

**MYOCARDIAL AND CEREBRAL
PRESERVATION DURING OFF-PUMP
CORONARY ARTERY SURGERY**

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Academic Dissertation to be presented with the assent of the Faculty of Medicine, University of Oulu, for public discussion in the Auditorium I of Oulu University Hospital, on January 28th, 2006, at 12 noon.

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Abstract

Interest in off-pump coronary surgery and ischaemic preconditioning has been increasing. The aim of this study was to evaluate surrogate indicators of haemodynamic, myocardial, and cerebral outcome during off-pump surgery and preconditioning.

Haemodynamics and myocardial preservation were monitored in a pilot study of twelve patients undergoing off-pump coronary surgery. Indicators of myocardial metabolism and tissue injury as well as cerebral damage were evaluated in a randomized study of thirty-three patients undergoing on-pump (11) or off-pump surgery with (11) or without (11) preceding myocardial ischaemic preconditioning for five minutes followed by reperfusion for five minutes.

The pilot study showed minimal haemodynamic changes and myocardial derangements during off-pump surgery as evaluated intraoperatively based on transcardiac differences of ATP degradation products and lactate and postoperatively based on MB mass of creatine kinase and troponin T.

In the following studies, myocardial ischaemic metabolism was evaluated intraoperatively by measuring transcardiac differences of ATP degradation products, lactate, and pH, which increased significantly from the baseline values in all study groups. However, the maximum values of lactate and pH were significantly higher in the cardiopulmonary bypass group ($p = 0.02$ and $p = 0.007$, respectively). There were no statistical differences between the preconditioning and non-preconditioning groups. Myocardial tissue injury was evaluated by postoperative leakage of MB mass of creatine kinase and troponin I. Their peak values were significantly higher ($p < 0.001$ and $p = 0.008$) after cardiopulmonary bypass (15.1 $\mu\text{g/l}$ and 13.8 $\mu\text{g/l}$) than after off-pump surgery without preconditioning (6.3 $\mu\text{g/l}$ and 5.2 $\mu\text{g/l}$). The respective values were 14.8 $\mu\text{g/l}$ and 7.4 $\mu\text{g/l}$ after preconditioning, and there were no statistically significant differences between the off-pump groups with and without preconditioning. Cerebral damage was evaluated based on the intra- and postoperative serum concentrations of neuron-specific enolase, which were corrected with respect to haemolysis. The corrected values were significantly higher after on-pump than off-pump surgery ($p = 0.003$ and $p = 0.005$).

In conclusion, multi-vessel off-pump coronary artery surgery is a haemodynamically feasible procedure offering better myocardial preservation compared to on-pump surgery. Ischaemic preconditioning of the myocardium does not seem to improve myocardial preservation in off-pump surgery. The slightly lower levels of neuron-specific enolase also suggest less cerebral damage.

Keywords: adenosine, brain, ischemic preconditioning, myocardium, off-pump coronary artery bypass, phosphopyruvate hydratase

**There are no perfect men in this world.
Only perfect intentions.**

Pen Densham:
Robin Hood; Prince of Thieves (1991)

To my farther and my mother

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Turku, December 2005

Hannu Penttilä

Abbreviations

AMI	acute myocardial infarction
ATP	adenosine triphosphate
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CI	confidence interval
CK-MBM	mass of MB fraction of creatine kinase
CPB	cardiopulmonary bypass
Cx	circumflex coronary artery
DC	direct current
ECG	electrocardiogram
IPC	ischaemic preconditioning
LAD	left anterior descending coronary artery
LIMA	left internal mammary artery
MIDCAB	minimally invasive direct coronary artery bypass
NSE	neuron-specific enolase
OPCAB	off-pump coronary artery bypass
PTCA	percutaneous transluminal coronary angioplasty
RCA	right coronary artery
TnI	troponin I
TnT	troponin T

List of original articles

This thesis is based on the following original papers, referred to in the text by their Roman numerals:

- I Penttilä HJ, Lepojärvi MVK, Kaukoranta PK, Kiviluoma KT, Ylitalo KV & Peuhkurinen KJ (1999) Myocardial metabolism and hemodynamics during coronary surgery without cardiopulmonary bypass. *Ann Thorac Surg* 67: 683–688.
- II Penttilä HJ, Lepojärvi MVK, Kiviluoma KT, Kaukoranta PK, Hassinen IE & Peuhkurinen KJ (2001) Myocardial preservation during coronary surgery with and without cardiopulmonary bypass. *Ann Thorac Surg* 71: 565–571.
- III Penttilä HJ, Lepojärvi MVK, Kaukoranta PK, Kiviluoma KT, Ylitalo KV & Peuhkurinen KJ (2003) Ischemic preconditioning does not improve myocardial preservation during off-pump multi-vessel coronary surgery. *Ann Thorac Surg* 75: 1246–1253.
- IV Kaukoranta PK, Penttilä HJ, Kiviluoma KT, Peuhkurinen KJ, Penttilä I & Lepojärvi MVK: Serum concentrations of neuron-specific enolase after coronary surgery with and without cardiopulmonary bypass. (Submitted).

Articles I–III are reprinted with permission from the Society of Thoracic Surgeons.

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1 Introduction

Cardiac surgery has been widely regarded as one of the most important medical advances of the 20th century. At present, it is hard to believe that the first successful cardiac operation, closure of an atrial septal defect, was performed not more than 53 years ago (Lewis & Taufic 1953), and that the first CABG was only done 45 years ago (Goetz *et al.* 1961). The first CABGs were performed without CPB (Favaloro 1968, Favaloro 1969, Favaloro *et al.* 1970, Johnson & Lepley Jr 1970), but the development of cardioplegia (Gay & Ebert 1973) led to widespread use of CPB to facilitate coronary artery surgery, and the beating heart technique was almost forgotten.

CPB has been reported to be harmful in many ways, however. The interaction between blood and foreign surfaces activates the complement system and neutrophils, with inflammatory responses (Butler *et al.* 1993), and CPB adversely affects both platelet count and platelet function (Zilla *et al.* 1989, Woodman & Harker 1990).

Myocardial protection during the aortic cross-clamp period may sometimes be difficult and ultimately depends on adequate distribution of cardioplegia to all parts of the myocardium (Partington *et al.* 1989a, Partington *et al.* 1989b). Abnormal septal motion (Akins *et al.* 1984), a decline in left ventricular systolic function (Roberts *et al.* 1980, Mangano 1985, Gorcsan III *et al.* 1994), and deleterious effects on diastolic function (Wehlage *et al.* 1990, Öwall *et al.* 1992, Houltz *et al.* 1996) have been documented after cardioplegia.

The incidence of postoperative neurological deficits has increased at the same time as overall mortality has declined (Gill & Murkin 1996). Of the patients who undergo cardiac surgery, 5.2% suffer strokes and 26–80% have short-term and up to 37% persistent cognitive dysfunction (Borowicz *et al.* 1996, Stump *et al.* 1996). On the other hand, similar moderate-to-severe neuropsychological dysfunction is not observed after major peripheral vascular surgery which does not require CPB (Shaw *et al.* 1987). Increasing age, prolonged CPB time, hypertension, diabetes, and previous neurological disease are regarded as risk factors (Borowicz *et al.* 1996, Stump *et al.* 1996, Utley 1996). Neurological injury is considered to be due to microembolization from the surgical field or the CPB system (Utley 1996) and ischaemia to cerebral hypoperfusion (Taylor 1998). Over 60% of the microemboli detectable by ultrasound at the common carotid artery have been shown to appear during the manipulation of the heart and the aorta (Stump *et al.*

1996). The systemic inflammatory response due to CPB has been suggested to cause cognitive dysfunction, which is in accordance with the swelling of cerebral tissue observed after cardiac surgery (Harris *et al.* 1993, Taylor 1998).

Although the adverse effects of CPB are mostly minor and reversible, patients with significant preoperative functional impairment of various organ systems may not tolerate the deleterious effects of CPB. Therefore, renewed interest in the beating heart technique, especially MIDCAB, arose in the late 1980s. On the other hand, the coronary artery to be grafted is usually occluded during the suturing of the distal anastomosis when CABG is performed on a beating heart. Evidence from studies of major coronary artery occlusion in the canine model has shown the safe coronary artery occlusion time to be about 15 to 20 min (Reimer & Jennings 1979).

IPC, defined as protection of the myocardium by a short ischaemic period before a subsequent longer period of ischaemia, was first described by Murry and colleagues (Murry *et al.* 1986). Since that, the phenomenon has been confirmed in numerous animal studies, but despite intensive research, its basic cellular mechanisms are not yet fully understood (Perrault *et al.* 1996, Yellon *et al.* 1998). Preinfarction angina in humans has been found to act like IPC: it preserves left ventricular function even without collateral coronary artery circulation (Nakagawa *et al.* 1995). PTCA has been a popular model in studying IPC in humans, but the results are conflicting (Deutsch *et al.* 1990, Ylitalo *et al.* 1996, Eltchaninoff *et al.* 1997). In CABG performed with CPB, IPC has been found to be effective during intermittent aortic cross-clamping (Yellon *et al.* 1993, Alkhulaifi *et al.* 1994) or with normothermic or mild hypothermic cardioplegia, but not with cold cardioplegia (Valen *et al.* 1996, Cleveland *et al.* 1997, Cremer *et al.* 1997), although several conflicting results also exist (Kolocassides *et al.* 1994, Perrault *et al.* 1996, Kaukoranta *et al.* 1997, Lu *et al.* 1997). There is evidence that other organs also benefit from ischaemic preconditioning, and an inter-organic protective effect, possibly mediated neuronally, has also been suggested (Perrault & Menasché 1996).

The aim of this study was to evaluate the haemodynamic and myocardial safety of coronary artery surgery on a beating heart, to compare myocardial and cerebral preservation between OPCAB and on-pump surgery, and to evaluate the effects of IPC during OPCAB.

2 Review of the literature

2.1 Historical aspects

2.1.1 Historical aspects of open heart surgery

After a period of laboratory research on dogs, the first successful cardiac operation, closure of an atrial septal defect, was performed only 53 years ago, in 1952, by Dr. Lewis. The operation was performed under direct vision by means of inflow stasis and moderate total-body hypothermia (Lewis & Taufic 1953), which technique later came into routine use (Swan *et al.* 1953). Because this technique enabled only simple repairs of the heart, there was a need for a technique allowing more complex operations. The first attempts to use a heart-lung machine with a pump and heterogeneous lung oxygenators (Dennis *et al.* 1951, Campbell *et al.* 1956) had poor results and did not arouse interest among cardiac surgeons. Instead, operations performed by means of controlled cross-circulation (Warden *et al.* 1954) were successful and were hence received with great enthusiasm, but the technique could be used only in paediatric surgery. The usage of a Gibbon type oxygenator with lower pump flow (Kirklin *et al.* 1955) and the development of disposable oxygenators (Lillehei *et al.* 1956) significantly improved the results of extracorporeal circulation and increased the number of indications for cardiac surgery. Rediscovery of the bubble oxygenator was a success and marked the beginning of the CPB era. These oxygenators are still in use, although membrane oxygenators are replacing them. The first pump was the multi-cam activated Sigmamotor pump, but roller pumps gained more popularity because of their ease of use and reliability.

2.1.2 Historical aspects of CABG

The Roman Stoic philosopher, Lucius Annaeus Seneca (4 BC–65 AD), gave the first written description of the symptoms of an anginal attack in himself. Angina was treated with sedatives and alcohol before nitroglycerine was discovered at the turn of the 19th century. Efforts at surgical treatment began with cervico-thoracic sympathectomy to

break neuronal connections and thyroidectomy to reduce metabolic needs. The earliest attempts at myocardial revascularization were based on providing collateral circulation to the heart by implanting the pectoral muscle or omentum into the pericardium, by producing adhesions between the pericardium and the epicardium with magnesium silicate (talc powder), by ligating the mammarian arteries, and by shunting the pulmonary artery and the left atrium. (Schiff 1990). Vinberg introduced a more advanced technique in 1946. He implanted the internal mammary artery directly into the myocardium of the left ventricle. The internal mammary artery formed an anastomosis with the left coronary artery system in four months. (Vinberg 1946).

Development of cardiac catheterization in 1929 and selective coronary angiography in 1959 (Shiff 1990) enabled the further development of coronary surgery. Advanced coronary surgery was started with coronary endarterectomy (Bailey *et al.* 1957), and the first successful clinical CABG was performed in 1960 by Robert H. Goetz. He used a non-suture technique to connect the right mammary artery to the right coronary artery on a beating heart by means of a tantalum ring (Goetz *et al.* 1961). Four years later, Garrett performed an aorto-coronary bypass with a saphenous vein graft (Garrett *et al.* 1973), and this technique was adopted and widely presented by Favaloro and Johnson (Favaloro 1968, Favaloro 1969, Favaloro *et al.* 1970, Johnson & Lepley Jr 1970). The patients were prepared for extracorporeal circulation, but they were operated without it, whenever possible. The need for a non-beating, bloodless surgical field and the development of cardioplegia (Gay & Ebert 1973) led to the widespread use of CPB to facilitate coronary artery surgery, and the beating heart technique was almost forgotten. Only a few individual cardiac surgeons continued to operate on a beating heart, mainly for economic reasons.

2.2 Myocardial ischaemia-reperfusion

The conventional definition of ischaemia focuses on the imbalance between myocardial oxygen supply and demand. Ischaemia, however, involves three components: hypoxia, decrease in substrate supply, and accumulation of harmful catabolites, such as lactate and hydrogen ion (Jennings & Reimer 1991). The severity of ischaemic injury is determined by the duration of ischaemia, the extent of collateral blood flow offsetting ischaemic changes, the ambient oxygen demand of the myocardium, and various preischaemic factors (Butchard *et al.* 1980).

2.2.1 Duration of ischaemia

The distinction between global ischaemia, imposed by aortic cross-clamping (and cessation of cardioplegia delivery), and regional ischaemia secondary to coronary artery occlusion is important, as the contribution made by each of the three pathologic determinants may vary and alter the time course of the development of injury. The oxygen demand of a regionally ischaemic myocardium greatly exceeds that of a globally ischaemic myocardium (Allen *et al.* 1986, Gayheart *et al.* 1989), possibly due to the

greater wall stress encountered in the ischaemic segment during systolic paradoxical bulging.

2.2.2 Extent of blood flow deficit

In regional ischaemia, the degree of collateral blood flow will proportionally reduce the severity of ischaemia and slow down its pathologic time course (Scharper *et al.* 1987). Collateral vessels will also aid the delivery of antegrade cardioplegia in the case of severe or total stenosis. During CPB, however, the collateral blood flow originating from cardiac and extracardiac sources represents only 2% to 4% of normal coronary blood flow. This is sufficient to wash out the cardioplegic solution and to reduce its effectiveness, while being in itself insufficient to satisfy the myocardial oxygen and metabolic demands. (Brazier *et al.* 1975).

2.2.3 Myocardial oxygen demand

The main determinants of myocardial oxygen demand are the pressure-volume area, heart rate, and inotropic state. The oxygen demand of the dyskinetic segment of a beating heart is decreased to 70% of normal during the periods of both ischaemia and reperfusion (Gayheart *et al.* 1989). The oxygen supply/demand mismatch during CPB may be reduced by cardiac arrest, hypothermia, and decompression of the heart by left ventricular venting (Mills *et al.* 1985). Normothermic electromechanical arrest reduces myocardial oxygen consumption to 20% of the basic value, and hypothermia reduces it further to 5% at a temperature of 22 °C (Buckberg *et al.* 1977).

2.2.4 Ischaemia-reperfusion injury

Reperfusion injury can be defined as pathology that is extended, accelerated, or expressed *de novo* from the profile observed during ischaemia, resulting from events occurring after the initiation of reperfusion. However, reperfusion injury is difficult to distinguish from ischaemic injury, because there is no reperfusion without ischaemia.

The reperfusion process is modifiable by interventions initiated at the time of reperfusion. During CPB, it is easier to modify the condition and composition of reperfusion by the delivery and composition of cardioplegia. The possibilities to modify reperfusion are much more limited while the heart is beating.

It is well known that ischaemia and reperfusion produce myocardial contractile dysfunction (Vinten-Johansen *et al.* 1985, Vinten-Johansen *et al.* 1988, Nakanishi *et al.* 1991). Reperfusion injury in the early postoperative period may be an important co-factor in the development of myocardial stunning, defined as postischaemic contractile dysfunction in the absence of morphological injury or necrosis (Braunwald & Kloner 1982). Arrhythmias are a well-known complication of reperfusion, their incidence and

severity being, however, related to the severity of the preceding ischaemia. Reperfusion arrhythmias occur after short intervals of normothermic ischaemia and are reduced as irreversible injury and electrical excitability develop upon more prolonged ischaemia. (Manning & Hearse 1984).

A number of mechanisms have been implicated in reperfusion injury, including the generation of oxygen-derived free radicals and their metabolites, activation of neutrophils and platelets, intracellular calcium accumulation, and development of microvascular injury with impaired blood flow producing a no-reflow phenomenon. However, it must be kept in mind that the degree of reperfusion injury is determined by the severity of the preceding ischaemia. (Ferrari *et al.* 1986, Hearse & Tosaki 1988, Opie 1989).

2.2.4.1 *Oxygen-derived free radicals*

Oxygen-derived free radicals are highly reactive with a broad spectrum of biological materials, including carbohydrates, amino acids, phospholipids, and DNA and are potentially toxic to cells (McCord 1985). The injury includes peroxidation of the lipid components of cellular membranes leading to damage to mitochondria and the sarcoplasmic reticulum and disruption of the endothelium (Krause & Hess 1984, Hess *et al.* 1984). These elements of myocellular injury contribute significantly to the pathologic process involved in postischaemic dysfunction (Bolli 1991), arrhythmias (Manning & Hearse 1984, Nejima *et al.* 1989), morphological injury (McCord 1985), and necrosis (Hammond & Hess 1985, Simpson & Lucchesi 1987).

2.2.4.2 *Neutrophils*

Neutrophils mediating the inflammatory response are regarded to play a central role in myocardial ischaemic-reperfusion injury. The extent of postischaemic injury is proportional to the extent of neutrophil accumulation (Nakanishi *et al.* 1992). Activated neutrophils are a primary source of deleterious oxygen-derived free radicals. The activation of neutrophils may induce degranulation, proteolytic enzyme release, and stiffening of neutrophils. This may promote microembolization leading to impediments in regional blood flow distribution or a no-reflow phenomenon (Engler 1989, Ko *et al.* 1991). Finally, neutrophils have been indirectly implicated in the aetiology of postischaemic oedema (Engler *et al.* 1986).

2.2.4.3 *Calcium*

The excessive intracellular and intramitochondrial accumulation of calcium ions is caused by several mechanisms during reperfusion. The intracellular calcium ion overload has a number of deleterious effects that may lead to severe myocellular damage and necrosis. High-energy phosphate stores may be depleted by both an acceleration of ATP utilization by calcium ion activated ATPases and a reduction in mitochondrial ATP

production. Increased intracellular calcium levels may activate catalytic key enzymes that catalyze injurious processes leading to membrane disruption. Furthermore, elevated intracellular calcium levels in the myocyte may alter the calcium kinetics of excitation-contraction coupling or calcium cycling between the contractile apparatus and the sarcoplasmic reticulum, leading to contracture, i.e. a stone heart. (Walsh & Tormey 1988, Opie 1989, Jennings & Reimer 1991).

2.2.4.4 *No-reflow phenomenon*

Coronary perfusion pressure and blood flow will determine, in part, the functional and morphologic destiny of the ischaemic-reperfused myocardium. Ischaemia sets the microcirculation to a "leaky" state, which allows both extravasation of fluid and intracellular water accumulation. However, during ischaemia, the absence of perfusion pressure prevents larger-scale migration of fluids, but during reperfusion, Starling forces favor fluid migration, leading to oedema. The combined effects of endothelial cell swelling and extravascular compression of capillaries by tissue oedema may cause severe impairment of microvascular perfusion and precipitate the no-reflow phenomenon. Gradual restoration of coronary perfusion pressure has been found to reduce the myocardial infarct size and to improve postischaemic systolic and diastolic function. (Opie 1989, Vinten-Johansen *et al.* 1992).

2.3 Deleterious effects of CPB

Although CPB and cardioplegia have greatly facilitated coronary artery surgery, they have been reported to be harmful in many ways. The interaction between blood and foreign surfaces activates the complement system and neutrophils, leading to an inflammatory response, and CPB adversely affects the haemostatic system. Postoperative neurological deficits are a significant problem, and myocardial protection during the aortic cross-clamping period may sometimes be difficult.

2.3.1 *Myocardium*

Coronary blood flow is reduced during CPB with non-pulsatile flow, a situation that always exists in extracorporeal circulation before and after aortic cross-clamping, when the heart is kept empty of blood to avoid a work load on the heart. After the cross-clamping period, when the patient is warmed up, the myocardium is extremely sensitive to ischaemia-reperfusion injury. The use of pulsatile blood flow during CPB increases coronary blood flow significantly (Ündar *et al.* 1999, Pêgo-Fernandes *et al.* 2000).

Myocardial protection against ischaemia during aortic cross-clamping consists of a reduction of oxygen demand and a washout of deleterious metabolites with cardioplegia. Interruption of electro-mechanical activity reduces the myocardial oxygen demand, and a

further reduction is achieved by cooling the myocardium. Oxygen supply is also possible by using blood cardioplegia. Various cardioplegic solutions, crystalloid or blood, and various infusion routes, antegrade, retrograde, or combined ante-retrograde, have been used.

A total failure of myocardial protection is always possible and obviously causes a myocardial infarction and a dramatic impairment of ventricular function. Myocardial function has been reported to be impaired during CPB and cardioplegia even when no difficulties in applying myocardial protection have occurred. A decline in left ventricular systolic function, particularly in the anteroseptal wall with compensatory hyperkinesia in the posterolateral wall, is frequently documented after CPB and cardioplegia. It has been reported to last from several hours to several weeks and even months. (Roberts *et al.* 1980, Mangano 1985, Hamouratidis *et al.* 1988, Gorcsan III *et al.* 1994). Abnormalities of interventricular septal motion after CPB are present in 60% to 100% of patients (Righetti *et al.* 1977, Vignola *et al.* 1979, Akins *et al.* 1984). Deleterious effects of CPB on left ventricular diastolic function have also been reported (Wehlage *et al.* 1990, Öwall *et al.* 1992), although conflicting results exist (Houltz *et al.* 1996). Modified ultrafiltration counteracts the impairment of left ventricular function (Chaturvedi *et al.* 1999). Atrial fibrillation is a common dysrhythmia after CABG, but it is not caused by CPB only (Saatvedt *et al.* 1999).

2.3.2 Brain

Cerebral injury after cardiac surgical procedures is a well-known and increasingly prevalent problem. The incidence of neurological complications has been reported to vary between 0.8% and 5.2% for stroke, between 23% and 83% for short-term, and up to 37% for persistent decline in cognitive function (Shaw *et al.* 1987, Borowicz *et al.* 1996, Gill & Murkin 1996, Nussmeier 1996, Stump *et al.* 1996, Utley 1996, Taylor 1998, Almassi *et al.* 1999, John *et al.* 2000, Puskas *et al.* 2000, van Wermeskerken *et al.* 2000). Cognitive decline is suggested to be due to CPB, as moderate to severe cognitive dysfunction has not been found in patients having major vascular operations not necessitating CPB (Shaw *et al.* 1987).

Stroke increases the duration of stay in an intensive care unit and hospital. Patients with stroke have six- to tenfold in-hospital mortality and also higher mortality at six months (Almassi *et al.* 1999, John *et al.* 2000). In a prospective study on 10,860 patients, Puskas *et al.* found patients with perioperative stroke to have an in-hospital mortality rate of 23% and decreased one- (64% versus 94%) and five-year (44% versus 81%) actuarial survival rates, longer hospital stays, and increased costs (Puskas *et al.* 2000).

A variety of factors, may potentially cause cerebral injury during cardiac operations and CPB, in particular. These include macroembolism, microembolism, impairment of cerebral blood flow, and systemic inflammatory response.

2.3.2.1 Predictors of cerebral injury

The type of operation affects strongly the risk of perioperative stroke. The risk is higher during open-heart surgery than during CABG, but the highest risk has been reported in combined CABG and open-heart surgery (Nussmeier 1996, Taggart *et al.* 1997b, Almassi *et al.* 1999). There are several other predictors of stroke, the most important being a history of preceding cerebrovascular disease, atherosclerotic ascending aorta, and increasing age, which is an important predictor, as operations on elderly patients are increasing in number. However, patients of 70 years of age or older have a five-year survival rate of over 80%, and their quality of life is similar to the population's normative scores. (Khan *et al.* 2000, Goto *et al.* 2000, Puskas *et al.* 2000). Other factors found to increase the risk for cerebral injury are female gender, hypertension, peripheral vascular disease, chronic obstructive pulmonary disease, renal insufficiency, diabetes, use of diuretics or bronchodilators, cigarette smoking, urgent or emergency surgery, prolonged CPB time, perioperative hypotension, lack of sinus rhythm at weaning from CPB, postoperative need for inotropic support longer than 30 minutes, and atrial fibrillation (Borowicz *et al.* 1996, Gill & Murkin 1996, Nussmeier 1996, Utley 1996, Taylor 1998, Almassi *et al.* 1999, John *et al.* 2000, Puskas *et al.* 2000).

2.3.2.2 Embolization

Macroembolism may consist of a massive amount of air introduced into the arterial line of the CPB system, intracardiac or intravascular thrombus release during the operation, or release of atheromatous debris from the ascending aorta, which has been increasingly recognized as a source of complications during cardiac operations (Utley 1996, Taylor 1998).

Gaseous microemboli occur in every operation requiring CPB and usually originate from the oxygenator, reservoirs, pumps, or the cardiac chambers. Other microemboli may develop from the residue of destroyed erythrocytes, leucocytes, platelets, serum lipids, fibrin and fibrin degradation products, denaturated proteins, atheromatous matter, and microparticles of plastic or other material from the disposable components. (Stump *et al.* 1996, Utley 1996).

The microembolic load during CPB is associated with early neuropsychological deficits, but not with stroke (Stump *et al.* 1993, Sylivris *et al.* 1998, Diegeler *et al.* 2000), and it may also impair regional autoregulation of cerebral blood flow (Sunngurtekin *et al.* 2000). A different mechanism might be responsible for stroke and cognitive dysfunction (Sylivris *et al.* 1998). Most studies implicate that the highest microembolic load appears during aortic manipulation due to cannulation, cross-clamping, declamping, side clamping, and decannulation, during manipulation of the heart, and when going on- and off-pump (Nussmeier 1996, Stump *et al.* 1996). In addition, reinfusion of blood aspirated by cardiomy suction has been suggested to produce lipid emboli (Brooker *et al.* 1998).

However, almost half of the embolic load during heart surgery is not directly associated with surgical procedures. The increased release of microemboli with bubble oxygenators compared to membrane oxygenators suggests that the majority of

microemboli are gaseous in nature. (Taylor 1998). This is supported by the fact that peaks of embolus formation are detected during perfusionist interventions, i.e., blood samplings and drug injections, and air entry into the reservoir via the venous line (Taylor *et al.* 1999, Willcox *et al.* 1999).

Cannulation of the distal aortic arch instead of the ascending aorta may diminish the embolic load, especially during perfusionist interventions (Borger *et al.* 1999). The use of arterial line filters of 40 μm or an aortic cannula equipped with a filter decreases the particulate embolic load, but gaseous microemboli are not filtered (Taggart *et al.* 1997a, Reichenspurner *et al.* 2000). The aortic filter is inserted immediately before declamping of the aorta and removed after discontinuation of CPB, and it captures particulate emboli of predominantly atheromatous origin (Reichenspurner *et al.* 2000).

2.3.2.3 Impairment in cerebral blood flow

Impairment of cerebral blood flow is another probable mechanism predisposing to cerebral injury (Hall *et al.* 1999). The management of blood carbon dioxide tension during CPB and hypothermia affects cerebral blood flow. In α -stat management, blood carbon dioxide tension values are uncorrected by temperature, and the blood carbon dioxide content is thus constant. Blood carbon dioxide tensions are corrected by temperature in pH-stat management, and carbon dioxide is added into the gas inflow to increase the blood carbon dioxide content.

Although physiologic blood flow rates are approximately 3 to 3.2 $\text{l/m}^2/\text{min}$, pump flow rates during CPB are customarily set at 2.2 to 2.4 $\text{l/m}^2/\text{min}$ and, during hypothermia, even below this. The reduction of whole body oxygen consumption enables the reduction of pump flow to 1.6 $\text{l/m}^2/\text{min}$ at the core temperature of 28 $^{\circ}\text{C}$ and to 1.2 $\text{l/m}^2/\text{min}$ at 20 $^{\circ}\text{C}$. Physiological cerebral blood flow is 40 to 60 $\text{ml}/100\text{g}/\text{min}$ and ranges from 20 to 60 $\text{ml}/100\text{g}/\text{min}$ during CPB. (Taylor 1998). The constant cerebral blood flow is a consequence of cerebral autoregulation being preserved during α -stat management of blood carbon dioxide tension. Cerebral autoregulation has been found to be intact at perfusion pressures of 20 to 100 mmHg, i.e., cerebral blood flow is independent of pressure changes and dependent upon cerebral oxygen consumption. Pressure levels allowing intact cerebral autoregulation are increased in patients with a preoperative history of hypertension, and cerebral blood flow is only dependent on perfusion pressure when the pH-stat protocol is used. (Murkin *et al.* 1987, Taylor 1998). However, blood pressure below 50 mmHg during CPB is found to be associated with a decreased incidence of stroke or coma compared with blood pressure above 50 mmHg, indicating that hypoperfusion is not the primary cause of stroke (van Wermeskerken *et al.* 2000). Haemodilution increases the cerebral blood flow (Plöchl *et al.* 1999).

The results of using pulsatile pump flow as a more physiologic method during CPB are controversial with respect to the increase in cerebral blood flow compared to non-pulsatile pump flow (Cook *et al.* 1997, Ündar *et al.* 1999), even when cerebral oxygenation assessed by means of jugular venous oxygen saturation is better preserved with pulsatile flow (Mutch *et al.* 2000). However, pulsatile flow has been found to have

no effects on cerebral outcome based on serum concentrations of S-100 protein (Ashraf *et al.* 1998a).

2.3.2.4 Other factors affecting the brain

Normothermia during CPB has been reported to decrease the oxygenation of jugular bulb and regional cerebral blood (Kadoi *et al.* 1999), to increase cerebral embolization (Cook *et al.* 2000), and to increase cerebral damage (Gaudino *et al.* 1999). No correlation has been found, however, between systemic temperature during CPB and the size of stroke (Engelman *et al.* 2000). The increased embolic load due to normothermia may be reduced by arterial line filtration, which has been found to decrease cerebral injury during normothermic CPB (Taggart *et al.* 1997a).

By using magnetic resonance imaging, Harris and his colleagues observed cerebral oedema in 8 out of 8 patients immediately after CPB. Oedema was present in three patients as late as 6 to 18 days after CPB, but no cognitive deficits were associated. Microembolization and increase in capillary permeability due to a CPB-derived systemic inflammatory reaction have been suggested to be the possible mechanisms. (Harris *et al.* 1993, Taylor 1998).

Impaired blood-brain barrier due to CPB is mentioned frequently in cardiac surgical literature, although CPB with non-pulsatile flow has been shown to have no effects on it (Laursen *et al.* 1986, Gillinov *et al.* 1992). Pulsatile flow during CPB, however, seems to decrease the permeability of the blood-brain barrier (Laursen *et al.* 1986).

2.3.3 Inflammatory response

Inflammatory response is one of the basic defence systems of the body, but it is exceedingly deleterious when uncontrolled. It is reasonable to postulate that all patients undergoing CPB develop an inflammatory response of some degree. After the exposure of blood to the artificial surfaces of the CPB circuit, an inflammatory response is activated, including complement, kallikrein cascade, and leukocyte activation. (Butler *et al.* 1993, Taylor 1996, Brasil *et al.* 1998, Fransen *et al.* 1998, Gu *et al.* 1998, Sonntag *et al.* 1998, Strüber *et al.* 1999). Neutrophils play an important role in the inflammatory response, monocytes may release systemic inflammatory cytokines, and intestinal mucosal injury due to splanchnic vasoconstriction during CPB allows leakage of endotoxins into the bloodstream (Butler *et al.* 1993, Fransen *et al.* 1998, Morse *et al.* 1998, Asimakopoulos *et al.* 1999).

The systemic inflammatory response in cardiac surgical patients is manifested as lung injury or acute respiratory distress syndrome in the worst case (Asimakopoulos *et al.* 1999, Ilton *et al.* 1999, Yamazaki *et al.* 1999), neutrophil-mediated myocardial ischaemia-reperfusion injury with no-reflow phenomenon (Sawa *et al.* 1998, Ilton *et al.* 1999), and a post-pump or post-perfusion syndrome with multi-organ failure. Manifestation of the post-pump syndrome consists of hyperthermia and leukocytosis, increased capillary permeability and accumulation of interstitial fluid, circulatory

dysregulation, especially hyperdynamic circulation, metabolic derangement, and organ dysfunction (Butler *et al.* 1993, Cremer *et al.* 1996). There is evidence from a porcine model that both CPB and endotoxin release are crucial to the deleterious manifestations of the inflammatory response. CPB has been found to activate the inflammatory system, causing pulmonary neutrophil sequestration without lung injury, but exposure to otherwise benign doses of endotoxin resulted in activation of the sequestered neutrophils, causing post-pump and acute respiratory distress syndromes. (Picone *et al.* 1999). Mesenteric dysfunction, mediated by complement C5a, has also been associated with CPB (Tofukuji *et al.* 2000).

A centrifugal pump has been shown to induce a more severe inflammatory response and complement activation than a roller pump (Ashraf *et al.* 1998b, Baufreton *et al.* 1999). Hypothermic CPB (28°C) does not produce a more profound inflammatory response than moderately hypothermic (32°C) or normothermic (37°C) CPBs (Birdi *et al.* 1999), although controversial results exist (Grünenfelder *et al.* 2000). Modified ultrafiltration has been shown to reduce the concentration of inflammatory markers during hypothermic CPB (Grünenfelder *et al.* 2000). The results of using a heparin-coated CPB circuit and a heparin- or silicone-coated oxygenator principally reveal a decrease in the cytokine release or inflammatory response (Schreurs *et al.* 1998, Ozawa *et al.* 2000, Shimamoto *et al.* 2000), although controversial results also exist (Horton *et al.* 1999, Defraigne *et al.* 2000). Arterial or venous line leukocyte filtration, corticosteroids, and aprotinin have been used to reduce the inflammatory response and organ reperfusion injury, but the results are controversial (Butler *et al.* 1993, Gu *et al.* 1999, Bull *et al.* 2000, Defraigne *et al.* 2000). A bilateral (left and right) CPB circuit and the use of the patient's own lung as an oxygenator have been shown to reduce the activation of the inflammatory reaction and to improve the respiratory index with reduction of the intrapulmonary right-to-left shunt (Richter *et al.* 1999).

2.3.4 Impairment of the coagulation system

CPB adversely affects both platelet count and platelet function. Platelet count decreases to about 50% due to aggregation and haemodilution caused by the priming volume of the CPB circuit. Platelets have been shown to undergo degranulation and morphological transformation leading to impairment of their function, which is suggested to be a consequence of the initial platelet activation due to contact with the surface of the CPB circuit. Other contributing factors are the use of salicylates and other antiplatelet agents, heparin, and hypothermia. The recovery of platelet function after CPB takes a few hours, but the normalization of platelet count takes a few days. (Zilla *et al.* 1989, Woodman & Harker 1990, Kestin *et al.* 1993, Kawahito *et al.* 1999, Bidstrup *et al.* 2000). The aggregation of platelets is divided into first-phase aggregation, which produces small aggregates, and second-phase aggregation, when the small aggregates grow in size. There is evidence that CPB may inhibit this second-phase aggregation with an increasing number of small aggregates. Thus, platelet function is not totally impaired, but some degree of aggregation ability remains and is inducible by strong stimuli. (Kawahito *et al.* 1999).

Plasma concentrations of coagulation factors are reduced in respect to haemodilution, with the exception of von Willebrandt factor, which decreases more. The concentrations of coagulation factors, however, usually remain at haemostatic levels. (Woodman & Harker 1990). Activation of coagulation and fibrinolysis has been shown to be associated with CPB (Hunt *et al.* 1998).

However, 3 to 5% of cardiac surgical patients bleed due to surgery, and a reoperation is needed for haemostasis. The treatment of coagulation dysfunction consists of transfusions of blood products and various perioperative chemotherapies (Woodman & Harker 1990, Bidstrup *et al.* 2000), but the use of circuits coated with heparin or other materials may not bring any benefits (Borgdorff *et al.* 1999, Kumano *et al.* 1999).

2.4 Studies on OPCAB

After CPB had become an established technique for CABG, only a few surgeons performed CABG on a beating heart. Among these surgeons were Benetti in Argentina (Benetti *et al.* 1991), Buffolo in Brazil (Buffolo *et al.* 1985, Buffolo *et al.* 1990), Ankeney in Cleveland (Ankeney 1975), and Archer in Texas Heart Institute (Archer *et al.* 1984).

2.4.1 Primary reports

Initially, OPCABs were performed via a conventional sternum-splitting incision without commercial stabilizers to facilitate the suturing of the distal anastomoses. The surgical field was stabilized with sutures or occlusive slings above and below the site of the distal anastomosis, and left ventricular wall movement and heart rate were decreased with β -blocking or calcium-blocking agents or adenosine. (Westaby & Benetti 1996). In the mainly retrospective studies, off-pump surgery was found to decrease mortality, morbidity, hospital stay, and the need for blood transfusions (Buffolo *et al.* 1990, Benetti *et al.* 1991, Pfister *et al.* 1992). Occlusion of a coronary artery during the suturing of the distal anastomosis seemed to be well tolerated based on the preservation of myocardial mitochondria (Benetti *et al.* 1991) and the lower incidence of low output state and myocardial infarction (Pfister *et al.* 1992). Interventricular septal function was also better maintained after OPCAB (Akins *et al.* 1984). Graft patency rates were of some concern, however, since the suturing of the distal anastomoses is distinctly more difficult on a beating heart. Before the use of tissue stabilizers, graft patency rates ranged from 75% to 93% (Ankeney 1975, Buffolo *et al.* 1985). Archer and his colleagues studied graft patency in 191 patients by recording the appearance of myocardial infarction after single coronary artery bypass procedures. After bypass grafting on LAD, they found as high an infarction rate as 18.7% and hence concluded that LAD was not a suitable artery to be bypassed without CPB (Archer *et al.* 1984). Laborde and his co-workers measured postoperative blood flows of the bypass grafts to LAD by an ultrasonic method and found the on-pump grafts to reach maximal blood flow on the sixth postoperative day, while the off-pump grafts reached equal flow on the first day (Laborde *et al.* 1989).

2.4.2 *Re-arrival of OPCAB*

2.4.2.1 *Haemodynamic changes and myocardial outcome*

At the turn of the 1990s, there was a general tendency towards minimal trauma in many sectors of the surgical field. Increasing awareness of the deleterious effects of CPB and the promising preliminary reports of the few surgeons performing CABG on a beating heart facilitated the new arrival of off-pump surgery, especially in the form of MIDCAB.

During OPCAB, the coronary artery to be bypassed is usually occluded for the time needed for the suturing of the distal anastomosis, and the heart may also be displaced. Occlusion of a coronary artery for 15 to 20 minutes is well tolerated in a canine model (Reimer & Jennings 1979). Displacement of the beating heart has been shown to increase heart rate, systemic vascular resistance, pulmonary pressure, and left and right filling pressures and to decrease arterial pressure, cardiac output and index, and left ventricular stroke volume (Gründeman *et al.* 1997, Mathison *et al.* 2000, Nierich *et al.* 2000, Menon *et al.* 2002, Torracca *et al.* 2002, Yetman *et al.* 2002). Kotoh *et al.* found left ventricular wall motion abnormalities even without rotation of the heart in four out of 34 MIDCAB patients evaluated by means of intraoperative transoesophageal echocardiography (Kotoh *et al.* 1999). Torracca *et al.* showed that exposure of the LAD area produced impairment of left ventricular relaxation only, whereas exposure of the lateral and posterior ventricular wall produced a decrease of left ventricular contractile state together with impairment of relaxation, as evaluated by means of pressure-volume loops (Torracca *et al.* 2002). Vassiliades and his colleagues studied retrospectively 1420 elective OPCAB procedures, of which 23 patients required immediate CPB due to haemodynamic collapse. Ten of the 23 patients suffered haemodynamic collapse while grafting was being done in the Cx area and seven during grafting of the main RCA. There were also significantly more patients with small body surface area, CAD of New York Heart Association class 3–4, cardiomegaly, preoperative AMI, and RCA grafts in the collapse group. They concluded that the causes of haemodynamic collapse were ischaemic, mechanical, or a combination of both. (Vassiliades *et al.* 2002b). In their prospective investigation of 500 patients, Mishra *et al.* found patients with ejection fraction under 25%, AMI less than 1 month previously, congestive heart failure, and preoperative haemodynamic instability to constitute the high-risk group for the institution of an intra-aortic balloon pump or conversion to CPB during multivessel OPCAB (Mishra *et al.* 2003). Edgerton *et al.* found re-do operation, congestive heart failure, and the surgeon's experience to predict conversion to CPB in their cohort study and emergency conversion to increase the risk for perioperative mortality, postoperative cardiac arrest, multisystem organ failure, vascular complications, and perioperative AMI compared to initially on-pump started CABG (Edgerton *et al.* 2003).

The release of myocardial injury markers and cytokines, the incidence of low output state and myocardial infarction, and the preservation of interventricular septal function, however, show left ventricular impairment to be more pronounced after CPB and cardioplegia than after surgery on a beating heart (Table 1). In the case of impaired left ventricular function and recent myocardial infarction, OPCAB as well as CABG without aortic cross-clamping and cardioplegia have been shown to preserve the myocardium

better than conventional surgery with CPB and cardioplegia (Benetti *et al.* 1996, Sternik *et al.* 1997, Antunes *et al.* 1999, Mohr *et al.* 1999). In the study of Benetti and his colleagues, 1420 patients were operated on a beating heart, 32 of them after myocardial infarction and one in cardiogenic shock. Early graft patency was 100%, and transmural myocardial biopsies showed a marked reduction in signs of mitochondrial and myofibril damage in comparison to the initial stage. (Benetti *et al.* 1996). Mohr *et al.* evaluated 57 patients who had undergone OPCAB after myocardial infarction. 57% of the patients needed an urgent operation, 22% were in cardiogenic shock, and 31% required preoperatively an intra-aortic balloon pump. Early return of angina occurred in 12% of the patients. Perioperative mortality was 1.7%, and the one- and five-year survival rates were 94.7% and 82.3%, respectively. The authors concluded that OPCAB is a safe operation in patients with preoperative myocardial infarction. (Mohr *et al.* 1999). Sternik and his co-workers compared the beating heart and CPB techniques in patients with left ventricular ejection fraction below 35%. They found higher one- and two-year actuarial survival rates after operation on a beating heart with a tendency toward a lower incidence of perioperative myocardial infarction and a diminished need for intra-aortic balloon pump. (Sternik *et al.* 1997). Pasini and his colleagues found OPCAB to significantly improve cardiac function without affecting myocardial metabolism in the case of a hibernating myocardium with a low ejection fraction of $25\% \pm 0.7\%$ (Pasini *et al.* 2001). OPCAB has also been shown to decrease the need for postoperative inotropic medication and the release of the MB fraction of creatine kinase in elderly patients, even in the case of incomplete revascularization (Kilo *et al.* 2001a).

2.4.2.2 Cerebral outcome

Neuropsychological tests and serum concentration of S-100 protein have most commonly been used for the evaluation of cerebral outcome. Cognitive outcome has mainly been found to be similar or better after OPCAB compared with on-pump surgery. However, the patient series have been small with respect to the insensitiveness of the neuropsychological test batteries, and most studies have been non-randomized (Table 2). The non-randomized clinical study by Anderson and his colleagues, in which S-100B protein was used to evaluate cerebral injury, showed a tenfold increase in the release of S-100B immediately after CPB compared with OPCAB (Anderson *et al.* 1999). This, however, might be due to contamination by the blood suctioned from the surgical field (Jönsson *et al.* 1999). In the randomized study of Diegeler *et al.* on 40 patients, cerebral outcome was better after off-pump than on-pump surgery based on neuropsychological tests and serum concentrations of S-100 protein. Also, the microembolic load was lower during OPCAB. (Diegeler *et al.* 2000). Neurologic and cognitive tests have shown the use of CPB to be a predictor of short- and long-term cognitive brain dysfunction after CABG (Kilo *et al.* 2001b, Schmitz *et al.* 2003). OPCAB has also been shown to be associated with a decreased cerebral microembolic load and increased cerebral perfusion compared with on-pump CABG (Lee *et al.* 2003, Lund *et al.* 2003). In a few large retrospective studies, the risk for stroke has been found to be 1.8–4 times higher after on-pump CABG compared with OPCAB (Buffolo *et al.* 1996, Patel *et al.* 2002, Stamou *et*

al. 2002). Avoidance of aortic manipulation during OPCAB did not diminish the risk for stroke any further (Patel *et al.* 2002).

Table 1. Studies on myocardial preservation during OPCAB compared with on-pump CABG.

Study group	Number of patients and study method	Means of the study and the results	End result
Akins <i>et al.</i> (1984)	22, prospective, randomized	Septal function ↑	+
Pfister <i>et al.</i> (1992)	440, retrospective, non-randomized	Low output states ↓	+
Buffolo <i>et al.</i> (1996)	8751, retrospective, non-randomized	Arrhythmias ↓	+
Birdi <i>et al.</i> (1997)	28 ^M , prospective, non-randomized	TnI release ↓	+
Ascione <i>et al.</i> (1999a)	80, prospective, randomized	TnI release ↓, atrial fibrillation ↓	+
Krejca <i>et al.</i> (1999)	38, prospective, randomized	TnI release ↓	+
Lönn <i>et al.</i> (1999)	32, prospective, randomized	TnI release ↓	+
Wan <i>et al.</i> (1999)	44, prospective, non-randomized	Cytokine and TnI releases ↓	+
Cartier <i>et al.</i> (2000)	2170, retrospective, cohort	Myocardial infarctions ±	±
Kilger <i>et al.</i> (2000)	87, prospective, non-randomized	CKMBM and TnI releases ↓	+
Ascione <i>et al.</i> (2001a)	253, retrospective (renal insuff.)	Inotropic need ↓	+
Calafiore <i>et al.</i> (2001)	1837, retrospective	Myocardial infarctions ↓, inotropic need ↓, CKMBM release ↓	+
Cleveland <i>et al.</i> (2001)	129857, retrospective	Postoperative cardiac arrest ↓	+
Kilo <i>et al.</i> (2001a)	88, retrospective, cohort (≥ 75 years)	Inotropic need ↓, CKMBM release ↓	+
Magee <i>et al.</i> (2002)	8449, retrospective	Myocardial infarctions ↓	+
Thielmann <i>et al.</i> (2005)	188, prospective, non-randomized	TnI, CK/CK-MB, and myoglobin releases ↓	+

M = MIDCAB; + indicates a better and - a worse outcome in off-pump surgery and ± an equal outcome obtained with both techniques; ↑ indicates an increase in the study parameter or a better outcome in the OPCAB group and ↓ a decrease or a worse outcome, respectively, in all of the tables 1–5.

Table 2. Studies on cerebral preservation during OPCAB compared with on-pump CABG.

Study group	Number of patients and study method	Means of the study and the results	End result
Malheiros <i>et al.</i> (1995)	81M, prospective, non-randomized	Neuropsychological tests \pm	\pm
Buffolo <i>et al.</i> (1996)	8751, retrospective	Complications \downarrow	+
Browne <i>et al.</i> (1997)	16M, prospective, non-randomized	Neuropsychological tests \pm	\pm
Andrew <i>et al.</i> (1998)	80M, prospective, non-randomized	Neuropsychological tests \pm	\pm
Anderson <i>et al.</i> (1999)	44M, prospective, non-randomized	S-100 protein (end of CPB) \downarrow	(+)
Taggart <i>et al.</i> (1999)	75, prospective, non-randomized	Neuropsychological tests \pm	\pm
Diegeler <i>et al.</i> (2000)	40, prospective, randomized	Neuropsychological tests \uparrow , S100 protein \downarrow	+
Ascione <i>et al.</i> (2001a)	253, retrospective (renal insuff.)	Stroke \downarrow	+
Calafiore <i>et al.</i> (2001)	1837, retrospective	Cerebrovascular accidents \pm	\pm
Cleveland <i>et al.</i> (2001)	129857, retrospective	Cerebrovascular accidents \downarrow , stroke \downarrow	+
Hirose <i>et al.</i> (2001)	178, retrospective (age \geq 75 years)	Stroke \downarrow	+
Kilo <i>et al.</i> (2001b)	308, prospective, non-randomized	P300 auditory-evoked potentials \uparrow	+
Hoff <i>et al.</i> (2002)	229, retrospective (age \geq 80 years)	Stroke \downarrow	+
Patel <i>et al.</i> (2002)	1730, retrospective	Stroke \downarrow	+
Stamou <i>et al.</i> (2002)	10389, retrospective	Stroke \downarrow	+
Lee <i>et al.</i> (2003)	60, prospective, randomized	Rey auditory verbal learning test \uparrow , cerebral microemboli \downarrow and perfusion \uparrow	+
Lund <i>et al.</i> (2003)	52, prospective, randomized	Cerebral microemboli \downarrow , neuropsychologic tests \pm	+
Schmitz <i>et al.</i> (2003)	251, prospective, non-randomized	Neurologic and neurocognitive test \uparrow	+

Table 3. Studies on inflammation and coagulation during OPCAB compared with on-pump CABG.

Study group	Number of patients and study method	Means of the study and the results	End result
Inflammation			
Brasil <i>et al.</i> (1998)	20, prospective, non-randomized	Tumour necrosis factor α release \downarrow	+
Fransen <i>et al.</i> (1998)	16, prospective, non-randomized	Neutrophil activation \downarrow , interleukin-6 \pm , C-reactive protein \pm	\pm
Gu <i>et al.</i> (1998)	35 ^M , prospective, randomized	Leukocyte elastase \downarrow , platelet β thromboglobulin \downarrow , complement C3a \downarrow	+
Sonntag <i>et al.</i> (1998)	35, prospective, non-randomized	Complement activation \downarrow	+
Picone <i>et al.</i> (1999)	22, porcine model (CPB+endotoxin)	Neutrophil sequestration \downarrow , pulmonary outcome \uparrow	+
Strüber <i>et al.</i> (1999)	24 ^M , prospective, non-randomized	Complement activation \downarrow , cytokine release \downarrow , fluid balance \downarrow	+
Ascione <i>et al.</i> (2000)	60, prospective, randomized	Interleukin-8 \downarrow , neutrophil count \downarrow , Complement activation \pm ,	+
Matata <i>et al.</i> (2000)	20, prospective, randomized	Complement activation \downarrow , interleukin-8 \downarrow , tumour necrosis factor α \downarrow	+
Coagulation			
Pfister <i>et al.</i> (1992)	440, retrospective, non-randomized	Blood transfusions \downarrow	+
Gu <i>et al.</i> (1998)	35 ^M , prospective, randomized	Blood loss \downarrow	+
Lönn <i>et al.</i> (1999)	32, prospective, randomized	Blood loss \downarrow	+
Nader <i>et al.</i> (1999)	122, prospective, non-randomized	Blood loss \downarrow , blood products \downarrow	+
Cartier <i>et al.</i> (2000)	2170, retrospective, cohort	Blood loss \downarrow , blood transfusions \downarrow	+
Koutlas <i>et al.</i> (2000)	273, retrospective, cohort	Blood transfusions \downarrow	+
Calafiore <i>et al.</i> (2001)	1834, retrospective	Blood loss \downarrow , blood transfusions \downarrow	+
Hoff <i>et al.</i> (2002)	229, retrospective (age \geq 80 years)	Blood transfusions \downarrow	+
Ascione <i>et al.</i> (2001a)	253, retrospective (renal insuff.)	Blood loss \downarrow , blood transfusions \downarrow	+
Ascione <i>et al.</i> (2001b)	200, prospective, randomized	Blood loss \downarrow , blood transfusions \downarrow	+
Cleveland <i>et al.</i> (2001)	129857, retrospective	Blood loss \downarrow	+
Magee <i>et al.</i> (2002)	8449, retrospective	Reoperations due to bleeding \downarrow , blood products \downarrow	+

Table 4. Studies on lung, renal, and gastrointestinal track preservation and on infection during OPCAB compared with on-pump CABG.

Study group	Number of patients and study method	Means of the study and the results	End result
Lung			
Buffolo <i>et al.</i> (1996)	8751, retrospective	Complications ↓	+
Lichtenberg <i>et al.</i> (2000)	30 ^M , prospective, non-randomized	Vital capacity, forced expiratory volume ↑, mechanical ventilation ↓	+
Cleveland <i>et al.</i> (2001)	129857, retrospective	Prolonged mechanical ventilation ↓	+
Hirose <i>et al.</i> (2001)	178, retrospective (age ≥ 75 years)	Respiratory failure ↓	+
Magee <i>et al.</i> (2002)	8449, retrospective	Prolonged mechanical ventilation ↓	+
Staton <i>et al.</i> (2005)	200, prospective, randomized	Compliance ↓, gas exchange ↑, extubation time ↓	+
Kidney			
Ascione <i>et al.</i> (1999b)	50, prospective, randomized	Glomerular and tubular function ↑	+
Gamoso <i>et al.</i> (2000)	690, prospective, non-randomized	Perioperative change in creatinine clearance ±	±
Ascione <i>et al.</i> (2001a)	253, retrospective (renal insuff.)	Serum creatinine and urea ↓	+
Cleveland <i>et al.</i> (2001)	129857, retrospective	Acute renal failure ↓	+
Magee <i>et al.</i> (2002)	8449, retrospective	Acute renal failure ↓	+
Stallwood <i>et al.</i> (2004)	2199, retrospective	Acute renal failure ↓	+
Gastrointestinal track			
Velissaris <i>et al.</i> (2003)	45, prospective, randomized	Gastric intramucosal pH ↓, gastric-arterial carbon dioxide difference ±	-
Sanisoglu <i>et al.</i> (2004)	1146, retrospective	Gastrointestinal complications and mortality ±	±
Infection			
Ascione <i>et al.</i> (2000)	60, prospective, randomized	Overall incidence of infections ↓	+

Table 5. Studies on the effects of OPCAB on mortality and economics compared with on-pump CABG.

Study group	Number of patients and study method	Means of the study and the results	End result
Mortality			
Buffolo <i>et al.</i> (1990)	593, prospective, non-randomized	3 year overall mortality ↓	+
Buffolo <i>et al.</i> (1996)	8751, retrospective	In-hospital mortality ↓	+
Sternik <i>et al.</i> (1997)	117, retrospective	Perioperative mortality ±, one- and two-year actuarial survival ↑	+
Arom <i>et al.</i> (2000)	3521, retrospective	Perioperative mortality: Low risk ±, medium risk ±, high risk +	+
Cartier <i>et al.</i> (2000)	2170, retrospective, cohort	Perioperative mortality ±	±
Koutlas <i>et al.</i> (2000)	273, retrospective, cohort	Perioperative mortality ↓	+
Calafiore <i>et al.</i> (2001)	1837, retrospective	Perioperative mortality ↓	+
Cleveland <i>et al.</i> (2001)	129857, retrospective	Perioperative mortality ↓	+
Hirose <i>et al.</i> (2001)	178, retrospective (age ≥ 75 years)	1, 2, and 3 years survival ±	±
Hoff <i>et al.</i> (2002)	229, retrospective (age ≥ 80 years)	Perioperative mortality ↓	+
Kilo <i>et al.</i> (2001a)	88 retrospective, cohort (≥75years)	In-hospital mortality ↓	+
Magee <i>et al.</i> (2002)	8449, retrospective	Perioperative mortality ↓	+
Economy			
Buffolo <i>et al.</i> (1996)	8751, retrospective	Material ↓, hospital stay ↓	+
Gu <i>et al.</i> (1998)	35 ^M , prospective, randomized	Hospital stay ↓	+
Magovern <i>et al.</i> (1998)	115 ^M , retrospective	Hospital costs ↓	+
Ascione <i>et al.</i> (1999c)	80, prospective, randomized	Material ↓, hospital stay ↓, morbidity ↓	+
Calafiore <i>et al.</i> (1999)	227, retrospective	ICU stay ↓, hospital stay ↓	+
Reichenspurner <i>et al.</i> (1999)	475/125/121, retrospective	Costs ↓ (CPB/off-pump/MIDCAB)	+
Koutlas <i>et al.</i> (2000)	273, retrospective, cohort	Hospital stay ↓	+
Calafiore <i>et al.</i> (2001)	1837, retrospective	Morbidity ↓, ICU stay ↓, hospital stay ↓	+
Hirose <i>et al.</i> (2001)	178, retrospective (age ≥ 75 years)	Major complications ↓, ICU stay ↓, hospital stay ↓	+
Hoff <i>et al.</i> (2002)	229, retrospective (age ≥ 80 years)	Hospital stay ↓	+

Table 6. Graft patency rates after coronary surgery with and without CPB.

Study group	Numbr of patients	Time of examination	Graft patency rate
CPB			
Buffolo <i>et al.</i> (1996)	30 (LIMA-LAD)	Before discharge	93.4% ^A
Lazzara <i>et al.</i> (1999)	6	Intraoperative	100% ^B
Puskas <i>et al.</i> (2004)	184/153 (622/511 grafts)	30 days / 1 year	99.0% / 93.6% ^C
OPCAB			
Ankeney (1975)	63	Postoperative (vein-RCA/LAD) (LIMA-LAD)	79% / 75% 93%
Buffolo <i>et al.</i> (1985)	41	Postoperative	83.9%
Benetti <i>et al.</i> (1991)	54	≤1 month (vein/LIMA)	93% / 87.5%
Tashiro <i>et al.</i> (1993)	12	Postoperative	89%
Benetti <i>et al.</i> (1996)	5 (post AMI)	1-30 days	100%
Buffolo <i>et al.</i> (1996)	30 (LIMA-LAD)	Before discharge	93.4% ^A
Fitzgibbon <i>et al.</i> (1996)	5065 grafts	Postoperative (vein/LIMA)	88% / 95%
	3993 grafts	1 year	81% / 91%
	1978 grafts	5 years	75% / 80%
Gurné <i>et al.</i> (1996)	38	±9 days	100%
Calafiore <i>et al.</i> (1999)	67	33±35 days	98.9%
Bedi <i>et al.</i> (2000)	35	Before discharge	97.8%
Bhan <i>et al.</i> (2000)	96 (160 grafts)	Before discharge (all/LIMA)	95.0% / 97.9%
Wiklund <i>et al.</i> (2000)	130	Before discharge	96% ^D
Ömeroğlu <i>et al.</i> (2000)	81	24-61 months (vein/LIMA)	47.1% / 95.6%
Puskas <i>et al.</i> (2001)	167	Before discharge	98.8%
Puskas <i>et al.</i> (2004)	184/153 (622/511 grafts)	30 days / 1 year	97.7% / 95.8% ^C
MIDCAB			
Benetti <i>et al.</i> (1995)	15	Before discharge	100%
Subramanian <i>et al.</i> (1995)	63	30 hours	95.2%
Elbeery <i>et al.</i> (1998)	50	Intraoperative	93%
Goldstein <i>et al.</i> (1998)	26	Intraoperative	65.4%
Cremer <i>et al.</i> (1999)	205	Early	98%
DePaulis <i>et al.</i> (1999)	12	1-2 days/6 months	100% / 100%
Diegeler <i>et al.</i> (1999a)	37/205	Intra-/postoperative	98% / 98%
	116	Six months	97.5%
Diegeler <i>et al.</i> (1999b)	221/130	2-4 days/6 months	96.8% / 95.4%
Lazzara <i>et al.</i> (1999)	10	Intraoperative	91% ^B
Lloyd <i>et al.</i> (1999)	14/9	1-3 days/6 months	100% / 100%
Mack <i>et al.</i> (1999)	100	Intra-/postoperative	99%
Gill <i>et al.</i> (2000)	51/32	6 hours/9.6months	96.3% / 95.4%
Oliveira <i>et al.</i> (2002)	104	Before discharge	98.1%
Wiklund <i>et al.</i> (2000)	130	Before discharge	88% ^D

All the MIDCABs are LIMA-LAD bypasses and all the OPCAB were made via sternotomy. Upper case letters A, B, C, and D indicate the results of the same comparative study. Post AMI = Operations after acute myocardial infarction.

2.4.2.3 Preservation of other organs

Impairment of blood coagulation and whole body inflammatory reaction are diminished by the off-pump technique compared with on-pump CABG (Table 3). Although all the results show the superiority of the beating heart technique, the value of these results is somewhat decreased because of the usually non-randomized nature of the studies. Al-Ruzzeh and his colleagues found higher neutrophil counts after OPCAB compared with on-pump, but the neutrophils in the OPCAB group showed decreased activation when measured by CD11b levels (Al-Ruzzeh *et al.* 2003). Consequently, OPCAB can be recommended to patients at an increased risk for bleeding (Jehovah's witnesses, re-do procedures, and coagulation abnormalities) and whenever the systemic inflammatory response is considered especially harmful for the patient. Recent studies have even revealed a possible state of hypercoagulability due to increased fibrinogen and platelet activity lasting for 1 to 3 days after OPCAB (Moller & Steinbruchel 2003, Quigley *et al.* 2003). On the other hand, CPB has been shown to impair the antiplatelet effect of aspirin after the operation, possibly due to increased platelet turnover that was not present after OPCAB (Zimmermann *et al.* 2005).

The results of global oxygen metabolism are controversial, however. Velissaris *et al.* showed superior oxygen metabolism associated with OPCAB compared with on-pump CABG, but Parolari *et al.* found no differences in oxygen metabolism to be associated with the two surgical techniques based on oxygen consumption, delivery, and extraction (Parolari *et al.* 2003, Velissaris *et al.* 2003). There are also a few studies showing the beating heart technique to decrease the risk for infections and to improve the preservation of the lung and the kidney, but the results concerning the gastrointestinal track are controversial (Table 4).

Perioperative mortality has been found to be 0 to 3.8% in primary OPCAB and 3.4 to 5.2% in reoperations, and it is similar or decreased compared with on-pump CABG (Table 5) (Fanning *et al.* 1993, Moshkovitz *et al.* 1995, Mohr *et al.* 1997, Moshkovitz *et al.* 1997, Tasdemir *et al.* 1998, Hill *et al.* 2000). However, compared with on-pump surgery, the incidence of perioperative mortality is lower, especially in elderly (Koutlas *et al.* 2000, Kilo *et al.* 2001a, Hoff *et al.* 2002) and high-risk patients (Arom *et al.* 2000) operated off-pump, while the incidence is equal in patients with a low or medium risk (Arom *et al.* 2000) and in diabetic patients (Magee *et al.* 2001). Morbidity is lower (Ascione *et al.* 1999c) and one- to three-year actuarial survival rates higher after off-pump than on-pump CABG, although morbidity increases with increasing age (Stamou *et al.* 2000). In a recent study of Immer *et al.*, quality of life has been shown to be better after OPCAB with respect to both physical and emotional role functioning compared with on-pump CABG (Immer *et al.* 2003). Ascione and his colleagues also reported a lower incidence of stroke, blood loss, inotropic requirement, and serum creatinine and urea after OPCAB in patients with nondialysis-dependent renal insufficiency compared with conventional surgery (Ascione *et al.* 2001a).

Age of 70 years or higher, diabetes mellitus, bronchial asthma, pulmonary vascular disease, unstable angina, recent myocardial infarction, left main coronary artery stenosis, emergency operation, re-do operation, calcified aorta, non-use of internal mammary artery, poor quality of LAD, and ignored disease of the Cx system during OPCAB have

been found to be predictors of increased perioperative mortality and are mainly the same predictors as in CABG with CPB (Moshkovitz *et al.* 1995, Moshkovitz *et al.* 1997, Tasdemir *et al.* 1998, Stamou *et al.* 2000).

OPCAB has been proved to be more economical than the CPB technique. No disposable equipment is needed for CPB, although there is some increase in the costs of operations due to the requirement for stabilizers. However, morbidity, need for blood transfusions, and intensive care unit and in-hospital stays are decreased by the beating heart technique (Table 5).

2.4.2.4 Development of off-pump surgery

There has been great concern about graft patency with the beating heart technique, as the suturing of the distal anastomoses on a moving target is more difficult than on a non-beating heart during CPB. Graft patency rates are shown summarized in table 6. Four studies compared the quality of grafts between on- and off-pump bypass with sternotomy and MIDCAB, showing similar patency rates for sternal incision on- and off-pump and somewhat lower rates for MIDCAB (A, B, C, and D in Table 6). The incidence of perioperative AMI associated with OPCAB has been 1.0% to 3.6% (Moshkovitz *et al.* 1995, Mohr *et al.* 1997, Moshkovitz *et al.* 1997, Tasdemir *et al.* 1998, Cartier *et al.* 2000, Puskas *et al.* 2001), which is equal to that obtained with on-pump surgery (Buffolo *et al.* 1996, Cartier *et al.* 2000). 7.7% to 12.5% of patients after OPCAB have been shown to develop early return of angina (Moshkovitz *et al.* 1995, Moshkovitz *et al.* 1997, Mohr *et al.* 1999).

Commercial stabilizers and moist air blowers have been developed to facilitate the suturing of the distal anastomoses and thereby to improve their quality (Kappert *et al.* 1999, Nierich *et al.* 1999, Pavie *et al.* 1999, Poirier *et al.* 1999, Karamanoukian *et al.* 2000). The use of intracoronary shunt has also been shown to improve graft patency from 90% to 100% and to decrease the need for intervention during the first six postoperative months (Menon *et al.* 2002). Izzat and his co-workers used intraoperative coronary angiography during OPCAB to improve the final quality of the graft anastomoses. Intraoperative angiography permitted the surgeon immediately to revise, if necessary, any graft abnormality and thus potentially to eliminate the need for an early reoperation. In that study, three out of 42 grafts required revision. (Izzat *et al.* 1999). The study group of Goldstein found an amazingly high number of problems in graft quality in their study on MIDCAB. They performed surgical revision for five out of 26 patients due to anastomotic obstruction or graft kinking, and four patients were treated with PTCA via the graft. (Goldstein *et al.* 1998). Naturally, any surgeon operating on a beating heart must be experienced. The learning effect improves graft patency rates after a short learning curve, and the training in the beating heart technique should be carried out via CABG with CPB (Falk *et al.* 1999, Karamanoukian *et al.* 2000).

When a coronary artery is occluded on a beating heart, there is always a relative urgency to complete the distal anastomoses to diminish the coronary occlusion time and the possible myocardial ischaemia time. In the case of ischaemia, an intracoronary flow-through catheter has been used widely in cases where the patient does not respond to

intravenous nitroglycerine, and many surgeons currently use it routinely during the suturing of all distal anastomoses. Coronary shunting has been shown to counteract the haemodynamic changes and the decrease in left ventricular contractility (Lucchetti *et al.* 1999, Menon *et al.* 2002, Yeatman *et al.* 2002). It may also help to avoid conversion to CPB and the development of myocardial infarction in the case of severe ischaemia manifested as bradycardia, total atrio-ventricular block, and hypotension (van Aarnhem *et al.* 1999). Instead of using the intracoronary flow-through catheter, Bedi *et al.* used retrograde coronary perfusion of arterial blood from the ascending aorta with a coronary sinus catheter to allow a longer time for coronary occlusion. They found the blood coming from the coronary opening to be similar to that during retrograde blood cardioplegia infusion, indicating retrograde perfusion of the myocardium. Signs of myocardial ischaemia were infrequent. (Bedi *et al.* 2000). Guyton and his co-workers developed a pump-assisted graft perfusion technique with the possibility of pressure regulation to restore arterial blood to the distal coronary beds immediately after the completion of the distal coronary anastomosis. It also provides a possibility for supplemental additives for myocardial resuscitation, myocardial vasodilatation, and enhancement of myocardial performance. (Guyton *et al.* 2000). Vassiliades and his colleagues found both passive and active pump-aided aorto-coronary shunts to reduce postoperative TnI release, but the active shunt was better in maintaining the cardiac index and mixed venous oxygen saturation (Vassiliades *et al.* 2002a).

One of the most important limitations of OPCAB is that all the coronaries may not be accessible with this technique. A left ventricular assistive device (Hemopump®) has been used experimentally to increase the number of coronaries suitable for this technique. However, it has not increased the number of bypass grafts suitable for this technique, but has been found to improve myocardial function, possibly counteracting the need for drawbacks to CPB, and also to increase coronary blood flow and pressure (Lachterman *et al.* 1990, Sweeney *et al.* 1992, Lönn *et al.* 1994a, Lönn *et al.* 1994b, Lönn *et al.* 1999). An intra-aortic balloon pump and a right ventricle support (Enabler circulatory support system®) have also been found to decrease intraoperative haemodynamic instability and conversion to cardiopulmonary bypass (Sharony *et al.* 2002, Christenson *et al.* 2003). Instead, integrated myocardial revascularization with PTCA, called hybrid operation, widens the indications of OPCAB. In this strategy, surgery is followed by PTCA or vice versa, and the results have been promising. (Fonger 1999, Lloyd *et al.* 1999, Zenati *et al.* 1999, Riess F-C *et al.* 2002).

Two meta-analyses of OPCAB compared with on-pump CABG have been published after the completion of the present trials. The larger of these meta-analyses included 53 randomized and non-randomized prospective and retrospective studies on 46 621 patients (Reston *et al.* 2003), while the smaller included 18 exclusively randomized studies on 1 584 patients (van der Heijden *et al.* 2004). Reston and his colleagues found statistically significantly lower rates of AMI, stroke, reoperation for bleeding, renal failure, atrial fibrillation, and wound infection and a reduction in the length of hospital stay after OPCAB. Mid-term angina recurrence did not appear to differ between treatments, although trends were seen toward lower reintervention rates with on-pump CABG and lower mortality with OPCAB. (Reston *et al.* 2003). In their meta-analysis, van der Heijden *et al.* obtained favorable results for OPCAB for mortality, stroke, and AMI

without statistical significance at short- and long-term follow-up (van der Heijden *et al.* 2004).

2.4.3 MIDCAB

The number of patients eligible for MIDCAB is even smaller than that for off-pump surgery through sternotomy, as only one to two distal anastomoses with no proximal aortic anastomoses can be sutured with this technique. The suturing of the distal anastomoses may also be more difficult due to the small incision compared to off-pump surgery done through sternotomy. A single comparative study by Wiklund *et al.* shows a decreased patency rate after MIDCAB (Table 6). Anaesthesia is also more demanding for MIDCAB. There may be additional problems in ventricular pacing, myocardial defibrillation, and conversion to CPB, if needed. Single-lung ventilation may also be required. (Gayes *et al.* 1996, Greenspun *et al.* 1996, Gayes & Emery 1997, Wasnick & Acuff 1997).

MIDCAB has been shown to decrease the need for mechanical ventilation, dyspnea, stress evaluated with psychosomatic scales, and the levels of serum stress hormones and to increase vital capacity, forced expiratory volume, and activity scores after the operation compared with sternotomy, but the results on postoperative pain are controversial (Grossi *et al.* 1999, Guliemos *et al.* 1999a, Guliemos *et al.* 1999b, Lichtenberg *et al.* 2000). Stanbridge and Hadjinikolaou found more restenoses and acute myocardial infarctions after MIDCABG than after sternotomy in their meta-analysis of over 6000 patients. The quality of anastomoses to RCA was inferior compared to LAD after MIDCAB, but the quality of anastomoses improved with the use of a tissue stabilizer. (Stanbridge & Hadjinikolaou 1999). Studies comparing MIDCAB with PTCA showed graft patency rates of 96–98% and 71–88%, respectively, six months after the intervention along with slightly higher costs of MIDCAB (Cisowski *et al.* 2002, Drenth *et al.* 2002).

2.5 Preconditioning with ischaemia

IPC is defined as protection of the myocardium by short ischaemic periods preceding a subsequent longer period of ischaemia. The important question is whether IPC occurs in humans. If it does, new therapeutic strategies for cardiovascular medicine could be developed.

2.5.1 Mechanisms and mediators

IPC was first described by Murry *et al.* to decrease the size of myocardial infarction after ischaemia of 40 minutes' duration, but not after 3 hours of ischaemia, and to delay ATP depletion in a canine model (Murry *et al.* 1986). Yellon and his colleagues confirmed the

finding of ATP preservation in CABG (Yellon *et al.* 1993) and Vuorinen and his colleagues in a rat model (Vuorinen *et al.* 1995). IPC has also been shown to attenuate myocardial apoptosis and neutrophil accumulation (Wang *et al.* 1999), though controversial results also exist (Wu *et al.* 2003b).

Despite intensive research on IPC, the underlying mechanisms are still mostly unknown. Adenosine, acetylcholine, catecholamines, angiotensin, bradykinin, endothelin, and opioids have been suggested as triggers and protein kinase C, tyrosine kinase, and ATP-sensitive potassium ion channels (K^{+}_{ATP}) as mediators of IPC (Kloner & Yellon 1994, Perrault & Menasché 1996, Meldrum 1997, Yellon *et al.* 1998). According to one hypothesis, a brief period of ischaemia depletes glycogen stores through the accumulation of lactate and protons, which are then washed out during the following reperfusion period. The glycogen stores remain substantially depleted, and lactate accumulation and pH fall are assumed to be delayed when the glycogen-depleted myocardium is exposed to more prolonged ischaemia. (Schaefer *et al.* 1995, Yellon *et al.* 1998).

A critical coronary artery stenosis (Kapadia *et al.* 1997) or the presence of collateral coronary blood flow (Murry *et al.* 1986) does not abolish the protective effect of IPC. Sakata *et al.* did not find a similar protective effect of IPC when collateral flow was seen, nor did they find any improvement in myocardial function in the case of no collateral flow (Sakata *et al.* 1997). There are also results indicating that IPC acutely recruits collateral coronary blood flow after the first coronary occlusion (Kloner & Yellon 1994). Deep hypothermia abolishes the protective effect of IPC, but there are controversial results of moderate hypothermia (Perrault & Menasché 1996, van den Doel *et al.* 1998, Takeshima *et al.* 1999). Of the different anaesthetics, at least preadministration of enflurane (Penta de Peppo *et al.* 1999), isoflurane (Belhomme *et al.* 1999), and sevoflurane (Julier *et al.* 2003) seems to act analogously with the protective effect of IPC in humans. Repeated low doses of dipyridamole similarly mimic the IPC effect (Pacini *et al.* 1996).

The ischaemic time required for preconditioning is of the order of two to fifteen minutes (Kloner & Yellon 1994), and the required reperfusion period is over two minutes (Tanaka *et al.* 1996). Up to four repetitions of the IPC cycle have been shown to reduce infarct size in rabbits, but more repetitions seem to increase it (Iliodromitis *et al.* 1997).

Preconditioning has also been found to have a delayed protective component emerging within a few hours to three days. Other organs except the kidney have been found to benefit from IPC, and there is also evidence of inter-regional and inter-organ protection, which is possibly neuronally mediated. (Perrault & Menasché 1996, Yellon *et al.* 1998). Especially the spinal cord has been studied intensively with promising results (Zvara *et al.* 1999, Abraham *et al.* 2000).

2.5.2 Clinical studies of IPC

Preinfarction angina in humans has been found to act like IPC, producing a reduced infarct size, as indicated by lower enzyme efflux, better left ventricular function, improved short-term prognosis, and better clinical outcome (Anzai *et al.* 1994, Iwasaka *et al.* 1994, Kloner *et al.* 1995, Nakagawa *et al.* 1995).

PTCA has been a popular model to study IPC in humans. The results of IPC trials confirm that electrocardiographic changes of ischaemia, anginal pain, and release of lactate are less marked upon repeated balloon inflations than during the first inflation (Deutch *et al.* 1990, Criber *et al.* 1992, Eltchaninof *et al.* 1997), although conflicting results also exist (Ylitalo *et al.* 1996).

In CABG performed with CPB, preconditioning has been found to be effective during intermittent aortic cross-clamping (Yellon *et al.* 1993, Alkhulaifi *et al.* 1994, Jenkins *et al.* 1997) or with normothermic or mild hypothermic cardioplegia, but not with cold cardioplegia (Valen *et al.* 1996, Cleveland *et al.* 1997, Cremer *et al.* 1997). However, several conflicting results also exist (Perrault *et al.* 1996, Kaukoranta *et al.* 1997, Lu *et al.* 1997, Illes *et al.* 1998, Lu *et al.* 1998, Li *et al.* 1999, Wu *et al.* 2000b). In a rat model, IPC alone has a similar protective effect as cardioplegia (Kolocassides *et al.* 1994), and it also ensures optimal myocardial protection whenever the delivery of cardioplegia is impaired (Galiñanes *et al.* 1995).

In a study by Malkowski and his colleagues, IPC did not improve left ventricular function during MIDCAB with bypass grafting to LAD (Malkowski *et al.* 1998). Similar results were obtained by Bufkin *et al.* on coronary occlusions in dogs simulating the suturing of distal anastomoses, but they found decreased myocardial accumulation of neutrophils after IPC (Bufkin *et al.* 1998). Wu and his colleagues have studied intensively the effects of IPC in humans during and after on- and off-pump CABG. They found IPC to attenuate the decrease of cardiac function (Wu *et al.* 2000b, Laurikka *et al.* 2002, Wu *et al.* 2003b), heart rate elevation, and episodes of supraventricular and ventricular tachycardia, but not atrial fibrillation (Wu *et al.* 2003a). IPC did not attenuate apoptosis (Wu *et al.* 2003b) and the generation of free radicals, although it turned out to protect against the stunning of the heart (Wu *et al.* 2001) and to decrease the postoperative release of TnI (Laurikka *et al.* 2002). According to their studies, recent unstable angina before CABG might act as an IPC stimulus via the delayed mechanism of preconditioning (Wu *et al.* 2000a). However, aging and preischaemic use of β -blockers seem to abolish the effect of IPC (Bartling *et al.* 2003, Suematsu *et al.* 2004).

2.6 Biochemical markers of myocardial ischaemia

Lactate production and pH fall are widely accepted indicators of ischaemic metabolism. The decline in cellular ATP during ischaemia is also well documented (Rovetto *et al.* 1975, Catinella *et al.* 1983). Increased venous concentration of adenosine and its catabolites have also been shown to correlate with any decrease in myocardial energy. This has been demonstrated during ischaemia and also during an increased myocardial workload. (Manfredi & Sparks Jr 1982, Kiviluoma *et al.* 1986, Raatikainen *et al.* 1991). All these markers: transmural pH difference, myocardial lactate production, and arterio-venous differences of ATP degradation products have been previously used as indicators of myocardial energy metabolism during ischaemia and reperfusion (Peuhkurinen *et al.* 1991, Landymore *et al.* 1992, Nissinen *et al.* 1993, Raatikainen *et al.* 1997).

The half-life of adenosine is 0.6 to 1.5 seconds in the case of physiological plasma concentrations. Adenosine is rapidly eliminated by erythrocytes, which convert adenosine preferentially to adenine nucleotides, and measurement of adenosine release may therefore underestimate the actual rate of adenosine formation. Dipyridamole does not alter the basal adenosine level, but completely blocks its uptake (Möser *et al.* 1989).

2.7 Biochemical markers of myocardial tissue injury

The detection of myocardial tissue injury after CABG remains a diagnostic challenge for physicians. Patients with perioperative AMI may present non-diagnostic ECGs, as in contrast to non-surgical patients, their AMI is predominantly non-Q-wave in nature. The appearance of segmental wall motion abnormalities is regarded as a sensitive and specific means to diagnose myocardial ischaemia and AMI, but it requires experience and is therefore subject to error. Furthermore, it is even less accurate in the case of non-ischaemic wall motion abnormalities. There are a few myocardial injury markers, of which troponins have proven to be both sensitive and specific. (Tatschl *et al.* 1998).

It is well known that the MB fraction of creatine kinase is not 100% cardiospecific, although CK-MBM is more sensitive and specific. Cross-reaction with skeletal muscle produces a significant source of error, as the surgery is associated with skeletomuscular trauma. TnT is more specific and sensitive than CK-MBM, but it is elevated in renal failure and may also interact with the troponins of skeletal muscle. The specificity of TnT for the diagnosis of AMI has been reported to range from 78% to 98%. TnI is even more specific than TnT for the diagnosis of AMI, as it is more rarely elevated in renal failure and does not cross-react with skeletal muscle troponins. (Mair *et al.* 1993, Alyanikian *et al.* 1998, Tatschl *et al.* 1998).

Following AMI, TnT starts to increase from the first hour after the onset of symptoms, and this initial release comes to an end after 32 hours, the peak value occurring at a median time of 14 hours. This is followed by a second peak around the fourth day. TnI starts rising after four to six hours and reaches its peak value at a median time of 18 to 19 hours after the insult. TnI is normalized after six to seven days, and compared to TnT, it has more rarely a second peak. Of these three markers, CK-MBM has the shortest time interval for the diagnosis of AMI. (Tatschl *et al.* 1998).

The cut-off or limit values of perioperative AMI have been proposed to be 30 µg/l for CK-MBM (Alyanikian *et al.* 1998), 3.5 µg/l to 3.9 µg/l for TnT (Mair *et al.* 1993, Carrier *et al.* 2000), and 8.3 ng/l to 15 µg/l for TnI, depending on the reagent used in the measurements (Alyanikian *et al.* 1998, Sadony *et al.* 1998, Tatschl *et al.* 1998).

2.8 Biochemical markers of cerebral damage

Eventually, neuropsychological tests demonstrate the clinical end-point of the patients' neurological condition, but they require large study groups, are laborious to carry out, and involve a few sources of error. Single-case definitions of cognitive dysfunction are strongly influenced by regression toward the mean. Thus, patients with high preoperative

scores tend to regress downward even in the absence of real change, and patients with low preoperative scores tend to improve, thereby requiring a much larger true decline. This is avoided by using group means, two to three tests, and a control group with the same tests at the same time points, but this can mask individuals who have deteriorated and makes the test pattern even more laborious. (Browne *et al.* 1999). Magnetic resonance imaging is an objective and promising method to study the cerebral effects of CABG, but it is expensive and may be hazardous during the early postoperative phase (Deslauriers *et al.* 1996). A sensitive and selective biological marker would be an objective and exact method to evaluate cerebral damage. There are a few biological markers reflecting neurological events, of which S-100 protein and NSE are the most promising.

S-100 protein is normally not present in serum, but appears after a stroke, subarachnoidal haemorrhage, and head injury (Persson *et al.* 1987). However, recent studies have shown mediastinal fat, muscle, and bonemarrow contain high levels of S-100 protein (Andersson *et al.* 2001). Infusion of blood bleeding in mediastinum will result in infusion of S-100 protein and will interfere with the early measurements of serum S-100 levels. There are several studies suggesting that S-100 protein predicts brain damage, but not cognitive dysfunction (Wimmer-Greinecker *et al.* 1998, Rasmussen *et al.* 1999), although controversial results also exist (Jönsson *et al.* 1999, Herrmann *et al.* 2000).

NSE, the $\gamma\gamma$ -isoform of enolase, is a glycolytic enzyme with a molecular weight of 77 000 Daltons localized in neurons and regarded as brain-specific. However, it is used predominantly as a tumor marker for small-cell lung cancer, neuroblastoma, and malignancies of neuroendocrine origin, and hence, it is not entirely brain-specific. NSE is also present in platelets and erythrocytes, and haemolysis can therefore substantially interfere with the NSE values of cerebral origin. The plasma half-life of NSE is suggested to be between 20 and 48 hours. (Johnsson 1996). Serum levels of NSE have been found to correlate with infarct size after a stroke (Missler *et al.* 1997).

NSE has been found to correlate with the extent of haemolysis after CPB of only 20 minutes, but not after extended periods of CPB, suggesting that the release from the brain also contributes to the total concentrations (Johnsson 1996). Johnsson *et al.* found a significant correlation between serum concentrations of NSE and haemolysis induced *in vitro*, but during CPB of two hours the correlation was weak, and there was also a correlation between the serum concentrations of NSE and CPB time (Johnsson *et al.* 2000). Their results are, however, in controversy with the other studies on NSE (Gao *et al.* 1997, Rasmussen *et al.* 1999). Serum levels of NSE have been found to correlate with neurological complications (Johnsson *et al.* 1995) and cognitive dysfunction (Wimmer-Greinecker *et al.* 1998, Rasmussen *et al.* 1999, Ebert *et al.* 2000) after CPB.

3 Purpose of the present research

The aims of this research were:

1. To evaluate the haemodynamic and myocardial safety aspects of temporary occlusions of the coronary arteries and occasional rotation of the contracting heart during off-pump coronary artery surgery. (I).
2. To evaluate myocardial preservation during off-pump multi-vessel coronary artery surgery compared with on-pump surgery (II).
3. To evaluate the effects of ischaemic preconditioning of the myocardium during off-pump multi-vessel coronary artery surgery on myocardial preservation (III).
4. To evaluate cerebral preservation during off-pump multi-vessel coronary artery surgery compared with on-pump surgery (IV).

4 Patients and methods

4.1 Patients and study design

The trials were approved by the Ethical Committee of Oulu University Hospital, and the study series was collected between October 1996 and June 1999. The trial I included twelve and the trials II–IV thirty-three patients with CAD eligible for CABG without CPB, from whom written informed consent had been obtained. The inclusion criteria in the trials were non-on-call operation and coronary stenoses technically suitable for OPCAB as evaluated by the operating surgeon. The exclusion criteria were ongoing ischaemia, acute myocardial infarction less than one month previously, poorly controlled diabetes, serum creatinine level higher than 150 $\mu\text{mol/l}$, symptomatic internal carotid artery stenosis, history of cerebral disease, chronic atrial fibrillation, aortic or mitral valvular disease and in the study I, also ejection fraction less than 40%. The pilot study (I) of twelve patients was a prospective follow-up study, and all the patients were operated on a beating heart (pilot group). The studies II–IV were performed simultaneously, and thirty-three patients were randomized to be operated as follows: eleven patients with CPB (CPB group), eleven off-pump without preceding IPC of the myocardium (OPCAB group), and eleven off-pump with preceding IPC (IPC group). There were no drop-outs during the studies, but two patients were excluded from the CK-MBM and TnI assessments due to perioperative AMI (Fig. 1). No formal power analysis was performed, as it was not known how large differences were to be expected in the biological markers. Randomization was carried out by closed mixed labels. Randomization for individual patient was done after the surgeon had decided to include the patient in the study, and after written informed consent had been given by the patient. The surgeon was always blinded to the study group of the patient until the beginning of the operation. The patient was always informed of the mode of operation afterward. However, the staff of the operating theater were informed of the surgical technique to be used on the afternoon before the day of operation. This was due to the need for preliminary arrangements in the operating theater. The anaesthesia technique was similar in all groups.

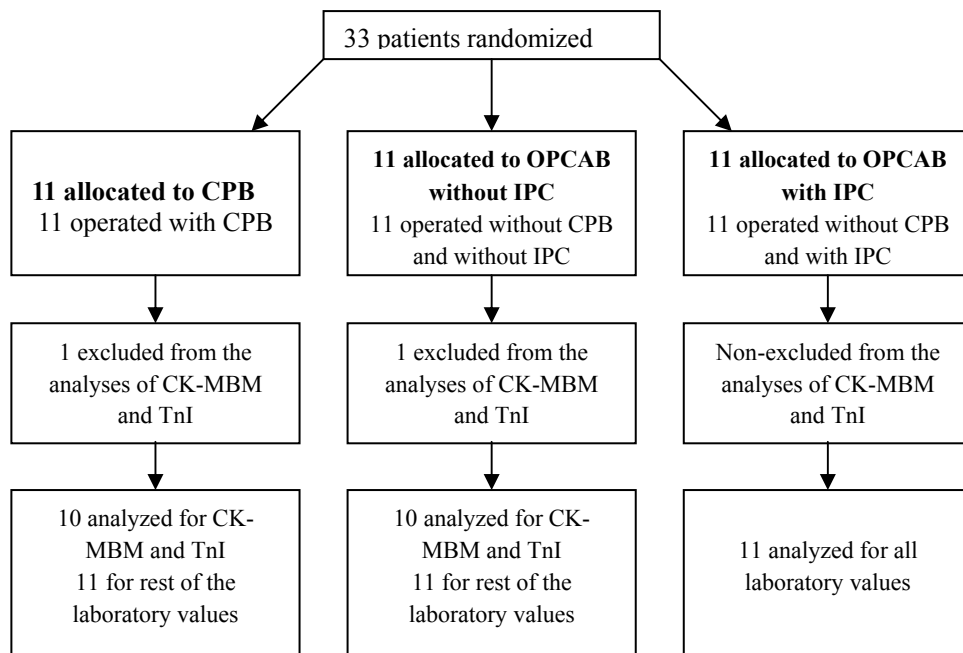


Fig. 1. Flow diagram of patient distribution.

4.2 Anaesthesia technique

All the patients were anaesthetized and the CPBs performed by the author, with the exception on two cases in study I, where the procedures were performed by Päivi Kaukoranta, Oulu University Hospital, Oulu, Finland. All medications, except salicylates, were allowed without interruption until the day of the operation. Salicylates were withdrawn one to two weeks before the operation, except in one patient in the pilot group, one in the CPB group, one in the OPCAB group, and three in the IPC group. Premedication consisted of oral diazepam (10 to 20 mg) and intramuscular morphine (6 to 15 mg). The radial artery was cannulated, and a pulmonary artery catheter with the thermodilution technique (SP510TH Thermodilution Catheter, Ohmeda Inc., Murray Hill, NJ) (I) or continuous monitoring of cardiac output and mixed venous oxygen saturation (Baxter Swan-Ganz Ccombo, Baxter Healthcare Corporation, Edwards Critical Care Division, Irvine, CA) (II–IV) was introduced. Anaesthesia was induced with propofol (0.9 to 2.8 mg/kg) and fentanyl (3.2 to 7.7 µg/kg). Muscle relaxation was achieved with pancuronium (0.07 to 0.13 mg/kg). The patients were ventilated with 30 to 50% oxygen in air, and anaesthesia was maintained with propofol (1.3 to 5.3 mg/kg/h), alfentanil (17 to 59 µg/kg/h), and sevoflurane (0.3 to 1.9 minimal alveolar concentration).

4.3 CPB and cardioplegia

The patients in the CPB group were anticoagulated with 3 mg/kg of heparin, and the activated clotting time was maintained above 480 seconds with additional heparin. Heparinization was reversed with protamine sulphate (3 mg/kg) with extra boluses if needed. A roller pump (Stöckert Caps, Stöckert Instrument, Germany) and a hollow fiber membrane oxygenator (Compactflow, Dideco, Mirandola, Italy) were used. The CPB circuit was primed with physiologic sodium chloride, Ringer solution, and mannitol, and the priming solution was circulated for at least ten minutes in the CPB circuit through a pre-bypass screen filter of 0.2–0.5 μm (PP3802, Pall Biomedical, Portsmouth, England). The pump flow rate was maintained above 2.3 l/m² during CPB. 40 to 60% oxygen in air was used to maintain the continuously monitored arterial line blood oxygen tension at 20–25 kPa, and normoventilation was maintained using α -stat carbon dioxide tension management. Perfusion pressure was maintained above 50 mmHg with phenylephrine hydrochloride during CPB and systemic blood pressure above 60 mmHg during the rest of the operation. The patients were cooled to 33 °C and rewarmed to normothermia before CPB was discontinued.

Intermittent antegrade delivery of aspartate-glutamate-enriched blood cardioplegia was used. A commercial cardioplegia set (CE 008, Dideco, Mirandola, Italy) was used to mix the cardioplegic solution and blood in a proportion of 1:9. The pressure of the aortic root during infusion was maintained at 40–50 mmHg and the temperature of blood cardioplegia at 33 °C, with the exception of the normothermic initial arresting and terminal infusions.

4.4 Patient care in OPCAB

The patients operated without CPB were anticoagulated with an initial heparin dose of 1 mg/kg, and additional heparin was given as needed. Activated clotting time was maintained above 300 seconds, and heparinization was reversed with protamine sulphate (30–100 mg). The patients were normoventilated, maintaining the blood oxygen tension at 20 to 25 kPa. The mean arterial blood pressure was maintained above 50 mmHg with phenylephrine hydrochloride and enhanced fluid infusion during the construction of the anastomoses and above 60 mmHg during the rest of the operation. Myocardial ischaemia, if present in ECG monitoring, was treated with intravenous nitroglycerine. If the patient did not respond to nitroglycerine, an intracoronary flow-through catheter was inserted (CTS Flo Coil Shunt, Cardiothoracic Systems Inc., Cupertino, CA). After the harvesting of the vein grafts, the patients were actively heated by placing a thermoblanket on the lower body to raise the core temperature above 36 °C.

4.5 Surgical technique

All operations were performed by the same experienced cardiac surgeon (Martti Lepojärvi, Oulu University Hospital, Oulu, Finland). A conventional midline sternum splitting incision was made, and a coronary sinus catheter (Pediatric RCSP Cannula, Grand Rapids, MI) was introduced through the right atrial wall before the suturing of the first anastomosis or prior to the start of CPB.

In the off-pump groups, pericardial traction sutures and elevating gauze pads were used to facilitate visibility and access to either the left or the right side of the heart. Haemostatic silastic loops (Retract-O-Tape, Quest Medical Inc., Allen, TX) placed proximally and distally to the anastomosis were used to stabilize and obstruct the coronary artery in the study I and for IPC (III). A commercial mechanical suction stabilizer (Octopus, Medtronic, Medtronic Inc., MN) and a moist air blower were used to facilitate the construction of the distal anastomoses, and coronary artery probes were used to obstruct the target artery and to diminish bleeding in the studies II–IV. To reduce heart rate and the amplitude of ventricular wall movement, most of the patients in the study I were given boluses or continuous infusion of esmolol. The proximal anastomoses of vein grafts were sutured with the aid of a partially occluding aortic side clamp in the order of the needs of the patients between or after the suturing of the distal anastomoses.

IPCs consisted of an ischaemic period of 5 minutes followed by a reperfusion period of 5 minutes. The first IPC was performed before the first coronary artery closure for the suturing of the distal anastomosis and the second before the second closure. The following coronary closures were performed without preceding preconditioning (Fig. 2).

CPB was established with a single two-stage right atrial cannula and an ascending aortic cannula. A cardioplegic cannula with additional venting and pressure-monitoring channels (DLP Inc, Grand Rapids, MI) was used for intermittent antegrade delivery of blood cardioplegia. During the construction of the anastomoses, cardioplegia was interrupted for short periods to improve visibility. Both the distal and the proximal anastomoses were accomplished during a single period of aortic cross-clamping.

4.6 Laboratory analyses

4.6.1 Sampling design

Intraoperative blood samples for lactate, pH, and ATP degradation products were withdrawn simultaneously from the arterial line and the coronary sinus catheter (T_0 – T_4 in Fig. 2). Oxygen and carbon dioxide tensions and oxygen saturation of haemoglobin were also measured, and mixed venous samples were withdrawn in the study I. After the operation, ECGs were recorded and the serum concentrations of CK-MBM and TnT (I), or TnI (II–IV) were monitored (T_0 and T_5 – T_{10} in Fig. 2). Contrary to the schema in fig. 2, the postoperative recordings in the pilot study (I) were performed 2, 4, 6, and 12 hours after the removal of the side-clamp and on the next two mornings. The serum

concentrations of NSE (IV) were recorded intra- and postoperatively (T_0 , T_4 , and T_6 - T_8 in Fig. 2).

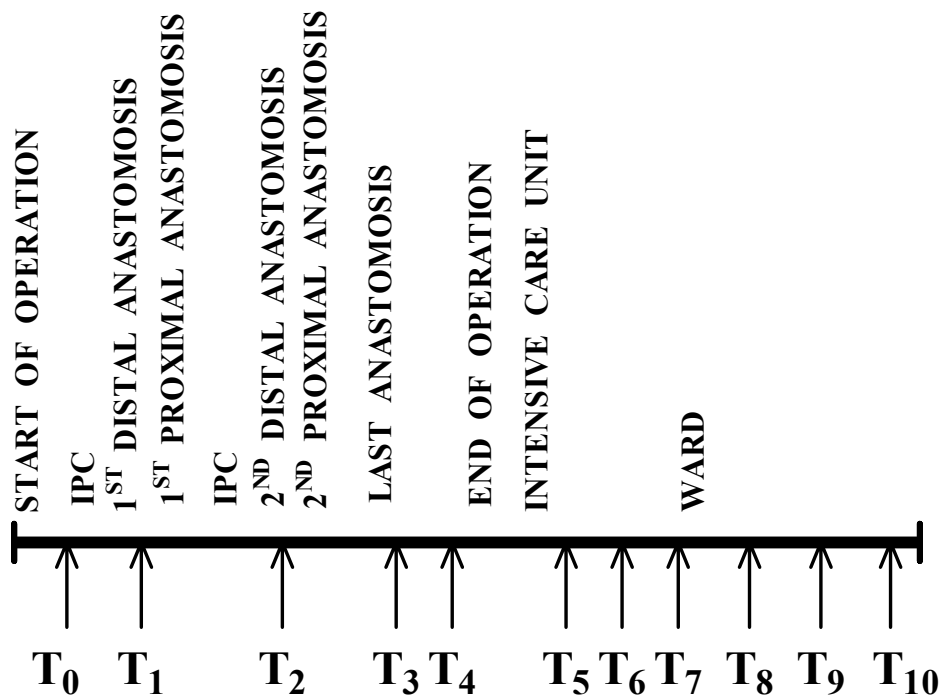


Fig. 2. Study design and blood sampling schedule. T_0 = before bypass grafting; T_1 - T_2 = immediately after the suturing of the first and the second distal anastomoses; T_3 - T_4 = 5 and 15 minutes after the suturing of the last anastomosis; T_5 - T_6 = 2 and 8 hours after the suturing of the last anastomosis; T_7 - T_{10} = the 1st to 4th postoperative day.

4.6.2 ATP degradation products

To measure the plasma levels of ATP degradation products (adenosine, inosine, hypoxanthine, and xanthine), blood samples of 5 ml were drawn into a syringe containing one ml of dipyridamole solution (1.1 mg/ml) and centrifuged directly, and the acidified plasma (3 ml of plasma in 0.5 ml of 60% perchloric acid) was neutralized with 2 mol/l potassium hydroxide / 0.5 mol/l triethanolamine hydrochloride. The extracts were stored at -20 °C for later analysis by high-pressure liquid chromatography as described by Nissinen and Raatikainen (Nissinen *et al.* 1993, Raatikainen *et al.* 1997). Transcardiac concentration differences of ATP degradation products were calculated.

4.6.3 *Neuron-specific enolase*

The blood samples for NSE assays were centrifuged, and the serum was separated to be frozen at -70°C and stored for later analysis. NSE was determined with a time-resolved fluoroimmunoassay DELFIA NSE Kit (Wallac Co, Turku, Finland) (Rasmussen *et al.* 1999). This assay shows no interference with erythrocyte enolase, but gross haemolysis interferes with the determination of brain-originated enolase. The detection limit is $1.0\ \mu\text{g/l}$. The values of serum NSE concentrations were corrected with the NSE from haemolysed erythrocytes by the following equation: $\text{NSE} (\mu\text{g/L}) = 4.89 + 9.78 \times \text{serum free haemoglobin (g/L)}$ (Johnsson *et al.* 2000).

4.6.4 *Other laboratory analyses*

Oxygen and carbon dioxide tensions, pH, and oxygen saturation of haemoglobin were determined with a 288 blood gas system (Ciba-Corning, Medfield, MA), and oxygen content was calculated as $1.39 \text{ haemoglobin concentration} \times \text{oxygen saturation} + 0.003 \text{ oxygen tension}$. Myocardial and systemic oxygen extractions were calculated from the values of oxygen content.

Lactate was assayed using an electrode-based lactate analyzer (YSI model 1500; Yellow Springs Instrument Co, Inc, Yellow Springs, OH), and transcardiac and arterio-venous differences were calculated.

CK-MBM and TnI were analyzed using the micro-particle enzyme immunoassay technology (AxSYM, Abbott Laboratories, Abbott Park, IL). TnT was analyzed by a manual version of enzyme-linked immunosorbent assay specific for cardiac TnT (Boehringer Mannheim, Mannheim, Germany).

Serum free haemoglobin was determined by the optical density at $540\ \text{nm}$, which has the maximal haemoglobin absorption capacity, and it was reduced with the optical density at the correction wavelength of $690\ \text{nm}$. The limit for normal value is $0.162\ \mu\text{g/l}$.

4.7 *Perioperative monitoring of patients*

Myocardial ischaemia was evaluated by continuous automatic monitoring of the ST segment at the modified leads V5 and II and by observing the appearance of a V wave in the pulmonary artery wedge pressure curve. Heart rate, mean arterial pressure, and cardiac output by the thermodilution technique (I) or continuous monitoring with recording of mixed venous oxygen saturation (II–IV) were measured, and the cardiac index was calculated.

The ECGs were recorded postoperatively (T_5 - T_{10} in Fig. 2) and evaluated by the same experienced cardiologist (Keijo Peuhkurinen, Kuopio University Hospital, Kuopio, Finland), who was blinded to the patients' perioperative course. Perioperative myocardial infarction was defined as the appearance of a significant new Q wave, left bundle-branch

block or poor R wave progression and a significant elevation of CK-MBM and TnT (I) or TnI (II–IV) levels.

4.8 Statistical analyses

The statistical analyses were performed using the Statistica package software, version 5.1 (StatSoft, Tulsa, OH). The t-test for independent changes was applied to single continuous variables and a cross-table to single categorical variables to test the differences between the groups. ANOVA with Scheffe's *post hoc* test (I) or contrast analysis (II–IV) was used to analyze the time-dependent variance within the groups and the differences between the groups when repeated measures were made. In the case of non-normal distribution, non-parametric Kruskal-Wallis test was used. The data are presented as means and 95% confidence interval in the text and as medians, 25% and 75% percentiles, and non-outlier ranges in the figures. Significance was assumed when the p value was less than 0.05.

5 Results

5.1 Perioperative characteristics

The study groups had similar preoperative characteristics and perioperative courses, with the exception of a longer total grafting time in the off-pump CABG groups compared with the aortic occlusion time in the CPB group and a lower core temperature in the CPB group. The CPB patients received higher doses of heparin, resulting in significantly longer activated coagulation times and, consequently, higher doses of protamine sulphate (Table 7). The mean CPB time was 73.8 min (CI, 60.9 to 86.7 min). The mean ischaemia time for the first two distal anastomoses was 13.6 min (CI, 11.7 to 15.4 min) in the IPC group, 15.2 min (CI, 12.5 to 17.9 min) in the OPCAB group, and 6.9 min (CI, 5.2 to 8.6 min) in the CPB group ($p < 0.001$).

5.2 Pilot study of OPCAB

During the suturing of the anastomoses, the transcardiac concentration differences of ATP degradation products increased modestly to 5.60 $\mu\text{mol/l}$ (CI, 1.12 to 10.09 $\mu\text{mol/l}$) ($p = 0.026$) and lactate to 0.17 mmol/l (CI, 0.00 to 0.35 mmol/l) ($p = 0.004$). The highest value of the transcardiac pH difference was 0.05 (CI, 0.03 to 0.06). Two patients were considered to be ischaemic and received intravenous nitroglycerin. There were no significant changes in heart rate, but mean arterial pressure and the cardiac index decreased to the lowest values of 58 mmHg (CI, 52 to 63 mmHg) ($p = 0.002$) and 1.9 l/min/m² (CI, 1.5 to 2.3 l/min/m²). Two patients developed atrial fibrillation after sternotomy, probably as a consequence of manipulation of the atria. Both were converted to sinus rhythm by DC shock at 10–20 J with myocardial surface electrodes. There were no significant changes in systemic oxygen extraction or arterio-venous pH differences. Mixed venous oxygen saturation of haemoglobin remained higher than 60%, and no significant systemic lactate production was recorded during or after the operation.

Postoperatively, the highest mean CK-MBM and TnT values of 13.4 $\mu\text{g/l}$ and 0.31 $\mu\text{g/l}$ were observed on the first postoperative morning. Haemodynamics remained

satisfactory with five patients receiving low doses of dopamine, mainly for treatment of modest hypotension. Two patients had hyperdynamic circulation, one had mild hypertension, and two developed atrial fibrillation. One patient was reoperated because of bleeding, and one was considered to have suffered a minor postoperative AMI. There were no other major complications during the one-week hospital stay.

Table 7. Patients' preoperative characteristics and perioperative course (means and CIs or numbers).

Study group (Trial / number of patients)	Pilot (I/11)	CPB (II, IV/11)	OPCAB (II, III/11)	IPC (III/11)	OPCAB +IPC (IV/22)
Age (y)	58.5 (52.3–64.5)	59.2 (53.0–65.4)	59.5 (53.3–65.8)	59.0 (53.9–64.0)	59.3 (55.6–62.9)
Body mass index (kg/m ²)	26.1 (23.9–28.2)	29.0 (25.8–32.1)	27.2 (25.9–28.5)	30.6 (27.2–34.0)	28.9 (27.1–30.7)
NYHA class (II/II/IV)	5/6/1	1/10/0	1/10/0	0/10/1	1/20/1
Diseased vessels (1/2/3)	2/8/2	1/5/5	1/6/4	0/5/6	1/11/10
Myocardial infarctions (0/1/2)	8/3/1	7/3/1	6/5/0	6/3/2	12/8/2
Ejection fraction < 50%	0	0	1	2	3
Bypass grafts / patient (n)	2.4 (2.1–2.7)	3.3 (2.4–4.2)	2.8 (2.3–3.3)	3.1 (2.4–3.8)	3.0 (2.6–3.4)
Operation time (min)	215 (194–236)	211 (188–233)	231 (207–254)	242 (209–275)	236 (218–255)
Total grafting / aortic occlusion time (min)	86 (74–98)	58* (44–72)	110 (95–125)	108 (83–134)	109 (96–123)
Total ischaemia time (min)	45.8 (39.9–51.8)	31.1 (20.2–42.0)	41.6 (34.5–48.6)	50.3 (41.9–58.7)	45.9 (40.5–51.3)
Lowest body temperature (°C)		33.2* (33.0–33.5)	35.0 (34.7–35.2)	35.3 (34.9–35.7)	35.1 (34.9–35.4)
Heparin dose (mg/kg)	1.1 (0.9–1.3)	4.3* (4.0–4.7)	1.8 (1.5–2.1)	1.8 (1.4–2.1)	1.8 (1.6–2.0)
Protamine sulphate (mg/kg)	0.9 (0.7–1.1)	3.3* (3.3–3.5)	0.7 (0.6–0.8)	0.6 (0.5–0.7)	0.6 (0.6–0.7)
ACT (seconds)	269–333	505–758*	261–345	280–371	270–358

ACT = Activated coagulation time; * = $p < 0.001$. Statistical analyses were only performed between the CPB, OPCAB, and IPC groups.

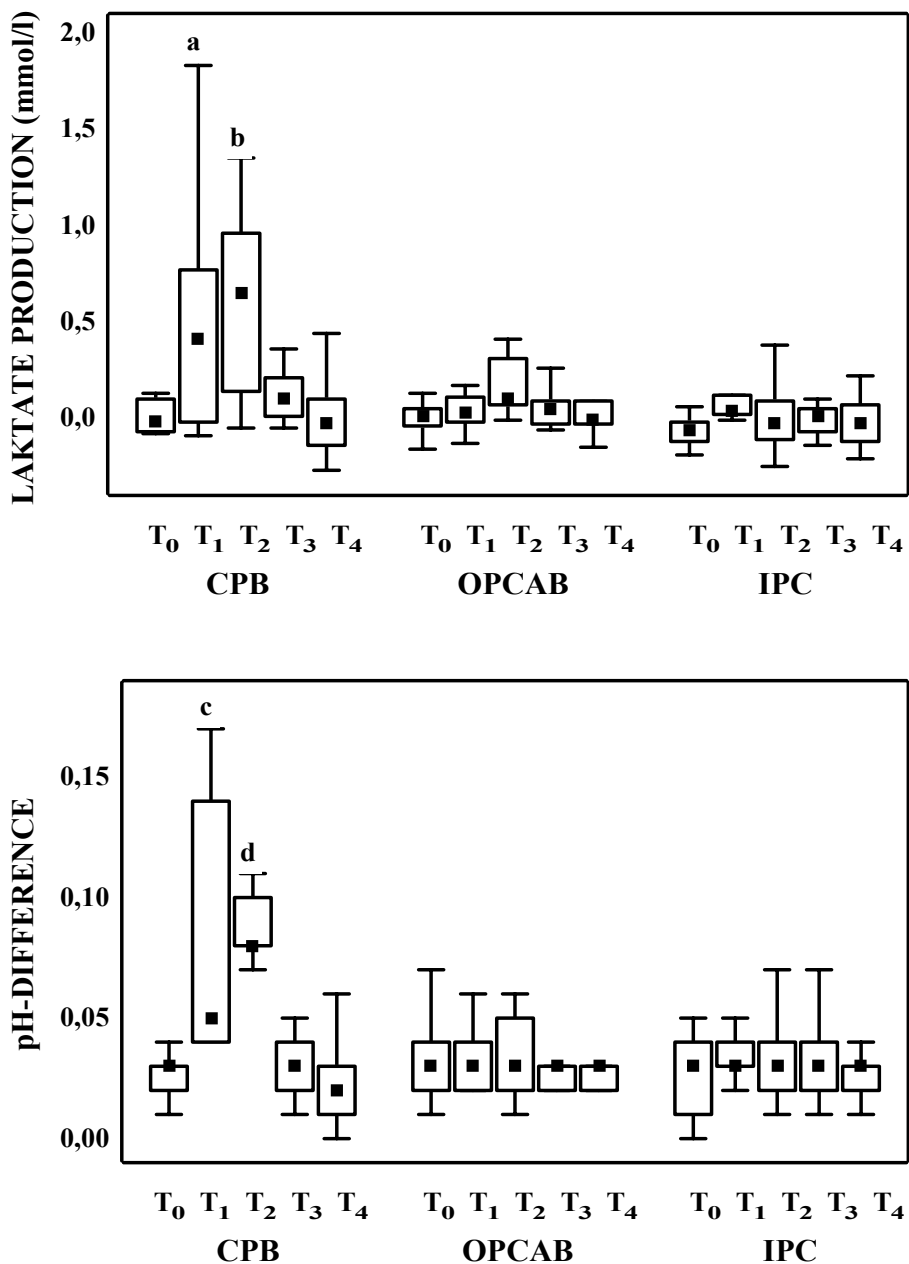


Fig. 3. Myocardial lactate production and transcardiac pH difference (median, 25% and 75% percentiles, and non-outlier range). T₀-T₁₀ indicate sampling times (Fig. 2) and the letters a, b, c, and d significant differences (between the CPB and OPCAB groups) ($p = 0.02$, $p = 0.01$, $p = 0.007$, and $p < 0.001$, respectively).

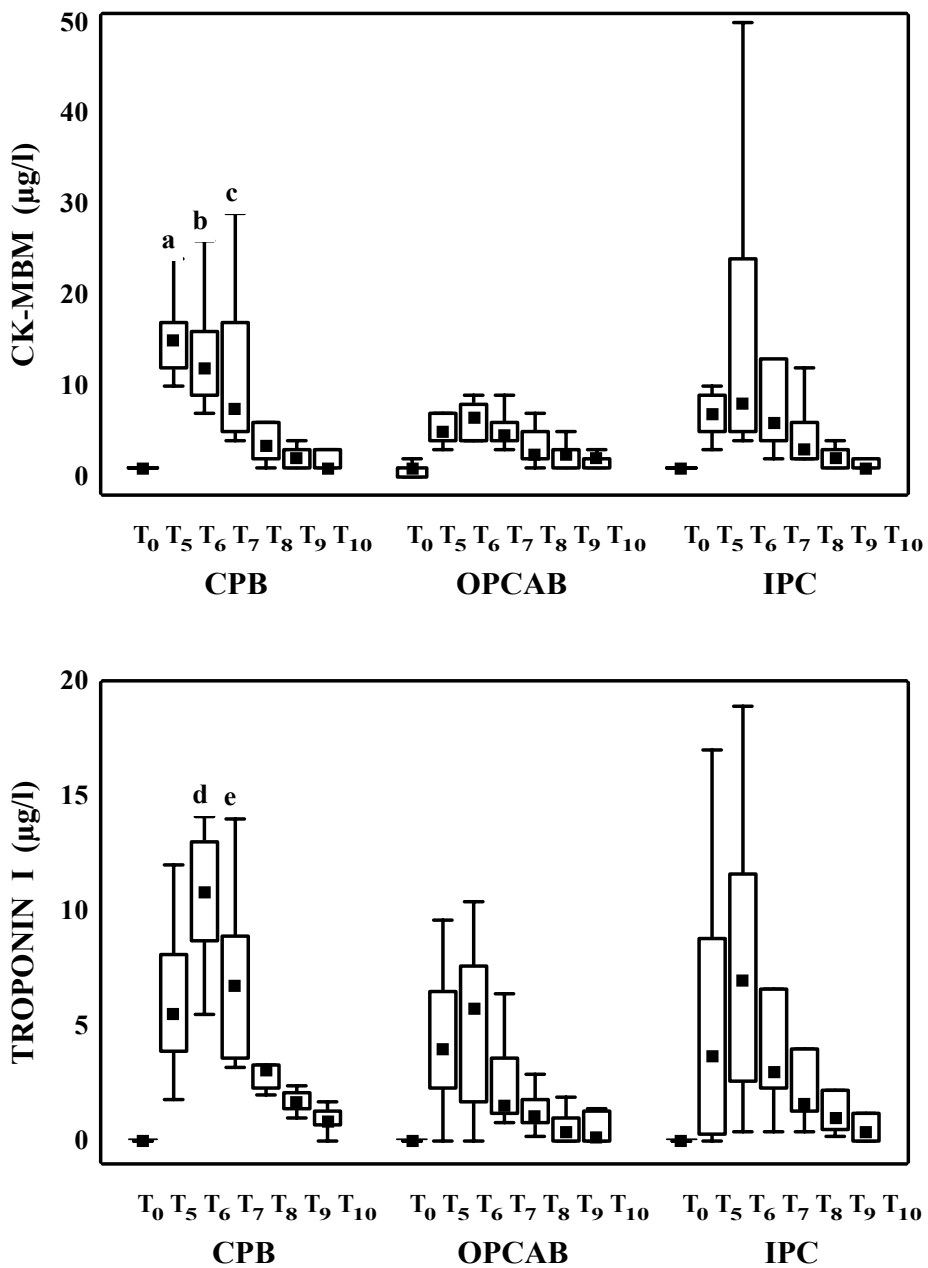


Fig. 4. Plasma levels of CK-MBM mass and troponin I (median, 25% and 75% percentiles, and non-outlier range). T₀-T₁₀ indicate sampling times (Fig. 2) and the letters a, b, c, d, and e significant differences (between the CPB and OPCAB groups) ($p < 0.001$, $p = 0.002$, $p = 0.04$, $p = 0.002$, and $p = 0.008$, respectively).

5.3 Markers of myocardial metabolism and tissue injury

Transmyocardial differences in total ATP degradation products increased significantly during the suturing of the first two distal anastomoses in all groups ($p = 0.02$ for CPB, $p = 0.04$ for OPCAB, and $p = 0.004$ for IPC). The highest values of ATP degradation products were $18.41 \mu\text{mol/l}$ (CI, 2.00 to $34.82 \mu\text{mol/l}$), $9.86 \mu\text{mol/l}$ (CI, 1.39 to $18.33 \mu\text{mol/l}$), and $13.12 \mu\text{mol/l}$ (CI, 0.89 to $25.36 \mu\text{mol/l}$), respectively. There were no statistically significant differences between the groups, however.

Myocardial net lactate production increased from the initial values to the maximum of 0.56 mmol/l (CI, 0.25 to 0.87 mmol/l) in the CPB group ($p = 0.001$), being 0.17 mmol/l (CI, 0.07 to 0.27 mmol/l) in the OPCAB group ($p = 0.003$) and 0.09 mmol/l (CI, 0.01 to 0.17 mmol/l) in the IPC group ($p = 0.05$). The highest value of the transcardiac pH difference was 0.08 (CI, 0.06 to 0.10) in the CPB group and 0.03 (CI, 0.02 to 0.05) in the OPCAB and IPC groups. The increase from the basic value of pH difference was statistically significant in each group ($p < 0.001$, $p = 0.007$, and $p = 0.002$, respectively). Myocardial lactate and acid production was significantly higher in the CPB group after the suturing of the first two distal anastomoses ($p = 0.02$ and $p = 0.01$ for lactate production, and $p = 0.007$ and $p < 0.001$ for pH difference) compared with the OPCAB group. There were no statistically significant differences in lactate production or the pH difference between the OPCAB and IPC groups (Fig. 3).

The maximum serum concentration of CK-MBM was $15.1 \mu\text{g/l}$ (CI, 12.1 to $18.1 \mu\text{g/l}$) in the CPB group, $6.3 \mu\text{g/l}$ (CI, 5.0 to $7.6 \mu\text{g/l}$) in the OPCAB group, and $14.8 \mu\text{g/l}$ (CI, 4.9 to $24.7 \mu\text{g/l}$) in the IPC group. CK-MBM levels were significantly higher in the CPB group at two ($p < 0.001$) and eight ($p = 0.002$) hours after the construction of the anastomoses and on the first postoperative day ($p = 0.04$) compared with the OPCAB group. The highest values of TnI were $13.8 \mu\text{g/l}$ (CI, 6.1 to $21.4 \mu\text{g/l}$), $5.2 \mu\text{g/l}$ (CI, 2.6 to $7.8 \mu\text{g/l}$), and $7.4 \mu\text{g/l}$ (CI, 3.7 to $11.2 \mu\text{g/l}$), respectively. TnI levels were significantly higher in the CPB group at eight hours after the construction of the anastomoses ($p = 0.002$) and on the first postoperative day ($p = 0.008$) compared with the OPCAB group. There were no statistically significant differences in CK-MBM or TnI levels between the OPCAB and IPC groups (Fig. 4).

5.4 Cerebral injury markers

The highest values of NSE serum concentrations corrected for plasma free haemoglobin were $3.8 \mu\text{g/l}$ (CI, 0.7 to $6.9 \mu\text{g/l}$) on the first postoperative day in the beating heart group and $6.3 \mu\text{g/l}$ (CI, 4.7 to $8.0 \mu\text{g/l}$) 15 minutes after the completion of the last anastomosis in the CPB group. The serum concentrations of NSE were significantly higher in the CPB group 15 minutes ($p = 0.003$) and eight hours ($p = 0.005$) after the suturing of the last anastomosis (Fig 5).

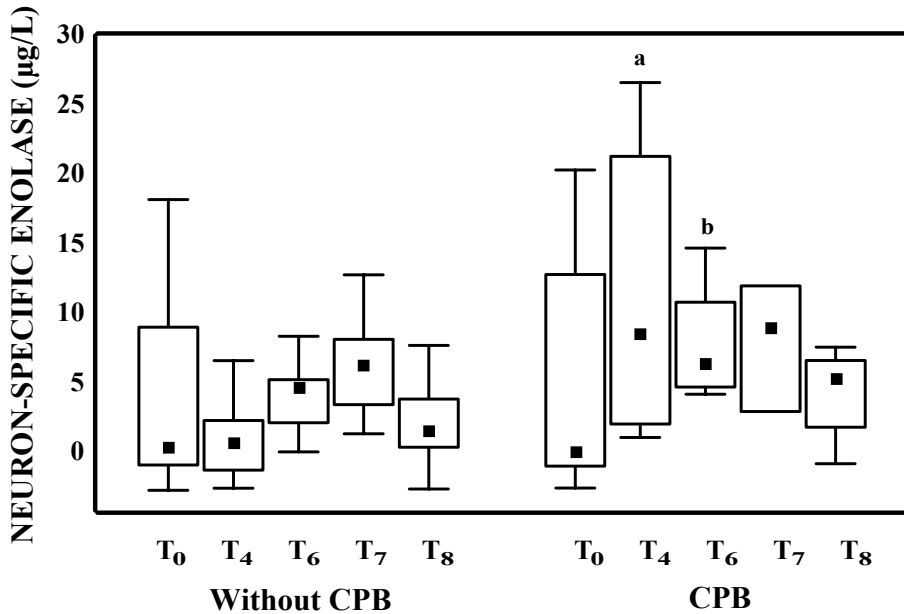


Fig. 5. Serum concentrations of neuron-specific enolase corrected for haemolysis (median, 25% and 75% percentiles, and non-outlier range). T₀, T₄, and T₆-T₈ indicate sampling times (Fig. 2) and the letters a and b indicate statistically significant differences between the groups ($p=0.003$ and $p=0.005$, respectively). The group without CPB consists of the two beating heart groups (OPCAB and IPC).

5.5 Perioperative course

Four patients in both beating heart groups (OPCAB and IPC) received intravenous nitroglycerine, and two of these patients (one in each group) also had an intracoronary flow-through catheter inserted. One patient in the OPCAB group received nitroglycerine to decrease his modestly elevated pulmonary artery pressure, and the others were considered to be ischaemic. All the patients received phenylephrine hydrochloride to maintain the mean arterial pressure above 50 mmHg, and three patients (one in each group) were defibrillated to restore sinus rhythm.

One patient in the CPB and one in the OPCAB groups had a perioperative AMI. Both developed inferolateral Q waves and had markedly elevated values of CK-MBM (273 µg/l and 120 µg/l) and TnI (277.5µg/l and 89.4µg/l). Three patients in the CPB group, one in the OPCAB group, and three in the IPC group developed atrial fibrillation after the operation, and they were converted to sinus rhythm. Six patients in the CPB group, two in the OPCAB, and three in the IPC group received low doses of dopamine mainly for the treatment of mild hypotension. Only one patient in the CPB group had a cardiac index below 2.2 l/m². One patient in the IPC group had a postoperative minor cerebral infarction. The recovery of the patients with AMI and cerebral infarction was uneventful, and there were no other major complications during the one-week in-hospital period.

6 Discussion

6.1 Methodological aspects

This series of one descriptive trial and one randomized prospective trial with three groups was planned to evaluate the myocardial and haemodynamic stability of OPCAB (I), to compare on- and off-pump CABG for myocardial (II) and cerebral (IV) preservation, and to evaluate the myocardial effects of IPC during OPCAB (III).

The studies II–IV were originally planned separately. However, the nature of the control group in trial III was equal with the study group in trial II. The nature of the control and study groups in trial IV was also equal to the control group in trial II and the combination of the study groups in the trials II and III, respectively. At that time, OPCAB was not such a routine operation as it is at present, and patients with CAD eligible for OPCAB were fewer in number and harder to recruit. To intensify the collection of patients into this study, recruitment was done simultaneously by combining the equal groups (Fig. 6). Afterward, all study groups were tested together for inter-group differences to ensure justification of the resplitting of the groups into the originally planned trials.

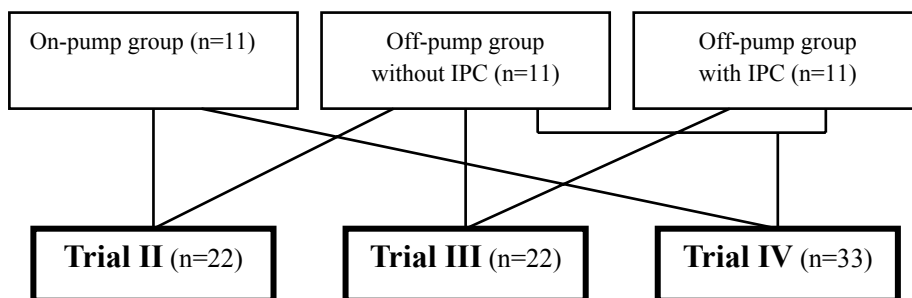


Fig. 6. Comparison between the study groups in the trials II–IV. IPC = ischaemic preconditioning of the myocardium.

Myocardial preservation during the operation was evaluated in terms of transcardiac differences of ATP degradation products, pH, and lactate. Lactate and pH are widely accepted biological markers of ischaemic metabolism. A decrease in the myocardial tissue concentration of ATP is associated with an increase of serum ATP degradation products, and their evaluation is a less traumatizing method than measurements of myocardial ATP concentrations from tissue biopsies. Adenosine is rapidly metabolized or taken up by red blood cells, and dipyridamole was therefore used in the stopping solution to prevent adenosine metabolism *in vitro* in the sampling syringes (Nissinen *et al.* 1993). The patients also received dipyridamole before the operation. Transcardiac differences were calculated from the arterial and coronary sinus blood concentrations, which may have produced a dilution effect and some underestimation of regional ischaemia.

Myocardial tissue injury was evaluated based on postoperative serum concentrations of CK-MBM and with a more specific myocardial injury marker, TnT (I) or TnI (II–IV). Two patients were considered to have had a perioperative myocardial infarction, and they were excluded from the analyses of CK-MBM and TnI. This was considered justified, as the purpose of this study was to compare two different surgical techniques for their capacity of tissue protection in patients with an uncomplicated perioperative course.

Intermittent antegrade mild hypothermic blood cardioplegia with normothermic arresting and terminal infusions was chosen for the CPB group, since this mode of cardioplegia, in our hands, has provided the best myocardial protection during CPB (Raatikainen *et al.* 1997, Kaukoranta *et al.* 1998).

The strength of the stimulus of IPC to initiate preconditioning in humans is largely unknown. A cycle of five-minute ischaemia followed by five-minute reperfusion was used in this study, as it is the most frequently recommended cycle and also acts as a test occlusion for ischaemic changes before the occlusion for the suturing of the distal anastomosis. Conceivable chemical preconditioning of the anaesthetics, dipyridamole and neosynephrine hydrochloride, used in this study may confuse the results, but all the groups were equal in this respect, and the aim of this study was to evaluate the effects of IPC in clinical practice.

Cerebral damage was evaluated by means of the serum concentrations of NSE, which is specific for neuronal injury. Neuropsychological tests, eventually, reveal the clinical endpoint of cerebral outcome, but they are laborious and require large study groups. They have also been shown to have a tendency towards the mean when the tests are repeated (Browne *et al.* 1999). NSE has been found to correlate with neuropsychological outcome (Rasmussen *et al.* 1999). However, it has been used predominantly as a tumor marker for small-cell lung cancer, neuroblastoma, and malignancies of neuroendocrine origin, and gross haemolysis interferes with the NSE analysis (Johnsson 1996). Patients with known malignancies were not included in this study, and the NSE of haemolysed erythrocyte origin was estimated and subtracted from the measured values of NSE (Johnsson *et al.* 2000).

6.2 Pilot study of OPCAB

The study I was a pilot study to define the myocardial and haemodynamic effects of OPCAB, when the coronary artery to be bypassed is occluded on a beating heart during the suturing of the distal anastomoses, and the heart is rotated. There was myocardial net production of ATP degradation products, lactate, and acid during the operation, suggesting worsening of the average myocardial energy state. However, these productions were significantly lower than those seen in the earlier studies performed in this hospital with CPB and cardioplegia (Nissinen *et al.* 1993, Raatikainen *et al.* 1997), but slightly higher than during PTCA (Peuhkurinen *et al.* 1991). Although these patient groups were not strictly comparable, the average myocardial energy state during CABG on a beating heart seemed to be at least equally well or even better maintained compared with on-pump CABG and cardioplegia.

The transient decreases of the mean arterial pressure to 50 mmHg and of the cardiac index below 2.0 l/min/m² were well tolerated, although systemic extraction of oxygen tended to increase slightly. Mixed venous blood oxygen saturation remained above 60%, which was regarded as the threshold for satisfactory circulation. The almost constant levels of systemic pH and lactate also indicated sufficient circulation.

There were no remarkable increases in the TnT and CK-MBM levels during the follow-up period of two days, demonstrating an absence of significant myocardial damage. One patient developed haemodynamically uneventful postoperative AMI with some suspicion of proximal LAD thrombus formation as a consequence of difficulties and jamming in connection with probing the artery.

6.3 Myocardial preservation

The importance of myocardial preservation during CABG cannot be overemphasized. Total failure in myocardial preservation with the current cardioplegia techniques is an exceptional, but often fatal complication of coronary surgery. Inadequate myocardial preservation with no difficulties in cardioplegia delivery is, however, more common. On the other hand, during OPCAB, the coronary artery to be bypassed is usually occluded for the suturing of the distal anastomoses while the heart is beating and may be rotated. The pilot study showed better myocardial preservation during OPCAB compared with the earlier clinical studies with CPB, which indicated more careful implementation of the study with a randomized trial.

A significant amount of myocardial release of lactate occurred in both groups (CPB and OPCAB) during the suturing of the anastomoses. Lactate production was significantly higher in the CPB group. Myocardial lactate production returned to the basal level in the OPCAB group and close to the basal level in the CPB group within 15 minutes after the construction of the anastomoses, indicating rapid recovery of metabolism in each group. The transcardiac pH difference also increased in both groups, indicating deterioration of anaerobic energy metabolism. However, the net acid release was more prominent during CPB.

There was a significant, although slight, increase in the net release of ATP degradation products in both groups, showing the overall energy state of the myocardium to be relatively well maintained during the suturing of the first two bypass grafts. There were no statistically significant differences between the groups. The ischaemia period for the first two bypasses in the CPB group was significantly shorter than that in the OPCAB group, but the ischaemia in the CPB group was global in nature. This is important, since the average myocardial energy state seems to be maintained better during OPCAB than CPB and blood cardioplegia.

Postoperatively, CK-MBM and TnI levels increased in each group, but the increases were significantly higher in the CPB group, indicating more prominent myocardial injury. This result is in accordance with the other studies of TnI levels after off- and on-pump CABG (Birdi *et al.* 1997, Ascione *et al.* 1999a, Krejca *et al.* 1999, Lönn *et al.* 1999, Wan *et al.* 1999).

6.4 Myocardial ischaemic preconditioning

Murry and his co-workers reported IPC to decrease the size of myocardial infarction after ischaemia of 40 minutes, but not of 3 hours, and to delay ATP depletion in a canine model (Murry *et al.* 1986). Yellon and his colleagues confirmed the finding of ATP preservation in coronary artery bypass surgery performed with the intermittent aortic cross-clamping technique (Yellon *et al.* 1993). Although the phenomenon has not been clinically studied during OPCAB, many cardiac surgeons intentionally predispose the beating myocardium to regional short-term ischaemia prior to occluding the coronary artery, hoping to utilize the benefits of IPC.

The increases in myocardial lactate production and the transcardiac pH difference were slight, and there were no statistically significant differences between the groups, suggesting that IPC does not improve myocardial preservation, although myocardial lactate production tended to be slightly lower in the IPC group. The effect of IPC may be confused by the possible chemical preconditioning of anaesthetics and neosynephrine hydrochloride, but overall, the benefits of IPC seem to be rather limited in terms of changes in myocardial energy metabolism.

There were no statistically significant differences between the two off-pump groups in the postoperative levels of CK-MBM and TnI. However, there was a slight tendency for higher levels with larger variations of both markers in the IPC group, although the possibility of false negative result cannot be excluded. There were 2.8 distal anastomoses and coronary artery occlusions without IPC and 3.1 distal anastomoses and 5.1 coronary occlusions with IPC, including the two occlusions for preconditioning. Thus, the larger number of coronary occlusions and the tendency to longer cumulative ischaemia time may explain the tendency to the slightly higher level and larger variation of myocardial injury markers in the IPC group.

6.5 Cerebral preservation

The serum concentration of NSE corrected for haemolysis was slightly but statistically significantly higher in the CPB group immediately and at eight hours after bypass grafting. This result may indicate increased neuronal damage during CABG with CPB, but its clinical significance remains to be estimated in larger clinical studies.

Earlier studies show conflicting results in comparing cerebral outcome after these two operative techniques, but none show a worse outcome after OPCAB. There are numerous non-randomized studies, which all show no differences between on- and off-pump operations in respect to neuropsychological changes or levels of biological cerebral injury markers (Malheiros *et al.* 1995, Browne & Taggart 1997, Andrew *et al.* 1998, Taggart *et al.* 1999, Anderson *et al.* 1999). However, the non-randomized nature of these studies may contribute to the results.

There are only a few prospective randomized studies comparing cerebral outcome after on- and off-pump CABG. In the study of Diegeler *et al.*, there was a better cerebral outcome after OPCAB in the evaluations of both the neuropsychological tests and S-100 protein (Diegeler *et al.* 2000). Lee and his colleagues found more cerebral microemboli during on-pump CABG and reduced cerebral perfusion with lower auditory verbal learning after operation compared with OPCAB (Lee *et al.* 2003). Lund *et al.* also found a significant reduction in the number of cerebral microemboli, but this was not associated with better neuropsychological performance after OPCAB compared with on-pump CABG (Lund *et al.* 2003). Cerebral complications have also been shown to be fewer after OPCAB compared with conventional surgery (Buffolo *et al.* 1996, Schmitz *et al.* 2003).

6.6 Perioperative course

Nine patients out of 34 in the off-pump groups were considered to be ischaemic during the operation, and all but two responded to low doses of intravenous nitroglycerine. The two non-responders had an intracoronary flow-through catheter inserted. Two patients developed intraoperative atrial fibrillation reversible with DC shock in the pilot study, but no instances of intraoperative atrial fibrillation were seen in the later trials. All the patients in the off-pump groups as well as in the CPB group needed small intravenous doses of phenylephrine to maintain their blood pressure. There were no remarkable haemodynamic changes in any of the patients, and there was no need for conversion to CPB.

One patient in the IPC group developed a small postoperative cerebral infarction after completing the study protocol for NSE, i.e. two days after the operation. There were three perioperative myocardial infarctions, one in each group except in the IPC group. The number of patients is, however, so small that no conclusions can be drawn. Six patients out of 34 in the off-pump groups and four out of 11 in the CPB group developed postoperative atrial fibrillation. The high frequency of dopamine infusion after the operations reflects only the aggressive maintenance of blood pressure in this hospital and not necessarily the need for inotropic support. The recovery of the patients with AMI and

cerebral infarction was uneventful, and there were no other major complications during the one-week in-hospital period.

6.7 Comparison of the results with the literature

As these studies were preliminary in character, they included a relatively small number of patients. In addition, they were completed several years ago. Therefore, it is reasonable to compare the results of this study with the results of more recent trials.

At the time when the first trial on haemodynamic changes and myocardial metabolism during OPCAB (I) was started, there was only one previous study available on the safety of OPCAB. This study showed coronary occlusion for 15 to 20 minutes to be well tolerated in a canine model (Reimer & Jennings 1979). This study showed a significant decrease of cardiac index, which, however, was well tolerated, as shown by the recording of mixed venous oxygen saturation and systemical acid balance and lactate production. Since that time, these haemodynamic changes have been confirmed in several studies by measuring various parameters (Mathison *et al.* 2000, Nierich *et al.* 2000, Menon *et al.* 2002, Torracca *et al.* 2002, Yetman *et al.* 2002). Kwak and his colleagues recently studied the haemodynamics of 30 patients undergoing OPCAB. They found a significant reduction in the right ventricular cardiac output and ejection fraction during anastomosis of the obtuse marginal coronary arteries. There was no significant change in these parameters during anastomosis of LAD and RCA. They also confirmed our result of no significant change in mixed venous oxygen saturation by measuring it continuously with a pulmonary artery thermodilution catheter (Kwak *et al.* 2004).

The second trial of this study (II) was primary in nature as well. The main results were better cardiac metabolism during OPCAB, measured by means of transcardiac lactate production and acid balance, and reduced TnI and CKMBM release after OPCAB, indicating less myocardial injury. At the time when the trial was started, there were only a few, mainly non-randomized trials on septal function, low output states, and arrhythmias (Table 1), all suggesting the superiority of OPCAB (Akins *et al.* 1984, Pfister *et al.* 1996, Buffolo *et al.* 1996). At present, there are several randomized and non-randomized trials confirming the results of this study on reduced release of TnI and CKMBM after OPCAB (Ascione *et al.* 1999a, Krejca *et al.* 1999, Lönn *et al.* 1999, Wan *et al.* 1999, Kilger *et al.* 2000, Calafiore *et al.* 2001, Kilo *et al.* 2001a). A recent non-randomized matched study carried out by Thielmann *et al.* on 198 patients revealed significantly lower TnI and MB fractions of creatine kinase but not myoglobin levels after OPCAB compared with on-pump CABG. There was no significant difference between the operative techniques regarding early haemodynamics in terms of cardiac index, systemic vascular resistance index, and left ventricular stroke work index. (Thielmann *et al.* 2005). However, conflicting results of postoperative haemodynamics exist in the form of decreased inotropic need after OPCAB (Ascione *et al.* 2001a, Kilo *et al.* 2001a).

IPC has been widely studied, and contradictory results have been reported for several years. The results of this study with a 5-minute coronary occlusion followed by a 5-minute period of reperfusion showed no benefit on myocardial energy metabolism or myocardial injury during OPCAB based on myocardial lactate and acid productions and

postoperative release of TnI and CKMBM (III). By now, several studies on IPC during OPCAB have failed to show any improvement of left ventricular function (Malkowski *et al.* 1998, Bufkin *et al.* 1998). Wu and his colleagues have studied intensively IPC during off- and on-pump procedures (Wu *et al.* 2000b, Wu *et al.* 2001, Wu *et al.* 2003b). One of their studies is largely identical with present study on IPC during OPCAB. It is a prospective randomized study with 32 patients and shows better postoperative recovery of the mean cardiac stroke volume index, reduced Tni release, and a tendency toward lower levels of MB fraction of creatine kinase after IPC. As preconditioning, LAD was occluded twice for a 2-minute period followed by 3-minute reperfusion. (Laurikka *et al.* 2002). The conflicting results may be due to the different IPC cycles used in these two similar studies, as it is largely unknown what kind of IPC cycle should be used to facilitate the benefits of IPC. Bartling *et al.* recently showed IPC to have no cardioprotective effects on senescent humans (Bartling *et al.* 2003). This could affect our results, as the mean ages of the patients with and without IPC were 59.0 and 59.5 years, respectively. Chronic beta-blocker treatment has been shown to interfere with the cardioprotective function of IPC (Suematsu *et al.* 2004). The patients in present study were allowed to continue their treatment with beta-blockers until the day of operation, which may also have counteracted the effects of IPC.

In the trial IV of this study, cerebral preservation measured with serum concentrations of NSE seemed to be better after OPCAB compared with on-pump CABG (IV). On the whole, the studies of cerebral preservation have yielded conflicting results (Table 2). In general, studies involving different measurements show equal or better cerebral preservation after OPCAB compared with on-pump CABG. At present, the incidence of stroke only has been shown, without controversy, to be decreased after OPCAB (Ascione *et al.* 2001a, Hirose *et al.* 2001, Hoff *et al.* 2002, Patel *et al.* 2002, Stamou *et al.* 2002).

7 Conclusions

The results of these studies allow the following conclusions to be drawn:

1. The changes in myocardial energy metabolism during coronary artery occlusion and rotation of the heart during off-pump surgery are mild and transient in nature, and the operation is haemodynamically well tolerated. Based on this study of a small patient series, off-pump coronary surgery seems to be a safe operation for selected patients.
2. Myocardial preservation with respect to metabolic changes and tissue injury is significantly better during off-pump coronary surgery compared with on-pump surgery and intermittent antegrade mild hypothermic blood cardioplegia. This may be important when choosing the best strategy for myocardial protection during coronary artery bypass grafting, at least in selected cases.
3. Preconditioning with regional ischaemia of five minutes followed by reperfusion of five minutes does not seem to be able to prevent metabolic derangement or to reduce myocardial tissue injury during multi-vessel coronary artery bypass grafting on a beating heart and cannot be routinely recommended.
4. Off-pump coronary artery surgery produces a smaller increase in the serum concentration of neuron-specific enolase, suggesting less neuronal damage, compared with conventional on-pump surgery with mild hypothermic CPB. However, the clinical significance of this result remains to be estimated in studies of neuropsychological function in larger patient series, before off-pump coronary surgery can be recommended as the primary surgical choice for patients at risk for cerebral complications.

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