Hemodynamic Collapse after Coronary Artery Bypass Grafting

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ACADEMIC DISSERTATION

To be publicly discussed, with permission of the Medical Faculty of the University of Helsinki, in Auditorium XIV in the main building of Helsinki University, on November 21st, 2014, at 12.00 o´clock.

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To my children Onni, Eino and Iines

Abstract

Myocardial infarction and sudden hemodynamic collapse after coronary artery bypass surgery are major complication associated with high mortality and morbidity. There are many well-established risk stratification systems to assess the risk of mortality and morbidity after cardiac surgery. These risk scores, however, do not predict severe immediate postoperative complications such as sudden hemodynamic collapse.

This study is based on a comprehensive analysis of patients who suffered from hemodynamic collapse during the immediate course after coronary artery bypass surgery between 1988 and 1999 in Helsinki University Hospital. One matched control patient was selected for every study patient. Patients, who did not survive, underwent a medicolegal autopsy and a rubber cast angiography was performed to reveal possible surgical errors in myocardial revascularization. Patients who were still alive in 2009 were traced with respect to mortality data and a health-related quality of life questionnaire was sent to the living patients and to the controls. In addition, a comparison was made between patients who suffered from postoperative hemodynamic collapse and patients who underwent a postoperative angiography due to persistent myocardial ischemia. Angiography was introduced in 2000 and this patient series was collected prospectively between 2000 and 2007.

This thesis consists of four studies (I-IV). The specific goals were to explore possible predictive factors of sudden hemodynamic collapse (I), to reveal the possible surgical errors that led to hemodynamic collapse and fatal outcome with the means of an autopsy (II), to find out the impact that postoperative angiography has on the incidence of postoperative hemodynamic collapse, and the rate of mortality, and morbidity of patients (III), and finally to investigate the quality of life of patients surviving hemodynamic collapse and open resuscitation in comparison with an age- and sex-matched national reference population (IV).

The results suggest the following: Sudden hemodynamic collapse after CABG is a hazardous complication with high mortality. Inadequate tissue perfusion, postoperative myocardial ischemia, and increased need for inotropic as well as mechanical support are predictive of hemodynamic collapse. (I)

Secondly, technical graft complications are a major underlying cause of postoperative hemodynamic collapse following CABG. Post-mortem angiography improves the accuracy of autopsy diagnostics of fatal graft complications. The cause of death could be established in every case. (II)

Thirdly, use of early postoperative angiography in case of hemodynamic compromise or myocardial ischemia reduces the rate of emergency reoperations and decreases morbidity and mortality. It also allows treatment with intravascular medication. (III)

Fourthly, patients who survive a severe hemodynamic collapse, open cardiac massage, and emergency reoperations have a similar prognosis as matched control patients. They also have good health-related quality of life that is comparable with age- and sex-matched national reference population as long as 15 years postoperatively. (IV)

Contents

List of original publications

This thesis is based on the following publications:

I   Karhunen JP, Sihvo EI, Suojaranta-Ylinen RT, Rämö OJ, Salminen US. Predictive factors of hemodynamic collapse after coronary artery bypass grafting: a case-control study. J Cardiothorac Vasc Anesth 2006;20:143-8.

II   Karhunen JP, Karhunen PJ, Raivio PM, Sihvo EI, Vainikka TL, Salminen US. Medico-legal autopsy in postoperative hemodynamic collapse following coronary artery bypass surgery. Forensic Sci Med Pathol 2011;7:9-13.

III   Karhunen J, Raivio P, Maasilta P, Sihvo E, Suojaranta-Ylinen R, Vento A, Salminen US. Impact of early angiographic evaluation on the frequency of emergency reoperations after coronary bypass surgery. Scand J Surg 2010;99:173-9.

IV   Karhunen JP, Jokinen JJ, Raivio PM, Salminen US. Long-term survival and quality of life after cardiac resuscitation following coronary artery bypass grafting. Eur J Cardiothorac Surg 2011;40:249-54.

The publications are referred to in the text by their Roman numerals.

Abbreviations

CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CI	Cardiac index
CK-MB	Creatinine kinase MB isoenzyme
CPB	Cardiopulmonary bypass
CPR	Cardiopulmonary resuscitation
cTnI	Cardiac troponin I
cTnT	Cardiac troponin T
ECG	Electrocardiography
HRQoL	Health-related quality of life
IABP	Intra-aortic balloon pump
ICU	Intensive care unit
IMA	Internal mammary artery
LIMA	Left internal mammary artery
LV	Left ventricle
LV-EF	Left ventricular ejection fraction
NYHA	New York Heart Association
MI	Myocardial infarction
OCM	Open cardiac massage
PCI	Percutaneous coronary intervention
PMI	Perioperative myocardial infarction
RA	Radial artery
SD	Standard deviation
SE	Standard error

1 Introduction

The development of the coronary artery bypass grafting (CABG) operation is one of the greatest surgical achievements of the 20th century. Millions of patients have undergone CABG since it was introduced into clinical practice in the 1960's. Since then, CABG has been performed regularly and the number of procedures has increased dramatically. During the last 40 years, the CABG operation has become one of the most successful and most frequently performed surgical procedures.

The first reported clinical CABG operation was performed in 1960 at Van Etten Hospital in Bronx, New York, where a right mammary artery to right coronary artery bypass was performed using a non-suture tantalum ring technique. In 1962, David Sabiston Jr performed the first reported aorto-coronary bypass grafting procedure with a saphenous vein graft. However, the patient died three days postoperatively of stroke and autopsy revealed a thrombosed proximal anastomosis. Sabiston reported his procedure as late as in 1974 (Mueller 1997). The first sutured mammary artery to coronary artery bypass in a human subject was performed in 1964 by the Russian surgeon, Vasiliy Kolesov, in Leningrad (Kolesov 1965). Kolesov grafted the left internal mammary artery (LIMA) to the left anterior descending artery. The first successful human vein bypass graft operation was performed later in 1964 by Garret in Houston, but like Sabiston, Garret reported it years later, in 1973 (Mueller 1997). Furthermore, the Argentinean surgeon, Rene Favaloro, began the systematic clinical use of saphenous vein CABG at the Cleveland clinic in 1967 (Favaloro 1971) and is therefore often credited for the advancement of CABG surgery (Mueller 1997).

Pharmacological treatment, myocardial protection, and surgical techniques have improved greatly during past decades. At the same time the patient population undergoing CABG has become older and the patients have more risk factors. Numerous risk score stratification systems have been created to predict operative risk (Parsonnet 1989, Higgins 1992, Tremblay 1993, Hattler 1994, Tu 1995, Greaves 1996, Pons 1997, Nashef 1999, Hannan 2006, Wu 2012, Nashef 2012). However, these risk scores predict overall mortality or morbidity after CABG, rather than the individual, immediate postoperative risk of hazardous complications such as sudden hemodynamic collapse and the need for resuscitation.

The first few hours after the CABG operation are the most crucial ones. Sudden hemodynamic collapse after CABG is an adverse event with high mortality and an incidence that ranges from 0.7 % to 3 % (Fairman 1981, McKowen 1985, El-Banayosy 1998, Anthi 1998, Guney 2009). Its cause is often bleeding and cardiac tamponade, which are easy to diagnose and to treat. However, graft complications are also possible culprits of this dreadful event and immediate angiography or reoperation due to graft occlusion or graft spasm is frequently required (El-Banayosy 1998, Anthi 1998, Asher 2004, Fukui 2005, Guney 2009, Lorusso 2012, Laflamme 2012). The mortality risk after sudden hemodynamic collapse is 30 % - 50 % and these patients frequently have severe complications (Fairman 1981, El-Banayosy 1998, Guney 2009, LaFlamme 2012). Overall early mortality rates at 3 months after CABG range from 1 % to 3 %. Postoperative morbidity rates for stroke, renal, pulmonary, and cardiac failure, bleeding, and wound infection vary from 1 % to 2 % (Fairman 1981, El-Banayosy 1998, Nashef 1999, Nashef 2012).

The benefit and impact of cardiac operations are not measured only with extended life expectancy and cardiac survival but also with a more subjective measurement, health-related quality of life (HRQoL). Interest in patients' subjective recovery after surgical procedures is increasing and studies on this subject are being published in every field of surgery. Also studies concerning postoperative HRQoL after CABG have been reported (Järvinen 2003, Loponen 2007, Jokinen 2008). However, no published data exist concerning the quality of life of patients who have undergone postoperative resuscitation and reoperation after CABG.

2 Review of the literature

2.1. Importance of cardiovascular disorders

Treatment of cardiovascular disorders has improved during the last decades. This has significantly decreased the cardiac mortality. However, cardiovascular diseases are still the main cause of death in Finland, comprising more than 40 % of all deaths (Tilastokeskus 2009a). Coronary artery disease (CAD) caused approximately one out of every four deaths (219/100,000) in Finland in 2007 (Tilastokeskus 2009a). This figure is slightly higher in comparison to the USA, where one out of every five deaths was due to CAD ant the total number of deaths caused by CAD was 445,687 patients (148/100,000) (Lloyd-Jones 2009). It has been estimated that in 2009 altogether 785,000 new myocardial infarctions (MI) were diagnosed in USA. This means nearly 2200 MIs per day. This difference only emphasises the importance of CAD treatment in Finland.

In 2004, 59,159 patients needed treatment for diagnosed CAD in Finland. Altogether 13,771 patients were treated for MI, while 75,964 patients were treated in hospital due to myocardial ischemia or angina pectoris. This accounted for 660,085 patient hospital days in 2004. The treatment of CAD, therefore, is an enormous burden and major source of costs for the Finnish health care system. Most patients manage with optimal medical treatment, but in 2008, altogether 35,527 coronary catheterizations or interventions were performed in Finland. These included 22,913 coronary angiographies, 8,597 percutaneous coronary interventions, and 4,017 CABG procedures.

2.2. Hemodynamic collapse after CABG

2.2.1 Etiology of hemodynamic collapse

Hemodynamic collapse with cardiac arrest is not usually caused by a single reason. Rather, it is caused by many pathophysiological mechanisms which potentiate each other (El-Banayosu 1998, Guney 2009). Possible graft failures include twisting of the graft, and a narrow or occluded anastomosis, which may lead to this severe complication (Weman 1999). Also, other than graft-related causes such as incomplete revascularization, pericardial tamponade, bleeding, reperfusion injury, or inadequate myocardial

preservation may start a vicious circle leading to myocardial ischemia and further infarction which may cause uncontrollable arrhytmias and hemodynamic collapse (Fairman 1981, El-Banayosy 1998, Fabricius 2001, Guney 2009, LaFlamme 2012).

2.2.2. Incidence of hemodynamic collapse

The incidence of hemodynamic collapse and cardiopulmonary resuscitation (CPR) in the immediate postoperative period after cardiac surgery varies from 0.7 % to 3 % (Fairman 1981, McKowen 1985, El-Banayosy 1998, Anthi 1998, Guney 2009, LaFlamme 2012). Of these patients 20 % to 60 % undergo further emergency reopening of the median sternotomy for open cardiac massage and for the diagnosis and treatment of the underlying cause of the hemodynamic collapse (Raman 1989, El-Banayosy 1998, Anthi 1998, Guney 2009). Cardiac tamponade leads to reoperation in 1% to 5% of patients after open heart surgery (Russo 1993, Grumann 2012). Atrial arrhythmias are not as dangerous as ventricular arrhythmias and can usually be treated or prevented with beta-blockers or amiodarone (Halonen 2006, Halonen 2010). Ventricular tachyarrhythmias however are the precipitating mechanism of unexpected cardiac arrest in almost half of the cases after cardiac surgery, with the underlying cause of arrhythmia being perioperative MI (PMI) (Anthi 1998, Thielmann 2006, Laflamme 2012).

2.2.3. Predictors of hemodynamic collapse

Preoperatively elevated cardiac troponin T (cTnT) levels have been reported to reveal patients with a higher risk of PMI (Carrier 1998). Diagnostic tools used to diagnose MI, such as the occurrence of chest pain, changes in electrocardiography (ECG), occurrence of new Q-waves, or changes in molecular parameters such as creatinine kinase MB isoenzyme (CK-MB) cannot be used with accuracy after CABG due to numerous confounding factors altering these parameters (Boden 1983, Yokoyama 2000, Diderholm 2002).

Cardiac troponin I (cTnI) is a known biomarker for myocardial cell damage in patients undergoing cardiac surgery. A minor rise after cardiac surgery is normal. The peak of cTnI is reached 6-8 hours after declamping of the aorta (Etievent 1995, Carrier 2000, Alter 2005). In 2001 Eigel et al. studied the release of cTnI at the end of the CABG procedure

and found that increased levels of cTnI at the end of surgery, before cessation of CPB, were a strong predictor of adverse events after CABG. Adverse events in this study were defined as the onset of MI and/or death peri- or postoperatively (Eigel 2001). In patients undergoing CABG, a peak in cardiac cTnI predicts mortality and morbidity (Fellahi 2003). Alter et al. reported in 2005 that an increace in leucocyte count (> 14000 G/L at the end of surgery) with either ST-elevations in ECG or CK-MB concentrations over 35 U/L at 6 hours after CABG could be predictive of MI.

Developments in intraoperative data acquisition systems have provided tools to record hemodynamic data more accurately and more precisely (Hollenberg 1997). This has led to the finding of an association between intraoperative ECG ST-segment changes and intraoperative hemodynamics in patients with PMI (Jain 1998). Reich et al. reported in 1999 that intraoperative hemodynamic abnormalities, including pulmonary hypertension, hypotension during CPB, and post CPB pulmonary diastolic hypertension, were independent predictors of mortality, stroke, and also PMI. These hemodynamic parameters were stronger independent predictors in comparison to preoperative risk factors (Reich 1999).

Recent studies have proved microdialysis to be an excellent tool to evaluate myocardial metabolism during heart surgery and have shown that measurement of interstitial glutamate release with microdialysis during and after heart surgery could be useful for identifying ongoing ischemia (Pöling 2006, Liu 2010)

2.2.4. Risk-scoring

There are numerous models that assess both preoperative factors as well as perioperative events to evaluate and predict individual outcome and risk of CABG (Parsonnet 1989, Higgins 1992, Tremblay 1993, Hattler 1994, Tu 1995, Greaves 1996, Pons 1997, Nashef 1999, Hannan 2006, Wu 2012, Nashef 2012). Preoperative factors, which raise the risk of morbidity and mortality after the operation include left main CAD, impaired left ventricular (LV) function, three-vessel disease, unstable angina, recent MI, and emergency operation. Also, the female sex is an independent risk factor (Nashef 1999, Vaccarino 2002, Regitz-Zagrosek 2004, Blankstein 2005, Madan 2011, Nashef 2012). However, although predictive of PMI, most of the preoperative variables measured rarely

predict the early outcome and adverse events such as hemodynamic collapse or cardiac arrest in the immediate post-operative course in an individual patient. There are also numerous studies that have attempted to find predictors of perioperative and early major postoperative complications such as post-operative arrhythmias, postoperative MI, hemodynamic collapse, and cardiac arrest (Anthi 1998, El-Banayosy 1998, Carrier 1998, Alter 2005). All these studies have focused on predicting and preventing these adverse events. However, none of the studies have provided a useful or reliable tool for this purpose. Also, it is widely believed that intra-operative management contributes importantly to outcome, but which intraoperative variables should be measured, it is not well known (Vincent 2004).

2.2.5. Role of conduits

The superiority of LIMA to left anterior descending coronary artery (LAD) revascularization when compared with saphenous vein grafting was documented already over 25 years ago (Loop 1986). However, because of fear of complications, bilateral IMA grafting has not been used often. Recent studies, however, demonstrate the benefit for long-term survival of bilateral IMA grafting over single IMA grafting (Puskas 2012, Dorman 2012).

There has been debate and controversy of the role of the radial artery (RA) as a graft in CABG. A few recent reports have shown an increase in postoperative ischemia with the use of LIMA in combination with the RA when compared with the use of saphenous vein combined with the LIMA graft (Palolari 2000, Apostolidou 2001). This increase in ischemia rates might also increase PMI incidence and lead to events such as hemodynamic collapse, cardiac arrest, and resuscitation.

The use of the RA as a graft for coronary revascularization was first introduced in 1973 by Carpentier and associates (Carpentier 1973), but at that time the experience was disappointing because of the high rate of graft failures leading to PMI and resuscitation (Fisk 1976, Curtis 1975). The poor results were probably due to the unavailability of antispasmodic drugs as all arterial grafts, especially the RA, are known to have a spasm tendency in the early phase after CABG (Acar 1991, Jones 1998). Another reason for the graft failures might have been due to the harvesting techniques used as the role of the preservation of the endothelial function during harvesting was not known at that time

period (Luscher 1991). The use of the RA as a coronary graft was proposed again in 1992 by Acar et al. (Acar 1992) after the finding that some of the grafts implanted as early as in 1972 were still patent 15 years later. Encouraging early patency rates were obtained during this new era, and were associated with an improved harvesting technique together with the use of calcium channel blockers or other vasodilators to prevent perioperative and postoperative spasm of the graft (Calafiore 1995, Chen 1996, Da Costa 1996).

Early use of the RA was abandoned because of major complications. However, in the later experience mid- and long-term patency results have been dramatically more favourable compared with venous grafting (Possati 1998, Acar 1998, Dimitrova 2012, Cao 2013, Habib 2012). Bhan et al. reported also excellent early results in 1999 (Bhan 1999). The use of the RA can facilitate complete arterial myocardial revascularizations, and moreover, its morphometric features allow it to reach virtually any coronary artery, to perform multiple distal anastomoses in sequential fashion, and sometimes to obtain two separate grafts by dividing one RA of adequate length. It has also been shown that it is possible to construct composite arterial conduits by proximally anastomizing the RA to the internal IMA.

These findings support the use of the RA over the saphenous venous graft. Increased knowledge of medication and postoperative treatment of patients with RA grafts has led to similar early postoperative complication rates in patients with RA and vein grafts. Mid- and long-term results favor the use of arterial grafts over venous grafts.

2.2.6. Treatment of hemodynamic collapse

There are guidelines for procedures in case of hemodynamic collapse and cardiac arrest after cardiac surgery (Dunning 2009). However, decisions and treatment are done individually in every case. This is evident from the variation of timing of emergency resternotomy from a few minutes up to 40 minutes after the beginning of resuscitation (Fairman 1981, Roussou 1994, Guney 2009). Treatment usually begins in the intensive care unit (ICU) with closed chest cardiopulmonary resuscitation and efficient medication. When this treatment is not sufficient, resternotomy and open chest cardiac massage is performed. Further reoperation and evaluation of grafts is often required as well (Anthi

1998, Fairman 1981, Roussou 1994, Birdi 2000, Pottle 2002, Guney 2009). The timing of thoracotomy is critical because unnecessary delay may lead to non-improved survival (Sanders 1985, Sanders 1985, Laflamme 2012). Because of the high incidence of mechanical and correctable underlying causes of hemodynamic collapse and the relatively low morbidity, it is justified to perform resternotomy aggressively (Fairman 1981, McKowen 1985, Anthi 1998, Birdi 2000, Laflamme 2012). Furthermore, Guney et al. reported better short- and long-term results in patients who underwent re-revascularization compared with patients who underwent non-invasive interventions in the ICU following cardiac arrest after CABG. This retrospective study consisted of 148 consecutive patients suffering from postoperative cardiac arrest between 1998 and 2004 (Guney 2009) Emergency resternotomy in the ICU has also been reported to be safe and cost-effective (Kaiser 1990, Fiser 2001, Charalambous 2006).

2.2.7 Impact of hemodynamic collapse on outcome

   Brown et al. recently reported that 7 % of all CABG patients experienced major complications in a patient population of over 100,000 patients (Brown 2008). These complications included hemorrhage or postoperative shock, reoperation, postoperative adult respiratory distress syndrome, new-onset of hemodialysis, postoperative stroke, postoperative infection, and septicemia. Postoperative complications are associated with high mortality (Glance 2007). Over 50 % ofPatients suffering from postoperative hemodynamic collapse resulting in subsequent resuscitation suffer from major complications such as renal, gastrointestinal, neurological dysfunction and infections (Fairman 1981, El-Banayosy 1998). A non-cardiac arterial complication, limb ischemia, may occur after insertion of the intra-aortic balloon pump (IABP) (El-Banayosy 1998).

   Although developments in operative techniques, such as off pump surgery and better understanding of peri- and postoperative care, have decreased early mortality, death still remains one of the major complications after CABG. The overall mortality rate after CABG ranges from 1 % to 3 % and the female sex is at a higher risk (Cleveland 2001, Plomondon 2001, Puskas 2007, Nashef 2012). Furthermore, patients with sudden unexpected postoperative hemodynamic collapse after CABG face a mortality risk that ranges from 30 % to 50 %, regardless of the cause of hemodynamic collapse (Fairman 1981, El-Banayosy 1998, Anthi 1998, Guney 2009).

As the patients suffering from sudden hemodynamic collapse after CABG undergo CPR, it is reasonable to compare the results with other studies regarding CPR. Kouwenhoven et al. published the first report of CPR in 1960. Since then, many studies has been published concerning in-hospital CPR (Sandroni 2004, Gombotz 2006, Suraseranivongse 2006). In-hospital mortality rates in these studies vary from 80 % to up to 94 %. However, only few reports of hemodynamic collapse and CPR after CABG have been published (Fairman 1981, McKowen 1985, El-Banayosy 1998, Anthi 1998, Guney 2009). Mortality rates in these reports are more favourable, ranging from 30 % to 50%. This is probably due to the environment in which the resuscitation takes place, as all patients recovering from cardiac operations are treated in a special ICU, an most often both an anesthesiologist and a cardiac surgeon is available on call. The underlying cause may be a graft failure that can be corrected in an emergency reoperation (Guney 2009).

2.3. Postoperative angiography

When signs of postoperative myocardial ischemia are present and early graft failure after CABG is suspected, postoperative angiography is a possible tool investigating the cause of ischemia. Moreover, the morbidity risk of this procedure low, under 1 % (Greaves 1996). Chest pain with common signs of myocardial ischemia including ECG ST-segment alteration, rise of CK/CK-MB, and troponin usually allow diagnosing unstable angina or MI under native conditions (Morey 2000, Pollack 2003, Ryan 1999). However, these criteria frequently fail in patients immediately after CABG. The difficulty of defining postoperative ischemia leads to difficulties in decision-making regarding the necessity of postoperative angiography.

For these reasons, there is no consensus on the indication of angiography subsequent to CABG. Many studies suggest different indications for postoperative angiography such as ST segment elevations in the ECG associated with CK/CK-MB enzyme ratio elevations (Fabricius 2001) and ST segment alteration associated with the rise of CK-MB over the level of 80 U/L (Rasmussen 1997). Also, the rise of cTnI has been shown to be an indicator for PMI and should therefore be an indication for angiography. However, studies on postoperative cTnI were not designed to investigate the indication for angiography (Etievent 1995, Carrier 2000, Eigel 2001, Holmvang 2002, Alter 2005). All cardiac necrosis biomarkers have an inevitable delay when the biomarker release occurs 4-6 hours

after ischemia (Alyanakian 1998, Alter 2005). This is a major limitation of biomarker use in the diagnostics of postoperative ischemia. When the cause of ischemia is graft failure its onset is immediately after the primary operation. ST level alterations may also be due to pericardial trauma, electrolyte imbalance, or transient hypoxia in the immediate postoperative phase (Yokoyama 2000, Alter 2005). Therefore, ST level elevation as a sole marker cannot be considered a reliable indicator of postoperative ischemia. Alter et al. studied the role of leukocyte count elevation at the end of surgery and levels over 14000 G/L seemed to predict postoperative ischemia when ST segment elevation was also observed (Alter 2005). This finding should be considered an indication for postoperative angiography. Also poor myocardial function in transesophageal echocardiography is suggestive of myocardial ischemia (Adams 2001).

The indications for postoperative angiography are not clear and the decision is often made individually in each case with signs of postoperative ischemia. Angiography allows planning of the possible immediate reoperation, when the culprit lesion is identified (Fabricius 2001, Alter 2005). Furthermore, in cases of graft spasms, intra-graft nitro-glycerine injections may be performed immediately. In addition, cardiac catheterization allows re-revascularization with emergency PCI that may limit myocardial cellular damage when compared to a reoperation (Thielmann 2006).

2.4. Autopsy

2.4.1. Medigo-legal autopsy after fatal outcome

In Finland, autopsy is frequently performed to patients who have undergone major surgery prior to death. As this is not the case in most other countries, it is difficult to find reports concerning autopsy findings of patients with fatal outcome after CABG (Lee 1997, Zehr 1997, Goodwin 2000). Post-mortem autopsy rates are low as in the report of Zehr et al. in 1997 with an autopsy rate of 24 %. This may be due to various factors. There may be the misconception that the clinical cause of death is accurate (Lee 1994). In addition, there

may be fear of legal litigation if unexpected findings are revealed in autopsies, especially when patients are more optimistic of the benefits of operation than the surgeon (Underwood 1989, Whittle 2007). Surgical failures are reported even more seldom (Weman 1999, Goodwin 2000), as the rate of surgical failure in the work by Weman et al. was 54.7 % compared with 4.8 % in the report by Goodwin. However, autopsy reveals an unsuspected cause of death in 7 % – 15 % (Barendregt 1992, Lee 1997, Zehr 1997, Goodwin 2000).

2.4.2. Role of post-mortem cast angiography

Post-mortem cast angiography has been used to detect cerebral arterial thromboses with a sensitivity of 92 % (Saimanen 2001) and also to visualize possible complications after abdominal surgery (Karhunen 1989). In The Helsinki University Central Hospital post-mortem cast angiography also has been used in cases of CABG with fatal outcome in autopsies. In this technique solidifying rubber with lead oxide as a contrast medium is applied (Weman 1999). It provides detailed data of the anastomoses and on the condition of the grafts and native vessels.

2.5. Quality of life

2.5.1. Quality of life after hemodynamic collapse and resuscitation

Measuring the quality of life is challenging, as it is a complex concept with multidimensional aspects and for this reason. In medical research, health related quality of life (HRQoL) is widely used. Ascertaining the quality of life and prognosis of survivors after cardiac resuscitation is important. If the quality of life after survival from resuscitation after cardiac surgery were poor, the extend of the treatment of postoperative hemodynamic collapse should be carefully considered.

Survival rates after resuscitation are low. It is also known, that cardiac resuscitated patients often suffer from severe complications, such as renal, gastrointestinal, and especially neurological dysfunction that inevitably influence to patients´ future cognitive, physical, and social functioning (Miranda 1994, El-Banayosy 1998, Wachelder 2009, Moulaert 2010). Studies concerning the quality of life after resuscitation are published in

growing numbers. The results vary. However, most of the reports provide evidence that most survivors enjoy a moderately impaired to excellent quality of life that is comparable with the normal population (De Vos 1999, Stiell 2003, Bunch 2003, van Alem 2004, Lundgren-Nilsson 2005, Horsted 2007). Modest impairment of QoL usually is caused by cognitive deficits, typically some memory problems with, in some cases, motor deficits (Cobbe 1996, Saner 2002). However, in other reports, a number of survivors suffer from impaired mental and physical functioning and HRQoL (Wachelder 2009).

Although the occurrence of hemodynamic collapse and resuscitation is associated with high mortality and morbidity rates, long-term survival and especially the HRQoL of survivors have not been documented.

2.5.2 Health survey instrument

The RAND-36 Item Health Survey instrument has a standardized questionnaire and it has specified mean and standard deviation values for different dimensions of quality of life for both sexes and age cohorts. It has also been applied to a random population in Finland and is therefore validated for the Finnish adult population. There are altogether eight dimensions in the RAND-36 which measure physical functioning, role limitation because of physical impairment (role-physical), pain, general health, vitality, social functioning, role limitation because of emotional impairment (role-emotional), and mental health. The scoring is made on a scale from 0 to 100, in which 0 denotes to maximal limitation in the patient´s physical and social functioning.

3 Objectives of the present study

The goal of this study was to answer the following questions:

I   What are the preoperative, intraoperative and postoperative risk factors for postoperative hemodynamic collapse and in which way could postoperative hemodynamic collapse be predicted?

II   What are the causes of postoperative hemodynamic collapse?

III   Does early graft patency evaluation in case of postoperative myocardial ischemia reduce the frequency of open cardiac massage (OCM) and mortality?

IV   What is the prognosis of hemodynamic collapse following CABG and resulting in OCM? Especially, what is the quality of life of the survivors?

4 Patients and methods

4.1. Study settings

This study is a composition of four studies carried out at the Department of Cardiothoracic Surgery in the Helsinki University Central Hospital. The ethics committee of the Helsinki University Central Hospital has approved the study.

4.2. Patient enrolment

From 1988 to 1999 a total number of 8807 patients underwent an isolated CABG operation. During this period, annual mortality rates ranged from 1.1 % to 4.3%. Of these patients, all who suffered from hemodynamic collapse and underwent emergency resternotomy were included in this study, with the exception of patients who suffered from hemodynamic collapse because of hemorrhage or pericardial tamponade. These patients were excluded from the study. The final study group consisted of 76 patients, who all underwent emergency resternotomy and OCM after postoperative hemodynamic collapse following CABG. This group was named the "OCM group". Medical records were retrieved and analyzed retrospectively.

From this same time period, one matched control patient with an uneventful postoperative recovery was selected for each study patient. The operation of each control patient was performed during the same three-month time period as the operation of the study group patient. The characteristics of these matched groups are presented in Table 1. In both groups, 1 patient was operated on the beating heart on-pump, while St Thomas cold cardioplegia was used for myocardial protection in all other patients. These two patient groups, both consisting of 76 patients, were matched according to six preoperative factors: sex, age, diabetes, number of diseased vessels, LV ejection fraction (EF), and New York Heart Association (NYHA) classification (Table 2). After patient selection, the medical records of altogether 152 patients were retrieved and analysed. Two of the medical records were found to be incomplete with some missing detail of data, one in both groups. Both groups consisted of 43 male patients and 33 female patients. No statistically significant differences existed between the groups in the non-matched variables either (Table 1.).

After a matched pair analysis, an additional 128 patients were randomly selected from patients operated during the same time period for regression analysis. The purpose of this patient group was to increase the statistical power of the study. For the analysis only the variables that differed significantly in the comparison between the study group and the matched control group were used. This additional control group consisted of 95 (74%) male patients and 33 (26%) female patients with a mean age of 61.7 ± 0.74 years.

Between 2000 and 2007 altogether 5251 isolated CABG operations were performed with early mortality ranging from 2.0 % to 4.7 %. Of these 5251 patients 1276 (24.3 %) were females. From this period, data of all patients who experienced hemodynamic collapse, resternotomy, and OCM were prospectively collected. In addition, all patients who underwent postoperative angiographic evaluation due to persistent myocardial ischemia were evaluated. This patient group consisted of altogether 13 (36%) patients with reoperation (Reoperation group) and 23 (64%) who underwent postoperative angiography (Angiography group). Thus, 36 (0.7%) patients were analyzed and this group was named "Angiography era group". This group consisted of 28 (78 %) male patients and 8 (22%) female patients. Preoperative characteristics of this group are shown in Table 1. Of the Angiography era group, 5 patients were operated on off-pump, while others underwent CPB and received cold blood cardioplegia for myocardial protection during aortic cross-clamping. The mean age in this group was 64.0 ± 1.56 years. The patient characteristics of this group are shown in Table 1.

These four study groups were analyzed in four published reports. In the first study, the first three patient groups were analyzed. In the second study only the first patient group was analyzed. In the third study, the first, the second, and the fourth patient groups were used while in the last study, the first and the second patient groups were analyzed.

Table 1. Matching of 76 OCM group patients and 76 Control group patients. In addition, preoperative characteristics of Angiography era patients are given. Data are expressed as mean (±SD) or percentage (%).

	Control group (n=76)	p-value (control/ OCM)	OCM = Pre-angiography era (n=76)	p-value (OCM/Angio)	Angiography era (n=36)
Matched variables					
Age (years)	59 ± 0.96	0.13	58.2 ± 1.04	<0.01	64.0 ± 1.56
Gender					
Male	57 %	1.00	57 %	0.03	78 %
Female	43 %	1.00	43 %	0.03	22 %
Diabetes	24 %	0.49	19 %	ns	28 %
NYHA classification	3.0 ± 0.08	0.10	3.2 ± 0.07	ns	2.94 ± 0.14
Left ventricular EF (%)	57 ± 1.76	0.11	55 ± 1.76	ns	49 ± 2.02
No. of diseased vessels	2.73 ± 0.06	0.25	2.26 ± 0.9	ns	2.61 ± 0.10
Additional variables					
Smoking history	46 %	0.09	57 %	ns	40 %
Diagnosed hypertension	50 %	0.73	47 %	ns	47 %
Cerebrovascular disease	9 %	0.56	12 %	ns	6 %
Renal disease	3 %	0.29	8 %	ns	3 %
Lung disease	3 %	0.10	8 %	ns	6 %
LV hypertrophy	16 %	1.00	16 %	ns	21 %
Previous CABG	4 %	0.56	5 %	ns	0 %
Cleveland risk score	1.91 ± 0.28	0.12	2.36 ± 0.32	ns	2.72 ± 0.49

NYHA= New York heart association, EF=Ejection fraction, CABG=Coronary artery bypass grafting, LV =Left ventricle

Table 2. NYHA classification

NYHA I: No symptoms and no limitation in ordinary physical activity, e.g. shortness of   breath when walking, climbing stairs etc.

NYHA II: Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.

NYHA III: Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest.

NYHA IV: Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.

4.3. Methods

From each patient group, with the exception of the additional control group, altogether 73 preoperative, intraoperative, and postoperative variables were collected into database and analyzed. These variables are given in Table 3. For the additional control group consisting of 128 patient, only 10 variables that were significantly different in the comparison between the OCM group and the control group were selected to increase statistical power. The variables analyzed for this group were age, gender, pH value, base excess, cardiac index (CI) immediately after perfusion and postoperatively, and post-operative use of adrenaline, inodilatator, or dopamin. All of values in all groups had to be measured at least 30 minutes before hemodynamic collapse. Limits for the various variables are as follows: low CI was defined as CI < 2.0 L/min/m2, and tachycardia as heart rate > 120. The criteria for postoperative ischemia was ST segment elevation > 2 mm. Hypotonia was defined as systolic blood pressure < 80 mmHg and diastolic blood pressure < 60 mmHg. Filling pressure was considered elevated when central venous pressure was > 15 mmHg or diastolic pulmonary artery pressure was > 20 mmHg. The use of inotropic support was defined as follows: epinephrine (0.02 mg/L), dopamine (0.02 mg/mL), or nitroglycerin (0.1 mg/mL) (no use, 1-15 mL/h and over 15 mL/h). The use of other drugs and intra-aortic balloon pump (IABP) was registered. Renal disease was considered to be present when S-creatinine was > 125μmol/l.

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4.3.1 Study I

The first study focused on the comparison of the first two patient groups (OCM group and control group) with regard to all of the variables given in Table 3. The purpose of this study was to find possible predictors of sudden hemodynamic collapse. After the initial comparison, data of the additional 128 patients were randomly selected from the same time period were used for testing of variables that differed statistically significantly in the matched pair analysis.

Table 3. Preoperative, intraoperative , and postoperative variables.

Preoperative	Intraoperative	Postoperative
Age	Cardiopulmonary bypass time	Timing of CPR
Gender	Aortic cross-clamp time	Tachycardia
Diabetes	Mean perfusion pressure	Hypotonia
Height	Perfusion temperature	Low cardiac index
Weight	Number of perfusions	High filling pressure
BMI	Amount of cardioplegia	Oliguria
Previous MI	Bleeding	Body temperature
Universal arterious sclerosis	Number of bypasses	Shivering
NYHA classification	Number of arterial grafts	Myocardial ischemia
Left ventricular EF (%)	Number of venous grafts	Nitro-glycerine infusion
No of diseased vessels	Number of IMA grafts	Dopamine infusion
Diseased Left main coronary	Number of radialic grafts	Epinephrine infusion
Smoking history	Number of complex grafts	Norepinephrine infusion
Diagnosed hypertension	Number of proximal anastomosis	Phosphodiesterase inhibitor
Cerebrovascular disease	Nunmer of distal anastomoses	Timing of extubation
Renal disease	Endarterectomy	Findings in resternotomy
Lung disease	Low cardiac index after CPB	Procedures in resternotomy
Left ventricular hypertrophy	Tachycardia	ICU stay
Previous CABG	Intra-aortic balloon pump	Hospital stay
Preoperative hemoglobin	Post-CPB blood gas analysis:	Complications
Timing of operation	Base Excess	Infection
Emergency/elective	pH	Amputation
Cleveland risk score	pO2	Additional surgery
	pCO2	Neurological
	Hemoglobin	Renal complication
		Heart complication
		Lung complication
		Gastrointestinal complication

BMI=body mass index, MI=myocardial infarction, EF=ejection fraction, CABG=coronary artery bypass grafting, CPB=cardiopulmonary bypass, ICU=intensive care unit

4.3.2. Study II

In the second study, only the study group (OCM group) was used. The purpose of this study was to identify possible surgical errors that lead to hemodynamic collapse. All patients with fatal outcome (n= 35) after hemodynamic collapse and resternotomy underwent medico-legal autopsy. In addition to the dissection of the coronary arteries and grafts, a post-mortem cast angiography was performed in all but three autopsies. This technique uses solidifying rubber with lead oxide as a contrast medium (Weman 1999). The records of autopsies with cast angiography were analysed in detail. The post-mortem angiographies were also re-analyzed. A surgical complication was considered to have occurred, when an occluded or narrow anastomosis, graft twisting, or dissection of the site of an anastomosis was encountered during autopsy.

4.3.3. Study III

The third study focused on evaluating the impact of the use of postoperative angiography on the incidence of hemodynamic collapse after CABG. A comparison was made between the OCM group and the group collected prospectively between 2000 and 2007. For clarity, the OCM group in this study was named the "Pre-angiography era group" and the more recent group was named as the "Angiography era group". Of the preoperative characteristics patient age differed significantly between the groups as Angiography era patients were older (58.2 years versus 64.0 years, p=0.002). Also the female gender was less frequent in the Angiography era (43.4 % versus 22.3 %, p=0.03). Other patient characteristics are shown in Table 1. The matched control group from the first study (I) was used in the third study for comparison of the hemodynamic collapse risk score, published in the first study (I).

4.3.4. Study IV

The fourth study was carried out to investigate the long-term survival and quality of life of patients surviving after sudden hemodynamic collapse and resternotomy after CABG. The OCM group and the co
ntrol group of the time period between 1988 and 1999 were analyzed in this study. In Finland mortality data are continuously updated in the National Causes of Death Register.

All patients from the two groups were traced from this archive for overall mortality in December 2009. Medical records of all patients were re-analysed and data concerning cardiac re-interventions was updated during the follow-up period.

Quality of life measurements were made with the RAND-36 Item Health Survey questionnaire (Aalto 1999). At the time of the study, 26 out of the 41 patients who were discharged from the hospital were alive in the OCM group and 45 out of 76 control patients were alive. The questionnaire was mailed to all living patients. Because seven patients from both groups seven patients were not reached or refused to participate, the follow-up rate in the two groups was 73 % (19/26) and 84 % (38/45), respectively. The mean follow-up time was 14.5 ± 3.3 years for the patients in OCM group and 15.6 ± 3.7 years for the control group. The mean age of the patients was 70 ± 9 years and 72 ± 7 years, respectively.

4.3.5. Graft-analysis

As the role of graft complications is important for this study, the patency of the grafts was analyzed in great detail. In addition to inspection and palpation, graft patency was assessed with flow measurements during the emergency reoperations. A surgical graft failure was considered to have occurred when there was a narrow or occluded anastomosis, graft twisting or dissection of the site of an anastomosis. A plain thrombosis of the graft was not considered to be a surgical complication if the graft and the anastomosis seemed to be technically intact. The second study (II) documented data of graft failures obtained in autopsies and post-mortem cast angiographies of patients in the OCM group who died. These findings were compared with the findings of emergency reoperations. Furthermore, in the third study (III), the findings of reoperations of Pre-angiography era (OCM group) patients were compared in detail with the findings of reoperations and angiographies of the Angiography era patients.

4.3.6. Statistics

In all of the studies (I –IV) the study settings and the comparisons made were different. Therefore, various statistical tools were used in this thesis.

In study I, intraoperative and postoperative factors were compared in a matched-pair design. Conditional logistic regression analysis (Stokes 1995) was used with the 1 sample t-test. McNemar´s exact test and Wilcoxon singed ranks test were used for nonparametric measurements. Mean and standard error were the descriptive statistics. Level of 5% was considered as the level of statistical significance. Significant parameters from the matched-pair analysis were collected from the additional 128 patients. Logistic regression analysis was performed using the data from 76 primary control patients, and 128 additional patients (n=204), and the OCM group patients (n=76). Possible incidence effect on parameter estimates was evaluated in data simulations, which included all control patients but only 2 to 4 patients from the OCM group. From the findings of the data simulations and logistic regression analysis, a simple risk score with three variables including postoperative CI, postoperative myocardial ischemia, and pH levels was created.

In study II, the data were expressed as percentages of cases or as means ± SD. P-values less than 0.05 were considered statistically significant. Comparisons were made with Fisher's exact test.

In study III, the data are given as means ± SE of mean. Pearson's Chi-Square test was used to evaluate nominal variables, while additional data were compared between the groups with independent t-test and when multiple groups were analysed ANOVA with Newman-Keuls pot-hoc test was used. Commercial statistical software packages were used to perform the computations (Statistica Version 8, Statsoft, Cytel Software Corporation, Cambridge, MA).

In study IV, the SPSS version 16.0 software (SPSS inc., Chicago, IL, USA) was used for statistical analysis. Quantitative data that were normally distributed were given as means ± standard deviation and skewed data as medians with IQR. For the RAND-36 instrument, summary scores and 95 % confidence intervals were calculated for the OCM group and for the control group. These data were compared with the Finnish age- and sex-matched reference population. For parametric data, the unpaired Student's t-test was used and for nonparametric data the Mann-Whitney U-test was used. Kaplan-Meier survival analysis was used for survival analysis and the log-rank test was used to evaluate the difference between the groups. p-values < 0.05 were considered statistically significant.

5 Results

5.1. Predictors of hemodynamic collapse (I)

Predictive factors of sudden hemodynamic collapse were pursued in a matched case-control study between the OCM group and the control group. The OCM group patients had significantly longer CPB times ($p=0.002$) compared with the controls, although, the aortic cross-clamp times were not statistically significant different ($p=0.23$). In both groups cold blood cardioplegia was used in 8 patients while all other patients received St. Thomas cold crystalloid cardioplegia for myocardial protection. Immediately after CPB, the cardiac index (CI) was significantly lower in the OCM group ($p=0.05$) as was the level of pH ($p=0.0057$) and base excess (BE) ($p=0.0014$). Postoperative myocardial ischemia detected in ECG was more frequent in the OCM group (32.9 %) than the control group (7.8 %) ($p=0.001$). OCM group patients also needed both mechanical (IABP $p<0.005$) and medical support (epinephrine $p<0.001$) more frequently. IABP insertion was intraoperative in each of the 8 cases. Detailed peri- and postoperative variables are given in Table 4. In addition to the data of the OCM group and the control group, also the data of the Angiography era group for the measured variables are given in this table.

5.1.1. Risk score formula (I, III)

After the comparison between the OCM group and the control group, an additional group of 128 patients were randomly selected from the same time period and the parameters with significant differences in the matched-pair analysis were retrieved. When the data was added, logistic regression analysis showed correlation between low CI, postoperative myocardial ischemia, low pH levels and the risk of hemodynamic collapse. For these variables, the area under the receiver operating characteristic curve (ROC-curve) was 0,73. Based on these results a simple risk score formula was created, in which pH was scored: 0 = pH > 7.35, 0.5 = pH 7.30 to 7.35, 1 = pH 7.25 to 7.30 or 1.5 = pH < 7.25. Low CI and postoperative ischemia scored according to their appearance; 0 = no, 1 = yes. Correlation of risk score points and need for open cardiac massage is shown in table 6, publication I, page 146. Although 18 (15%) patients in the OCM group scored 0.0 risk

score points, they ended up in hemodynamic collapse.   Risk Score formula: pH
(0/0.5/1/1.5) + PI (0/1) + low CI (0/1).

Table 4. Peri- and postoperative variables in all patient groups.

	Control group n=76	p-value (OCM vs. control)	OCM = Pre-angiography era n=76	p-value (OCM vs. Angiography era)	Angiography era n=36
Perioperative					
CPB time (min)	94.6 ± 4.1	0.005	110.0 ± 4.3	ns	101.0 ± 9.2
Aortic cross clamp time min	55.0 ± 2.8	0.24	58.8 ± 2.4	ns	62.8 ± 4.4
Low cardiac index post CPB	7 (8.7 %)	0.05	14 (18.1 %)	ns	8 (22.2 %)
Off-pump procedure	0 (0 %)	1.00	0 (0 %)	<0.001	5 (13.9 %)
postoperative					
use of:					
* Epinephrine infusion (%)	29 (38.1 %)	0.001	48 (63.2 %)	ns	72.2
* Dopamine infusion (%)	40 (52.6 %)	0.84	42 (55.2 %)	<0.0001	0
* Norepinephrine infusion (%)	5 (6.7 %)	0.06	9 (11.8 %)	<0.0001	80.6
* Inodilatator infusion (%)	2 (2.7 %)	0.06	7 (9.2 %)	0.03	25.0
* Nitro-glycerine infusion (%)	52 (68.4 %)	0.05	64 (84.3 %)	ns	75.0
* IABP (%)	0 (0 %)	0.005	9 (11.8 %)	ns	8.3
Myocardial ischemia (%)	6 (8.0 %)	<0.0001	25 (32.9 %)	< 0.0001	74.3
Hypotension (%)	71 (93.4 %)	1.00	71 (93.4 %)	< 0.0001	20.0
High filling pressure (%)	29 (38.1 %)	0.48	35 (46.1 %)	0.02	22.9
Low cardiac index (%)	14 (18.2 %)	0.13	23 (30.2 %)	ns	42.9

OCM=open cardiac massage, CPB=cardiopulmonary bypass, IABP=intra-aortic balloon pump

5.2. Mortality, survival, and morbidity after hemodynamic collapse (I,II,III,IV)

A major proportion of the OCM group patients (57/76, 75 %) suffered hemodynamic collapse and underwent OCM during the first 5 postoperative hours (Figure 1). Sixty-two patients (82%) underwent further emergency cardiac reoperation while 14 patients (18 %)

died before the emergency reoperation. Overall early mortality of the OCM group was 46 % (35/76) compared with 0 % in the control group ($p<0.0001$). Also late survival at 5, 10, 15, and 20 years after the operation was significantly different between the two groups, as overall survival rates were 50 %, 49 %, 40 %, and 18 % for the OCM group, and 95 %, 74 %, 59 % and 49 % for the control group, respectively ($p<0.0001$). However, the late survival rates were 93 %, 90 %, 74 %, and 33 % in the OCM group and 95 %, 74 %, 59 %, and 49 % in the control group, when the early mortality of the OCM group was excluded. The difference was not significant ($p=0.60$).

Cardiac-related overall survival rates were 50 %, 49 %, 41 %, and 18 % in the OCM group and 94 %, 83 %, 71 %, and 61 % in the control group, respectively ($p<0.0001$). When early mortality of the OCM group was excluded, the corresponding cardiac survival was 95 %, 95 %, 78 %, and 35 % in the OCM group and 94 %, 83 %, 71 %, and 61 % in the control group, respectively ($p=0.64$) Overall late non cardiac-related deaths occurred in 15 patients of 152 (10 %). In the OCM group, non cardiac-related mortality was 3 % compared to 17 % in the control group ($p=0.092$).

The OCM group patients suffered from all complications more frequently than the control group patients. The rate of different complications is given in Table 5. OCM group patients also required a longer ICU stay, hospital stay, and ventilation time, that is 5.5 $\pm$ 0.7 days ($p<0.0001$), 13.1 $\pm$ 1.6 days ($p=0.28$), and 4.1 $\pm$ 0.6 days ($p<0.0001$), respectively, when the corresponding times for the control group patients were 2.1 $\pm$ 0.1 days, 12.3 $\pm$ 0.4 days, and 1.0 $\pm$ 0.02 days, respectively

Table 5. Complications of OCM group patients and control group patients during the primary hospital stay.

	OCM group (n=76)	Control group (n=76)	*p*-value
Infection	17 (22.4%)	4 (5.3%)	0.002
Additional surgery	22 (28.9%)	3 (3.9%)	<0.0001
Cerebral complication	18 (23.7%)	3 (3.9%)	0.0002
Stroke	11 (14.5%)	0 (0%)	0.0003
Renal complication	11 (14.5%)	0 (0%)	0.0003
Pulmonary complication	25 (32.9%)	4 (5.3%)	<0.0001
GI complication	3 (3.9%)	0 (0%)	0.04
Myocardial infarction	70 (92.1%)	15 (19.8%)	<0.0001
Lower limb amputation	2 (2.6%)	0 (0%)	0.08

GI= gastro intestinal

Figure 1. Timing of open cardiac massage during the immediate postoperative course after coronary artery bypass grafting in the 76 OCM group patients.
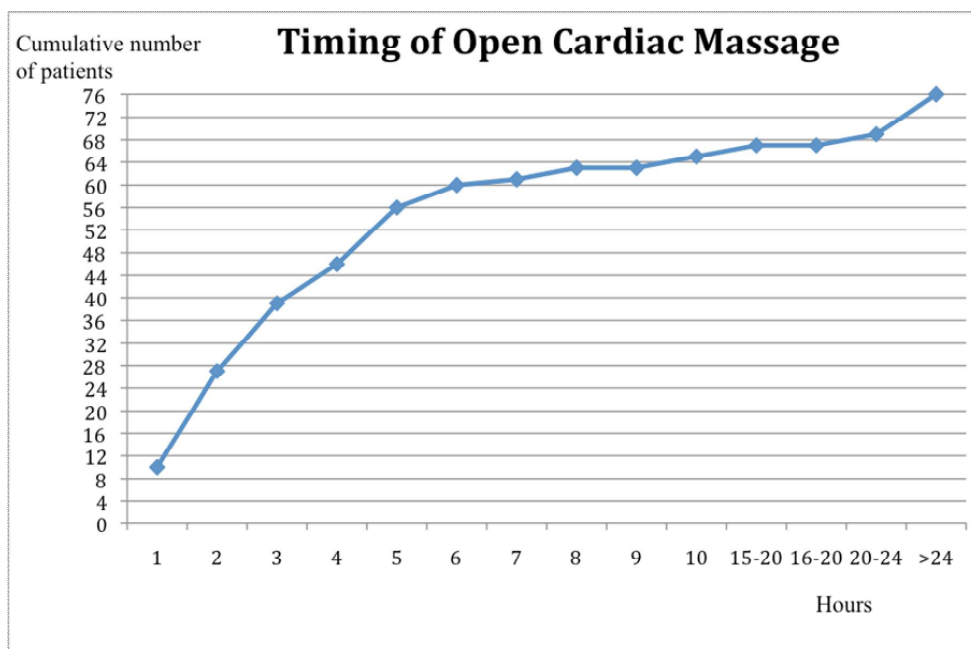
5.2.1. Cardiac survival (IV)

After discharge, during long-term follow-up, there was no significant difference in either the rate or timing of cardiac re-interventions between the OCM group and the control group. Re-CABG was performed in five (7%) of the patients of the OCM group while only one (1%) re-CABG was performed in the control group. The difference was not significant (p=0.10). The time frame of the operations was not significantly different (p=0.08) either. The mean/median time to reoperation was 8.5 ± 3.7 years in the OCM group and the single patient in the control group underwent re-CABG 18.1 years postoperatively. In the OCM group four (5%) patients received a pacemaker, while six (8%) pacemakers were implanted in the control group patients. Percutaneous coronary intervention (PCI) procedures were performed in two (3 %) patients of the OCM group and in four (5 %) patients of the control group. In the OCM group, one (1 %) laser re-vascularisation procedure was performed 4.5 years after primary surgery, and 1 (1 %) patient in the control group received a heart transplant 7.8 years after CABG.

5.2.2. Causes of death (II, IV)

An autopsy was performed in all 35 deceased patients to reveal the cause of death. Among the patients who died in the OCM / Pre-angiography era group, the underlying cause of death was cardiac-related in every patient. Acute myocardial infarction, which was diagnosed in 29 patients (82.9 %), was the most common immediate cause of death. Autopsy also revealed contributing factors, not detected prior to death: A pulmonary complication was diagnosed in three (8.6 %) patients prior to death while pulmonary oedema was detected in 20 (57.1 %) patients at autopsy. Furthermore, ten (28.6 %) cerebral complications were observed in autopsies while neurological problems were detected in nine (25.7 %) patients prior to death. Altogether five (14.3 %) patients were anuric clinically, however, only two (5.7 %) renal infarctions were found in autopsies. Causes of death with contributing factors are given in table 6 for patients who died immediately, for patients who died before the emergency operation (n=14), and for patients who died after the emergency reoperation (n=21).

Table 6. Cause of in-hospital death and contributing factors of 35 OCM group patients, and late cause of death of the 41 OCM patients with primary survival and of the 76 matched control patients. Follow-up periods were 14±3.3 years and 15±3.7 years postoperatively.

Cause of death	Immediate death (n=14)	Death after emergency operation (n=21)	*p*-value	Survivors (n=41)	Controls (76)
Immediate cause					
Perioperative MI	13 (92.8 %)	16 (76.2 %)	ns		
Acute cardiac insufficiency	1 (7.1 %)	1 (4.8 %)	ns		
Acute graft thrombosis	0 (0 %)	1 (4.8 %)	ns		
Coronary artery disease	0 (0 %)	1 (4.8 %)	ns		
Cerebral infarction	0 (0 %)	1 (4.8 %)	ns		
Severe arrhythmia	0 (0 %)	1 (4.8 %)	ns		
Contributing factor					
Pulmonary oedema	7 (50 %)	13 (61.9 %)	ns		
Cerebral infarction	1 (7.1 %)	9 (42.9)	0.02		
Renal infarction	2 (14.3 %)	0 (0 %)	ns		
Infection	2 (14.2 %)	1 (4.8 %)	ns		
Multiorgan failure	3 (21.4 %)	6 (28.6 %)	ns		
Late cause of death (20 y)					
Cardiac				13 (31.7%)	18 (23.7%)
Non-cardiac				2 (4.8%)	13 (17.1%)

MI=myocardial infarction

5.2.3. Impact of postoperative angiography (III)

After the introduction of postoperative angiography, the incidence of sudden hemodynamic collapse and emergency resternotomy after CABG decreased from 0.86 % (76/8807) to 0.34 % (13/5251) (*p*<0.001). Furthermore, in-hospital mortality also decreased from 46.1 % (35/76) to 22.2 % (8/36) (*p*=0.015), although early mortality of the patients in the Angiography era who underwent emergency resternotomy without postoperative angiography (Reoperation group) was 46.2 % (6/13), which was equal to the Pre-angiography era mortality. In the Angio group of the Angiography era early mortality was 8.7 % (2/23).

The only complication rate that differed significantly between the Pre-angiography era and Angiography era patients was the rate of MI (92.1% vs. 63.8 %, *p*<0.001). However, during the Angiography era the rate of complications was higher in the Reoperation group than in the Angio group. Complications and treatment times of the various study groups are shown in Table 7.

Table 7. Hospital stay and operative complications of patients of the various study groups. The Angiography era group is further divided into patients who underwent angiographic evaluation (Angio group) and into patients, who were immediately reoperated (Reoperation group).

| | Matched control group (n=76) | OCM = Pre-Angiography era (n=76) | Angiography era (n=36) | *p*-value (OCM vs.Ang) | Angiography era (n=36) | |
					Angio group (n=23)	Reoperation group (n=13)
ICU stay (d)	2.14 ± 1.02	5.53 ± 0.68	5.72 ± 0.98	ns	4.0 ± 0.76	8.8 ± 2.17
Hospital stay (d)	12.3 ± 3.71	13.1 ± 1.63	12.2 ± 1.54	ns	9.9 ± 0.96	16.5 ± 3.91
Ventilation time (d)	1.0 ± 0.17	4.1 ± 0.63	3.37 ± 0.84	ns	2.7 ± 0.63	5.7 ± 1.98
Complications						
Infection	4 (5.3%)	17 (22.4%)	6 (17.1%)	ns	1 (4.3%)	5 (41.7%)
Additional surgery	3 (3.9%)	22 (28.9%)	5 (14.3%)	ns	2 (8.7%)	3 (25.0%)
Cerebral complication	3 (3.9%)	18 (23.7%)	3 (8.6%)	ns	2 (8.7%)	1 (8.3%)
Renal complication	0 (0%)	11 (14.5%)	7 (20.0%)	ns	3 (13.0%)	4 (33.3%)
Pulmonary complication	4 (5.3%)	25 (32.9%)	14 (40.0%)	ns	8 (34.8%)	6 (50.0%)
GI complication	0 (0%)	3 (3.9%)	3 (8.6%)	ns	0 (0%)	3 (25.0%)
Cardiac complication	15 (19.7%)	70 (92.1%)	23 (63.8%)	< 0.001	12 (52.2%)	11 (84.6%)
Lower limb amputation	0 (0%)	2 (2.6%)	1 (2.9%)	ns	1 (4.3%)	0 (0%)
In-hospital death	0 (0%)	35 (46.1%)	8 (22.2%)	0.015	2 (8.7%)	6 (46.2%)

ICU= intensive care unit, GI= gastro intestinal

5.3. Grafts used (I, II, III)

The types of grafts used in various patient groups are given in Table 8. The only significant difference between the groups was in the use of sequential grafts, which were used more frequently in the later years (Angiography era) (*p*=0.025). Furthermore, the use of internal mammary artery grafts tended to be more frequent in the Pre-angiography era, although this difference was not significant (*p*=0.058). The use of arterial grafts in females decreased in the Angiography era patients, however the difference was not significant

either. The number of arterial grafts used in female patients in the Pre-angiography era group was 1.27 ± 0.10 while it was 1.00 ± 0.33 in the Angiography era group.

Table 8. Graft characteristics of patient groups undergoing isolated CABG. Pre-angiography era = OCM group and the Matched control group patients were operated on between 1989 and 1999, while the Angiography group patients were operated on during 2000 to 2007. The only significant difference was the more frequent use of sequential grafts during the Angiography era compared with the OCM group (p=0.025).

	Matched control group (n=76)	Pre-angiography era = OCM group (n=76)	Angiography era (n=36)
Number of bypasses			
All bypasses	3.38 ± 0.10	3.34 ± 0.11	3.19 ± 0.17
arterial	1.33 ± 0.08	1.36 ± 0.10	1.17 ± 0.13
venous	2.03 ± 0.17	1.97 ± 0.15	1.89 ± 0.17
IMA	1.13 ± 0.06	1.14 ± 0.06	0.94 ± 0.07
Radial artery	0.13 ± 0.05	0.22 ± 0.07	0.22 ± 0.10
Gastroepiploic artery	0.03 ± 0.02	0.01 ± 0.01	0 ± 0
Number of sequential grafts	0.26 ± 0.05	0.25 ± 0.06	0.61 ± 0.11
Number of endarterectomies	0.04 ± 0.02	0.026 ± 0.02	0 ± 0

IMA= internal mammary artery

5.4. Graft complications and repairs (II, III)

The grafts were evaluated in the OCM / Pre-angiography era group and in the Angiography era group. Occluded anastomoses were observed significantly more often in the Angiography era patients (p=0.043). In 16 of the 62 (25.8%) evaluated patients of the Pre-angiography era, the reason for hemodynamic collapse was considered to be a graft spasm while in the Angiography era, four graft spasms were objectively visualized at angiography in addition to one graft spasm observed at emergency reoperation. All four

graft spasms observed at angiography, were successfully treated with an intra-graft nitro-glycerine injection. The findings of the reoperations and angiographies are given in Table 9.

When the findings from the reoperations and post-mortem investigations of the 35 non-survivors of the OCM group were combined, the underlying cause was found to be a surgical graft complication in altogether 14 cases (40 %). The incidence of surgical graft complications was slightly lower among survivors, as a correctable surgical graft failure was found in 13 (31.7 %) of 41 survivors (p=0.34). Patent postoperative graft findings with no evident complication in the grafts were observed more frequently in the Angiography era group. However, the difference was not significant.

Findings in emergency reoperations led to additional grafting in 33 (53.2 %) of the OCM / Pre-angiography era patients, while seven (20 %) patients in the Angiography era received additional grafting. This difference was significant (p=0.006). Of these seven Angiography era patients, four (17.4 %) were Angio group patients and the additional grafting was performed in an operation following angiography. Three (25 %) patients in the Reoperation group received additional grafts. There was also a significant difference in the rate of graft revisions between the Pre-angiography era patients and the Angiography era patients. A graft revision was performed in 24 (38.7 %) patients in the Pre-angiography era and in four (11.4 %) patients of the Angiography era patients (p=0.013). In the Angiography era, a graft revision was performed in one (4.3 %) patient in the Angio group while this was true for three patients (25 %) in the Reoperation group. Furthermore, a percutaneous coronary intervention was adequate treatment for five (14.3 %) of the Angiography era patients. Four (11.4 %) of these patients received an intra-graft nitro-glycerine injection successfully and a stent was inserted in one (2.9 %) patient.

Table 9. Graft findings in reoperations in the Pre-angiography era patients and graft findings in reoperations and angiographies in the Angiography-era patients. Between the Pre-angiography era and the angiography era, only the number of occluded anastomoses or grafts was significantly different (p=0.043). In the Pre-angiography era, 14 patients died prior to emergency reoperations, while in the Angiography era 1 patient died before the reoperation

| | Pre-angiography era (n=62) | Angiography era (n=35) | Angiography era (n=35) | |
			Angio-group (n=23)	Reoperation group (n=12)
Number of patients having				
graft thrombosis	13 (17%)	3 (8.5%)	3 (13.0%)	0 (0%)
graft twisting	5(8.1%)	1 (2.9%)	0 (0%)	1 (8.3%)
narrowed anastomosis	8 (12.9%)	2 (5.7%)	1 (4.3%)	1 (8.3%)
occluded anastomosis / graft	2 (3.2%)	5 (14.3%)	3 (13.0%)	2 (16.7%)
tight graft	4 (6.5%)	0 (0%)	0 (0%)	0 (0%)
graft spasm in angiography	-	4 (11.4%)	4 (17.4%)	-
graft spasm considered in reoper	16 (25.8%)	1 (2.9%)	-	1 (8.3%)
No graft flow (if measured)	15 (24.2%)	6 (17.1%)	3 (13.0%)	3 (25.0%)
Hematoma occluding graft	2 (3.2%)	0 (0%)	0 (0%)	0 (0%)
No pathological findings	21 (33.9%)	16 (45.7%)	11 (47.8%)	5 (41.7%)

5.4.1. Autopsy and cast-angiography findings of grafts (II)

Autopsy was performed in all of the 35 deceased patients of the OCM group. Post-mortem cast-angiography was performed in all except three of these patients. In these patients the assessment of the grafts was based on the autopsy alone. One patient had thrombosis of all three venous grafts, while in the other 2 patients the grafts were considered to be intact. Seven (20%) patients had no pathological findings of the grafts at autopsy and also seven (20%) patients had graft thrombosis without any evidence of underlying surgical failure. Altogether 11 (31%) patients had thrombosis of their grafts. In two (5.7%) patients graft twisting was observed in cast-angiography but not seen during

autopsy dissection. Autopsy dissection revealed a minor thrombosis in a narrowed anastomosis, which was considered occluded in the cast-angiography. Differences in the findings of the autopsies and cast-angiographies are shown in article II, Table 3, page 11.

5.5. Quality of life (IV)

The mean follow-up time of the OCM group was 14.5 ± 3.3 years, the longest follow-up being 22.0 years. The corresponding figures for the control group were 15.6 ± 3.7 years and 21.8 years, respectively. At the time of the study, the mean age of the patients was 70 ± 9 years in the OCM group and 72 ± 7 years in the control group. The RAND-36 scores showed that the patients had achieved a good quality of life. When the groups were compared with each other and with a sex- and age-matched Finnish adult population, the RAND-36 scores were equal regarding all physical, mental, and social HRQoL dimensions (article IV, Figure 2, page 252).

6 Discussion

6.1. Predicting outcome (I)

The first part of the study demonstrates that postoperative hemodynamic collapse and the subsequent need for emergency reoperation and OCM is a dreadful complication with high mortality and morbidity. Early mortality of 46 % in the present study is comparable with earlier reports with mortality figures ranging from 30 % to 50 % (Fairman 1981, El-Banayosy 1998, Guney 2009). Although numerous risk scores for postoperative mortality and morbidity after myocardial revascularization have been created, these often fail to predict immediate postoperative collapse. In this study, patients scored relatively low in the Cleveland risk score system, which further emphasises the difficulty of predicting early problems after CABG in an individual patient. The Cleveland risk score system was used in our department at the time of the study. In addition to risk scores for primary cardiac surgery, also a score for the prognosis after IABP insertion in cardiac surgery has been published (Hausmann 2002). Advanced age, long aortic cross-clamp times, increased need for inotropic support, low CI, low mean arterial pressures and mixed venous saturations, in addition to high filling pressures, all increased mortality of patients requiring IABP insertion (Hausmann 2002). Moreover, in primary cardiac surgery, long-term survival may be predicted by gender, type of surgery, preoperative and postoperative cTnT levels, and aortic cross-clamp time (Lehrke 2004).

In the present study, predictive factors for sudden hemodynamic collapse appeared to be prolonged CPB time, low postoperative CI, poor tissue perfusion based on low pH and BE levels, myocardial ischemia, and the need for mechanical and/or inotropic support. However, the choice of graft material or the number and complexity of bypasses did not have any effect on the risk of hemodynamic collapse. Because aortic cross-clamp times were equal, the longer CPB times could be a consequence of hemodynamic problems intraoperatively. Patients having signs of poor myocardial function should be carefully evaluated. Transesophageal echocardiography effectively evaluates pericardial tamponade, as well as myocardial areas having poor motion as a sign of ischemia (Adams 2001). For further evaluation of graft malfunction, postoperative angiography gives detailed information of grafts (Adams 2001, Fabricius 2001, Alter 2005). As the prediction of

hemodynamic collapse is difficult, a risk score system was created, which might provide support for the decision to use diagnostic or surgical interventions before the collapse occurs.

The risk score was created using the original OCM group, the matched controls, and the additional 128 controls. It was calculated for all groups in this study. In the analysis, the area under ROC curve was only 0.73, which does not give strong power. Furthermore, the Pre-angiography/OCM group scored 0.90, while the Angiography era group scored 1.13 and the control group matched with the Pre-angiography era group scored 0.43. The Score of the Angiography era group was higher than the score of the OCM/Preangiography era group. The formula gives 1 point for postoperative ischemia. As myocardial ischemia is an indication for angiography, patients undergoing angiography could be expected to have higher scores. Moreover, the presence of only myocardial ischemia and low cardiac index is scored, which is a limitation, because the severity of ischemia and low output varies significantly. In addition, 18 (24%) of the OCM group patients scored zero points but suffered hemodynamic collapse. As the threshold to perform angiography is lower than the threshold to perform a reoperation, there are probably patients in the Angiography era group, who might have been treated successfully conservatively during the pre-angiography period. Furthermore, because the risk score formula was based on data from the pre-angiography period, it predicts subsequent hemodynamic collapse, but not the need for postoperative angiography. Moreover, because postoperative angiography might improve patient survival and decrease morbidity, it is fare to admit that our risk score formula clearly needs modification to answer the needs of modern postoperative care. The formula, as it is, lacks clinical relevance.

Ventricular tachyarrhythmias have been reported to be the precipitating mechanism in almost half of the patients who suffered unexpected cardiac arrest after cardiac surgery (Anthi 1998). Furthermore, the underlying cause for arrhythmias was perioperative MI (Anthi 1998). The most common cause for infarction has been reported to be early graft failure (Anthi 1998, El-Banayosy 1998, Guney 2009), which was also the case in our study as half of the patients who underwent immediate reoperation had early graft thrombosis or some other form of graft failure. The patients with no obvious technical graft failure had better early survival rate than the patients with graft complications. In addition, the long-term survival of patients who survived was equal to that of the control group.

Since the underlying cause of hemodynamic collapse in almost half of the patients was a graft malfunction, earlier investigative measures or surgical intervention while the patient is hemodynamically stable would undoubtedly result in a lower rate of hemodynamic collapse and need for resuscitation. When signs of poor tissue perfusion and myocardial ischemia are seen and there is need for increased inotropic support, a patient should be a candidate for re-interventions.

6.2. Surgical failure and causes of death (II)

The second part of the study concentrated on the post-mortem findings of the patients in the OCM group died with special emphasis to possible technical graft failures. Bosma et al reported prospective data of medical errors of 12,121 patients admitted to the surgical ward. Of these patients, 735 (6.1%) had a documented error. Errors leading to permanent injury occurred in 41 patients (4.7%) and five patients (0.6%) died (Bosma 2011). Earlier reports of surgical failures resulting in fatal outcome after CABG are scarce (Weman 1999, Goodwin 2000). In Finland, the autopsy rate after fatal outcome after major surgical interventions has been almost 100 %. Reports have shown autopsy rates as high as 84-88 % (Lee 1997, Goodwin 2000), but there are also reports with rates as low as 24.5 % (Zehr 1997). All these reports, however, demonstrate the importance of autopsy after surgical death as autopsy reveals an unsuspected cause of death in 14 % to 25 % of cases (Barendregt 1992 Lee 1997, Zehr 1997, Goodwin 2000). In the present study, the cause of death was revealed in every case.

Technical graft complications were observed in 40 % of the deceased patients and this supports the notion that graft complications are the most common underlying cause of hemodynamic collapse after CABG. An earlier report from our institution with detailed autopsy analysis demonstrated a stronger association between graft complications and death (Weman 1999). This is partly explained by the fact that in the earlier report by Weman et al. a graft thrombosis without a predisposing surgical error was considered a graft complication, while in the present study, only thromboses due to clear technical failures were considered graft complications. These figures are significantly higher than the frequency of surgical failure of 4.8 % reported by Goodwin et al. in 2000 (Goodwin 2000). This difference may partly be explained by the use of post-mortem cast angiography, which gives detailed information of the condition of the grafts and the

anastomosis (Weman 1999). However, most of the technical failures in the present study were detected by autopsy dissection. Cast angiography revealed 2 graft twists not detected by dissection.

Autopsy also revealed contributing factors not detected clinically. The rate of pulmonary edema in the autopsies was 57.1 %, while pulmonary complications were diagnosed only in 8.6 % of patients prior to death. This discrepancy may be due to the rapid development of pulmonary edema with acute cardiac failure and rapid fluid administration during cardiac resuscitation. This phenomenon could be expected especially in patients suffering immediate death after resuscitation and in patients who died during reoperation. Not surprisingly, autopsy demonstrated multiorgan failure in patients who survived the emergency reoperation and died later and in patients, who lived several days before the postoperative hemodynamic collapse.

Unexpected complications, especially unexpected postoperative death, may lead to malpractice claims and litigation. Therefore, medico-legal autopsy provides a neutral investigation of the cause of death. It also often convinces the relatives of the patients because a professional, who was not participating in the treatment of the patient prior to death, performs the autopsy. This may limit litigation. Even in cases with technical graft failure resulting in death, there were no legal consequences in this study.

Autopsy with careful dissection of the coronary arteries and grafts is important in revealing possible technical failures in grafting as well as in ascertaining the cause of death and possible contributing factors. Furthermore, post-mortem cast angiography improves the diagnostics of graft complications and is useful in combination with dissection of the coronary arteries in autopsy.

6.3. Impact of postoperative angiography on outcome (III)

The main result of the third part of the study was that early postoperative angiography evaluation of patients showing signs of persistent myocardial ischemia after CABG seemed to result in a lower rate of emergency operations. It also decreased postoperative morbidity and mortality. The improvements and changes in operative techniques in the Angiography era as well as improved intensive care treatment and monitoring might influence these results. However, the mortality and morbidity of the patients in the Angiography era who underwent an emergency reoperation without preceding

angiography were similar to the mortality and morbidity of patients in the Pre-angiography era. Cardiac morbidity in the Angiography era group was significantly lower in comparison to the Pre-angiography era group. In the Angiography era group only 64 % of patients were diagnosed with MI in contrast to 92 % of patients in the Pre-angiography era group. Furthermore, the frequency of MI varied within the Angiography era group as 85 % of the Reoperation group patients in the Angiography era were diagnosed with MI. The reduction of other complications was not significant, although the frequency of renal, gastrointestinal, and pulmonary complications tended to be higher in the Pre-angiography era group.

Female sex is considered to be an isolated risk factor for mortality after CABG (Nashef 1999, Nashef 2012). The proportion of female patients decreased significantly during the Angiography era (43 % vs. 22 %). This could be one of the reasons for the lower mortality and morbidity rates in the Angiography era group. In addition, the less frequent use of arterial grafts in female patients in the later patient population might have led to a lower early morbidity and mortality as arterial grafts are known to have an early spasm tendency especially in female patients (Acar 1991).

Only a few studies have focused on the indication of postoperative angiography following CABG (Alyanakian 1998, Alter 2005). The use of cardiac biochemical markers, such as CK-MB, cTnI, and cTnT, causes an inevitable delay, as levels of these markers peak 4-6 hours after myocardial ischemia (Alyanakian 1998). In the first study, postoperative hemodynamic collapse occurred during the first five postoperative hours in 75 % of the cases and therefore biomarkers of myocardial necrosis could not have been utilized. Immediate postoperative elevation of leukocyte count in association with ECG ST-segment elevation has been reported to be useful (Alter 2005).

In conclusion, angiography provides a tool to evaluate possible graft malfunction during the early postoperative course when signs of myocardial ischemia have been observed in ECG. It also allows catheter-based procedures, such as injection of intra-graft nitro-glycerine or stent insertion to be performed, as was the case in four patients in this study. Furthermore, if catheter-based procedures are not possible, angiography findings allow detailed planning of the immediate reoperation.

6.4. Long-term survival and quality of life (IV)

Long-term data about HRQoL and survival of patients who have undergone resuscitation, resternotomy, and emergency reoperation after CABG have not been reported previously. The major finding of the fourth part of the study was that patients surviving sudden hemodynamic collapse resulting in resuscitation and emergency reoperation in the immediate postoperative course after CABG achieve equal long-term survival and equal HRQoL in comparison with control patients. Furthermore, the HRQoL of these patients was comparable with an age- and sex-matched Finnish reference population. This finding is consistent with earlier studies reporting good quality of life six months to eight years after cardiopulmonary resuscitation not related to cardiac surgery (Kuilman 1999, Wachelder 2009). However, reports of inferior quality of life in comparison with the general population after cardiopulmonary resuscitation have also been published (Nichol 1999). Studies regarding early major postoperative complications after CABG are still scarce and the follow-up period of patients surviving the complications have been only up to 36 months (El-Banayosy 1998, Guney2009). Furthermore, these studies focus on mortality and morbidity, not on HRQoL.

Improvement of HRQoL following CABG have been reported earlier (Järvinen 2003, Loponen 2007), but the follow-up time of these studies was only 18 months. Our study, however, measured HRQoL similar to general population at 15 years postoperatively of both the study patients and the 76 control patients having postoperative course without major complications. In the studies by Loponen and Järvinen, elderly patients didn't receive permanent improvement in HRQoL. However, Jokinen et al. reported a prospective study in 2008, with follow-up of 8 years, and found the HRQoL in elderly patients undergoing cardiac surgery to be equal with age- and sex-matched controls (Jokinen 2008).

Long-term survival was similar between the OCM group and the control group when the early 30-day mortality of the OCM group was excluded. All patients who primarily survived in the OCM group underwent additional emergency cardiac surgery. This may be an explanation for the excellent results in long-term survival and HRQoL. According to a previous report, patients suffering cardiac arrest after CABG and undergo re-revascularization have better result in follow-up when compared with the patients having re-interventions in the intensive care unit (Guney 2009).

Interestingly, during the follow-up time of the OCM and matched control groups, no significant differences were found in either percutaneous or re-CABG interventions. There was a tendency for more frequent re-CABG in the OCM group (5 vs. 1, p=0.10), but probably due to the small number of patients, the difference was not significant. The incidence of non-cardiac causes of death of the control group in the follow-up period tended to be higher than in the OCM group (17% vs. 3 %). However, this difference did not reach the level of significance either.

The excellent result in both survival and also in the HRQoL of the resuscitated patients emphasises maximum efforts to be used to rescue patients suffering from sudden hemodynamic collapse in early postoperative course after CABG.

6.5. Limitations of the study

Being a retrospective setting for the most part, was the major limitation of this study. Only few data were missing regarding preoperative, perioperative and postoperative variables, as well as concerning resuscitation and emergency reoperations and, furthermore, the autopsies. However, with a prospective setting we could have enlarged the focus of the study to measure also the cost effectiveness during the follow up period. The other limitation of the study is the relatively low number of patients. But as the incidence of this hazardous complication is quite low and the time period of patient enrolment was 20 years, from 1988 to 2007, we could find only 89 patients suffering from unexpected hemodynamic collapse leading to resuscitation and resternotomy, in addition to 23 patients evaluated with postoperative angiography. Furthermore, even the changes in the operative techniques and peri- and postoperative patient treatment and monitoring have occurred, would longer time period, thus larger number of patients, result in problems in data comparison. From this point of view, the study setting should be a multicenter prospective study, with the limitation, that the treatment strategies, graft selection and peri- and postoperative patient care vary between the different cardiac centers.

The initially retrospective study design and the small number of patients were limitations especially for the long-term HRQoL study. The number of patients alive in 2009 was 26 in the OCM group and 45 in the control group, and the loss of participation was 20 %. Thus the results of the HRQoL may be overestimated, because the patients who

either had died, or were unable to participate might have had the poorest HRQoL. However, the 95 % confidence intervals were calculated, and probably there would not have been any statistical differences between the groups, even if the patient populations had been larger. Causes of death, mortality and data of cardiac procedures such as percutaneous interventions or surgery were collected successfully of the patient questionnaires in addition from the hospital and National Center of Statistics Records. Unfortunately, data concerning recurrent angina and myocardial infarction was unsuccessfully obtained and, thus, not included.

Conclusions

1. Risk factors for hemodynamic collapse following CABG appeared to be: long CPB time, low postoperative pH and BE levels, low cardiac index, postoperative myocardial ischemia and need for mechanical support (IABP). We created a formula for hemodynamic collapse prediction, however, as patient treatment methods have chanced after that, the formula is not suitable for modern clinical work. Predicting hemodynamic collapse still remains a challenge.

2. Surgical graft complication resulting in myocardial ischemia and low cardiac index is the most common underlying cause for sudden hemodynamic collapse resulting in need of emergency resternotomy and OCM. Graft complication was frequently observed as well in patients with fatal outcome and in those, who survived. Other graft problems, such as graft spasm may also lead to myocardial ischemia, arrhythmias and hemodynamic collapse.

3. Early angiography in cases with sings of postoperative poor tissue perfusion following CABG leads to exact diagnosis of possible graft malfunction and provides a tool to perform intra-arterial interventions. Furthermore, when percutaneous interventions are not sufficient, angiographic findings allow better planning of the possible immediate reoperation.

4. Early mortality after hemodynamic collapse resulting in OCM after CABG was 46 %. Patients who survived cardiac resuscitation and emergency reoperation achieved similar long-term prognosis in terms of survival and cardiac interventions as the pair-matched control patients. In addition, 15 years postoperatively, they had a good HrQol, similar to that of age- and sex-matched national reference population.

8 Finnish Summary

Sydänlihasinfarkti ja sitä seuraava hemodynaaminen romahdus sepelvaltimo-ohitusleikkauksen jälkeen on vaarallinen komplikaatio, johon liittyy korkea kuolleisuus ja sairastavuus. Sepelvaltimokirurgian jälkeistä kuolleisuuden ja sairastavuuden arvioimista varten on kehitetty monia riskipistejärjestelmiä. Näiden järjestelmien heikkous on kuitenkin se, että ne eivät ennusta välittömiä leikkauksen jälkeisiä vakavia komplikaatiota, kuten hemodymaanista romahdusta.

Tämä tutkimuskokonaisuus perustuu mittavaan analyysiin sepelvaltimokirurgisista potilaista, joiden hemodynamiikka romahti välittömässä leikkauksenjälkeisessä vaiheessa vuosien 1988 ja 1999 välillä Helsingin Yliopistollisessa keskussairaalassa. Jokaiselle tutkimuspotilaalle valittiin esitiedoiltaan vastaava (matched) kontrollipotilas samalta ajanjaksolta. Niille, jotka kuolivat, suoritettiin oikeuslääketieteellinen ruumiinavaus, johon kuului kumivarjoaineella tehtävä sepelvaltimoiden varjoainetutkimus selvittämään mahdollisia kirurgisia virheitä sepelvaltimoiden siirteissä. Vuonna 2009 elossa oleville potilaille ja heidän kontrollipotilailleen lähetettiin elämänlaatukyselykaavake. Tämän lisäksi vertailtiin hemodynaamisen romahduksen saaneita potilaita potilaisiin, joille tehtiin varhaisen sydänlihasiskemian vuoksi varjoainekuvaus välittömässä leikkauksenjälkeisessä vaiheessa. Angiografiatutkimus-käytäntö aloitettiin vuonna 2000 ja potilasaineisto on tältä osin kerätty vuosien 2000 ja 2009 välillä.

Tämä tutkimus koostuu neljästä osatutkimuksesta (I-IV). Tavoitteena oli selvittää ennakoivia tekijöitä, jotka johtavat hemodynaamiseen romahdukseen sepelvaltimokirurgian jälkeen (I). Tavoitteena oli myös selvittää oikeuslääketieteellisellä ruumiinavauksella mahdolliset kirurgiset virheet jotka johtivat hemodynaamiseen romahdukseen ja mahdollisesti kuolemaan (II). Lisäksi selvitettiin, vaikuttiko sepelvaltimoleikkauksen jälkeinen varjoainetutkimus kuolleisuuteen, sairastavuuteen ja teho-osastolla tapahtuneiden elvytysten määrään (III). Lopuksi selvitettiin hemodynaamisesta romahduksesta selvinneiden potilaiden pitkäaikaiselämänlaatua (IV).

Tulokset osoittavat, että yhtäkkinen hemodynaaminen romahdus sepelvaltimokirurgian jälkeen on vaarallinen komplikaatio, johon liittyy suuri kuolleisuus. Kudosten riittämätön verensaanti, leikkauksen jälkeinen sydänlihaksen iskemia ja lisääntynyt verenkiertoa ja sydämen tehoa lisäävien lääkkeiden tarve, kuten myös verenkiertoa tehostavien

lisälaitteiden tarve ennustavat kohonnutta riskiä leikkauksen jälkeiselle hemodynaamiselle romahdukselle (I).

Tekninen virhe sepelvaltimoiden ohituksessa osoittautui suurimmaksi syyksi leikkauksen jälkeiselle hemodynaamiselle romahdukselle. Kuoleman jälkeinen sepelvaltimoiden varjoainekuvaus parantaa oikeuslääketieteellisen ruumiinavauksen diagnostiikkaa kuolemaan johtaneissa sepelvaltimo-ohitussiirteiden ongelmissa. Kuolinsyy pystytään selvittämään kaikissa tapauksissa. (II)

Leikkauksen jälkeisen huonon hemodynamiikan tai sydänlihaksen iskemian takia tehdyt sepelvaltimoiden varjoainekuvaukset vähensivät avointa sydänelvytystä sekä sitä seuraavien hätäleikkausten määrää, kuten myös kuolleisuutta ja sairastavuutta. Varjoainetutkimus antaa myös mahdollisuuden hoitaa sillä diagnosoituja ongelmia, kuten sepelvaltimosiirteen supistumista suonensisäisellä lääkityksellä. (III)

Potilaat, jotka selviävät vakavasta hemodynaamisesta leikkauksenjälkeisestä romahduksesta ja hätäleikkauksesta, saavuttavat kontrollipotilaisiin verrattuna vastaavan pitkäaikaisennusteen. Myös elämänlaatu on vertailukelpoinen kontrollipotilaiden kanssa, kuten myös ikä- ja sukupuolivakioitujen verrokkien kanssa vielä 15 vuotta leikkauksen jälkeen. (IV)

9 Acknowledgements

10 References

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