7

Current Evidence of On-Pump Versus Off-Pump Coronary Artery By-Pass Surgery

Kim Houlind
Dept. of Vascular Surgery,
Kolding Sygehus - Little Belt Hospital
Denmark

1. Introduction

Conventional coronary artery by-pass grafting (CCABG) performed using cardioplegic arrest and cardiopulmonary by-pass is a very well documented treatment for ischemic heart disease. The operation often relieves chest pain and it improves survival for patients with triple- vessel disease and left main coronary artery disease.

Since it was introduced in the late 1960´es, CCABG has become one of the most commonly performed operations. In 2007, an estimated 408.000 surgical coronary revascularizations were performed in the United States alone (1)

Given the ageing populations in large parts of the world, CCABG is also increasingly being offered to elderly patients and to patients with co-morbidities. As a consequence, a significant number of operated patients suffer major or minor complications. Concerns have been raised that the use of cardiopulmonary by-pass (CPB) could cause neuro-cognitive dysfunction. Also, CPB has been linked to myocardial, renal and pulmonary damage. Several mechanisms have been suggested: Manipulation of the aorta during cannulation and clamping may cause dislodgment and embolization of atherosclerotic deposits, cardiac arrest may induce myocardial damage, and the long-lasting and repeated contact of blood with the non-biological surfaces of filters and tubing of the heart- lung- machine induce mechanical wearing of the formed elements and biochemical over-activation of the immune- and coagulation systems

Development of the Off-pump Coronary Artery By-pass (OPCAB) technique has been driven by concerns of these possible side-effects from CPB. On the other hand, concerns have been raised about whether the quality of anastomoses constructed "on the beating heart" - i.e. without cardiopulmonary by-pass and cardioplegic arrest – would be as good as that of the anastomoses performed during CCABG. The question remains controversial. Best estimates of the proportion of surgical coronary revascularizations performed as OPCAB in the United States is around 25%. Some surgical centres perform almost all coronary by-pass operations off-pump, while others hardly or never use this technique. Tradition and economy dictate that OPCAB is the preferred method in some parts of the developing world. In the beginning of the OPCAB-experience, evidence was limited to small, published series by individual surgeons (2-3). Although seemingly providing good results, these observations were hampered by the lack of a control group. Later studies from databases were difficult to interpret because the original intention-to-treat was not

recorded. This may have caused high-risk patients to be moved from one treatment group to the other (4-5).
From the late 1990ies to 2002 a significant technical development in stabilizing equipment led to a fast rise in the number of OPCAB procedures. From 2002 results from the first randomized studies failed to show a clear benefit and interest has cooled somewhat. A significant number of randomized studies have been conducted comparing very different end-points after OPCAB and CCABG. This chapter aims to review the results of these studies to assess the comparative effectiveness and safety of the two techniques.

2. Methods

Searching MEDLINE and Cochrane library using the terms » *OPCAB* «, » *off-pump* «, » *offpump* « OR »MIDCAB«, limited to English language june 23rd, 2010, provided 4788 abstracts that were read manually to find randomized, controlled trials. Two-hundred and twenty nine papers were retrieved and read before 90 papers, reporting results from 61 individual randomized, controlled trials, were identified.

3. Results

3.1 Effectiveness

Long term survival

The comparative long-term survival of OPCAB and CCABG is not well evaluated. The longest follow-up is in the OCTOPUS-study (6). Five years postoperatively 130/142 OPCAB-patients and 130/139 CCABG patients were alive (p=ns). Other studies with up to twelve months follow-up also failed to show any difference (7-13). Due to the relatively low risk of mortality associated with either operation, however, the statistical strength to detect any difference is not present in any of these studies.
The largest randomized study, the ROOBY-trial (14) showed a trend towards higher mortality in the OPCAB group at one year follow-up (4.1% vs. 2.9%, p=0.15) and a significant difference in cardiac deaths only (2.7% vs. 1.3%, p=0.03). On the other hand, another study with a mean 3.8 years follow-up of 300 patients showed a trend in the opposite direction with 5 deaths in the OPCAB-group and 10 in the CCABG-group (15).

Graft patency

Even with the use of contemporary cardiac stabilizers and intracoronary shunts, OPCAB remains more technically challenging than CCABG. Difficulties with positioning the heart may cause the surgeon to graft a less favourable part of the coronary artery. Performing the anastomosis is more difficult and may lead to stenosis at the anastomosis site. Furthermore, the coagulability of blood is increased after OPCAB compared to CCABG (16-20). Hence, a serious concern when introducing the OPCAB technique has been whether the number and quality of the grafts would be equivalent to what could be achieved using CPB.
In the vast majority of randomized, controlled trials, the OPCAB-patients tended to receive a lower number of grafts than the patients operated using CPB. In the largest studies and in a meta-analysis this difference was statistically significant (13-14, 21, 22) with a mean difference of 0.1-0.3 grafts. Several studies compared the number of grafts compared to a preoperative plan. In most of these studies, no difference was found (8-9,12, 14, 23), a few studies showed a difference in favour of CCABG, and one study found a difference in

favour of OPCAB (24). In this study, however, the absolute number of grafts was 0.2 lower in the OPCAB-group.
Allmost all of the earlier studies showed a trend towards poorer graft patency in OPCAB patients. A single, smaller study found this difference to be statistically significant (25). Also, the proportion of patent grafts in the largest study, the ROOBY-trial, was 82.6% in the OPCAB group and 87.8% in the CCABG group (p<0.01) (14). This difference, however, did not result in a higher number of myocardial infarctions in the OPCAB group.
In studies performed by few, dedicated OPCAB surgeons, the difference in number of grafts was very small and not statistically significant (12, 24). The study by Khan (25), the SMART study (14), and the Best Bypass Surgery Study (26) differentiated the findings and found a higher proportion of occluded grafts at right and circumflex territories and fewer occlusions in the LAD territory. Lingaas et al only found differences in graft patency between OPCAB and CCABG to be significantly different when comparing vein grafts as opposed to internal mammary artery grafts (10).

Recurrent or persistent chest pain

An important parameter is freedom from chest pain. In the Octopus trial (6, 24), 89.0% experienced freedom from chest pain in the OPCAB group compared to 89.3% in the CCABG-group (p=ns). At five years follow-up, these numbers were down to 82.3% and 87.7%, respectively (p=ns). At one year follow-up, ergometer testing was performed in 81% of the patients. It was found to be negative in 79.8% of CCABG patients and 83.1% of OPCAB patients (p=ns). In the SMART-study, chest pain was present at one-year follow-up in 0% of CCABG and 3% of OPCAB patients, respectively (p=ns) (12). In a separate publication, using a specific questionnaire on chest pain in the 400 patients involved in the BHACAS1 and BHACAS2-studies, no difference was found after a median follow-up of three years (27).

Reintervention

Given the lower number of patent grafts in the OPCAB groups, a greater need for coronary re-intervention might be expected. Only few of the published trials have had long enough follow-up for this question to be evaluated. In the BHACAS-1 study, three percent of both OPCAB and CCABG patients had had a reintervention – either percutaneous or surgical – within a median three years follow-up (7). The longest follow-up, which was published by the Octopus trialists, reported 7.7% of OPCAB-patients and 5% of CCABG patients to have undergone reintervention after five years (6). In the ROOBY-trial, the proportion undergoing reintervention was 4.6% in the OPCAB group and 3.4% in the CCABG group at one year follow-up. Neither individual studies nor metanalyses found thiese differences to be statistically significant (21, 26).

Quality of life

A number of studies compare self-reported, health related quality of life after OPCAB and CCABG. Medical Outcomes Study-Short Form 36 (MOS SF-36) is the most commonly used tool. In this questionnaire eight scales cover physical, mental, and social well-being (28). One study found a significantly higher score among CCABG-patients in one of the eight scales ("Role emotional") in contrast to another study who favoured OPCAB patients in the dimension "Social Relationships", using another questionnaire (29,30). In general, few significant inter-group differences have been found, given the multiple tests being performed.

On the other hand, a significant increase in self-reported, health related quality of life is invariably found in both groups comparing preoperative and postoperative status (24, 27, 31).

3.2 Safety

Periperative mortality

Most of the randomized trials have included either consecutive patients or patients with low perioperative risk due to young age, few comorbidities, and need for relatively few grafts. The expected operative mortality for this group of patients is too low for any of the randomized trials to have sufficient statistical strength to detect a difference between treatment groups. This is also true for metaanalyses of randomized trials.

Among the larger non-randomized studies, Cleveland et al. analyzed data from the Society of Thoracic Surgeons (STS) database (4). They included operations performed in 1998 and 1999 in 126 centers with experience in OPCAB surgery. A total of 118.140 CCABG and 11.717 OPCAB procedures were included. The risk adjusted mortality in this comparison was 2.94% in the CCABG group and 2.32% in the OPCAB group ($p < 0.0001$). Magee and co-workers compared the results of 6.466 CCABG and 1.983 OPCAB procedures in two American centres in 1998-2000 (5). In spite of a significantly higher preoperative morbidity in the OPCAB-group, mortality in the OPCAB group was 1.8% against 3.5% in the CCABG-group ($p = 0.002$). However, these comparisons were not performed according to the principle of intention–to-treat. This is a significant drawback, since patients who were converted to CCABG during the operation after initially attempting to perform OPCAB are analyzed as belonging to the CCABG group. Hence, the complications of the most complicated OPCAB-procedures were exported to the CCABG-group.

It is worth noting that one of the few randomized studies that specifically included high-risk patients who received an acute operation, found a significantly higher mortality in the CCABG group than in the OPCAB group (7.7% vs. 1.6%, $p=0.04$) (32). However, this study exclusively included patients who only needed grafting the LAD territory, which would be expected to favour OPCAB.

3.3 Other cardiac complications

Myocardial damage

None of the randomized studies or meta-analyses has documented any significant difference in the incidence of clinical peri-operative myocardial infarction. However, many randomized studies provide evidence of a lower, subclinical release of biochemical markers of myocardial damage among patient operated using OPCAB (12, 25, 32-42). This tendency is very robust across the different studies, and it is even preset in a study that showed a significantly higher proportion of graft occlusions in the OPCAB group (25). These differences are ascribed to ischemia and reperfusion with cardioplegia. Apart from creatinine-kinase type B (CK-MB) and Troponine T, also atrial natriuretic peptide and heart type fatty-acid binding protein tend to exhibit a higher raise after CCABG than after OPCAB (36). All of these differences, are, however in an order of magnitude smaller than what has so far been considered clinically relevant. By detailed measurement of left ventricular ejection fraction between groups, no inter-group differences were found (42). On the other hand, the long term follow-up of the OCTOPUS-study showed that the patients with the highest release of CK-MB had the highest

risk of experiencing a clinical myocardial infarction during the following year (43). A number of confounding issues may, however, be relevant.
In a study of myocardial biopsies, it was found that the concentration of reduced glutathion recovered more rapidly in CCABG than OPCAB patients (38). For the OPCAB-operations, a proximal snare was used for occlusion of the vessel while performing the anastomosis. This finding suggests that cardioplegia is better tolerated than occlusion. Still, a higher increase in CK-MB was found in the CCABG-group. Together, these findings suggest that the myocardium in the territory of the occluded vessel suffers more from occlusion but a less profound damage to the entire myocardium is caused by ischemia and reperfusion. Which of these two situations pose the largest threat to heart function is not clear. Gadolinium contrast enhanced magnetic resonance perfusion imaging, reflecting permanent damage to the myocardium, failed to detect a difference between treatment groups despite a higher release of Troponine- I in the CCABG-group (39). On this background, it was speculated whether some of the Troponine leak represented protein release from non-structurally bound cytosolic pools, rather than true myocardial necrosis. In another study, micro-dialysis was used to sample myocardial interstitial fluid during and after surgery (44). More abnormal values were found during CCABG than during OPCAB. It was not stated in the paper whether samples were taken within or outside the area of the temporally occluded vessel during OPCAB.

Atrial fibrillation

In the BHACAS-1 study, Heart rate and rhythm were continuously monitored for 72 postoperative hours. The incidence of postoperative atrial fibrillation was found to be 45% among CCABG patients as compared to 8% among patients operated with OPCAB ($p<0.001$) (45). A large number of later studies, including the BHACAS-2 study, have confirmed this tendency but with a much smaller difference between groups. The tendency is statistically significant in some of these studies and in meta-analyses (21).

Postoperative inotropic support and low cardiac output syndrome

Need for inotropic drugs after the operation may reflect either transient or permanent heart failure. Several, larger studies do not report this end-point (13-14), but among the ones that do, there is a trend towards a higher incidence in patients operated using cardiopulmonary by-pass. A meta-analysis of 16 studies including 1655 patients found a need for inotropic support postoperatively in 23.6% of CCABG and 15.1% of OPCAB patients ($p=0.04$)(21). Other studies report the incidence of "low cardiac output syndrome", defined as need for intra-aortic balloon pump, need for inotropic drugs or pressor drugs. One of the larger studies reports a significant difference (12), while others do not (13, 46).

3.4 Neurological complications

Stroke

Theoretically, the use of cardiopulmonary by-pass may cause stroke by a number of different mechanisms. These include the manipulation of the ascending aorta for cannulation and clamping, gaseous or particulate emboli formed in the by-pass circuit, and accidental interruption of flow.
Also, post-operative atrial fibrillation may cause strokes in spite of adequate antithrombotic treatment. For these reasons, an important argument for favouring OPCAB has been the intention to reduce the rate of peri-operative strokes.
In low risk patients, the risk of suffering a peri-operative stroke is between 1 and 1.5%. Hence, none of the individual, randomized, controlled trials have had the statistical strength

to prove a difference. A single meta-analysis only just managed to show a significant difference (47), but other analyses, comprising just as many or more trials and patients, failed to prove OPCAB superior (21). Therefore, until the time of the publication of the ROOBY-trial (14), evidence was ambiguous. In the ROOBY trial, however, the trend was opposite that of most earlier studies with 1.3% strokes in the OPCAB-group and 0.7% in the CCABG-group (p=0.28). In view of the large volume of this trial compared to all the other trials, it can no longer be stated that there is a clear trend in favour of OPCAB to reduce the rate of peri-operative strokes in younger, low-risk patients. It is, however, worth noting, that the OPCAB technique is still being developed in order to reduce stroke rate. An increasing number of surgeons favour a "no-touch-aorta" technique, placing proximal anastomoses end-to-side in a mammary artery graft rather than on the aorta itself. In addition, some centers aim to reduce the risk of embolisation due to atrial fibrillation by ligating the left atrial appendage. Excellent results have been produced, but not tested in randomized trials.

Neurocognitive dysfunction

Several randomized trials have used neuro-psychological or neuro-cognitive tests to detect perioperative cerebral damage lesser than overt stroke. In some of these studies, early postoperative testing favoured OPCAB (48-49) while others found no significant difference (50-53). Zamvar and coworkers, only including patients with triple-vessel disease, performed a battery of neuro-cognitive tests one week and ten weeks postoperatively, comparing with pre-operative test results. At both occasions, they found a significantly higher degree of neuro-cognitive dysfunction in CCABG-patients than in OPCAB-patients (54).

In the Octopus trial (6, 41, 49), a significant difference in favour of OPCAB was found after three months but not after one year nor after five years of follow-up. At five years follow-up, a more than fifty per cent decline in scores at neuro-cognitive testing was found in both groups, illustrating the fact that patients with ischemic heart disease in general have an increased risk of neurocognitive decline. A similar decline has been documented after three years in a non- surgical control group (55).

Surrogate end-points of brain damage are often used in randomized trials comparing OPCAB with CCABG. These include release of the S-100 peptide and detection of High Intensity Transcranial Doppler Signals (HITS) as well as changes in serum concentrations of different hormones.

When S-100 is detected in peripheral blood, it is seen as a marker of damage to, and increased permeability of, the blood-brain barrier. There is good evidence from randomized controlled trials that the increase of S-100 is higher after CCABG than after OPCAB (48, 51, 56). In two out of three studies these increases are compared to the results of postoperative, neurocognitive tests, but none of the studies showed any correlation between S-100 levels and neurocognitive function. In one of the studies one patient suffered a major stroke resulting in paralysis of an arm and a leg without a major increase in blood concentrations of S-100. Hence, the clinical significance of relase of S-100 is uncertain.

Characteristic high-intensity signals – HITS - can be detected by trans-cranial measurement of Doppler signals from the medial cerebral artery. The amount of HITS increase during manipulation of the aorta, especially during cannulation, clamping, and declamping. A lower number of HITS are observed at the beginning of cardiopulmonary by-pass. It is not clear, to what extent HITS represent particulate emboli being released from vessel walls, tubes or filters and what proportion of HITS are being generated by gaseous microemboli and turbulence. Several studies have demonstrated a larger amount of HITS in patients undergoing CCABG than in patients undergoing OPCAB (48, 53). One study showed a correlation between the number of HITS detected in the CCABG-group and the results of one out of three neurocognitive tests. This correlation, however, according to a figure in the publication, relies heavily on the results from one patient (48). No correlation was found with the results of any of the other two tests nor, in the OPCAB group, between the number of HITS and the results of any of the three tests. In a larger study, a lower neuro-cognitive score was found at discharge from hospital in patients who had undergone CCABG compared to patients operated with OPCAB-tecghnique (53). This difference was not found at six weeks and six months follow-up and no correlation was found between number of HITS and postoperative cognitive function.

To summarize, there is strong evidence of more HITS when performing CCABG than OPCAB. There is, however, no evidence that these HITS represent emboli or that they have any significance with regard to early or late postoperative cognitive dysfunction.

In another study, cerebral SPECT-scans revealed more evidence of microemboli after CCABG than after OPCAB (50). However, like in the case of HITS and S-100 release, this finding could not be shown to correlate with the performance of patients in neuro-cognitive tests.

One study suggests that changes in neuro-cognitive function and tendency to mental depression after both CCABG and OPCAB are related to disturbance of the circadian rhytms of cortisol and melatonine release (57). These disturbances are, though, also susceptible to other factors and they occur after both types of procedures. The clinical significance of this finding is not clear.

3.5 Renal function

Transient or permanent renal impairment are well known complications to cardiac surgery (58). This risk has be attributed to the systemic, inflammatory response, hypoperfusion of the kidneys during operation and, possibly, the non-pulsatile nature of flow during cardiopulmonary by-pass (59).

Clinically significant, new onset renal failure – defined either as need for dialysis or by increase in biochemical markers to pathological levels – occur at a rate of approximately 1-2 per cent of the low-risk patients typically included in randomized, controlled trials. None of these studies have, therefore, had the statistical strength to detect a difference in the incidence of this end-point between patients operated with OPCAB or CCABG. Even in a large meta-analysis by Cheng et al (21) showing an odds ratio of 0.58 in favour of OPCAB the confidence limits were too wide to allow statistical significance.

On the other hand, when comparing biochemical markers of sub-clinical renal damage, evidence from several clinical trials is in favour of OPCAB (11, 60-61). This difference is clear whether glomerular or tubular damage is compared (60). In one study, the difference between creatinine clearance after CCABG compared to OPCAB was especially high in patients with diabetes, hypertension and heart failure (11). In one trial, comparing patients operated using pulsatile flow in the cardiopulmonary by-pass circuit, no difference in postoperative renal function was found between patients operated with OPCAB and CCABG. This finding seems to confirm the theory that non-pulsatile flow contributes to the subclinical renal impairment often seen after cardiac surgery using cardiopulmonary by-pass (61).

3.6 Lung function

During cardiopulmonary by-pass, ventilation is commonly stopped to prevent the motion of the lungs interfering with surgery. During the early postoperative period patients who have

undergone cardiac surgery are prone to develop atelectasis. Theoretically, this may be prevented by OPCAB where the lungs are continuously ventilated.
Most of the authors addressing this question, found that postoperative ventilation times were longer for patients who underwent CCABG than for those who underwent OPCAB. There is good evidence from a meta-analysis for a lower incidence of chest infections and shorter postoperative need for ventilator assistance after OPCAB (21), although one study of low-risk patients contradicts this finding (23). Most of these studies may be biased by the fact that the staff members deciding the time when the patients should be weaned from the ventilator were not blinded with regard to the type of operation that had been performed. On the other hand, evidence is strengthened by the fact that the one study in which the staff was indeed blinded also found a shorter postoperative need of ventilation in the OPCAB group (12).
In two trials, patients with chronic obstructive pulmonary disease were studied specifically. In one of these studies, a significantly higher postoperative decrease in lung function was found among post-CCABG patients (62). In the other study, a shorter time to extubation and shorter stay in intensive care unit was found among OPCAB patients (63). Also, in a study of patients with recent myocardial infarction, a shorter ventilation time was documented for OPCAB-patients compared to CCABG-patients (32).
It has been suggested, that the mechanism behind impaired lung function after CCABG was changes in alveolar gas exchange as a result of increased interstitial oedema. This effect has, however, been specifically addressed by several studies finding that this effect is comparable in OPCAB and CCABG-patients and most significant during the first few postoperative hours (23, 42, 64-65).In a randomized comparison of patients with single- and double-vessel disease, a significantly higher veno-arterial shunting was found after cardio-pulmonary by-pass (23). It is still unknown whether this result can be generalized to patients with triple vessel disease where the OPCAB-technique is complicated by the need to manipulate the heart.

3.7 Gastro-intestinal complications

There is evidence from a single, large, randomized trial that the risk of gastro-intestinal complications - including ischaemic bowel, hepatic failure, gastric bleeding, perforated duodenal ulcer, acute cholecystitis, and acute pancreatitis - is higher after CCABG than after OPCAB (66). This study, however, excluded patients needing grafts to the circumflex territory. This selection can be expected to favour OPCAB. Other, larger, randomized trials either do not find this difference or do not report this endpoint (6-7, 12-14).

3.8 Inflammatory response

A generalized inflammatory response is activated by any sort of surgery, but is aggravated by cardio-pulmonary by-pass. The blood–air interface and the contact between the blood and the artificial surfaces of the CPB circuit play important roles. Cooling and heating as well as ischemia and reperfusion of the myocardium are other factors that tend to activate a systemic inflammatory response.
The inflammatory response includes both humoral and cellular elements. Randomized comparisons between CCABG and OPCAB shows the CCABG patients to have increased serum-levels of a multitude of different substances including tumor necrosis factor-alpha, interleukins 6 and 8, selectin, c-reactive protein, intracellular adhesion molecule – 1, and vascular endothelial growth factor (39,67-72). Also, the expression of a scavenger molecule on monocytes is significantly higher in "on-pump" patients (73). It has been proposed that

this inflammatory over-activation can be harmful and lead to organ failure and infections. No definitive coupling has, however been made in coronary artery by-pass patients between inflammatory markers and clinical outcome.
Similarly, oxidative stress is known to be higher in patients undergoing cardiopulmonary by-pass. Theoretically, this may cause tissue damage, but no practical clinical consequence has been proven in patients (74).

3.9 Blood loss and coagulation

Transfusions have been shown to be associated with substantial incremental increases in risks of mortality and morbidity for patients undergoing cardiac surgery. There is good evidence from a number of large, randomized trials that blood loss and need for transfusions is lower after OPCAB than after CCABG (7,15, 24, 45, 74-76). This finding is often explained by the activation and subsequent deactivation of platelets and humoral coagulation factors by the non-biological surfaces of the cardiopulmonary by-pass circuit. The alpha granules of the platelets are being depleted and the platelet count is reduced by dilution. Also fibrinolytic cascades are activated.
Some characteristics of the study protocols may, however, influence these results. Typically, different protocols for heparinization and reversion with protamine are used for the study groups, increasing bleeding tendency in the CCABG-groups. In addition, some studies apply a fixed value of haematocrit as an indication for transfusion. Because of dilution caused by the priming volume of the cardiopulmonary by-pass circuit this will increase the risk of transfusion in the CCABG-group compared to the OPCAB-group, even if this dilution were better treated using diuretics.

3.10 Cost-effectiveness

Some of the clinical trials have covered heath economic analyses up to twelve months after surgery. All these studies find OPCAB to be less costly while providing a similar gain of Quality Adjusted Life Years (12-13, 24, 29, 50). As an example, the Octopus study (24) found costs of OPCAB to be $13.069 versus $14.908 (P<0,01) at one year follow up for a one year QALY of 0,83 in the CCABG group versus 0,82 in the OPCAB group. Long term data on health economics are not available.

4. Summary

In conclusion, this review of currently published randomized controlled trials comparing outcomes after OPCAB and CCABG resulted in the following findings:

- There is no strong evidence that one treatment is superior with regard to preventing death from any cause, chest pain or reintervention for ischemia. There is evidence from one large, well performed study that the risk of cardiovascular death is higher at one year follow-up after OPCAB compared to CCABG. There is some evidence from large trials that patients undergoing OPCAB receive fewer grafts than patients undergoing CCABG, but this tendency is very small in studies performed in centres with a large experience in OPCAB. There is strong evidence that graft patency is lower after OPCAB, but not in very experienced centres.
- There is no evidence of a difference in peri-operative risk of mortality between the two treatments. There is strong evidence of a larger release of biochemical markers of

myocardial injury and of increased incidence of atrial fibrillation after CCABG but no difference in the incidence of clinically important myocardial infarctions.

There is conflicting evidence of increased need of inotropic or pressor drugs and of intra-aortic balloon pump after CCABG. There is strong evidence of increased release of biochemical markers of renal insufficiency after CCABG but not of postoperative need of dialysis.

There is conflicting evidence of differences in incidence of perioperative stroke. Limited evidence suggests that neuro-cognitive dysfunction is larger early after CCABG than after OPCAB. However, no difference is detected later than three months after the operation.

There is strong evidence of fewer chest infections and shorter ventilation times after OPCAB. Risk of peri-operative bleeding and need for transfusions is higher after CCABG than after OPCAB. There is conflicting evidence regarding increased risk of gastro-intestinal complications after CCABG.

There is strong evidence from a number of randomized, controlled trials that the inflammatory response and the oxidative stress is higher after CCABG than after OPCAB. However, the clinical significance of these findings remain unclear.

Finally, there is strong evidence that OPCAB is more cost-effective than CCABG at up to twelve months follow-up. Long term data on cost-effectiveness are not available.

5. References

[1] Roger VL, Go AS, Lloyd-Jones DM et al. Heart Disease and Stroke Statistics_2011 Update: A report from the American Heart Association. Circulation 2011;123:e18-e209

[2] Benetti FJ. Direct coronary surgery with sphenoid vein bypass without either cardiopulmonary bypass or circulatory arrest. J Cardiovasc Surg 1985;26:217-22

[3] Buffolo E, Andrade JC, Succi J et al. Direct myocardial revascularization without cardiopulmonary bypass. Thorac Cardiovasc Surg 1985:33;26-9

[4] Cleveland JC Jr, Shroyer AL, Chen AY, Peterson E, Grover FL. Off-pump coronary artery bypass grafting decreases risk-adjusted mortality and morbidity. Ann Thorac Surg. 2001;72(4):1282-8

[5] Magee MJ, Jablonski KA, Stamou SC, Pfister AJ, Dewey TM, Dullum MK, Edgerton JR, Prince SL, Acuff TE, Corso PJ, Mack MJ. Elimination of cardiopulmonary bypass improves early survival for multivessel coronary artery bypass patients. Ann Thorac Surg. 2002;73:1196-202

[6] van Dijk D, Spoor M, Hijman R, Nathoe HM, Borst C, Jansen EWL, Grobbee DE, de Jaegere PTP, Kalkman CJ for the Octopus Study Group. Cognitive and Cardiac Outcomes 5 Years After Off-Pump vs On-Pump Coronary Artery Bypass Graft Surgery. JAMA 2007;297(7):701-708

[7] Angelini GD, Taylor FC, Reeves BC, Ascione R.Early and midterm outcome after off-pump and on-pump surgery inBeating Heart Against Cardioplegic Arrest Studies (BHACAS 1 and 2): a pooled analysis of two randomised controlled trials. Lancet 2002; 359: 1194–99

[8] Czerny M, Baumer H, Kilo J, Zuckermann A, Grubhofer G, Chevtchik D, Wolner E, Grimm M. Complete Revascularization in Coronary Artery Bypass Grafting With and Without Cardiopulmonary Bypass. Ann Thorac Surg 2001;71:165–9

[9] Légaré J-F, Buth KJ, King S, Wood J, MD; Sullivan JA, Friesen HC, Lee J, Stewart K, Hirsch GM. Coronary Bypass Surgery Performed off Pump Does NotResult in Lower In-Hospital Morbidity Than Coronary Artery Bypass Grafting Performed on Pump. Circulation. 2004;109:887-892

[10] Lingaas PS, Hol PK, Lundblad R, Rein KA, Tønnesen TI, Svennevig JL, Hauge SN, Vatne K,Fosse E. Clinical and Angiographic Outcome of Coronary Surgery with and without Cardiopulmonary Bypass: A Prospective Randomized Trial. The Heart Surgery Forum 2003:302621

[11] Sajja LR, Mannam G, Chakravarthi RM, Sompalli S, Naidu SK, Somaraju B, Penumatsa RR. Coronary artery bypass grafting with or without cardiopulmonary bypass in patients with preoperative non–dialysis dependent renal insufficiency: A randomized study. J Thorac Cardiovasc Surg2007;133:378-88

[12] Puskas JD, Williams WH, Mahoney EM, Huber PR, Block PC, Duke PG, Stables JR, Glas KE, Marshall JJ, Leimbach ME, McCall SA, Petersen RJ; Bailey DE, Weintraub WS, Guyton RA. Off-pump vs conventional coronary artery bypass grafting: early and 1 year graft patency, cost, and quality-of-life outcomes. A randomized trial. JAMA 2004;291:1841-1849

[13] Straka Z, Widimsky P, Jirasek K, Stros P, Votava J, Vanek T, Brucek P, Kolesar M, Spacek R. Off-Pump Versus On-Pump Coronary Surgery: Final Results From a Prospective Randomized Study PRAGUE-4. Ann Thorac Surg 2004;77:789 –93

[14] Shroyer AL, Grover FL, Hattler B, Collins JF, McDonald GO, Kozora E, Lucke JC, Baltz JH, Novitzky D, for the Veterans Affairs Randomized On/Off Bypass (ROOBY) Study Group. On-Pump versus Off-Pump Coronary-Artery Bypass Surgery N Engl J Med 2009;361:1827-37.

[15] Karolak W, Hirsch G, Buth K, MSc, and J-F Legare. Medium-term outcomes of coronary artery bypass graft surgery on pump versus off pump: Results from a randomized controlled trial. Am Heart J 2007;153:689-95

[16] Ascione R, Williams S, Lloyd CT, Sundaramoorthi T, Pitsis AA, Angelini GD. Reduced postoperative blood loss and transfusion requirement after beating-heart coronary operations: A prospective randomized study. Ann Thorac Surg 1999;68:493– 8

[17] Paparella D, Galeone A, Venneri MT, Coviello M, Scrascia G, Marraudino N, Quaranta M, de Luca L, Schinosa T, Brister SJ, Activation of the coagulation system during coronary artery bypass grafting: Comparison between on-pump and off-pump techniques. J Thorac Cardiovasc Surg 2006;131:290-7

[18] Parolari A, Mussoni L, Frigerio M, Naliato M, Alamanni F, Galanti A, Fiore G, MD, Veglia F, Tremoli E, Biglioli P, Camera M. Increased prothrombotic state lasting as long as one month after on-pump and off-pump coronary surgery. J Thorac Cardiovasc Surg 2005;130:303-8

[19] Parolari A, Mussoni L, Frigerio M, Naliato M, Alamanni F, Polvani GL, Agrifoglio M, Veglia F, Tremoli E, Biglioli P, Camera M. The role of tissue factor and P-selectin in the procoagulant response that occurs in the first month after on-pump and off-pump coronary artery bypass grafting J Thorac Cardiovasc Surg 2005;130:1561-6

[20] Tanaka KA, Thourani VH, Williams WH, Duke PG, Levy JH, Guyton RA, Puskas JD Heparin anticoagulation in patients undergoing off-pump and on-pump coronary bypass surgery. J Anesth 2007;21:297–303

[21] Cheng DC, Bainbridge D, Martin JE, Novick RJ. The Evidence-based Perioperative Clinical Outcomes Research Group. Does Off-pump Coronary Artery Bypass Reduce Mortality, Morbidity, and Resource Utilization When Compared with Conventional Coronary Artery Bypass? A Meta-analysis of Randomized Trials. Anesthesiology. 2005;102(1):188-203
[22] Widimsky P, Straka Z, Stros P, Jirasek K, Dvorak J, Votava J, Lisa L, Budesinsky T, Kolesar M, Vanek T, Brucek P. One-Year Coronary Bypass Graft Patency A Randomized Comparison Between Off-Pump and On-Pump Surgery. Angiographic Results of the PRAGUE-4 Trial. Circulation. 2004;110:3418-3423
[23] Kochamba GS Yun KL, Pfeffer TA, Sintek CF, Khonsari S.Pulmonary Abnormalities After Coronary Arterial Bypass Grafting Operation: Cardiopulmonary Bypass Versus Mechanical Stabilization. Ann Thorac Surg 2000;69:1466 –70
[24] Nathoe HM, Dijk D, Jansen EWL, Suyker WJL, Diephuis JC, Boven WJ, Riviere AB, Borst C, Kalkman CJ, Grobbe DE, Buskens E, Jaegere PPT. A comparison of on-pump and off-pump coronary bypass surgery in low-risk patients. The New England Journal of Medicine 2003;348:394-402.
[25] Khan NE, De Souza A, Mister R, Flather M, Clague J, Davies S, Collins P, Wang D, Sigwart U, Pepper J. A Randomized Comparison of Off-Pump and On-Pump Multivessel Coronary-Artery Bypass Surgery. N Engl J Med 2004;350: 21-8.
[26] Møller CH, Perko MJ, Lund JT, Andersen LW, Kelbæk H, Madsen JK, Gluud, C, Steinbrüchel DA. Graft patency after off-pump versus on-pump coronary artery surgery in high-risk patients. Scandinavian Cardiovascular Journal, 2010; 44: 161–167
[27] Ascione R, Reeves BC, Taylor FC, Seehraa HK, Angelini GD.Beating heart against cardioplegic arrest studies (BHACAS 1 and 2): quality of life at mid-term follow-up in two randomised controlled trials. European Heart Journal 2004; 25: 765–770
[28] Bjorner JB, Kreiner S, Ware JE, Damsgaard MT, Bech P. Differential item functioning in the Danish translation of the SF-36. J Clin Epidemiol 1998;51:1189-202.
[29] Al-Ruzzeh S, George S, Bustami M, Wray J, Ilsley C, Athanasiou T, Amrani M. Effect of off-pump coronary artery bypass surgery on clinical, angiographic, neurocognitive, and quality of life outcomes: randomised controlled trial BMJ 2006;332:1365-72
[30] Jensen BO, Hughes P, Rasmussen LS, Pedersen PU, Steinbrüchel DA. Health-related quality of life following off-pump versus on-pump coronary artery bypass grafting in elderly moderate to high-risk patients: a randomized trial. European Journal of Cardio-thoracic Surgery 2006;30:294—299
[31] Tully PJ, Baker RA, Kneebone AS, Knight JL. Neuropsychologic and Quality-of-Life Outcomes After Coronary Artery Bypass Surgery With and Without Cardiopulmonary Bypass: A Prospective Randomized TrialJournal of Cardiothoracic and Vascular Anesthesia 2008;22:515-521
[32] Fattouch K, Guccione F, Dioguardi P, Sampognaro R, Corrado E, Caruso M, Ruvolo G. Off-pump versus on-pump myocardial revascularization in patients with ST-segment elevation myocardial infarction: A randomized trial. J Thorac Cardiovasc Surg 2009;137:650-7
[33] Gulielmos V, Menschikowski M, Dilla H-M, Ellera M, Thiele S, Tugtekina SM, Jarossb W, Schuelera S. Interleukin-1, interleukin-6 and myocardial enzyme response after coronary artery bypass grafting: a prospective randomized comparison of the

conventional and three minimally invasive surgical techniques. European Journal of Cardio-thoracic Surgery 2000;18:594-601
[34] Krejca M, Skiba J, Szmagala P, Gburek T, Bochenek A. Cardiac troponin T release during coronary surgery using intermittent cross-clamp with fibrillation, on-pump and off-pump beating heart. European Journal of Cardio-thoracic Surgery 1999;16: 337-341
[35] Chowdhury UK, Malik V, Rakesh Y Seth S, Ramakrishnan L, Kalaivani M, Reddy SM, Subramaniam GK, Govindappa R, Kakani M. Myocardial injury in coronary artery bypass grafting: On-pump versus off-pump comparison by measuring high-sensitivity C-reactive protein, cardiac troponin I, heart-type fatty acid–binding protein, creatine kinase-MB, and myoglobin release. J Thorac Cardiovasc Surg 2008;135:1110-9
[36] Malik V, Kale SC, Chowdhury UK, Ramakrishnan L, Chauhan S, Kiran U.Myocardial Injury in Coronary Artery Bypass Grafting On-Pump versus Off-Pump Comparison by Measuring Heart-Type Fatty-Acid–Binding Protein Release Tex Heart Inst J 2006;33:321-7
[37] Medved I, Anic D, Zrnic B, Ostric M Saftic I. Off-Pump versus On-Pump – Intermittent Aortic Cross Clamping – Myocardial Revascularisation:Single Center Expirience. Coll. Antropol. 2008;32:381–384
[38] Sahlman A, Ahonen J, Nemlander A, Salmenperä M, Eriksson H, Rämö J, Vento A. Myocardial metabolism on off-pump surgery; a randomized study of 50 cases. Scand Cardiovasc J 2003;37: 211–215,
[39] Selvanayagam JB, Petersen SE, Francis JM, Robson MD, Kardos A, Neubauer S, Taggart DP. Effects of Off-Pump Versus On-Pump Coronary Surgery on Reversible and Irreversible Myocardial Injury. A Randomized Trial Using Cardiovascular Magnetic Resonance Imaging and Biochemical Markers. Circulation. 2004;109:345-350.
[40] Serrano CV Jr, Souza JA, Lopes NH, Fernandes JL Nicolau JC, Blotta MHSL, Ramires JAF MD, Hueb WA. Reduced expression of systemic proinflammatory and myocardial biomarkers after off-pump versus on-pump coronary artery bypass surgery: A prospective randomized study. Journal of Critical Care 2010;25: 305–312
[41] van Dijk D, Nierich AP, Jansen EWL, Nathoe HM, Suyker WJL, Diephuis JC, van Boven W-J, Borst C, Buskens E, Grobbee DE, de Medina EOR, de Jaegere PTP, for the Octopus Study Group. Early Outcome After Off-Pump Versus On-Pump Coronary Bypass Surgery Results From a Randomized Study Circulation. 2001;104:1761-1766
[42] Vedin J, Jensen U, Ericsson A, Samuelsson S Vaage J. Pulmonary hemodynamics and gas exchange in off pump coronary artery bypass grafting Interact CardioVasc Thorac Surg 2005;4:493-497
[43] Hendrik M, Nathoe HM, Moons KGM, van Dijk D, Jansen EWL, Borst C, de Jaegere PTP, Grobbee DE, for the Octopus Study Group Risk and Determinants of Myocardial Injury During Off-Pump Coronary Artery Bypass Grafting. Am J Cardiol 2006;97:1482–1486
[44] Mantovani V Charles Kennergren C Bugge M, Sala A , Lönnroth P, Berglin E Myocardial metabolism assessed by microdialysis: A prospective randomized study in on- and off-pump coronary bypass surgery. International Journal of Cardiology 2010;143: 302–308

[45] Ascione R, Caputo M, Calori G, Lloyd CT, Underwood MJ,Angelini GD. Predictors of Atrial Fibrillation After Conventional and Beating Heart Coronary Surgery. A Prospective, Randomized Study. Circulation. 2000;102:1530-1535

[46] Møller CH, Perko MJ, Lund JT, Andersen LW, MD, Kelbæk H, Madsen JK, Winkel P, Gluud C, Steinbrüchel DA. No Major Differences in 30-Day Outcomes in High-Risk Patients Randomized to Off-Pump Versus On-Pump Coronary Bypass Surgery. The Best Bypass Surgery Trial. Circulation. 2010;121:498-504

[47] Wijeysundera DN, Beattie WS, Djaiani G, Rao V, Borger MA, Karkouti K, Cusimano RJ. Off-pump coronary artery surgery for reducing mortality and morbidity: meta-analysis of randomized and observational studies. J Am Coll Cardiol. 2005;46(5):872-82.

[48] Diegeler A, Hirsch R, Schneider F, Schilling L-O, MD, Falk V, Rauch T, Mohr FW. Neuromonitoring and Neurocognitive Outcome in Off-Pump Versus Conventional Coronary Bypass Operation. Ann Thorac Surg 2000;69:1162– 6

[49] van Dijk D, Jansen EWL, Hijman R, Nierich AP, Diephuis JC, Moons KGM, Lahpor JR, Borst C, Keizer AMA, Nathoe HM, Diederick E. Grobbee DE, De Jaegere PTP, Kalkman CJ, for the Octopus Study Group. Cognitive Outcome After Off-Pump and On-Pump Coronary Artery Bypass Graft Surgery. A Randomized Trial. JAMA. 2002;287(11):1405-1412

[50] Lee JD, Lee SJ, Tsushima WT, Yamauchi H, Lau WT, Popper J, Stein, A, Johnson D, Lee D, Petrovitch H, Dang CR. Benefits of Off-Pump Bypass on Neurologic and Clinical Morbidity: A Prospective Randomized Trial. Ann Thorac Surg 2003;76:18 –26

[51] Lloyd CT, Ascione R, Underwood MJ, Gardner F, Black A, Angelini GD. Serum S-100 protein release and neuropsycologic outcome during coronary revascularization on the beating heart: A prospective randomized study. J Thorac Cardiovasc Surg 2000;119:148-54

[52] Motallebzadeh R, Bland JM, Markus HS, Kaski JC, Jahangiri M. Neurocognitive Function and Cerebral Emboli: Randomized Study of On-Pump Versus Off-Pump Coronary Artery Bypass Surgery. Ann Thorac Surg 2007;83:475– 82

[53] Naseri MH, Pishgou B, Ameli J,Babaei E, Taghipour HR. Comparison of post-operative neurological complications between on-pump and off-pump coronary artery by-pass surgery Pak J Med Sci 2009;25:137-141

[54] Zamvar V, Williams D,Hall J, Payne N, Cann C, Young K, Karthikeyan S, Dunne J. Assessment of neurocognitive impairment after off-pump and on-pump techniques for coronary artery bypass graftsurgery: prospective randomised controlled trial. BMJ 2002;325:1268

[55] Selnes OA, Grega MA, Borowicz LM Jr, Barry S, Zeger S, Baumgartner WA, McKhann GM. Cognitive outcomes three years after coronary artery bypass surgery: a comparison of on-pump coronary artery bypass graft surgery and nonsurgical controls. Ann Thorac Surg. 2005 Apr;79(4):1201-9.

[56] Wandschneider W, Thalmann M, Trampitsch E, Ziervogel G, Kobinia G, Off-Pump Coronary Bypass Operations Significantly Reduce S100 Release: An Indicator for Less Cerebral Damage? Ann Thorac Surg 2000;70:1577–9

[57] Yin Y-q, Luo A-l, Guo X-y, Li L-h Huang Y-g. Postoperative neuropsychological change and its underlying mechanism in patients undergoing coronary artery bypass grafting. Chin Med J 2007;120:1951-1957

[58] Andersson LG, Ekroth R, Bratteby LE, Hallhagen S, Wesslen O. Acute renal failure in the patient undergoing cardiac operation. Prevalence, mortality rate, and main risk factors. J Thorac Cardiovasc Surg 1989;98:1107-12
[59] Abu-Omar Y, Ratatunga C. Cardiopulmonary by-pass and renal injury. Perfusion 2006; 21:209-213
[60] Ascione R, MD, Lloyd CT, Underwood MJ, Gomes WJ, Gianni D, Angelini GD. On-Pump Versus Off-Pump Coronary Revascularization: Evaluation of Renal Function. Ann Thorac Surg 1999;68:493– 8
[61] Tang ATM, Knotta J,. Nanson J, Hsua J, Hawa MP, Ohri SK. A prospective randomized study to evaluate the renoprotective action of beating heart coronary surgery in low risk patients. European Journal of Cardio-thoracic Surgery 2002;22:118–123
[62] Güler M, Kırali K, Toker ME, Bozbug N Ömeroglu SN , Akıncı E, Yakut C. Different CABG Methods in Patients With Chronic Obstructive Pulmonary Disease. Ann Thorac Surg 2001;71:152–7
[63] Covino E, Santise G, Di Lello F, De Amicis V, Bonifazi R, Bellino I, Spampinato N: Surgical myocardial revascularization (CABG) in patients with pulmonary disease: Beating heart versus cardiopulmonary bypass. J Cardiovasc Surg (Torino). 2001;42(1):23-6.
[64] Cox CM, Ascione R, Cohen AM, Davies IM, Ryder IG, Angelini GD. Effect of Cardiopulmonary Bypass on Pulmonary Gas Exchange: A Prospective Randomized Study. Ann Thorac Surg 2000;69:140 –5
[65] Syed A, Fawzy H, Farag A, Nemlander A, Comparison of Pulmonary Gas Exchange in OPCAB Versus Conventional CABG. HeartLung and Circulation 2004;13:168–172
[66] Raja SG, Haider Z, Ahmad M. Predictors of gastrointestinal complications after conventional and beatingheart coronary surgery. Surg J R Coll Surg 2003:221-228
[67] Formica F, Broccolo F, Martino A, Sciucchetti J, Giordano V, Avalli L, Radaelli G, Ferro O, Corti F, Cocuzza C, Paolini G. Myocardial revascularization with miniaturized extracorporeal circulation versus off pump: Evaluation of systemic and myocardial inflammatory response in a prospective randomized study. J Thorac Cardiovasc Surg 2009;137:1206-12
[68] Nesher N, Frolkis I, Vardi M, Sheinberg N, Bakir I, Caselman F, Pevni D, Ben-Gal Y, Sharony R, Bolotin G, Loberman D, Uretzky G, Weinbroum AA,. Higher Levels of Serum Cytokines and Myocardial Tissue Markers During On-Pump Versus Off-Pump Coronary Artery Bypass Surgery J Card Surg 2006;21:395-402
[69] Onorati F, Rubino AS, Nucera S, Foti D, Sica V, Santini F, Gulletta E, Renzulli A. Off-pump coronary artery bypass surgery versus standard linear or pulsatile cardiopulmonary bypass: endothelial activation and inflammatory response European Journal of Cardio-thoracic Surgery 2010;37: 897—904
[70] Wildhirt SM, Schulze C, Conrad NE, Schütz A, Reichart B. Expression von TNF-alpha und löslichen Adhäsionsmolekülen nach koronarchirurgischen Eingriffen mit und ohne extrakorporaler Zirkulation. Z Herz- Thorax- Gefäßchir 2001;15:7–13
[71] Johannson-Synnergren M, Nilsson F, Bengtsson A, Jeppson A, Wiklund L. Off-pump CABG reduces complement activation but does not significantly affect peripheral endothelial function: a prospective, randomized study. Scand Cardiovasc J 38; 53–58, 2004

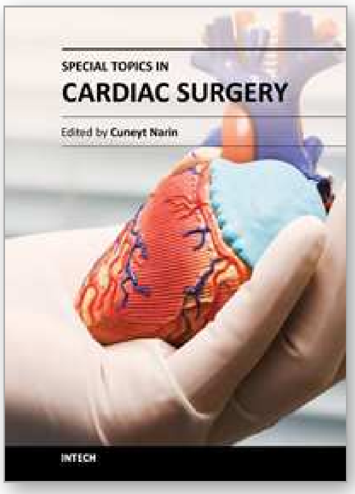
[72] Gu YJ, Mariani MA, Oeveren W v , Grandjean JG, Boonstra PW. Reduction of the Inflammatory Response in Patients Undergoing Minimally Invasive Coronary Artery Bypass Grafting. Ann Thorac Surg 1998;65:420–4

[73] Kolackova M, Kudlova M, Kunes P, Lonsky V, Mandak J, Andrys C, Jankovicova K, Krejsek J. Early Expression of FcγRI (CD64) on Monocytes of Cardiac Surgical Patients and Higher Density of Monocyte Anti-Inflammatory Scavenger CD163 Receptor in "On-Pump" Patients. Mediators of Inflammation 2008; 235461

[74] Akila, D'souza AB, Prashant V, D'souza V. Oxidative injury and antioxidants in coronary artery bypass graft surgery:Off-pump CABG significantly reduces oxidative stress. Clinica Chimica Acta 2007;375:147–152

[75] Puskas JD, Williams WH, Duke PG, Staples JR, Glas KE, Marshall JJ, Leimbach M, Huber P, Garas S, Sammons BH, McCall SA, Petersen RJ, Bailey DE, Chu H, Mahoney EM, Weintraub WS, Guyton RA. Off-pump coronary artery bypass grafting providescomplete revascularization with reduced myocardial injury, transfusion requirements, and length of stay: A prospective randomized comparison of two hundred unselected patients undergoing off-pump versus conventional coronary artery bypass grafting. J Thorac Cardiovasc Surg 2003;125: 797-808

[76] Medved I, Anic D, Zrnic B, Ostric M Saftic I. Off-Pump versus On-Pump – Intermittent Aortic Cross Clamping – Myocardial Revascularisation: Single Center Expirience. Coll. Antropol. 2008;32:381–384



Special Topics in Cardiac Surgery
Edited by Prof. Cuneyt Narin

ISBN 978-953-51-0148-2
Hard cover, 308 pages
Publisher InTech
Published online 29, February, 2012
Published in print edition February, 2012

This book considers mainly the current perioperative care, as well as progresses in new cardiac surgery technologies. Perioperative strategies and new technologies in the field of cardiac surgery will continue to contribute to improvements in postoperative outcomes and enable the cardiac surgical society to optimize surgical procedures. This book should prove to be a useful reference for trainees, senior surgeons and nurses in cardiac surgery, as well as anesthesiologists, perfusionists, and all the related health care workers who are involved in taking care of patients with heart disease which require surgical therapy. I hope these internationally cumulative and diligent efforts will provide patients undergoing cardiac surgery with meticulous perioperative care methods.