ischemia. Transesophageal ultrasound (System FiVe^R echocardiograph (GE Vingmed Ultrasound, Horten, Norway) was used.

Study of anastomotic quality

Patients underwent coronary angiography on the operating table after completion of the operation and after 3 months.

Statistical analysis

Data were analyzed using T-tests for continuous data, chi-square for categorical data and logistic regression for further analysis. Analyses were performed with SPSS software (SPSS Inc. Chicago, USA).

6. Results

6.1 Operative outcomes in OPCAB surgery

Preoperative risks

Preoperative risk factors were more common in OPCAB than ONCAB resulting in a non-significantly higher estimated mortality rate in OPCAB patients. The difference was not significant.

Operative procedures

All ONCAB patients were operated with median sternotomy and normothermic or mild hypothermic CPB. In OPCAB patients, a varied surgical approach was utilized. In paper 1, 54 of 172 patients had minimally invasive thoracotomy (MIDCAB) with single bypass to LAD, and 2 patients had lateral thoracotomy. In reoperative cases 16 of the OPCABs were MIDCABs.

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

Mortality and complications

Estimated mortality rate was higher and observed mortality lower in OPCAB, giving identical risk adjusted mortality in the paper 1 material and lower risk adjusted mortality for OPCAB in reoperations. None of the mortality differences were significant.

Complication rates were non-significantly lower in OPCAB in paper 1; the differences were significant when reoperations were reviewed separately. Cardiovascular and other complications were reduced. This was confirmed in paper 2, where 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

Risk factors and preoperative status

There were no differences in preoperative clinical status or in operative risk factors.

On table angiographic studies

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.

Postoperative angiographic studies

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 of 32 studied Symmetry^R grafts, 16 were occluded and 8 were stenotic. The differences between groups were highly significant.

Embolization by Trans Cranial Doppler

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 in the Symmetry^R group, and there was a 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

Septal ischemia during grafting of LAD

Patients with occlusion of LAD and retrograde filling through collaterals did not develop ischemia. Most patients with antegrade flow in LAD developed ischemia when LAD was snared, and there was significant difference in the measurements of myocardial strain in shunted and non-shunted patients. Ischemia was reversed in almost all shunted patients, while the majority of non-shunted patients remained ischemic until reperfusion. None of the patients developed hemodynamic instability during grafting of the LAD.

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

Anastomotic quality

There was a trend towards improved anastomotic quality in the shunt-group at on-table angiogram, but on postoperative angiography findings were similar. 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. The new lesions corresponded to the location of the proximal snares, which were applied to occlude the LAD.

7. Discussion

New surgical treatment modalities are presented with increasing frequency. The scientific community and commercial operators bring new procedures and medical devices to the market, offering improved outcomes for various disease processes. Health authorities and third party payers require evidence of efficacy and safety before approving and allowing reimbursement of new treatments and procedures. The authorities, device companies and the medical community share responsibility for optimizing safety and minimizing adverse effects (55). Simultaneously, improved therapies should not be unduly delayed. As medical care becomes increasingly expensive and complex, it will be more important to prove a treatment's impact on quality of life and cost (83). Manufacturers of medical devices are responsible for obtaining FDA- or CE- approval prior to market introduction (56). Well-designed clinical studies are essential for the determination of outcomes related to new procedures and devices. Long- term follow-up and post market surveillance is important for the evaluation of new procedures and products as demonstrated in the drug-eluting stent controversy (84).

The controlled, prospective, randomized study represents the “gold standard” for comparison of competing therapies, although even such studies may be biased (85). After introduction of a new method or a device, it may be unrealistic to conduct randomized studies, since data needed for planning may be unavailable, and the new treatment may not have been adequately defined. Observational studies may reveal more variable results than randomized studies (86), but are of value when prospective randomized study may be difficult or even unethical (87, 88).

At the initiation of OPCAB in Buffalo outcome data for the procedure was largely unavailable. The NY-State registry made it possible to compare perioperative outcomes of OPCAB and ONCAB (36, 37).

In this early phase it was important to establish whether OPCAB was as safe perioperatively as the ONCAB technique. There was no assessment of outcomes beyond 30 days or after discharge from the hospital.

These studies demonstrated that patients operated with OPCAB, had a non-significantly elevated risk profile, and similar risk adjusted mortality as ONCAB. Complication rates were lower in OPCAB reoperations. It was concluded that OPCAB had similar operative safety profile as ONCAB, and that avoidance of CPB might reduce complications. An analysis of a much larger dataset from the NY State Department of Health, which included almost 50 000 patients, confirmed lower mortality and complication rates for OPCAB (89).

There were serious limitations to our early study. Assignment to treatment groups was biased and determined by the operating surgeon. NY State data has shown that the surgeon is an important risk factor (90), not taken into account in our study. The rate of OPCAB use varied, and surgeons with better skills may preferentially have performed one type of surgery.

“Intention to treat” methodology was not used to establish the groups. Patients, whose operation started as OPCAB and were converted to ONCAB, were included in the ONCAB group. Patients prepared for ONCAB who intraoperatively had contraindications to CPB and operated with OPCAB, were included in the OPCAB group. Patients converted to ONCAB were known to have unfavorable outcomes (81), which could bias results since complications or death would be reported in the ONCAB group. Similarly, conversion from ONCAB to OPCAB could improve the results of ONCAB by removing high-risk patients from that group.

The lack of intermediate- and long-term follow up was another limitation of these studies, as was the lack of postoperative angiography. A lower number of grafts combined with decreased patency could cause earlier return of ischemia and need for reinterventions. This was confirmed in the publication from NY State Dept. of Health (89), which demonstrated increased reintervention rates in OPCAB. A study from Emory University with more than 12 000 patients demonstrated lower operative mortality and complication rates in OPCAB (91), and similar 10-year survival.

In spite of the limitations, the studies from Buffalo had importance, being among the first to evaluate OPCAB, utilizing a mandatory database. Other studies have shown improved operative results, especially in high risk patients (46), (92).

The group at Rikshospitalet in Oslo, with which our team from Buffalo kept close contact, designed a randomized study, comparing OPCAB and ONCAB. Outcomes, including graft patency, were similar (72, 93). In contrast, another randomized study showed benefits of OPCAB, both perioperatively and at midterm (94). Similarly, a large meta-analysis demonstrated perioperative benefits of OPCAB on mortality, complication rates and resource use (95). The Belgian surgeon P. Sergeant improved outcomes by changing and re-engineering his department to OPCAB (96). The perioperative benefits of OPCAB were limited to high-risk patients in our studies (97, 98), as have been demonstrated by others (92,99). It may be difficult to design randomized studies for such groups of patients (100).

The question of whether OPCAB would offer benefits to the average patient requiring coronary surgery, needed to be answered by a multicenter, controlled study.

The ROOBY study was designed to evaluate in a randomized partly blinded study important safety and efficacy issues related to CABG with or without CPB. Operative mortality,

complication rates, graft patency and long term survival were included in this carefully powered study, conducted in Veterans Administration hospitals (73). The ROOBY study demonstrated worse composite outcomes and lower patency rates of vein grafts in the OPCAB group (101). It was argued that the surgeons participating in the study did not have adequate exposure to OPCAB (102), but the ROOBY investigators had demonstrated that outcomes were independent of surgeon volume (101). In our experience intraoperative graft patency verification is important in OPCAB since 3- 5% of grafts may need revision (103), (104). Graft verification does not appear to have been required in the ROOBY study, and this may have affected graft patency.

The role of CPB in coronary surgery remains controversial. Several randomized studies including the just cited ROOBY study (93, 101), indicated that OPCAB did not provide any benefit compared to ONCAB, while observational studies indicated significant benefits of OPCAB especially in high-risk patients (97, 105, 106). One reason may be that the randomized studies usually did not include high- risk cases (107).

OPCAB has been technically more challenging than ONCAB due to the need for hemodynamic stability, stabilization (108) and positioning (109) of the heart during grafting. As technological solutions became available, OPCAB became more reproducible. The Symmetry^R device was designed to decrease embolization and stroke rates, since clamping of the aorta became unnecessary during construction of proximal anastomoses. Although initial results were promising (79, 80), case reports showed early occlusion in the connector (110). We designed a randomized study of risks and benefits of the connector, but found more occlusions of vein grafts in the pilot group and redesigned the study.

The device was used in 23 patients, a sequential group of 23 OPCAB had the proximal anastomoses performed by suturing and partial aortic clamping.

Vein grafts attached to the aorta with Symmetry^R connectors had a high rate of occlusion and stenosis (111). The obstructive process seemed to originate in the connector (112, 113). Other investigators confirmed the findings (114, 115), while Japanese patients fared better (116). Some received anti-thrombotic therapy in addition to aspirin, in contrast to the patients in our study. Ethnic factors influence the tendency to arterial thrombosis and thrombocyte reactivity (117, 118). This may have played a role (119) as may have endothelial damage (120). The construction of the Symmetry^R device left metal surfaces exposed to blood, giving potential for thrombogenicity and intimal hyperplasia (121).

The use of a differently constructed connector resulted in better patency (122). That device did not expose metal components to blood, and clopidogrel was administered after surgery possibly improving the results (123).

Previous investigations had shown reduction in the number of emboli during construction of proximal anastomoses with Symmetry^R connectors (124). The use of ONCAB as control was not optimal since ONCAB produced higher embolic counts than OPCAB (125). The hypothesis that use of the Symmetry^R connector decreased embolic counts (124) was not supported by our study (126). On the contrary, patients operated with connector had more gaseous- and a trend towards more solid- emboli than patients with hand-sewn anastomoses. The importance of emboli during heart surgery has been documented (127). The amount of gaseous emboli in the Symmetry^R group was surprising, but may have been due to a Venturi effect (128).

Prior to these studies, Symmetry^R had been used extensively. A small study like ours, which included serial graft angiography contributed significantly to the market withdrawal of a dangerous device. The study, in which 46 patients were included and only 23 received the connector, demonstrated the value of carefully planned clinical- and angiographic- studies for introduction of cardiovascular technology.

Patients with critical coronary artery disease are prone to develop myocardial ischemia during OPCAB. The practice of occluding native vessels during anastomotic construction may cause hemodynamic collapse, necessitating conversion to CPB (129, 130). Insertion of an intracoronary shunt during grafting may prevent ischemia, although it has been questioned whether the small lumen have adequate blood flow (131). We demonstrated that ischemia was prevented in most patients with antegrade flow in the LAD, while most patients operated without shunt were ischemic. Patients with occlusion and retrograde filling of LAD did not develop ischemia, since blood was supplied from collaterals. Relief of ischemia in shunted patients was not dependent on shunt-size. Shunts smaller than 1.5 mm were not used (131). Although no evidence of hemodynamic compromise or leak of cardiac enzymes was seen in the study patients who did not get shunt, ischemia impairs ventricular function (132) and may cause hemodynamic collapse reversible by shunt (54).

Endothelial damage and development of coronary lesions have been considered a possible complication of shunt use (133, 134). Occlusive snaring of arteries results in vessel damage in animal models (135) and lower angiographic patency rates (136). Patency rates in this study were similar or improved when shunts was used. On angiograms performed after three months 15 vessels had obstructive lesions, proximal to the anastomosis, corresponding to the occlusive snare. Similar changes were not seen distal to the anastomosis, indicating that the use of shunts did not cause permanent damage to coronary arteries.

8. Conclusion

1) Clinical studies using a public database indicated that OPCAB was as safe as ONCAB and demonstrated a reduced rate of complications in high-risk patients. Although the methodology used had significant limitations, later studies supported the finding that OPCAB can be performed with similar safety as ONCAB. However, many of these studies were retrospective and not well controlled. Randomized studies have not shown the same benefits as those seen in observational-, registry based-, and meta-analytical investigations.

Regarding the applicability of OPCAB to relatively lower risk patients, the ROOBY study has raised significant concerns about whether OPCAB can be recommended as a primary technique for most surgeons (101). The issue of whether the surgeons who participated in ROOBY had enough OPCAB experience was raised (102), but the authors studied this issue carefully and did not demonstrate any outcome difference between surgeons with varying OPCAB experience (101). Glance et al. used material from NY-State Database and found no volume effect on OPCAB results (137). Based on the study from Oslo (93) and the well-designed and much larger ROOBY-study, we conclude that OPCAB should not be recommended for general use, especially for low risk patients. High-risk patients seem to benefit from OPCAB in centers experienced with the procedure (107), corresponding to the findings from our early clinical studies.

2) Use of the proximal connector device, Symmetry^R, resulted in unacceptable patency of vein grafts attached to the aorta during OPCAB. In contrast to what was expected, microembolization increased with use of the device. The device has been removed from the market.

3) Intracoronary shunts prevented ischemia during grafting of the antegradely perfused LAD during OPCAB. Anastomotic quality was independent of shunt use. On the basis of this

study, a recommendation could be given for using intravascular shunt during construction of coronary anastomosis in OPCAB procedures.

We have demonstrated that investigations using clinical registries may be valuable during the introductory phase of new surgical procedures. The limitations of such studies are many, and randomized clinical trials are essential when outcomes of different surgical procedures are compared. Introduction of new devices and tools in surgical procedures must undergo thorough evaluation under controlled circumstances before being recommended for routine use.

9. Future Prospects

OPCAB and ONCAB are used globally to treat patients with coronary disease. Utilization of the procedures varies between countries, regions, institutions and surgeons. In the US, OPCAB penetration is about 20% of surgical volume, while Japanese surgeons perform 60 % of revascularizations as OPCAB. In Scandinavia the procedure is used in less than 10%. Elimination of CPB makes OPCAB less invasive than ONCAB, but the magnitude of the procedure is still significant, and as we have demonstrated in this thesis, the elimination of CPB does come with additional risks.

The further minimization of coronary revascularization may require endoscopic or robotic approaches (138, 139) and use of automated connectors (140) or semi-automated sutures (141). Although such technologies are available and have been used in relatively small series, the methods have not been subject to large scale controlled studies. Robotic coronary surgery is technically difficult and in little use (142). The outcomes from connector use are variable at best. Reliable connectors with proven intermediate and long-term patency could potentially revolutionize CABG by making totally endoscopic procedures simpler (143).

Performing CABG thoracoscopically without CPB, is still exceedingly difficult. The fact that certain individuals may be able to perform such procedures, does not mean that they should be promoted for general use.

Reducing invasiveness remains a goal in coronary surgery, and ideally large incisions and use of CPB should be eliminated. Attempts to realize this goal should not compromise the main purpose of coronary surgery, to prolong and improve quality of life. Well-planned and non-biased investigations must be important parts of the realization of our clinical and technological goals.

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