Coronary artery bypass grafting with and without extracorporeal circulation

A randomised trial with focus on cognitive function and health-related quality of life

PhD thesis
Birte Østergaard Jensen

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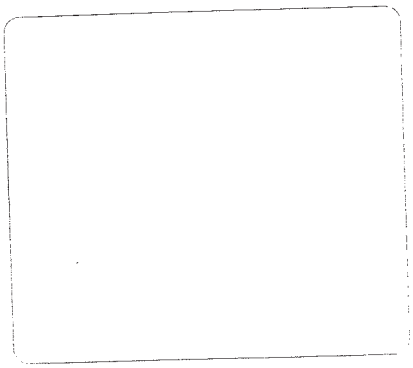

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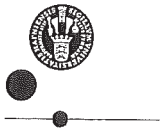


Faculty of Health Sciences
Copenhagen University
and
Department of Cardiothoracic Surgery
The Heart Centre
Copenhagen University Hospital, Rigshospitalet
2006

Not everything that can be counted counts,
and not everything that counts can be counted.
--Albert Einstein

IN LOVING MEMORY OF PIA
her wit, her precision,
her warmth and kindness
were inspirational

Preface

This thesis was planned and carried out during my employment as a PhD student from 2003 to 2006 at the Department of Cardiothoracic Surgery, The Heart Centre, Rigshospitalet, Copenhagen University Hospital, which gave me ideal working conditions in every way. My employment was financed by: The Copenhagen Hospital Corporation's Research Council and The Danish Heart Foundation. The study was additionally supported by grants from The Lundbeck Foundation.

First of all, I want to express my sincere gratitude to Daniel A. Steinbrüchel. He has been truly supportive throughout my entire training, and provided me the time and facilities to realise the research.

I owe many thanks to Pia Hughes for stimulating talks, valuable input and encouragement to complete the research as a part of the BBS Trial.

I am much obliged to Preben U. Pedersen for his stimulating enthusiasm, inspiring discussions and invaluable help. I am also very thankful to Lars S. Rasmussen for his excellent and professional help and for letting me use the ISPOCD test battery.

I want to thank the ward staff at the department of cardiothoracic surgery 3-15-2, 3 and 4 for their great support and willingness to offer me room and space during the entire course, in connection with inclusion and follow-up of patients.

Furthermore I want to thank my colleagues Sune Damgaard, Christian Møller and Nikolaj Lilleør at the research unit for creating a stimulating and friendly work environment. For that I am very grateful.

October 2006

Birte Østergaard Jensen

List of contents

Abbreviations

AMI	Acute Myocardial Infarction
BBS	Best Bypass Surgery Trial
CABG	Coronary Artery Bypass Grafting
CAD	Coronary Artery Disease
CCAB	Conventional Coronary Artery Bypass
CI	Confidence Interval
CPB	Cardiopulmonary Bypass
HRQoL	Health-related quality of life
IHD	Ischaemic Heart Disease
ISPOCD	International Study of Post-Operative Cognitive Dysfunction
MDI	Major Depression Inventory
MMSE	Mini Mental State Examination
MRI	Cerebral Magnetic Resonance Imaging
OPCAB	Off-pump Coronary Artery Bypass
QOL	Quality of life
RCT	Randomised clinical trial
SD	Standard Deviation
SF-36	Medical Outcomes Study Short Form 36

Original papers

This thesis is based on the following papers, which will be referred to by their Roman numerals:

I. Jensen BØ, Hughes P, Pedersen PU, Rasmussen LS, Steinbrüchel DA. Rationale and design of a randomized clinical trial of neurocognitive functions in moderate to high-risk patients undergoing conventional versus off-pump coronary artery bypass grafting. Unpublished material.

II. Jensen BO, Hughes P, Rasmussen LS, Pedersen PU, Steinbrüchel DA. Cognitive Outcomes in Elderly, High-Risk Patients After Off-Pump Versus Conventional Coronary Artery Bypass Grafting: A Randomized Trial. Circulation. 2006;113:2790-5.

III. Jensen BØ, Hughes P, Rasmussen LS, Pedersen PU, Steinbrüchel DA. Health-related quality of life following off-pump versus on-pump coronary artery bypass grafting in elderly moderate to high-risk patients: a randomized trial. Eur J Cardio-thoracic Surg. 2006;30:294-9.

Abstract

Background

Coronary artery bypass grafting (CABG) with the use of cardiopulmonary bypass (CPB) is one of the most common cardiovascular operations. However, there is a substantial risk of procedure-related postoperative complications. Besides a risk of mortality and adverse effect on cardiac, pulmonary and renal function, there is also a risk of major and minor cerebral deficits usually manifested as stroke or cognitive decline.

It has been suggested that the risk of cerebral dysfunction is less pronounced with off-pump coronary artery bypass grafting (OPCAB). This is a procedure where the distal graft anastomoses are performed on a beating heart without a heart and lung machine, aortic cross clamping, and cardioplegic arrest.

Previous trials comparing coronary artery bypass grafting with or without extracorporeal circulation have mainly enrolled selected patients at young age and low operative risk. Currently, there are no randomised trials including high-risk patients, e.g. elderly patients with serious co-morbidity, although this population might benefit the most from avoiding CBP.

Objectives and methods

Paper I — Description of the rationale, design and methodology of a randomised clinical trial that aims to compare off-pump to on-pump CABG surgery with respect to postoperative cognitive dysfunction and health-related quality of life.

Paper II — A randomised clinical trial assessing the effect of off-pump versus on-pump CABG surgery on cognitive function at three months postoperatively (n = 120).

Paper III — A randomised clinical trial assessing the effect of off-pump versus on-pump CABG surgery on health-related quality of life at three months postoperatively (n = 120).

Results

Paper I — Enrollment started in July 2002 and ended in December 2004. One hundred and twenty consecutive patients were randomly assigned to one of the two intervention groups.

Paper II — Cognitive dysfunction was identified in 7% of the patients in the off-pump group and 10% in the on-pump group 3 months postoperatively. No significant difference was found in the incidence of cognitive dysfunction between the groups, regardless of the definition applied.

Paper III No statistically significant differences were seen between off-pump and on-pump groups at three months postoperatively, except for changes in mean difference of role limitation due to emotional problems, which was improved in favour of the on-pump group. Depression scores remained unchanged within and between the two surgical groups.

Conclusions

The trial is a sub-study of the first randomised clinical trial examining moderate to high-risk patients undergoing coronary artery bypass surgery.

In elderly, high-risk patients, no significant difference was found in the incidence of cognitive dysfunction between off-pump and on-pump CABG groups three months after the surgery.

Both off-pump and on-pump patients improved in health-related quality of life scores after CABG surgery. No clinically relevant difference could be demonstrated in health-related quality of life between the intervention groups.

Introduction

This PhD thesis deals with a randomised clinical trial that investigates neurocognitive functions and perceptions of health-related quality of life in elderly, moderate to high-risk patients scheduled for elective or sub-acute coronary artery bypass grafting (CABG) at The Heart Centre, Copenhagen University Hospital, Rigshospitalet.

Postoperative cognitive dysfunction is a well-known complication of cardiac surgery, clinically manifested as problems with memory, concentration, and learning. The use of the heart-lung machine has been considered the most important component of the operation to avoid, especially in elderly moderate to high-risk patients. However, evidence for these postulates is still lacking.

This thesis is a sub-study of the Best Bypass Surgery (BBS) Trial (ClinicalTrials.gov identifier NCT00120991), that aims to compare conventional coronary artery bypass surgery using the heart-lung machine (CCAB) to off-pump coronary artery bypass grafting (OPCAB), with respect to peroperative and postoperative mortality and morbidity, in patients with a moderate to high predicted preoperative risk.

Background

Prevalence and incidence of coronary artery disease in the elderly

Coronary artery disease (CAD) is the leading cause of death worldwide. Although the disease has decreased in North America and many western European countries, it is still the cause of more than 7 million deaths each year worldwide (1).

In Denmark, it is assumed that approximately 150,000 to 200,000 out of 5.4 million inhabitants have CAD, of whom about 43,000 are treated in hospital or die each year. Although there is a marked decrease in the incidence rates of CAD among persons above the age of 75 years, approximately 14,000 elderly men and women are still hospitalised or die of the disease every year in Denmark (2). The decline in mortality and morbidity is not solely attributable to an actual decrease in the incidence of CAD, but also to improved treatment procedures including medical therapy, percutaneous coronary interventions, and coronary artery bypass grafting (CABG).

Surgical revascularization for CAD is among the most commonly performed operations in the world with more than 800,000 procedures annually worldwide. This accounts for more resources used in cardiovascular surgery than any other single procedure (3, 4). In 2003, CABG was performed on 600 per 1,000,000 inhabitants in Denmark, or in total 3385 procedures annually, of which 649 were on patients older than 75 years of age (2). These patients are at a higher risk of

mortality and morbidity than younger patients, because they generally have more co-morbidities and a decreased reserve capacity of most organ systems, making them more vulnerable to postoperative adverse effects on cardiac, pulmonary, renal and neurocognitive function.

CABG in elderly patients

Mortality

The evolution in surgical techniques and medical care has led to a less restrictive patient selection for CABG, which now is also offered to older and more ill patients. In the context of coronary surgery the term "elderly" is usually defined as patients at 70 years or older. These patients generally have more complex co-morbidities including diabetes, hypertension, cerebrovascular disease, peripheral vascular disease and renal dysfunction. These conditions might lead to increased fatal and non-fatal complications after CABG (4). A Canadian study investigated the operative mortality rate during a 15-year period showing an incidence of 2% among younger patients under the age of 70 years. In contrast, the overall operative mortality rate was 5% in the elderly patients, but the risk-adjusted operative mortality rate had decreased significantly for this group of patients over time, and for low and medium-risk patients it was found to be 3% (5).

CABG with the use of heart-lung machine

The surgical treatment for CAD has continuously progressed and developed ever since the earliest conception of the idea in 1880 (6). The initial direct implantation of vessels into the myocardium was performed in 1938, and after a series of inventive experimental attempts an effective heart-lung machine was available in the mid 1950s (6). Since the late 1960s it has been used routinely in operations for CAD (6). The treatment tends to relieve or minimise symptoms, to improve exercise tolerance and to increase survival in selected patient groups (4).

Mortality from elective surgery is approximately 2% - 4% depending on factors such as age, sex, left ventricular function, and the presence of other co-morbidities including diabetes, obesity, and hypertension. Patients with the most severe CAD gain most benefit from surgery and the gain is greatest in those with left main stem disease or triple vessel disease (7).

Compared to medical treatment, CCAB improves symptoms of angina and exercise capacity in addition to reducing the need for antianginal therapy e.g. nitrates, beta-blockers, and calcium channel blockers. More than 70% of the patients are free of angina at one year and 50% at five years postoperatively (8). Moreover, patients experience a better quality of life and less limitation in physical activity (9).

The technique includes aortic cross clamping and cold blood cardioplegic arrest which makes it possible to operate in a blood-free surgical field with an

immobilised heart. This improves the technical procedure when establishing the distal anastomoses.

Although the use of extracorporeal circulation has been simplified there are still several potentially harmful perturbations to normal physiologic systems including the effects on cardiac, pulmonary, renal and neurocognitive function (3). In fact, the heart-lung machine has been considered to be the most important component of the operation to avoid (10).

CABG without the use of heart-lung machine

Off-pump CABG was initially introduced in the early 1960s mainly due to the lack of extracorporeal circulation technology, and later in the early 1970s due to economic considerations (10). About 25% of all CABG operations in Denmark are now performed without a heart-lung machine (11). This is a procedure where the distal graft anastomoses are performed on a beating heart without a heart-lung machine, aortic cross clamping, and cardioplegic arrest.

With the introduction of a mechanical tissue stabilization device in the mid 1990s, it was possible to immobilise the target coronary arteries and thereby accurate surgery becomes feasible and the surgical challenges much easier (12).

The technique is considered to be less harmful to the patient, especially in terms of neurological complications, as the aorta is not cannulated and cross clamped. One study reported no strokes in any of 222 patients undergoing OPCAB with no aortic manipulation compared to a 4% stroke rate in an age-matched group undergoing CCAB (13). Patients with severe atherosclerotic aortic disease undergoing OPCAB are reported to have a significantly lower prevalence of stroke compared to matched patients undergoing CCAB (14, 15).

Neurological complications of CABG

Risk factors

Age is considered to be the strongest predictive factor of neurological and neuropsychological injury in cardiac surgery (16). Other variables as independent risk factors for stroke include chronic renal insufficiency, recent myocardial infarction, previous cerebrovascular accident, carotid artery disease, hypertension, diabetes, moderate to severe left ventricular dysfunction, low cardiac output syndrome, aortic calcification, and new onset atrial fibrillation, which adversely affect hospital mortality, prolonging the hospital stay (17, 18), and negatively impacting late death (19). Thus, it has been proposed that elderly patients would benefit most from OPCAB surgery in terms of reducing major neurological injury (20-22), particularly in the presence of severe aortic atherosclerosis and occult cerebrovascular disease, because aortic manipulation is reduced (23).

The risk of cognitive dysfunction following cardiac surgery has been well known for many years. The damage is supposed to be caused by microembolisation from

the heart-lung machine or by manipulating the aortic root, and on the basis of the general inflammatory response (16). Other factors such as prolonged hypoperfusion during CCAB or anesthesia (24), educational or occupational levels (25), and genetic factors (26, 27) have been pointed out as additional explanations.

Stroke

Perioperative neurological injuries are among the most devastating complications of CABG (20, 28). The two main clinical manifestations are stroke and cognitive dysfunction (29).

The incidence of postoperative stroke is reported to be about 2% - 5% (16, 18, 20, 30), and the adjusted 10-year survival is described as 27% for patients with stroke and 62% for patients without postoperative stroke (19).

Cognitive dysfunction

Postoperative cognitive dysfunction is a condition characterized by impairment of memory or concentration, detected by neuropsychological testing and clinically presenting with deficits in cognition and memory, representing a significant change from a previous level of functioning (31). The dysfunction includes impairment in concentration, memory, learning, psychomotor speed and visual construction (32-34). Patients report that they are "just not the same", involving problems with following directions, mental arithmetic and planning complex actions. Family members may also notice that a patient is more short-tempered, is less able to withstand frustration, and has wider mood changes (35).

Short-term cognitive dysfunction

It is shown in studies in which the patients were followed for a period of six months after CABG, that cognitive dysfunction usually decreases during the first weeks (36) or months (32, 37). The frequency of this short-term cognitive dysfunction varies between different studies from 22.5% (38) up to 79% (39) depending on the test methods applied (40-42), the composition of the target population (43) and study design (44).

Long-term cognitive dysfunction

Where the patients were followed for a longer period, studies indicate occurrence of persistent cognitive dysfunction after CCAB (43, 45-47). A longitudinal study found a 53% decrease in cognitive functions at discharge from hospital, 36% after six weeks, 24% after six months and 42% after five years (46). On the one hand this points towards a pattern of early improvement followed by a later aggravation predicted by the presence of early postoperative cognitive dysfunction. On the other hand, long-term cognitive function is found to be similar in the majority of

patients when comparing cognitive function among 125 patients five years after randomisation to either coronary surgery or angioplasty (41). However, none of the prospective studies mentioned reporting late cognitive decline included a control group.

In a prospective observational study neuropsychological performance of 140 patients undergoing CCAB did not differ from that of a comparable non-surgical control group of 92 patients with CAD at one year or three years after baseline examination (48). It is possible therefore that late cognitive decline is not only specific to the use of the heart-lung machine, but might also be caused by normal aging, development of Alzheimer's disease or other causes during the follow-up period (24).

Neurological complications of off-pump versus on-pump CABG

Meta-analyses of the few randomised clinical trials currently available comparing off-pump and on-pump CABG (Table 1) on the topic of short (2 weeks, 1 month and 3 months) (49-51), and long-term (1-2 years) follow-up have not been able to demonstrate a statistically significant difference in the composite outcome of mortality, stroke, myocardial infarction, and renal failure (52). In an overview of eight retrospective non-randomised observational studies it was not possible to reach any definitive conclusions regarding significant difference in incidence of stroke or transient ischaemic attacks between off-pump and on-pump groups (53). Evidence of cognitive dysfunction from randomised clinical trials comparing OPCAB with CCAB in elderly moderate to high-risk patients is still lacking.

A recent meta-analysis indicated that cognitive dysfunction was reduced by 44% at two to six months, but the effect was not sustained beyond 12 months (52). However, there are some limitations that must be taken into consideration in the interpretation of the analysis.

Firstly, these studies up to now have mainly included low-risk patients less than 70 years of age with one or two-vessel disease.

Secondly, the patients were not comparable regarding the number of grafts, as the patients allocated to off-pump surgery had significantly fewer distal vessels anastomosed.

Thirdly, the pooled data concerning cognitive function were based on 393 patients, and two thirds came from one study (54). In that study different anaesthetic techniques were used depending on the treatment allocation. Patients in the CCAB group received total intravenous anaesthesia including high-dose opioids, whereas 54% of the patients in the OPCAB group received thoracic epidural anaesthesia combined with low-dose opioids.

The influence of anaesthesia on postoperative cognitive dysfunction is still a controversial topic (55). The use of opioids has been associated with the development of postoperative cognitive dysfunction, whereas thoracic epidural anaesthesia has been found to reduce the stress response which might contribute

to less endogenous release of catecholamines and consequently prevent the development of postoperative cognitive dysfunction (56, 57). The detected 44% reduction in cognitive dysfunction in favour of the OPCAB technique might therefore be eliminated or precluded in future large-scale randomised trials taking these factors into account. However, one study only investigating patients with triple-vessel disease reported a marked reduction in cognitive decline in OPCAB patients at one week and 10 weeks postoperatively, compared to CCAB patients (58).

Table 1. An overview of three meta-analyses and one systematic review comparing off-pump to on-pump CABG in terms of neurological injuries

Author	Patients	Study type	Follow-up	Incidence of cognitive dysfunction	Composite outcome stroke, AMI and death
Cheng et al. 2005 (52)	N = 3369 allocated to OPCAB or CCAB	Meta-analysis 37 RCT	30 days, 6 months and >1 year	ND	NS
	N = 335 allocated to OPCAB or CCAB	Meta-analysis 3 RCT	30 days	40% OPCAB 50.6% CCAB NS (P = 0.3)	ND
	N = 393 allocated to OPCAB or CCAB	Meta-analysis 3 RCT	2-6 months	20.3% OPCAB 31.8% CCAB Significant (P = 0.01)	ND
	N = 334 allocated to OPCAB or CCAB	Meta-analysis 2 RCT	1-2 years	27.2% OPCAB 30.9% CCAB NS (P = 0.7)	ND
van der Heijden et al. 2004 (50)	783 OPCAB 801 CCAB	Meta-analysis 18 RCT	2 weeks, 1 month, 3 month and 1 year	ND	NS
Parolari et al. 2003 (49)	532 OPCAB 558 CCAB	Meta-analysis 9 RCT	30 days	ND	NS
van Dijk et al. 2000 (38)	N = 505 CABG Mean age 55-64 years	Review 4 cohort studies 2 intervention studies	2 months	22,5%	ND

RCT = randomised controlled trial, AMI = acute myocardial infarction, ND = not determined, NS = non significant

Off-pump versus on-pump CABG and health-related quality of life

At present, only a few studies have evaluated the effect of OPCAB versus CCAB on health-related quality of life. Due to the dependence on subjective perception, it has been difficult to assess an overall evaluation of quality of life among patients undergoing cardiac surgery. Factors such as increased age, female gender, persistent pain (more than three months) and poor quality of sleep have been associated with reduced quality of life outcome (59).

One study evaluating quality of life among 73 octogenarians undergoing CCAB reported that 89% were free of angina and 83% were totally independent in their physical activities of daily living after surgery (60).

In a multi-centre trial, 281 younger low-risk patients were randomly assigned to off-pump or on-pump CABG. Self-reported overall quality of life, as well as physical functioning, general health, vitality, role limitations due to emotional problems and general mental health showed statistically significant improvements in both groups at 1, 3, 6 and 12 months after surgery compared to one week before surgery. No differences were observed between the off-pump and on-pump groups (54).

Two other randomised trials reporting quality of life at 30 days and one year with a median follow-up of three years showed no differences between the surgical groups (61, 62).

None of the studies available so far examined differences in the incidence of depression before and after off-pump compared to on-pump surgery.

Depression is shown to affect mortality from myocardial infarction (63, 64), and the appearance of increased depressive symptoms at six months after CABG has been related to the occurrence of cardiac morbidity/mortality (65, 66). Preoperative emotional changes, including depression, have been reported in 27% to 47% of patients, and in 19% to 61% of patients after heart surgery (67). Depression does not explain or influence changes in neuropsychological test performance before and after CABG, but patients suffering from depression before the operation are more often continuously depressed after surgery (68-70). Moreover, awareness of cognitive dysfunction is a source of anxiety or depression in CABG patients (71, 72).

Summary

OPCAB procedure might result in a significant reduction of the risk of major and minor damage to the central nervous system in terms of stroke and cognitive dysfunction in elderly, moderate to high-risk patients. This might lead to experiences of better health-related quality of life and reduced depression. However, evidence for these postulates is preliminary and additional data are needed to explore differences in postoperative cognitive dysfunction and quality of life among elderly, moderate to high-risk patients treated with off-pump procedure compared to on-pump CABG surgery.

Aim

Paper I: To describe the design, methodology and rationale of a randomised clinical trial that aims to compare off-pump to on-pump CABG surgery with respect to postoperative cognitive dysfunction and health-related quality of life.

Paper II: To test the hypothesis that the incidence of postoperative cognitive dysfunction is equal after off-pump CABG versus on-pump CABG surgery.

Paper III To test the hypothesis that health-related quality of life is equal after off-pump CABG versus on-pump CABG surgery.

Materials and methods

Paper I

Based on a literature review and recommendations for improving the quality of reports of parallel group randomised trials (73), the paper describes the rationale and design of the present BBS sub-study. The aim was to evaluate the effect of off-pump versus on-pump CABG on cognitive functions, with possible subsequent impact on cardiac risk factors and health-related quality of life at 3 and 12 months postoperatively compared to preoperatively.

The trial includes elderly moderate to high-risk patients because this population is supposed to benefit most from OPCAB surgery in terms of reducing neurological injury. For details regarding inclusion and exclusion criteria please see paper I (74).

The choice of the neuropsychological tests was based on considerations in accordance with international guidelines of the assessment of neurobehavioral outcomes after cardiac surgery (75). In addition, specific culture and language problems were taken into consideration.

Cardiac risk factors were determined by changes in blood pressure, plasma lipids, body mass index, smoking habits and medical treatment. These data are being analysed and will not be reported in the present thesis.

Health-related quality of life was assessed using validated and reliable questionnaires, commonly used within cardiac surgery and psychiatry. Data concerning Expressed Emotion and Family Climate are being analysed and will not be reported in the present thesis.

The trial was powered on the basis of a reduction in cognitive impairment from 50% in the CCAB group to 20% in the OPCAB group. Consecutive patients fulfilling the inclusion criteria and none of the exclusion criteria were to be included from the BBS main trial. Further considerations regarding internal validity of the study related to blinding, statistical methods and follow-up were described and additionally discussed.

Paper II

The paper comprised 120 patients with known ischaemic three-vessel heart disease scheduled for elective or sub-acute CABG, who were ≥ 55 years of age, and who had a EuroSCORE (76) above or equal to 5. The patients were participating in the randomised, clinical BBS main trial that compares off-pump to on-pump treatment with respect to per- and postoperative mortality and morbidity, in patients with a moderate to high-predicted preoperative risk.

For details in surgical technique in the off-pump and on-pump groups see paper II (77).

We tested the hypothesis that the incidence of postoperative cognitive dysfunction was equal after off-pump versus on-pump surgery. The patients were neuropsychologically tested as described in paper II (77) and further detailed in the appendix (page 45). The incidence of in-hospital stroke was determined as described in appendix.

Cognitive dysfunction was defined as the occurrence of at least two deficits out of seven possible (Table 2). The seven possible deficits were: two possible deficits in A, B, C, and one possible deficit in D. For the two error scores, a deficit was defined as ≥ 4 additional errors postoperatively

compared to preoperatively out of 16 possible in B and ≥ 5 additional errors postoperatively compared to preoperatively out of 40 possible in C. For the remaining 5 variables, a deficit is defined as 40% postoperative deterioration in the neuropsychological test compared to preoperative tests results.

Table 2. The definition of cognitive dysfunction

Tests	**Memory**	**Cognitive speed, attention and flexibility**
A. Visual Verbal Learning	2 deficits	
B. Concept Shifting Task		≥4 errors or/and 1 deficit in time
C. Stroop Color Word Interference		≥5 errors or/and 1 deficit in time
D. Letter-Digit Coding		1 deficit

In addition, secondary analysis was performed based on two other common definitions of cognitive decline:

1. 20% decline in cognitive scores as compared with baseline
2. The ISPOCD definition (International Study of Post-Operative Cognitive Dysfunction), where changes in performance of seven parameters from the result of the four tests were calculated. For each individual test outcome, the average learning effect was subtracted from these changes and a Z score was obtained after division by the SD from an age-matched healthy control group. When two out of seven Z scores in individual tests or the combined Z score were 1.96 or more, patients were defined as having cognitive dysfunction.

Paper III

The paper comprised the same 120 patients included in paper II. After randomisation and before heart surgery, the patients were asked to fill in the Medical Outcomes Study Short Form 36 (SF-36) and Major Depression Inventory (MDI) diagnostic scale for self-reporting of health-related quality of life and symptoms of depression. If a patient was unable to complete the questionnaire, the principal investigator did interview administration. Three months after surgery the same questionnaires were mailed to the patients. For details regarding the assessment of health-related quality of life kindly see paper III.

We tested the hypothesis that health-related quality of life is equal after off-pump versus on-pump CABG surgery. Primary outcome was the change in SF-36 score.

All data were analysed according to randomisation on an intention to treat basis. Categorical variables were compared using Pearson's Chi-Square test or Fisher's exact test as appropriate. For continuous data, changes within the groups were analysed using paired t-test. Groups were

compared using unpaired t-test (for normally distributed data) or Mann Whitney's rank sum test (for data not normally distributed). A P value less than 0.05 was considered statistically significant.

Results

Paper I

Patient characteristics

From July 2002 to December 2004 120 patients were enrolled in the study. The average monthly recruitment was 7 patients. A total of 206 consecutive candidate patients were identified from the BBS study, and of these, 61 and 59 patients (58%) were randomly allocated to OPCAB or CCAB respectively. The reasons for exclusion of 56 patients were: logistic reasons (35 patients), not meeting inclusion criteria for cognitive testing (13 patients), and refusal to participate (8 patients). The three-month follow-up was completed in March 2005, and the twelve-month follow-up was completed in December 2005. In the present thesis the results from three months follow-up will be reported. Demographic data of the OPCAB and CCAB patients are presented in Table 3 and co-morbidity is described in Table 4.

Table 3. Demographic data at baseline

Variable	**OPCAB** (n = 61)	**CCAB** (n = 59)
Age, mean (SD), y	76 (4.8)	75 (4.2)
Sex, female, n (%)	26 (43)	22 (37)
Basic schooling		
7 years or less, n (%)	31 (51)	34 (58)
8 to 9 years, n (%)	16 (26)	18 (31)
10 years, n (%)	9 (15)	5 (9)
High school, n (%)	5 (8)	2 (3)
Education		
None, n (%)	17 (28)	30 (51)
Vocational, n (%)	35 (57)	28 (48)
University, n (%)	9 (15)	1 (2)
Marital status		
Living with a partner (%)	36 (59)	36 (61)
Separated/divorced (%)	7 (11.5)	5 (9)
Widow/widower (%)	18 (29.5)	18 (31)

Table 4. Description of co-morbidity at baseline

Variable	OPCAB (n = 61)	CCAB (n = 59)
Predisposition for IHD <55 years of age, n (%)	18 (31)	12 (20)
Diabetes, n (%)	11 (18)	11 (19)
Hypertension, n (%)	40 (66)	33 (56)
Previous myocardial infarction, n (%)	42 (69)	46 (78)
Previous neurological events*, n (%)	12 (20)	15 (25)
History of atrial fibrillation, n (%)	3 (5)	6 (10)
Ejection fraction, mean (SD)	49.8 (8.9)	48.6 (8.3)
EuroSCORE, mean (SD)	6.8 (1.6)	6.6 (1.6)

*Includes stroke and transient ischaemic attack

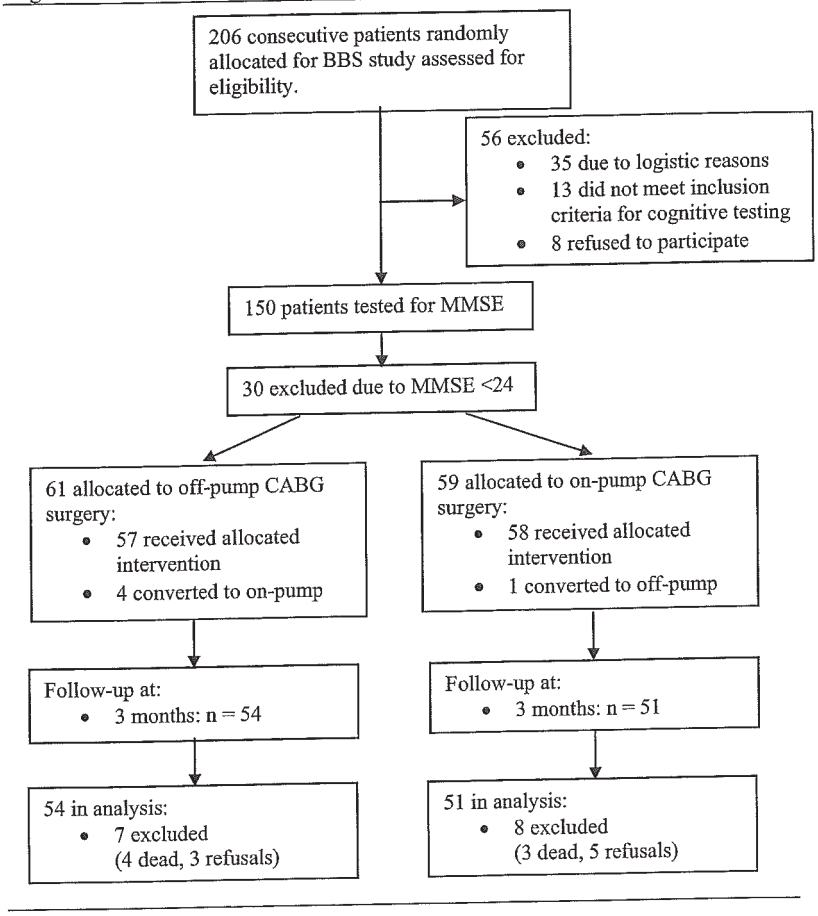
Paper II

Participant flow

At three months cognitive outcomes could be determined in 54 patients in the OPCAB group and 51 patients in the CCAB group. Because patients were included consecutively, the logistic reasons for the exclusion of 35 patients can be explained e.g. by the staff collecting data having a vacation or a day off, or patients not being available for baseline information due to inclusion late in the evening or just before operation, or patients living so far away from the hospital that follow-up was impracticable. The reasons for excluding 13 patients not meeting criteria for cognitive testing were: severe visual (3 patients) or auditory (1 patient) disorders, neuropsychological testing within the last year (1 patient), more than five drinks/units of alcohol per day (1 patient) current severe psychiatric disease (1 patient), poor comprehension of Danish (4 patients) and unwillingness to return for follow-up (3 patients). Furthermore, 30 of the eligible patients were excluded due to Mini Mental State Examination (MMSE) scores below 24.

One of the patients was converted during the OPCAB procedure due to haemodynamic instability. Three patients were a priori performed as on-pump cases, because the surgeon considered that the operation could not be performed successfully as OPCAB procedure in his hands. One of the 59 patients allocated to CCAB was converted to OPCAB due to severe calcification. At three months seven patients were dead and eight refused to participate in further cognitive tests (Figure 1).

Figure 1.



Cognitive outcomes

All data were analysed according to randomisation on an intention to treat basis. Data are presented as numbers and percents including confidence interval (CI). Postoperatively (in-hospital incidence) 1 non-fatal stroke was seen in the OPCAB group and 1 non-fatal stroke occurred in the CCAB group.

Applying our definition of at least two deficits out of seven possible compared to baseline, 7.4% (CI: 2.1% - 17.9%) of the patients in the OPCAB group and 9.8% (CI: 3.3% - 21.4%) of the patients in the CCAB group had cognitive dysfunction (P = 0.7).

Using the definition "20% decline in cognitive scores compared to baseline", the incidence of cognitive decline at three months was 20.4% (CI: 10.6% - 33.5%) of the patients in the OPCAB group and 23.5% (CI: 12.8% - 37.5%) of the patients in the CCAB group (P = 0.8). When cognitive dysfunction was defined according to a Z score ≥ 1.96, 26.0% (CI: 15.0% - 39.7%) of the patients in the OPCAB group and 21.6% (CI: 11.3% - 35.3%) of the patients in the CCAB group had cognitive dysfunction (P = 0.7). There was no significant difference in the incidence of neurocognitive decline between the two groups regardless of the definition applied. The incidence of cognitive dysfunction is presented in Table 5.

Table 5. Incidence of cognitive dysfunction

Definition	**OPCAB** (n = 54)	**CCAB** (n = 51)	**P =**
2 deficits out of 7 possible	7.4%	9.8%	0.74
(CI)	(2.1%-17.9%)	(3.3%-21.4%)	
20% decline in cognitive scores	20.4%	23.5%	0.81
(CI)	(10.6%-33.5%)	(12.8%-37.5%)	
Z score ≥ 1.96	26.0%	21.6%	0.65
(CI)	(15.0%-39.7%)	(11.3%-35.3%)	

CI = 95% confidence interval

Paper III

Health-related quality of life

The primary end point was the change in SF-36 score. Differences are presented with 95% CI. The SF-36 and MDI scores are presented with mean and standard deviation (SD) or number and percentage (%). Of the 57 patients available for follow-up in the OPCAB group three refused to fill in the questionnaires, and one patient out of the 56 available in the CCAB group refused to fill in the questionnaires at three months. Of the remaining 113 patients, a response was obtained from 109 (96.5%).

In both groups there was an improvement in health-related quality of life at three months. Except for role limitations due to emotional problems favouring the on-pump group (P = 0.04), no significant difference was found in the change of SF-36 scores between the two groups.

The number of patients with depressive symptoms remained unchanged in both groups from baseline to three months. No significant difference between the groups was found in the change of depressive symptoms.

Discussion

In this thesis we described the rationale, design and methodology of the randomised BBS Trial sub-study, with special reference to cognitive function and health-related quality of life.

We tested the hypothesis that the incidence of postoperative cognitive dysfunction is equal after off-pump versus on-pump CABG. Our results indicate that patients who underwent CABG surgery without a heart-lung machine showed no improved cognitive outcomes at three months postoperatively compared to patients who underwent an on-pump CABG procedure.

Additionally, we tested the hypothesis that health-related quality of life is equal after off-pump versus on-pump CABG. No clinically relevant difference between off-pump and on-pump surgery was found in SF-36 and MDI scores.

The above confirmation of our hypothesis leads to questions concerning limitations of the study with special references to the extent to which systematic error is minimised (internal validity) and the extent to which the results of the study provide a correct basis for generalisations to other circumstances (external validity).

Methodology

The concept of internal validity implies that the observed differences between groups of patients allocated to different interventions may, except for random error, be credited to the treatment under investigation. Bias related to internal validity falls into four categories concerning: selection bias, attrition bias, performance bias and detection bias (78).

Selection bias and attrition bias

The success of the randomisation depends on the allocation sequence and the concealment from investigators enrolling patients (79). Studies with inadequate generation of the allocation sequences are shown to overestimate the effect of the intervention by 50%, compared to studies with adequate generation of the allocation sequence. Studies with inadequate allocation concealment have been associated with a 30% overestimation of the intervention (80).

In this study the consecutive patients were centrally randomised to one of two groups by an external press-button telephone voice response system. In that way adequate concealment was ensured, as the investigator who admitted patients to the trial could not be aware of the upcoming assignments. At baseline there were no significant differences between the groups regarding age, sex, co-morbidity, smoking habits, and basic school education. However, in the OPCAB group the level of education tends to be higher, which is considered to be incidental (Table 3 and 4).

There might be a potential risk of selection bias since 56 out of 206 eligible patients were excluded after randomisation for logistic reasons, or due to specific criteria for cognitive testing or unwillingness to participate. Besides these, 30 out of 150 eligible patients scored less than 24 in MMSE (Figure 1). A natural explanation could be related to patient characteristics including age with associated arteriosclerosis that might equally well be manifested in other arteries than the coronary arteries. Thus, the exclusions might disqualify patients with a higher incidence of cognitive dysfunction than the study population. The presence of cognitive impairment in older

adults who refuse to participate or later on drop out of the study might be responsible for some refusals (81). Therefore, the incidence of cognitive dysfunction at 7.4% in the off-pump group and 9.8% in the on-pump group, as reported in Paper II, can be considered as a minimum.

As described in Paper II, four out of 61 patients allocated to off-pump were converted to on-pump. One of the patients was converted during off-pump procedure due to haemodynamic instability. Three procedures were performed as on-pump cases, because the surgeon considered that the operation could not be performed successfully as an off-pump procedure in his hands. One out of 59 patients allocated to on-pump was converted to off-pump due to severe calcification. The conversion of patients after their allocation to the treatment groups could introduce attrition bias with respects to differences related to prognosis (78), and excluding those patients from the analysis may lead to erroneous conclusion (73). We kept all patients in their original groups, regardless of their adherence to the study protocol. In that way the analyses were performed according to the intention to treat principle, thus avoiding selection bias.

The in-hospital death rate was 3% (1 OPCAB and 3 CCAB) and at the three-month follow-up 5.8% of the patients were dead (4 OPCAB and 3 CCAB). Besides these, three patients in the off-pump group and five patients in the on-pump group refused to participate in further cognitive testing. In addition some patients refused or renounced on individual tests in the test battery. In general, the dropout frequency is about 10% - 30% or even much higher, and it is recommended that the tests with missing scores should not be used for evaluation of cognitive function (82). By accounting for patient selection, and the fact that a large number of the patients were available for cognitive testing at the three-month follow-up as only 8 out of 113 (7%) refused to participate further, the possibility of attrition bias is not a major concern regarding the internal validity of this study. Moreover, the response rate on questionnaires measuring health-related quality of life was 96.5%, as only four out of 113 patients refused to participate further (Paper III).

Performance bias and detection bias

Blinding is difficult to achieve, especially in surgical trials (73), so therefore an "open" design is required and neither study personnel nor participants were blinded to the surgery performed. In order to minimise performance bias the assessment of outcomes and the data analysis were performed with blinding. There are weaknesses linked to the performance of cognitive testing, and many factors have to be taken into consideration (82).

The tests were performed in a standardised way by the principal investigator, and after proper instructions from a consultant. The sessions were held in a dedicated test room, parallel versions were applied, and only the patient and investigator were present. In spite of efforts to keep the environment and times consistent, this is extremely difficult in a highly specialised hospital setting as the logistic organization of patient flow can easily be interrupted by unforeseen events. As a consequence, some variation in procedure was inevitable. The tests were performed on the day of operation or the day before, and again about three months (88 days – 124 days) postoperatively. All follow-up tests were carried out at the hospital and the time and day of the test was arranged with regard to the patients' options and wishes.

The self-reported outcome was assessed the day before bypass surgery or on the day of operation and repeated three months after surgery. On both occasions, the patients completed the two SF-36 and MDI self-reported questionnaires. If a patient was unable to complete the questionnaire, the principal investigator did interview administration. Three months after the operation the same

questionnaires were mailed to the patients. The variation in scores of health-related quality of life may not only reflect variation of the individual person, but suggests consideration of the total surgical treatment and care from admission to completed outpatient rehabilitation.

Sample size and statistical power

A well designed prospective and randomised study is considered as a "gold standard" to give a true answer to the proposed question and the categories as mentioned are relevant to minimise systematic sources of bias (83). Other sources of bias in randomised trials can only be explained by chance (random errors), but the risk can be minimised by a sufficient sample size. This study was powered to demonstrate differences in cognitive functions between the two surgical groups. We assumed a composite outcome incidence to be about 50% in the CCAB group during a three to twelve-month period, with a possible reduction to 20% in the OPCAB group.

To demonstrate a reduction in cognitive impairment from 50% to 20% (with a significance level of 0.05 and an 80% power) would require 50 patients in each group. With an expected 20% drop out the total number of enrolled patients was 120. The risk of type 2 errors is important and a more modest reduction cannot be excluded, but a detection of a small difference would need to be investigated in a larger randomised study. The detection of a difference between 7% and 10% would require approximately 3000 patients if a type 2 error of 20% is accepted. Furthermore, the detection of a difference between scores of role limitations due to emotional problems (RE) at 54.6 and 59.8 would require approximately 2000 patients if a type 2 error of 20% is accepted (see paper III).

External validity

The value of clinical research to society depends on how the study population represents the population that is supposed to benefit from the research (84). Our study deals with elderly, high-risk patients scheduled for elective CABG and the results can only be valid for this population. According to our knowledge this is the first single-centre randomised study focusing on that specific topic. Therefore, there is a need for larger multi-centre trials in order to verify whether or not there is an improvement in cognitive function and health-related quality of life among off-pump patients compared to patients undergoing on-pump CABG surgery.

Outcome measures

The implementation of OPCAB technique in clinical practice during the last decade has been dependent of the individual surgeon's subjective preferences, where the cardiovascular community has been divided according to beliefs and distrust. At present about 30% of coronary revascularizations are performed as OPCAB surgery worldwide. Some centres perform more than 50% of the CABG surgery as off-pump technique, and some surgeons even achieve a level of 90%, where others do not use OPCAB at all (85). In Denmark, approximately 25% of CABG procedures are performed as OPCAB (11).

Despite the large number of publications evaluating the effect of OPCAB versus CCAB, only a few randomised trials have been completed up to now, mainly including low-risk patients with a EuroSCORE of 0 – 4, showing neither statistically significant differences in favour nor risk in the off-pump technique regarding the composite endpoint death, stroke and myocardial infarction.

Although an increasing number of patients with advanced age and other risk factors for neurocognitive injuries are being referred for CABG, this study is the first randomised trial investigating the effect of avoiding the heart-lung machine on cognitive function and quality of life in that specific population.

Cognitive dysfunction

As described in paper II, we found no difference between the two groups regarding incidence of cognitive dysfunction and stroke. It was anticipated, however, that at three months, the outcome would have been significantly improved in favour of the off-pump technique.

It is remarkable that in our study, the 9.8% - 23.5% variation in incidence of cognitive decline in the CCAB group (see paper II), depending on the definition used, is consistent with the previously reported incidence, from uncontrolled studies, of 4% - 47% in younger patients (mean age 55 years - 70 years) two months after the operation (38), as advanced age is the least controversial demographic risk factor for cognitive decline (34, 46).

In the ISPOCD study, the incidence of cognitive dysfunction was 13.8% at three months postoperatively, in a small sample of elderly patients (median 70 years, range 61-80) undergoing cardiac surgery (86, 87). Moreover, the lack of benefit from avoiding CPB was not expected, because the use of CPB is generally regarded as the main cause of cognitive decline and the effects are anticipated to be even more notable in older patients with more co-morbidity (51, 88).

Looking at the literature, the crucial step of finding a significant neurocognitive deficit is the definition itself. The definition varies and if a low threshold of deficit is used then more patients will have a deficit. This level is arbitrary from research group to research group and varies between a deterioration of 1 SD in one or more tests, a deterioration of 20% or 25% in at least one or two tests, to the use of standardized Z-score or composite Z-score (82, 89).

The definition of cognitive dysfunction in this study is more restrictive than the "20% criterion" and the definition using Z-score. In the analyses of the test results from our study, the evaluation of cognitive function is based on differences between pre- and postoperative performance. Therefore, the association between early and late cognitive outcome could be explained by regression towards the mean (90), because generally the use of scores favours patients with poor preoperative performance because of the "protective" effect of low baseline performance (82). On the other hand, the ISPOCD test battery is in accordance with the Statements of Consensus on Assessment of Neurobehavioral Outcomes after Cardiac Surgery (75) and tested for sensitivity in elderly patients undergoing CCAB (89). The error scores are considered as well, and learning effects were taken into account by including a control group of healthy volunteers.

The natural variability in performance during repeated neuropsychological testing can only be demonstrated by using a control group (82). Recently, a larger study (91) comprising 204 CABG patients (mean age 68.8 years) and 90 age and gender-matched healthy controls assessed the sensitivity and specificity of three commonly used statistical definitions of postoperative cognitive dysfunction. They demonstrated that the definition using a Z-score was superior in sensitivity and specificity compared to the definitions of 20% decline in 20% of the tasks and 1SD deviation decline on two or more tasks. These findings indicate that using the Z-score definition for secondary analysis contributes to a further verification of the results from our study.

We have noticed that the tendency for cognitive dysfunction is less, but not statistically significant, in the CCAB patients compared to OPCAB patients when using a Z score definition. This opposite direction from the two other definitions is notable, but might be explained by the definition itself, thus referring to relative and absolute changes in cognitive function.

The Octopus study was conducted on 281 younger patients at low risk using a definition of a 20% decrease in test performance in 20% of the tests. The primary analysis revealed an incidence of 25% of patients' suffering from cognitive decline at three months postoperatively, increasing to 32% after 12 months (54). A newly published paper (92), reports the re-analysis of the same data using an alternative definition of cognitive dysfunction including a control group of 112 healthy middle-aged subjects.

Cognitive decline was found in up to 28% of the control group and 31% in the CABG group, when the widely employed 20% definition was used. The use of 1SD definition revealed an incidence of cognitive dysfunction at 11% in the CABG group versus 14% in controls.

By including the control group the reliable change (RC) definition identified an incidence of 7.7% in the CABG group and 4.6% of controls. This 7.7% three-month incidence is very similar to the 9.9% found in the ISPOCD study with non-cardiac surgery patients (93). Thus, the authors conclude that previously reported incidences of cognitive dysfunction might be highly overestimated.

In addition, a Norwegian study (94) compared OPCAB and CCAB surgery to the frequency of new postoperative cerebral lesions and the prevalence of postoperative cognitive dysfunction in 120 middle aged patients (mean 65 years).

The authors used ten neuropsychological tests with six components, and defined the impairment to be 20% decrease in at least two tests compared to preoperative assessment. Cerebral magnetic resonance imaging (MRI) examination revealed no significant difference in the number of patients with new MRI lesions ($P = 0.17$) or in the number of patients with cognitive dysfunction (20.4% in the OPCAB versus 23.1% in the CCAB group) assessed by neuropsychological tests.

By comparison, in our study we found an incidence of 26.0% in the OPCAB group to 21.6% in the CCAB group when using the ISPOCD definition (Table 5). This relatively high incidence of cognitive dysfunction might therefore be explained by the increased age of our study population (mean 75.5 years, range 66-86), compared to the studies reported up to now. Furthermore it might additionally confirm that age is the primary risk factor for late cognitive dysfunction (93) in CABG patients, rather than conditions linked to the heart-lung machine.

Health-related quality of life

The success of cardiac surgery is not solely judged by its effects on mortality but also by its neuropsychological and emotional consequences, and by its influence on health-related quality of life (4, 95).

The concept of health-related quality of life is a relatively broad health outcome, referring to the physical, emotional and social well-being of an individual. Within health sciences there is a general agreement about this definition today, meaning that the concept is relatively well defined (96).

Previously published measurements of health-related quality of life at 1, 3, 6 and 12 months have been reported in four randomised trials mainly including younger patients at lower risk undergoing OPCAB versus CCAB (54, 61, 97-99). Additionally, one study obtained data from 328 of 401 randomised patients using a post-test-only design with a median follow-up at 3 years (24).

Different instruments such as EuroQOL-6, EuroQOL (original version), EuroQOL-5, SF-36 and the 16-item Quality of Life Scale-Norwegian were used, all showing that health-related quality of life improved in off-pump and on-pump groups over time, but there were no significant differences between the surgical groups regardless of the instruments used or the design of the study. The results as described in paper III are in accordance with the results described above.

The responsiveness to SF-36 scores has been correlated to age, and older patients tend to score lower than younger patients when the particular emphasis of the physical health scores centres on physical functioning, role limitations due to physical health problems, physical pain and general health (100). In our study, however, there was a marked improvement in in all eight SF-36 domains from baseline to three months. Baseline scores were clearly below the values in the background population, but after surgery several domains improved to a level equal to or even better than those of a comparable background population. Therefore, we cannot exclude the possibility that the patients wanted to please the health care providers (wish bias).

It is remarkable that only 7% and 8% of the patients respectively scored more than 2.5 at the MDI diagnostic scale (paper III). In contrast the prevalence of depression is estimated to be between 27% and 47% of patients scheduled for heart surgery, and between 19% and 61% of patients after the intervention. A plausible explanation might be that the studies up to now were largely completed in the mid-90s, when criteria for operation were more restrictive, and the course of the disease, from the first signs of symptoms until discharge from hospital, has become much shorter now. Another possible explanation could be the age of the study population, as younger persons might have a higher degree of anxiety when they are confronted with a life-threatening disease and its emotional consequences.

Conclusion

In a randomised trial, we investigated whether patients undergoing off-pump CABG procedure might benefit more from the surgery than patients undergoing on-pump CABG, with respect to postoperative cognitive function and health-related quality of life.

No significant difference was demonstrated in Paper II, in terms of postoperative cognitive dysfunction at the three-month follow-up, in 120 selected high-risk elderly patients, undergoing OPCAB versus CCAB surgery. The incidence of postoperative cognitive dysfunction remained similar between the groups, regardless of the definition used to detect the impairment. It was concluded that patients undergoing CABG surgery without CPB show no improvement in cognitive outcomes three months after the surgery compared to patients who undergo CCAB procedure. This study can be considered as valid justification for conducting a larger-scale randomised clinical multi-centre trial in order to obtain further verification for the generalization of the findings.

In Paper III, we demonstrated improvement in health-related quality of life within both surgical groups to the same level as a comparable healthy background population. Depression scores

remained unchanged within and between the two groups, regardless of whether the surgery was performed with or without a heart-lung machine. No clinically relevant difference between off-pump and on-pump bypass surgery could be demonstrated. Further investigations of health-related quality of life are nescessary in elderly, high-risk patients undergoing off-pump versus on-pump coronary bypass surgery.

Dansk resume

Konventionel bypassoperation på hjertets kranspulsårer med anvendelse af hjertelungemaskine er blandt de hyppigste operationer inden for hjertekirurgien. Der er imidlertid en substantiel risiko for postoperative komplikationer forbundet med proceduren. Udover risiko for øget dødelighed og skadelig påvirkning på hjerte-, lunge- og nyrefunktion er der risiko for større og mindre cerebral påvirkning i form af stroke eller kognitiv dysfunktion.

Koronar bypass operation uden anvendelse af hjertelungemaskine er en teknik som blev "genopdaget" midt i 90'erne, og som for øjeblikket anvendes ved ca. 25% af alle bypassoperationer på Rigshospitalet. Det er en procedure hvor etableringen af de distale graftanastomoser gennemføres på bankende hjerte og uden afklemning af aorta. To forskellige sugeapparater sikrer hæmodynamisk stabilitet og immobilisering af blodkarrene, medens der udføres kirurgi på hjertets bagside. Incitamentet til denne udvikling har været et ønske om at undgå nogle af de komplikationer der er forbundet med konventionel bypass kirurgi.

De hidtidige undersøgelser, hvor man har sammenlignet bypassoperation med eller uden hjertelungemaskine, har hovedsagelig omfattet udvalgte yngre patienter i lav risikogruppe. For nuværende findes ingen beskrivelser af randomiserede studier hvor man har inkluderet patienter i høj risikogruppe, som for eksempel ældre patienter med svære følgesygdomme. Dette til trods for at denne patientgruppe formentlig har størst gavn af at undgå tilkobling til hjertelungemaskinen. Med henblik på en nærmere afklaring af denne problemstilling, undersøgte vi effekten af bypassoperation med eller uden anvendelse af hjertelungemaskine på kognitive funktioner og helbredsrelateret livskvalitet hos ældre patienter i moderat til høj risikogruppe.

Afhandlingen baseres på tre (I-III) publikationer. I første publikation beskrives rationale og design for et randomiseret studie der har til formål at sammenligne bypassoperation med eller uden anvendelse af hjertelungemaskine på kognitive funktioner og helbredsrelateret livskvalitet. I anden publikation undersøges kognitive funktioner hos 120 patienter før og tre måneder efter bypass kirurgi. Patienterne fordeles i to grupper ved lodtrækning. Forekomsten af postoperativ kognitiv dysfunktion hos patienter opereret uden hjertelungemaskine sammenlignes med forekomsten af kognitiv dysfunktion hos patienter opereret med hjertelungemaskine. Data analyseres i forhold til tre forskellige definitioner på kognitiv dysfunktion. I tredje publikation sammenlignes de samme 120 patienters selvvurderede helbredsstatus og symptomer på depression. Sammenligningen foretages på basis af spørgeskemaer udfyldt før og efter hjerte operationen og i forhold til de to operationsteknikker.

I gruppen af patienter der blev bypass opereret uden hjertelungemaskine var forekomsten af kognitiv dysfunktion ikke statistisk signifikant forskellig fra gruppen af patienter som blev opereret med hjertelungemaskine, uanset hvilken definition der blev anvendt. Patienternes selvvurderede helbredsstatus var markant forbedret i begge grupper tre måneder efter operationen sammenlignet med før operationen. Niveauet svarer til det som ses hos en tilsvarende gruppe af raske danskere fra 75 år og opefter. Der var ingen statistisk signifikant forskel i helbredsstatus eller symptomer på depression blandt de patienter som blev opereret uden hjertelungemaskine, sammenlignet med dem som blev opereret med anvendelse af hjertelungemaskine.

Det konkluderes at: Denne afhandling omhandler det første randomiserede studie som har undersøgt hvorvidt bypass operation på bankende hjerte er bedre end bypassoperation med anvendelse af hjertelungemaskine. Dette er vurderet i forhold til kognitive funktioner og helbredsrelateret livskvalitet hos ældre patienter i høj risiko gruppe (publikation I). Der findes ingen forskel i

forekomsten af postoperativ kognitiv dysfunktion mellem de to patientgrupper, uagtet der anvendes tre forskellige definitioner til bedømmelse af dysfunktion (publikation II). Patienternes oplevelse af helbredsrelateret livskvalitet forbedres over tid uafhængig af de anvendte operationsteknikker. Der findes ingen klinisk relevant forskel mellem de to patientgrupper i helbredsrelateret livskvalitet eller symptomer på depression (publikation III).

Den her beskrevne problemstilling bør yderligere undersøges i et større multicenter studie med behørig randomisering og tilpas stratificering. Først når et sådant studie foreligger, vil det være muligt at afgøre hvorvidt bypassoperation med eller uden anvendelse af extracorporeal cirkulation er to ligeværdige operationsteknikker med hensyn til forekomsten af kognitiv dysfunktion og selvvurderet livskvalitet hos ældre patienter i højrisikogruppe.

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Appendix

The method to detect major and minor neurological injuries

Definition of stroke

Perioperative stroke vas defined as acute new neurological deficit that occurred during or after the CABG procedure, and established before discharge, resulting in death or lasting >24 hours and classified by a physician as a stroke. If at all possible, a neurologist should have evaluated the patient and diagnosed a stroke or a brain CT-scan demonstrating a new infarction with or without haemorrhagic transformation should be present. These data was obtained from patients' records.

Neuropsychological test battery

The neuropsychological test battery used, has been developed for the International Study of Post-Operative Cognitive Dysfunction that aimed to investigate the occurrence of long-term postoperative cognitive dysfunction in elderly patients after non-cardiac surgery (93). The choice of the neuropsychological tests is based on considerations according to the Statement of Consensus on Assessment of Neurobehavioral Outcomes after Cardiac Surgery (42, 75). This deals with deliberations concerning reliability and validity of measures, availability of normative data, brevity, sensitivity to relevant cognitive domains, availability of alternative forms, the physical effort required to perform the test and use in prior studies. Furthermore specific cultures and language problems were taken into consideration (31). Normative data are available (93) and the test battery has been translated into Danish and previously validated for sensitivity among patients undergoing CCAB surgery (89). Each single test is well known and has been used for years within neuropsychological and dementia research areas. High test-retest reliability coefficients are obtained and the learning effect is minimized because some tests exist in 3 parallel versions of same grade (82).

After randomisation and before inclusion in the study eligible patients were screened for dementia using:

Mini Mental State Examination (MMSE) (101). The test is divided into two sections and the first part covers orientation, memory and attention. The second part covers the ability to name, follow verbal and written commands, write a sentence spontaneously, and copy a complex polygon. The patient has to obtain a score of at least 24 points out of 30 possible points.

The actual test battery exists of the following four tests:

1. *The Visual Verbal Learning Test* (102) was used for assessment of memory based on a list of 15 well-known words. Each word is presented in about two seconds and the session is repeated tree times. The patient is asked to recall as many words as possible immediately after each session and also delayed recall after 15 to 25 minutes. The number of correct words and the number of errors is registered.

2. *The Concept Shifting Task* (103) consists of tree subtests that measure cognitive speed and flexibility. Each subtest consists of a white sheet of paper with a circular stain consisting of 16 circles by numbers or letters which is required to be crossed out in correct order and as fast as possible without errors. In the first subtest, the numbers from 1-16 has to be crossed

out in numerical order. In the second subtest the letters from A-P are crossed out in alphabetical order. The third subtest requires a continuous shift between the numbers 1-8 and the letters A-H. Time and number of errors for each subtest are registered.

3. *The Stroop Color Word Interference Test* (104) The test consists of tree subtests measuring attention and cognitive speed, in simple complex conditions. In the first subtest four rows with ten words of the colour names red, blue, green and yellow are printed in black on white paper. In the second subtest the same number of correspondingly coloured patches are printed and the colours have to be named. In the third test the colour names are printed in incongruously collared ink, e.g. the word blue can be printed in green. The colour of the ink has to be named. Each subtest has to be done as fast as possible preferably without errors. The time needed to read the colour names aloud and errors are registered.

4. *Letter-Digit Coding Task* was used to measure the speed of processing of general information. The patient is asked to fill in digits near letters according to a key presented at the top of the test sheet (with nine consonants in random order) and to work as fast as possible. The total number of correct digits in 60 seconds is registered.

Article I

Rationale and design of a randomized clinical trial of neurocognitive functions in moderate- to high-risk patients undergoing conventional versus off-pump coronary artery bypass grafting.

Rationale and design of a randomized clinical trial of neurocognitive functions in moderate- to high-risk patients undergoing conventional versus off-pump coronary artery bypass grafting.

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Abstract

Background: Neurological and neuropsychological complications after conventional coronary artery bypass grafting (CCAB) are a significant clinical problem with consequences for both short-and long-term postoperative prognoses. It has been suggested that the risk of a negative effect on cerebral function is less pronounced among patients who undergo off-pump coronary artery bypass grafting (OPCAB) rather than CCAB. However, evidence for these statements is preliminary and additional data are needed.

Methods: The study is a sub-study of the randomized Best Bypass Surgery Trial that compares OPCAB to CCAB treatment, with respect to peri- and postoperative mortality and morbidity in patients with a moderate- to high-predicted preoperative risk. We evaluate the effect of OPCAB versus CCAB on cognitive functions, with possible subsequent impact on cardiac risk factors and health-related quality of life at 3 and 12 months postoperatively compared to preoperatively. The primary outcome measure is cognitive dysfunction evaluated by neuropsychological tests. Secondary outcome measures are cardiac risk factors and health-related quality of life. The study is powered on the basis of a reduction in cognitive impairment from 50% in the CCAB group to 20% in the OPCAB group.

Results: Enrolment started in July 2002 and ended in December 2004. One hundred and twenty consecutive patients were randomly assigned to one of the two study groups.

Conclusions: This BBS sub-study is the first randomized clinical trial examining neurocognitive functions in moderate- to high-risk patients undergoing OPCAB versus CCAB surgery. The trial will contribute to the existing knowledge whether OPCAB might be a less harmful procedure compared to CCAB, with respect to postoperative cognitive function and health-related quality of life in elderly patients undergoing coronary artery bypass surgery.

Key words: Coronary artery bypass surgery; Off-pump; On-pump; Neurocognitive functions; Cognitive dysfunction; Health-related quality of life; Randomized clinical trial; Research design

Introduction

Coronary artery bypass grafting (CABG) with the use of cardiopulmonary bypass is one of the most common cardiovascular surgical procedures [1]. However, there is a substantial risk of procedure related postoperative complications. Beside a risk for mortality and adverse effect on cardiac, pulmonary and renal function, there is as well a risk of major (type 1) and minor (type 2) cerebral deficits usually manifested as stroke or cognitive decline [2]. The reported incidence of postoperative stroke is approximately 3% in patients undergoing conventional coronary artery bypass grafting (CCAB) surgery [3].

Postoperative cognitive dysfunction is a condition characterized by impairment of memory or concentration, detected by neuropsychological testing and clinically manifested by deficits in cognition and memory, representing a significant change from previous level of functioning [4]. The incidence of this cognitive decline varies between different studies from 3% to 80% depending on how the deficit is defined, test methods applied, the composition of the target population and study design [3, 5, 6]. In a systematic review, the pooled analyses of six highly comparable studies yielded a proportion of 23% of patients with cognitive dysfunction two months after CCAB [7]. Furthermore, neurocognitive deficits have been reported to affect up to 42% of patients five years after CCAB [5].

It has been suggested that the risk of negative effect on cerebral function is less pronounced among patients who undergo off-pump coronary artery bypass grafting (OPCAB) [8-10]. This is a procedure where the distal graft anastomoses are performed on a beating heart without a heart and lung machine, aortic cross clamping, and cardioplegic arrest [11]. In an overview of eight retrospective nonrandomized observational studies it was not possible to make any definitive conclusions regarding significant difference in incidence of stroke or transient ischemic attacks between OPCAB and CCAB groups [12]. There are randomized trials available examining the cerebroprotective effect of OPCAB versus CCAB, showing inconsistent results [13-18]. Recently, one larger multicenter randomized clinical trial in low-risk patients compared OPCAB to CCAB using a battery of 10 neuropsychological tests before and after surgery to determine cognitive outcome at 3 and 12 month postoperatively. Three months after the procedure cognitive decline occurred in 21% of the patients in the OPCAB group, and 29% of the patients in the CCAB group. The effects were limited and became negligible at 12 months [19]. A newly updated and comprehensive meta-analysis [20] of randomized trials found no significant difference for neurocognitive dysfunction at 30-day and beyond 12 months, but significant reduction was found at 2-6 months. However, these studies were in younger patients, whereas neurocognitive decline is strongly age dependent [21]. Other known risk factors for adverse cerebral outcome are manipulation of an atherosclerotic aorta, and the heart and lung machine [22]. It cannot be concluded that the heart and lung machine is an independent risk factor of cerebral complications following CCAB until large scale, randomized, studies with appropriate risk stratification are conducted [12, 23]. Especially there is a need of randomized trials including high-risk patients, e.g. elderly patients with serious co-morbidity, since it might be that this population will benefit the most of avoiding the heart and lung machine [24]. We evaluate the effect of OPCAB versus CCAB on cognitive functions in moderate- to high-risk patients at 3 and 12 months postoperatively compared to preoperatively. In addition, a possible subsequent impact on cardiac risk factors and health-related quality of life is evaluated relative to the reference treatment.

Trial design

The study is a sub-study of the randomized Best Bypass Surgery (BBS) Trial (ClinicalTrials.gov identifier NCT00120991) that aims to compare OPCAB to CCAB treatment with respect to per- and postoperative mortality and morbidity, in patients with a moderate- to high-predicted preoperative risk.

Ethics

The local Ethics Committee has approved the BBS main trial and a separate approval was obtained for this sub-study, subject to journal no. 01-079/02. The Danish Data Protection Agency has furthermore approved the BBS main Trial. The study is carried out according to the guidelines of the Helsinki II declaration [25]. All participating patients signed written informed consent.

Patient recruitment

Patients who fulfill the inclusion criteria and none of the exclusion criteria are enrolled in the study (Table 1). The study investigators screen all patients scheduled for CABG daily for eligibility.

Randomization and blinding

Consecutive patients are centrally randomized to one of two groups by an external press button telephone voice response system. The patients are stratified by the following characteristics: gender, age (55 to 65 years; > 65 years), diabetes mellitus and EuroSCORE (5-8; > 8) [26]. Patients are randomized in a 1:1 ratio to OPCAB or CCAB surgery. The assessors of outcomes and the staff undertaking data analysis are blinded for allocation.

Outcome measures

The primary outcome measure is cognitive dysfunction evaluated by neuropsychological tests assessing memory, sensorimotor speed, cognitive flexibility and different aspects of motor function.

Secondary outcome measures include cardiac risk profile and health-related quality of life.

Neuropsychological tests, cardiac risk, and health-related quality of life

The choice of the neuropsychological tests are based on considerations concerning reliability and validity of measures, availability of normative data, brevity, sensitivity to relevant cognitive domains, availability of alternative forms, the physical effort required to perform the test and use in prior studies [27-29]. Furthermore specific cultures and language problems are taken into consideration [4]. The test battery has been developed for the International Study of Post-Operative Cognitive Dysfunction (ISPOCD) that aimed to investigate the occurrence of long-term

postoperative cognitive dysfunction in elderly patients after major non-cardiac surgery. Normative data are available [30]. The test battery has been translated into Danish and previously validated for sensitivity among patients undergoing CCAB [31]. Each single test is well known and has been used for years within neuropsychological and dementia research areas. High test-retest reliability coefficients are obtained and the learning effect is minimized because some tests exist in 3 parallel versions of same grade [32, 33]. The battery comprises the following tests: Mini Mental State Examination [34] as a screening test for dementia before inclusion in the study. The patient must obtain a score of at least 24 points out of 30 possible points.

A. The Visual Verbal Learning Test is used for assessment of memory and it is based on a list of 15 words. The patient is asked to recall as many words as possible immediately after presentation and also delayed recall after 15 to 25 minutes [35].

B. The Concept shifting Task consists of tree subtests that measure cognitive speed and flexibility [36]. Time and number of errors are registered.

C. The Stroop Color Word Interference Test measures attention and cognitive speed, in simple and complex conditions [37]. Time and number of errors are registered.

D. The Letter-Digit Coding is a substitution exercise based upon the Symbol Digit Substitution task in the Wechsler Adult Intelligence Scale [38]. Within one minute as many fields as possible are completed. The number of correct completed fields is recorded.

The sessions are done in a separate test room, only the patient and investigator are present. Each test is performed in a standardized way by the principal investigator and parallel versions are applied.

Cardiac risk factors are determined by changes in blood pressure, plasma lipids, body mass index, smoking habits and medical treatment [39].

Health-related quality of life is assessed using 36-item Medical Outcomes Study Short Form (SF-36) measuring physical and mental health status [40-42]. Symptoms of depression are measured using the ICD-10 diagnostic scale [43-45]. Family relations are assessed using Expressed Emotion survey [46] and family climate questionnaire [47].

Sample size

We estimate that 50% of the patients in the CCAB group do have a neurological or neuropsychological complication (type 1 + type 2). Cognitive dysfunction (type 2) is defined as the occurrence of at least two deficits out of seven possible (Table 2). The seven possible deficits are: Two possible deficits in A, B, C, and one possible deficit in D. For the two error scores, a deficit is defined as ≥4 additional errors postoperatively compared to preoperatively out of 16 possible in B and ≥5 additional errors postoperatively compared to preoperatively out of 40 possible in C.

For the remaining 5 variables, a deficit is defined as a 40% postoperative deterioration in the neuropsychological test compared to preoperative tests result.

We expect that this frequency in the OPCAB group may be reduced to 20%. To demonstrate a reduction in cognitive impairment from 50% to 20% (with a significance level of 0.05 and a 80% power) would require 50 patients in each group [48]. With an expected 20% drop out the total number of enrolled patients is 120.

Statistical analysis

Demographic data will be reported as medians with range and proportions with 95% confidence interval. Changes between baseline values and postoperative values will be analyzed by means of a paired t-test for normally distributed data and Wilcoxons paired rank-sum test for non-normally distributed data. The clinical outcome data will be compared with an unpaired t-test or a Chi-Squared test depending on type of variable. Correlation analysis will be performed using Pearsons correlations coefficient or Spearmans rank correlation depending on distribution. A $p < 0.05$ is considered statistically significant. All subjects will be analyzed in the groups to which they are randomly allocated according to intention to treat analysis [48].

Current status of the trial

From July 2002 to December 2004 120 patients were enrolled. The average monthly recruitment for the study was 7 patients. A total of 206 consecutively candidate patients were identified from the BBS study, and of these, 61 and 59 patients (58%) respectively were randomly allocated to OPCAB or CCAB (Figure 1). Twelve months follow-up was completed in December 2005. Baseline characteristic of the randomized patients are listed in Table 3.

Discussion

The design of this trial differs from that of previous trials comparing the effect of OPCAB versus CCAB on cognitive functions. First, to our knowledge it is the only randomized clinical trial focusing on cognitive function in elderly moderate- to high-risk patients undergoing OPCAB compared to CCAB. Secondly, this trial investigates, whether a possible cognitive dysfunction does have a real impact on patient's perception and everyday life. Third, the decisive element in detection of postoperative cognitive dysfunction is how the deterioration is defined and how it is estimated. Looking at the literature, the crucial step of finding a significant neurocognitive deficit is the definition in its self. The definition varies and subsequently, as lower the threshold of deficit is determined, as more patients will have a deficit. This level is arbitrary from research group to research group and varies between a deterioration of 1 SD in one or more tests, a deterioration of 20% or 25% in at least one ore two tests, until using standardized Z-score or composite Z-score [31, 32]. If a possible decline in patients cognitive testing is a deficit or not may be less interesting. The most important aspect must be, if the decline is recognized as such by the patient and has a direct impact on postoperative rehabilitation and quality of life.

Our definition is more restrictive than an open definition (e.g. the deterioration of 1SD criterion or deterioration of 20% - 25% criterion) and a more conservative definition using standardized or composite Z-score. Another important element is a sensitive test battery and taking learning effects into account, hence including a control group of healthy volunteers [32]. The ISPOCD test battery is in accordance with the Statements of Consensus on Assessment of Neurobehavioral Outcomes after Cardiac Surgery [28] and tested for sensitivity in elderly patients undergoing CCAB [31]. In the analyses of the test results from our study, the evaluation of cognitive function will be based on differences between pre- and postoperative performance, and the error scores will be considered as

well. A secondary data analysis, based on the definition used in the ISPOCD study (when two Z-scores for single test parameters or the a combined Z-score is 1.96 or more) [30, 32], and a open definition using deterioration of 20% in two out of five tests will be performed as well [15, 19], and discussed according to the definition as described.

By the central randomization and consecutive enrollment of patients from the BBS Trial, efforts have been taken to minimize selection bias [49]. Blinding is difficult to obtain, especially in surgical trials [50] and neither study personnel nor participants can be blinded to the surgery performed, but the assessment of outcomes and the data analysis can be performed with blinding.

Another important possible complicating factor that needs to be considered is missing information related to patients who drop out of the study before the end [50]. Information regarding the status of patients lost to follow-up will be obtained and reported in a flow diagram [50]. If the proportion of patients is too great and falsely lead to more impaired patients in one group than the other a possible approach is to analyze data according to the principles of most optimistic and most pessimistic outcome [48].

The BBS Trial as well as the present BBS sub-study has received grants from non-profit organizations only and is investigator initiated and controlled. In this way biased assessment of the effect of the intervention from commercial sponsorship should be assured.

Conclusion

According to our knowledge this is the first study examining the effects of OPCAB compared to CCAB in elderly moderate- to high-risk patients with respect to postoperative cognitive dysfunction and impact on everyday life. This improved knowledge might contribute to the existing knowledge with respect to postoperative cognitive function and quality of life in elderly patients undergoing OPCAB versus CCAB.

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Table 1

Eligibility and exclusion criteria of the BBS trial sub-study population

BBS trial study population

Eligibility criteria:

1. Known ischaemic three vessel heart disease affecting one of the marginal coronary arteries
2. Age ≥ 55 years
3. Scheduled for elective or sub-acute CABG
4. EuroSCORE ≥ 5 and <17
5. The patient has signed written informed consent before randomization and surgery

Exclusion criteria

6. Previous heart surgery
7. Ejection fraction < 30 %
8. Unstable preoperative condition e.g. continuous infusion of inotropics on the day of the operation
9. Patient unable to give informed consent

From BBS trial patients are selected consecutively, but with the following restrictions:

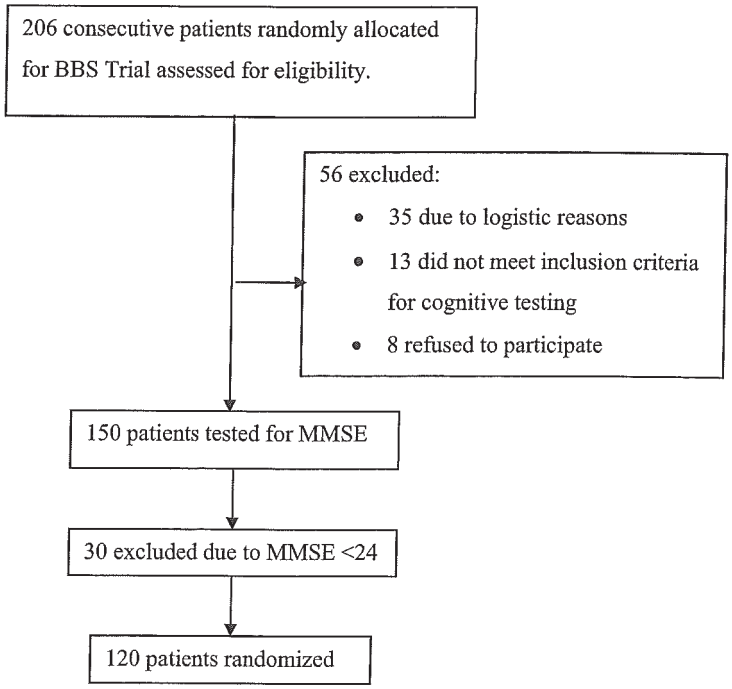
1. Mini Mental State Examination score under 24 points
2. Current severe psychiatric disease e.g. depression, psychosis or alcoholism. (patients currently using either antipsychotic or antidepressant drugs or imbibing more than 5 drinks/units of alcohol per day within the last 3 months).
3. Neuropsychological testing within the last year
4. Illiteracy
5. Poor comprehension of Danish
6. Severe visual or auditory disorder
7. Unwillingness to return for follow-up

Table 2

The definition of cognitive dysfunction.

Tests	Memory	Cognitive speed, attention and flexibility
A. Visual Verbal Learning	2 deficits	
B. Concept Shifting Task		≥4 errors or/and 1 deficit in time
C. Stroop Color Word Interference		≥5 errors or/and 1 deficit in time
D. Letter-Digit Coding		1 deficit

Figure 1 Flow chart for assessment of patient eligibility



MMSE, Mini Mental State Examination

Table 3

Baseline characteristics of the 120 patients included in the BBS sub-study

Mean age (SD), y	75.5 (4.5)
Female (%)	48 (40)
Co-morbidity	
Predisposition for IHD <55 years of age (%)	30 (26)
Diabetes (%)	22 (18)
Hypertension (%)	73 (61)
Previous myocardial infarction (%)	88 (73)
Previous stroke or TIA (%)	27 (23)
History of atrial fibrillation (%)	9 (8)
Current Smoker (%)	22 (18)
Former smoker (%)	71 (59)
Mean blood pressure/mm Hg	
Systolic (SD)	145 (25.3)
Diastolic (SD)	74 (11.7)
Mean body mass index/kg/m^2 (SD)	27 (4.6)
Mean lipid status/mmol/l	
Total cholesterol (SD)	4.69 (1.28)
HDL cholesterol (SD)	1.29 (.40)
LDL cholesterol (SD)	2.83 (1.08)
Triglyceride (SD)	1.67 (.89)
Unit of alcohol consumption per day	
0 (%)	63 (53)
1-2 (%)	42 (35)
3-4 (%)	15 (12)
Pensioner (%)	119 (99)
Post employment wages (%)	1 (1)

Basic school	
7 years or less (%)	65 (54)
8 to 9 years (%)	34 (28)
10 years (%)	14 (12)
High school (%)	7 (6)
Education	
None (%)	47 (39)
Vocational (%)	63 (53)
University (%)	10 (8)
Marital status	
Living with a partner (%)	72 (60)
Separated/divorced (%)	12 (10)
Widow/widower (%)	36 (30)

IHD, ischemic heart disease; *TIA,* transient ischemic attack

*The risk of myocardial infarction within the next 10 years

Article II

Cognitive Outcomes in Elderly High-Risk Patients After Off-Pump Versus Conventional Coronary Artery Bypass Grafting. A Randomized Trial

Cognitive Outcomes in Elderly High-Risk Patients After Off-Pump Versus Conventional Coronary Artery Bypass Grafting

A Randomized Trial

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Background—It has been suggested that the risk of cerebral dysfunction is less with off-pump coronary artery bypass grafting (OPCAB) than with conventional coronary artery bypass grafting (CCAB). However, evidence for this statement is preliminary, and additional insight is needed.

Methods and Results—The study was a substudy of the randomized Best Bypass Surgery trial that compared OPCAB with CCAB treatment with respect to intraoperative and postoperative mortality and morbidity in patients with a moderate to high level of predicted preoperative risk. The outcome was cognitive function. A total of 120 elderly patients (mean age 76 years, SD 4.5 years) underwent psychometric testing before surgery and at a mean of 103 (SD 15) days postoperatively with a neuropsychological test battery that included 7 parameters from 4 tests. Cognitive dysfunction was defined as the occurrence of at least 2 of the 7 possible deficits. Secondary analysis was performed on the basis of the definition of a 20% decline in cognitive scores compared with baseline, and with z score analysis. Cognitive dysfunction was identified in 4 of the 54 patients (7.4%, 95% confidence interval [CI] 2.1% to 17.9%) in the OPCAB group and 5 of the 51 patients (9.8%, 95% CI 3.3% to 21.4%) in the CCAB group. We found no difference in incidence of cognitive dysfunction between the groups regardless of the definition applied.

Conclusions—In elderly high-risk patients, no significant difference was found in the incidence of cognitive dysfunction 3 months after either OPCAB or CCAB. **(*Circulation*. 2006;113:2790-2795.)**

Key Words: cardiopulmonary bypass ■ cerebrovascular disorders ■ coronary disease ■ brain complication ■ cognitive function

Coronary artery bypass grafting with the use of cardiopulmonary bypass (CPB) is one of the most common cardiovascular operations.[1] However, there is a substantial risk of procedure-related postoperative complications. In addition to the risk for mortality and an adverse effect on cardiac, pulmonary, and renal function, there is a risk of major (type 1) and minor (type 2) cerebral deficits, usually manifested as stroke or cognitive decline.[2] The reported incidence of postoperative stroke is ≈3% of the patients undergoing conventional coronary artery bypass grafting (CCAB).[3]

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Postoperative cognitive dysfunction is a condition characterized by impairment of memory or concentration, which is detected by neuropsychological testing and which presents clinically with deficits in cognition and memory, representing a significant change from the patient's previous level of functioning.[4] The incidence of this cognitive decline varies among different studies from 3% to 80% depending on how the deficit is defined, the test methods applied, the composition of the target population, and the study design.[3,5,6] In a systematic review, the pooled analyses of 6 highly comparable studies yielded a proportion of 23% of patients with cognitive dysfunction 2 months after CCAB.[7] Furthermore, neurocognitive deficit has been reported to affect up to 42% of patients 5 years after CCAB.[5]

It has been suggested that the risk of cerebral dysfunction is less pronounced with off-pump CABG (OPCAB).[8–10] This is a procedure in which the distal graft anastomoses are performed on a beating heart without a heart and lung

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machine, aortic cross clamping, and cardioplegic arrest.[11] In an overview of 8 retrospective, nonrandomized observational studies, it was not possible to make any definitive conclusions regarding a significant difference in the incidence of stroke or transient ischemic attacks between OPCAB and CCAB surgery groups.[12] There are randomized trials available that examined the cerebroprotective effect of OPCAB versus CCAB surgery that showed inconsistent results.[13–19] A newly updated and comprehensive meta-analysis of 37 randomized trials found no significant difference for neurocognitive dysfunction at 30 days and beyond 12 months, but a significant reduction was found at 2 to 6 months postoperatively.[20] However, the studies were conducted in younger patients, whereas neurocognitive decline is strongly age-dependent.[21] Other known risk factors for adverse cerebral outcome are manipulation of an atherosclerotic aorta and CPB.[22] It cannot be concluded that CPB is an independent risk factor for cerebral complications after CABG until large-scale, randomized studies with appropriate risk stratification are conducted.[12,20,23] In particular, there is a need for randomized trials that include high-risk patients, eg, elderly patients with serious comorbidity, because this population might benefit the most by avoiding CBP.[11,24] The aim of the present study was to evaluate the effect of OPCAB versus CCAB surgery on cognitive function at 3 months postoperatively compared with preoperatively in elderly high-risk patients (EuroSCORE [European system for cardiac operative risk evaluation] ≥5),[25] with the hypothesis that the degree and frequency of postoperative stroke and cognitive dysfunction are reduced after OPCAB compared with CCAB.

Methods

Participants

The local ethics committee approved the study. The study is a substudy of the randomized BBS (Best Bypass Surgery) trial that aims to compare OPCAB with CCAB treatment with respect to intraoperative and postoperative mortality and morbidity in patients with a moderate to high predicted preoperative risk. Patients with known ischemic 3-vessel heart disease affecting 1 of the marginal coronary arteries who were scheduled for elective or subacute CABG at the Heart Center, Copenhagen University Hospital who were ≥55 years of age and who had a EuroSCORE ≥5 were candidates for inclusion in the study. They were not admitted to the study if any of the following criteria were present: (1) previous heart surgery; (2) ejection fraction less than 30%; (3) unstable preoperative condition, ie, continuous infusion of inotropic drugs on the day of the operation; or (4) patient unable to give informed consent. For the present substudy, patients were recruited consecutively from the BBS trial between July 2002 and December 2004, but with the following additional exclusion criteria: (1) Mini Mental State Examination score below 24 points; (2) current severe psychiatric disease ie, depression, psychosis, or alcoholism (patients currently using either antipsychotic or antidepressant drugs or imbibing more than 5 drinks/units of alcohol per day within the last 3 months); (3) neuropsychological testing within the last year; (4) illiteracy; (5) poor comprehension of Danish; (6) severe visual or auditory disorder; or (7) unwillingness to return for follow-up.

After written informed consent about the BBS trial was obtained, the patients were centrally randomized to 1 of 2 groups by an external touchtone telephone voice-response system. The patients were stratified by the following characteristics: gender, age (55 to 65 years or >65 years), diabetes mellitus, and EuroSCORE (5 to 8 or >8). Patients were randomized in a 1:1 ratio to OPCAB or CCAB surgery. The assessors of outcomes and the staff undertaking data analysis were blinded for allocation.

Intervention

In the OPCAB group, the revascularization procedure was performed on the beating heart with a stabilization of the target coronary arteries. When access to posterior coronary arteries was needed, a suction device lifted the heart. In case of suspicion of aortic calcification or plaque formation, the vein or radial grafts were anastomosed as T-grafts to the left internal mammary artery (LIMA) or a HeartString device (Guidant Corp, Santa Clara, Calif) was used to facilitate proximal graft-aortic anastomosis without clamping. In the CCAB group, the revascularization procedure was performed with the use of CPB in normothermia, an aortic cross clamp, and cold blood cardioplegic arrest. Patients with pronounced aortic calcifications were converted to OPCAB surgery, according to the BBS trial protocol. In case of macroscopically normal aorta, a side clamp was used for proximal anastomoses. When cross clamping revealed plaque formation, the proximal anastomoses were established before removal of the cross clamp. In both groups, the LIMA and saphenous vein grafts were composed of standard graft material. The same surgeons performed both procedures.

Neuropsychological Test Battery

The choice of the neuropsychological tests was made in accordance with the "Statement of Consensus on Assessment of Neurobehavioral Outcomes After Cardiac Surgery."[26,27] Furthermore, specific cultures and language problems were taken into consideration.[4] Normative data are available.[28] The test battery has been translated into Danish and validated previously for sensitivity among patients undergoing CCAB surgery.[29] High test-retest reliability coefficients have been obtained, and the learning effects are minimized because the test exists in 3 parallel versions.[30,31] The battery comprised the following tests: The Mini Mental State Examination[32] was used as a screening test for dementia after randomization and before inclusion in the study; the patient had to score at least 24 points out of a possible 30 points. The remaining tests were as follows: (A) Visual Verbal Learning test was used for assessment of memory that was based on a list of 15 words. The patients were asked to recall as many words as possible immediately upon viewing the list and after 15 to 25 minutes.[33] (B) The Concept Shifting Task consisted of 3 subtests that measure cognitive speed and flexibility.[34] Time to complete the test and the number of errors were registered. (C) The Stroop Color Word Interference Test measures attention and cognitive speed in simple and complex conditions.[35] Time and number of errors were registered. Finally, the Letter-Digit Coding (D) is a substitution exercise based on the Symbol Digit Substitution task in the Wechsler Adult Intelligence Scale.[36] Within 1 minute, as many fields as possible are completed. The number of correctly completed fields is recorded.

The sessions were done in a dedicated testing room, and only the patient and investigator were present. Each test was performed in a standardized way by the principal investigator, and parallel versions were applied.

Sample Size

We assumed a composite outcome incidence to be ≈50% in the CCAB group during a 3- to 12-month period, with a possible reduction to 20% in the OPCAB group. To demonstrate a reduction in cognitive impairment from 50% to 20% (with a significance level of 0.05 and 80% power) would require 50 patients in each group.[37] With an expected 20% dropout rate, the total number of enrolled patients was 120.

Definitions and Data Analysis

Cognitive dysfunction was defined as the occurrence of at least 2 of 7 possible deficits (Table 1). The 7 possible deficits were 2 possible deficits in A, B, and C and 1 possible deficit in D. For the 2 error scores, a deficit was defined as ≥4 additional errors postoperatively compared with preoperatively out of 16 possible in B and ≥5

TABLE 1. Definition of Cognitive Dysfunction

Tests	Memory	Cognitive Speed, Attention, and Flexibility
A. Visual Verbal Learning	2 Deficits	
B. Concept Shifting Task		≥4 Errors and/or 1 deficit in time
C. Stroop Color Word Interference		≥5 Errors and/or 1 deficit in time
D. Letter-Digit Coding		1 deficit

additional errors postoperatively compared with preoperatively out of 40 possible in C. For the remaining 5 variables, a deficit was defined as a 40% postoperative deterioration in the neuropsychological test compared with preoperative tests results.

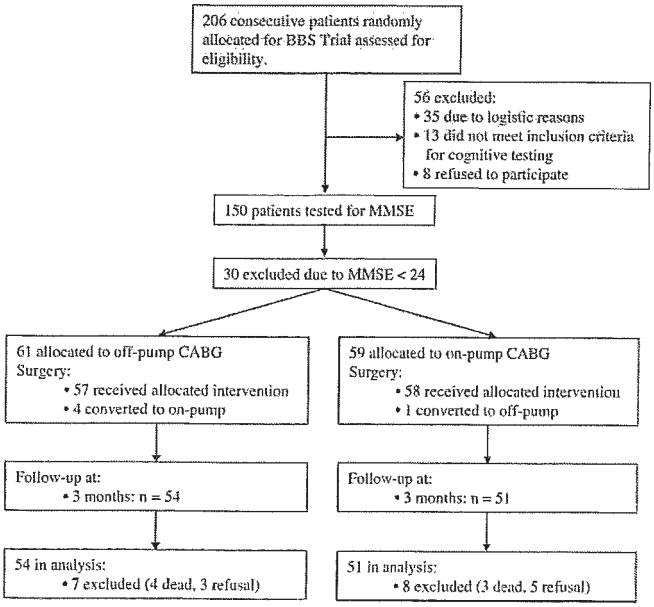
Secondary analysis was performed based on 2 other definitions of cognitive decline: (1) a 20% decline in cognitive scores compared with baseline[38] and (2) the ISPOCD (International Study of Post-Operative Cognitive Dysfunction) definition,[28] in which changes in the performance of 7 parameters from the result of the 4 tests were calculated. For each individual test outcome, the average learning effect was subtracted from these changes, and a z score was obtained after division by the SD from an age-matched healthy control group. When 2 of 7 z scores in individual tests or the combined z score were 1.96 or more, patients were defined as having cognitive dysfunction. (See Rasmussen et al[30] for details.) Differences in patient characteristics at baseline and frequency of cognitive dysfunction in the OPCAB and CCAB group were compared with χ^2 test and Fischer's exact test for categorical variables. Continuous data were compared with t test or Wilcoxon rank test as appropriate. Probability values less than 0.05 were considered statistically significant. All subjects were analyzed in the groups to which they were randomly allocated according to intention-to-treat analysis.

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Patient Population and Allocation

Between July 2002 and December 2004, 206 consecutive patients included in the BBS trial were evaluated for eligibility in the present study. In total, 13 patients did not meet criteria for cognitive testing because of severe visual (3 patients) or auditory (1 patient) disorders, neuropsychological testing within the last year (1 patient), more than 5 drinks/units of alcohol per day (1 patient), current severe psychiatric disease (1 patient), poor comprehension of Danish (4 patients), and unwillingness to return to follow-up (3 patients). Furthermore, 30 of the eligible patients were excluded due to having a Mini Mental State Examination score less than 24. Logistic reasons were responsible for the exclusion of 35 patients, eg, the staff who were responsible for data collection had vacation or a day off, patients were not available for baseline testing because of inclusion late in the evening or just before surgery, or patients lived so far away from the hospital that follow-up was impossible. Therefore, 120 patients were included in the present study. At 3 months, cognitive outcomes could be determined in 54 patients in the OPCAB group and 51 in the CCAB group. Seven patients had died, and 8 patients refused to participate in further cognitive tests (Figure). At baseline, there were no significant differences between the groups regarding age, sex, comorbidity, smoking habits, and basic school education; however, in the OPCAB group, the level of education was higher. Twenty-four percent of the patients had a EuroSCORE of 5 (12 OPCAB and 17 CCAB patients). The mean EuroSCORE for all patients was 6.68. Patients in the OPCAB group were on average 1 year older than those in the CCAB group and



Flow of patients through the trial. MMSE indicates Mini Mental State Examination.

TABLE 2. Baseline Characteristics of Patients According to Surgery Procedure

Variable	OPCAB (n=61)	CCAB (n=59)
Age, mean (SD), y	76 (4.8)	75 (4.2)
Sex, female, n (%)	26 (43)	22 (37)
Comorbidity, n (%)		
Predisposition for IHD <55 y of age	18 (31)	12 (20)
Diabetes	11 (18)	11 (19)
Hypertension	40 (66)	33 (56)
Previous myocardial infarction	42 (69)	46 (78)
Previous neurological complications*	12 (20)	15 (25)
History of atrial fibrillation	3 (5)	6 (10)
Ejection fraction, mean (SD)	49.8 (8.9)	48.6 (8.3)
EuroSCORE, mean (SD)	6.8 (1.6)	6.6 (1.6)
Current smoker, n (%)	10 (16)	12 (20)
Former smoker, n (%)	37 (61)	34 (58)
Basic school, n (%)		
7 y or less	31 (51)	34 (58)
8 to 9 y	16 (26)	18 (31)
10 y	9 (15)	5 (9)
High school	5 (8)	2 (3)
Education, n (%)		
None	17 (28)	30 (51)
Vocational	35 (57)	28 (48)
University	9 (15)	1 (2)

IHD indicates ischemic heart disease.
*Includes stroke and transient ischemic attack.

comprised slightly fewer men (Table 2). Perioperatively, the mean length of operation was 159 (SD 40) minutes in the OPCAB group and 152 (SD 30) minutes in the CCAB group. In the OPCAB group, the nontouch aorta technique (proximal T grafting plus right internal mammary artery) was used in 6 of 57 patients, the HeartString technique in 3 of 57, and a side clamp in the remaining 48 patients. In the CCAB group, proximal T grafting was used in 3 of 58, the 1-clamp technique in 5 of 58, and a side clamp in the remaining 50 patients. Four of 61 patients allocated to OPCAB were converted to on-pump CABG. One of the patients was converted during the OPCAB procedure owing to hemodynamic instability. Three procedures were performed as on-pump cases because the surgeon considered that the operation could not be performed successfully as an OPCAB procedure in his hands. One of the 59 patients allocated to CCAB was converted to OPCAB owing to severe calcification.

Duration of CPB in the CCAB group was 60 (SD 19) minutes, with 36 (SD 13) minutes of cross-clamp time. The incidence of postoperative atrial fibrillation was 57% (95% confidence interval [CI] 43.2% to 69.4%) in the OPCAB group and 55% (95% CI 41.5% to 68.3%) in the CCAB group. Postoperatively (in-hospital incidence), 1 nonfatal stroke was seen in the OPCAB group and 1 in the CCAB group.

Cognitive Outcome

The mean interval between operation and 3-month follow-up was 100 (SD 11) days in the OPCAB group and 106 (SD 18) days in the CCAB group (P=0.07). When we applied our definition of at least 2 of 7 possible deficits compared with baseline, 7.4% (95% CI 2.1% to 17.9%) of the patients in the OPCAB group and 9.8% (95% CI 3.3% to 21.4%) in the CCAB group had cognitive dysfunction (P=0.7).

When we used the definition of a 20% decline in cognitive scores compared with baseline, the incidence of cognitive decline at 3 months was 20.4% (95% CI 10.6% to 33.5%) of the patients in the OPCAB group and 23.5% (95% CI 12.8% to 37.5%) in the CCAB group (P=0.8). When cognitive dysfunction was defined according to a z score $\geq$1.96, 26.0% (95% CI 15.0% to 39.7%) of the patients in the OPCAB group and 21.6% (95% CI 11.3% to 35.3%) in the CCAB group had cognitive dysfunction (P=0.7). There was no significant difference in the incidence of neurocognitive decline between the 2 groups regardless of the definition applied.

Discussion

Our objective was to evaluate the effect of OPCAB versus CCAB on cognitive function in elderly high-risk patients at 3 months postoperatively. To the best of our knowledge, this is the first randomized study focusing on that specific topic. In addition, the present study is characterized by a high degree of internal validity in terms of accounting for patient selection, and a large number of the patients were available for 3-month follow-up, because only 8 of 120 refused to participate. The sample-size calculation was based on achieving a 60% reduction in cognitive decline at 3 months. The risk of type 2 error is important, and a more modest reduction cannot be excluded, but detection of a small difference would need to be investigated in a larger randomized study. The detection of a difference between 7% and 10% would require approximately 3000 patients if a type 2 error of 20% is accepted.

It is remarkable that 30 (20%) of 150 eligible patients were excluded because their Mini Mental State Examination score was <24 (Figure). One explanation could be related to patient characteristics, including age, with associated arteriosclerosis that might be manifested in arteries other than the coronaries. The groups were similar with regard to demographic characteristics. The difference in education is considered incidental (Table 2). The high incidence of atrial fibrillation did not differ significantly between the groups and can therefore be precluded as a confounder in terms of thromboembolic events.

We found no difference between the 2 groups with regard to incidence of cognitive dysfunction and stroke. It was anticipated, however, that at 3 months, outcome would have been significantly improved in favor of the OPCAB technique. It is remarkable that in the present study, the 9.8% to 23.5% variation in incidence of cognitive decline in the CCAB group (Table 3), depending on the definition used, is consistent with the previous reported incidence, from uncontrolled studies, of 4% to 47% in younger patients (mean age 55 to 70 years) 2 months after the operation,[7] because advanced age is the least controversial demographic risk factor for cognitive decline.[5,39] Moreover, the lack of benefit from avoiding CPB was not expected, because the use of CPB is generally regarded as the main cause of cognitive decline, and its effects are anticipated to be even more notable in older patients with more comorbidity.[40,41] Three other randomized

TABLE 3. Incidence of Cognitive Dysfunction

Definition	OPCAB, % (n=54)	CCAB, % (n=51)	*P*, OPCAB vs CCAB
2 Deficits out of 7 possible (95% CI)	7.4 (2.1–17.9)	9.8 (3.3–21.4)	0.74
20% Decline in cognitive scores (95% CI)	20.4 (10.6–33.5)	23.5 (12.8–37.5)	0.81
z Score ≥1.96 (95% CI)	26.0 (15.0-39.7)	21.6 (11.3-35.3)	0.65

studies that included younger, low-risk patients found no significant difference in cognitive function after 2.5 months[17] or 3 months[16,19] with OPCAB versus CCAB. In contrast, Zamvar et al[42] found significantly greater deterioration in cognitive scores in the on-pump group after 10 weeks using a battery of 9 neuropsychometric tests. Cognitive dysfunction was defined as deterioration of 1 SD from the baseline score of all patients. Recently, in a longitudinal study, 140 patients undergoing CCAB were compared with a control group of 92 demographically and medically similar nonsurgical patients with coronary artery disease who underwent cardiac catheterization with or without an angioplasty procedure.[43,44] No significant differences in cognitive outcomes were found between the groups at 3 months or at 1- or 3-year follow-up, which suggests that the previously reported early postoperative cognitive decline after CABG tended to be resolved before the 3-month examination.

Two retrospective observational studies examined patients with EuroSCORES >5 and found no benefit from OPCAB surgery related to the incidence of stroke.[45,46] A meta-analysis of 9 nonrandomized observational studies, which included 4475 elderly patients aged 70 years or older, 1253 of whom underwent OPCAB and 3222 of whom underwent CCAB, showed that the OPCAB technique was associated with a significantly lower incidence of stroke than the CCAB technique.[47] Because of the limited design of the studies included in the meta-analyses, and inconsistency with the results of the present study, further prospective randomized trials of sufficient size are required before a final conclusion can be drawn with regard to whether there is a cerebroprotective benefit from avoiding CPB in elderly high-risk patients.

The reasons for the limited differences in cognitive outcome between the treatment groups observed in the present study may be explained in several ways. When one examines the literature, the crucial step of finding a significant neurocognitive deficit is in determining the definition itself. The definition of a significant deficit varies, and the lower the threshold of "deficit" is determined to be, the more patients there will be who have a deficit. This level is arbitrary from research group to research group and varies from a deterioration of 1 SD in 1 or more tests, a deterioration of 20% or 25% in at least 1 or 2 tests, to the use of a standardized *z* score or composite *z* score.[29,30] The definition of cognitive dysfunction in the present study was more restrictive than the "20% criterion" and the definition with the *z* score. In the analyses of the test results from the present study, the evaluation of cognitive function was based on differences between preoperative and postoperative performance. Therefore, the association between early and late cognitive outcome could be explained by regression toward the mean,[48] because generally, the use of scores favors patients with poor preoperative performance because of the "protective" effect of low baseline performance.[30] On the other hand, the ISPOCD test battery is in accordance with the "Statements of Consensus on Assessment of Neurobehavioral Outcomes after Cardiac Surgery"[26] and has been tested for sensitivity in elderly patients undergoing CCAB.[29] The error scores were considered and learning effects taken into account by the inclusion of a control group of healthy volunteers.

Another explanation involves the short-term follow-up in the present study, because it has been suggested that improved cognitive outcome with an OPCAB procedure may only become clear in the long term. van Dijk et al[19] found an increasing incidence of cognitive decline from 3 to 12 months, and Newman et al[5] found cognitive decline in 24% of patients 6 months after CCAB, which increased to 42% after 5 years.

A final explanation might be that the OPCAB technique is a new source of cognitive dysfunction caused by decreased cerebral perfusion pressure during episodes of elevated central venous pressure and corresponding decreased arterial blood pressure, in connection with dislocation of the heart during surgical exposure of the posterior cardiac wall.[49] The influence of systemic mean arterial pressure during CPB and neurological outcome has been the subject of considerable debate. Commonly, a mean arterial pressure of 50 to 60 mm Hg when the patient is undergoing CPB is regarded as safe to avoid neurological complications, which corresponds to current guidelines at our institution.

In conclusion, the results of this randomized trial in 120 selected high-risk elderly patients suggest that patients who undergo CABG surgery without CPB have no improvement in cognitive outcomes at 3 months compared with patients who undergo a CCAB procedure.

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Disclosures

None.

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Editorial

Can Cognition Survive Heart Surgery?

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In this issue of *Circulation*, Jensen et al[1] report that cognitive difficulties were no fewer when off-pump (OPCAB) versus conventional (CCAB) coronary artery bypass grafting was used. This important investigation, a substudy of the Best Bypass Surgery Trial, is a randomized prospective controlled trial that compares OPCAB with CCAB. Although the numbers seem relatively small (ie, 120 elderly patients with a men age of 76 years), the study was carefully powered to show differences in cognitive function at a mean of 103 days of follow-up. Although one could quibble with the details of the neuropsychological tests chosen (mini-mental state examination as a screening test for dementia after randomization but before inclusion, visual verbal learning, concept shifting, Stroop color word interference test, letter-digit coding), the main result is unequivocal. The incidence of cognitive decline was roughly 8%, and no difference between OPCAB and CCAB was found. This disappointing result raises important questions about the mechanisms of neurological injury caused by cardiac surgery and what future strategies might entail.

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Early in the development of cardiac surgery, it was psychiatrists who first reported difficulties with thought content and process. Rizzo et al[2] reported on 32 patients under the care of Lewis Dexter (cardiologist) and Dwight Harken (cardiac surgeon) who underwent "finger fracture" valvuloplasty surgery for rheumatic mitral valve disease at the Peter Bent Brigham Hospital in Boston. These psychiatrists applied analytical explanations (eg, hysterical fantasies as the heart as a sexual organ, transference to the surgeon, depersonalization, narcissism) to their findings of disordered thinking in many of their patients. Only 50 years later, these explanations sound amusingly antique, but they mark the first organized recognition that the brain could suffer serious damage as a result of cardiac surgery.

The neurological complications of cardiac surgery fall into 2 major categories: those affecting the peripheral nervous system and those affecting the central nervous system. Although common and important, peripheral nervous system complications are not the subject of the Jensen et al[1] study. The central nervous system complications fall into 3 major categories: acute encephalopathy as a result of a disorder in the neurological systems that subserve consciousness (inattention, confusion, delirium, drowsiness, stupor, and coma, sometimes with seizures and/or myoclonus), overt stroke (the sudden or rapid onset of a neurological deficit in a vascular territory as a result of a cerebrovascular disease), and a chronic syndrome of cognitive decline (inattention, amnesia, aphasia, apraxia) that is often, but not always, associated with symptoms of depression (apathy, sadness, sleep disorder, anhedonia). As cardiac surgery has matured and become technically better, the incidence of acute encephalopathy and overt stroke has progressively declined to current levels in the best hands of <10% and <3%, respectively, but the problem of chronic cognitive decline has remained and in many ways has become the most important complication that plagues a significant minority of patients who have otherwise successfully survived heart surgery.

When extracorporeal circulation was introduced, it was implicated in the mechanism of brain damage from heart surgery,[3–5] and many efforts were made to protect the brain through the use of inline filtration systems meant to deal with what was believed to be the major mechanism of neurological damage, namely cerebral emboli.[6,7] Soon it became clear that central neurological complications of heart surgery were not limited to intracardiac (open heart) surgery but were seen in extracardiac (coronary artery bypass surgery) as well.[8] The precise prevalence of cognitive decline after coronary artery bypass grafting varies widely, presumably depending on the sensitivity of the neuropsychological tests used, but have been found by some to be much more prevalent than the roughly 8% found in the present study by Jensen et al.[1] Newman and colleagues,[9] who defined a significant decline as a 20% reduction from baseline, found a cognitive decline in 53% of patients at discharge, 36% at 6 weeks, 24% at 6 months, and 42% at 5 years. This interesting finding of late cognitive decline correlated with early cognitive impairment, indicating that that those patients who suffer cognitive deficits from the stress of cardiac surgery may have had an early form of a degenerative dementia (eg, Alzheimer disease). Others have not found an increased incidence in Alzheimer disease among those who suffer cognitive decline after cardiac surgery. Knopman et al[10] retrospectively analyzed 557 patients with dementia compared with age- and sex-matched control subjects; 24 dementia patients and 28 control subjects who had undergone CCAB. There was no association between cardiac surgery and Alzheimer disease. McKhann et al[11] compared 140 patients who underwent CCAB and 72 patients who underwent OPCAB with 2 control groups, 1 comprising 99 patients who had vascular disease but did not undergo surgery and 1 consisting of 69 age-matched normal control subjects. All groups except the normal control subjects showed a mild reduction in neuro-

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psychological scores, but there was no evidence of a surgically correlated dementia at 3 months or 1 year. In the study in this issue of *Circulation*, Jensen and colleagues tried to exclude a premorbid early dementia before including patients in the study, but the mini-mental state examination could be too coarse an instrument with which to detect such patients. Jensen et al[1] did not address the issue of whether there was a late progressive cognitive decline.

More modern techniques to assess the mechanism of central nervous system injury such are intraoperative transcranial Doppler[12] and diffusion-weighted MRI[13] have shown that cerebral emboli are the dominant mechanism of brain injury during cardiac surgery, even in the vast majority of patients who do not demonstrate the syndrome of overt stroke. Border-zone ischemia, resulting from hypotension, is a relatively rare mechanism of intraoperative brain injury, seen in only the most obvious cases of systemic hypotension during the procedure. Usually ischemic lesions, detected by diffusion-weighted MRI, seen in the so-called border zones are actually emboli in the terminal arterial territories, in which case the lesions are often strikingly asymmetrical, a finding that is rare in true border-zone (or watershed) regions affected during systemic hypoperfusion. Metabolic insults almost never explain the nature and persistence of the neurological deficits.

If, as Jensen et al[1] have shown in the present study, the incidence of cognitive decline is not reduced by performing OPCAB and if, as the overwhelming bulk of the evidence has shown, emboli are the major cause of the deficits, one is forced to inquire about the source and nature of the emboli. Clearly, the persistent problem with microemboli cannot be attributed to extracorporeal circulation as was originally believed. The use of inline filtration systems probably has had a beneficial effect by reducing embolic burden, but a persistent risk of stroke and more subtle brain damage persists despite the widespread use of these systems. It seems likely that manipulation of the heart and great vessels and clamping of the aorta, required to implant the grafts in OPCAB, even without breaching the cardiac chambers, is enough to release showers of microemboli. Only the fairly rare macroembolism produces an overt stroke (incidence <3%), whereas the nearly ubiquitous microemboli produce the more common acute syndrome of inattention, confusion, and delirium (agitated confusion) and the chronic syndrome of depression, apathy, inattention, and frank dementia. This hypothesis is supported by the evidence that the major risk factors for postoperative cognitive decline are age, hypertension, known cerebrovascular disease, and preoperative cognitive difficulties. It is likely that cardiac surgery is indeed a stress test for cerebral reserve, producing more cognitive difficulties in those destined to develop a dementia, even if that dementia is not classic Alzheimer disease.

Cardiac surgery is one of the great triumphs of 20th century medicine. It has become so apparently safe that coronary artery bypass grafting is now a routine procedure. The last remaining major complication is subtle cognitive failure that can lead to disabling loss of the ability to enjoy intellectual pursuits. As coronary artery bypass grafting is challenged by interventional methods for revascularization of the myocardium, perhaps all but the most emergent preoperative patients should be investigated using sophisticated neurocognitive tests and neuroimaging to identify those who may not be able to withstand the challenge of an inevitable shower of microemboli. Interventional techniques probably also produce some emboli, but the dose is likely to be much less, perhaps making these procedures safer for the high-risk patient who requires myocardial revascularization. Intraoperative measures that may affect the incidence of neurological deficit include ultrasonic assessment of the aorta to determine where mobile atheromatous material may reside to avoid these areas when placing the clamp and grafts, transcranial Doppler to monitor embolic activity in real time, and minimization of movement of the heart and great vessels during the procedure. Use of devices (eg, suction) that help to immobilize the heart during OPCAB so that the surgeon can sew in the grafts may paradoxically increase the risk of emboli and thus neurological deficit. Perhaps the trend to use OPCAB in high-risk patients has reached its peak and is declining. This study by Jensen et al[1] removes another apparent advantage of coronary artery bypass grafting on the beating heart, a procedure that is more difficult technically than CCAB, may result in less viable grafts, is challenging to teach to the next generation of cardiac surgeons, and apparently does not reduce the risk of the last remaining major side effect of surgical myocardial revascularization, that of cognitive decline.

In summary, the problem has been reduced to a rather simple one. Stroke, produced mostly by arterial source emboli, is the cause of heart surgery–induced cognitive failure. The clinical syndromes fall on a continuum. A few strokes (<3%) are gross and singular, producing an obvious deficit (eg, hemiplegia), but most are multiple. When the embolic burden is high (≈10%), an acute encephalopathy ensues. When the burden is lower, no deficit is noted in the acute period, but if the cerebral reserve is low (ie, there is an inevident premorbid brain disease such as hypertensive cerebrovasculopathy), then the patient suffers a nonprogressive cognitive deficit (≈8%). In the subgroup of patients in whom the premorbid disease is an inherently progressive disorder (eg, presymptomatic Alzheimer disease that is made manifest by the stress of cardiac surgery), the patient later undergoes a progressive cognitive decline (dementia). This continuum hypothesis explains the disparate results of many studies, because very much like the aphorism of the wise men and the elephant, each investigator was examining a separate part of the problem, but none could see the problem as a whole. All we have to do to deal with the problem of cognitive failure in cardiac surgery survivors is to reduce the burden of cerebral ischemia in those who are selected to undergo the procedure. OPCAB does not address the major issue, arterial source emboli, and thus, not surprisingly, does not address the problem. By selecting patients more carefully with preoperative cognitive and brain imaging methods and then by minimizing intraoperative cerebral emboli using methods that require less manipulation of the heart and aorta, the neurocardiologists of the future might finally save the mind of the cardiac surgery survivor.

Disclosures

None.

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Article III

Health-related quality of life following off-pump versus on-pump coronary artery bypass grafting in elderly moderate to high-risk patients: a randomized trial

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Health-related quality of life following off-pump versus on-pump coronary artery bypass grafting in elderly moderate to high-risk patients: a randomized trial

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Abstract

Objective: Previous trials comparing coronary artery bypass grafting (CABG) with or without extracorporeal circulation have mainly enrolled selected patients at younger age and low risk. Patient-reported health-related quality of life has not been significantly different. We compared health-related quality of life in elderly moderate to high-risk patients randomized to either off-pump or on-pump surgery. **Methods:** The study is a sub-study of the randomized Best Bypass Surgery Trial that compares off-pump to on-pump treatment, with respect to peri- and postoperative mortality and morbidity in patients with a moderate to high-predicted preoperative risk. After randomization and before heart surgery, 120 consecutive patients were asked to fill in the Medical Outcomes Study Short Form 36 (SF-36) and Major Depression Inventory (MDI) diagnostic scale for self-report of health-related quality of life. Three months after surgery, the same questionnaires were mailed to the patients. **Results:** The response rate was 96.5%. At baseline, the groups were comparable except for a difference in educational level. Both groups improved in all eight SF-36 domains from baseline to 3 months. No statistical differences were seen between the groups except for changes in mean difference of role limitation due to emotional problems, which was significantly ($P = .04$) improved in favour of the on-pump group. Depression scores remained unchanged within and between the two surgical groups. **Conclusions:** Both on-pump and off-pump patients improved in health-related quality of life scores after CABG surgery. No clinically relevant difference between the groups could be demonstrated.

Keywords: Coronary artery bypass surgery; Off-pump; On-pump; Health-related quality of life; Quality of life; Depression

1. Introduction

Patients aged 70 years or older undergoing coronary artery bypass grafting (CABG) with the use of a heart-lung machine (on-pump) are at a higher risk of mortality and morbidity than younger patients, because they generally have more co-morbidities and a decreased reserve capacity of most organ systems, making them more vulnerable to postoperative adverse effect on cardiac, pulmonary, renal and neurocognitive function [1]. Nevertheless, long-term survival and good functional improvement can be achieved in the elderly [2]. The success of cardiac surgery is not solely judged by its effects on mortality but also by its neuropsychological and emotional consequences, and by its influence on health-related quality of life (HRQoL) [2,3]. Changes in cognitive function have been associated with reduced HRQoL 1 year [3] and 5 years after cardiac surgery in terms of lower general health and a less productive working status [4]. A randomized study, using a post-test only design, compared medical treatment to invasive treatment in 113 patients with inducible ischemic heart disease. At an average follow-up of 36 months, more invasively treated patients had concentration difficulties but better HRQoL scores in the physical variables [5].

Depression is found to be an independent risk factor for cardiac events after CABG [6]. Patients suffering from depression before the operation are more often depressed after the surgery [7,8] and seem to have worse physical function and higher co-morbidity than patients with low depression score [9]. However, CABG appears to have a beneficial effect on psychological function and HRQoL for the

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majority of patients [10]. Due to the lack of a common definition and the dependence on subjective perception, it has been difficult to assess an overall evaluation of HRQoL among patients undergoing cardiac surgery [11]. Factors such as increased age, female gender, persistent pain (more than 3 months), and poor quality of sleep have been associated with reduced HRQoL outcomes [11]. As an alternative to on-pump surgery, off-pump CABG may improve selected clinical outcomes other than mortality in low to medium risk patients, but no significant difference between surgical groups in health status or HRQoL have been demonstrated in these patients up to now [12]. Evidence for corresponding statements is still lacking in elderly moderate to high-risk patients [1]. We have recently compared cognitive function in elderly moderate to high-risk patients at 3 months after off-pump and on-pump surgery, respectively, and found no significant difference between the groups for cognitive decline (unpublished data). In this study we compare HRQoL of 120 patients who were randomized either to off-pump or on-pump CABG surgery. HRQoL was measured by self-reported information on functional capacity in daily living including physical, emotional, social, mental, and psychological dimensions.

2. Materials and methods

2.1. Participants

The study is a sub-study of the randomized Best Bypass Surgery (BBS) Trial (ClinicalTrials.gov identifier NCT00120991) that aims to compare off-pump to on-pump CABG with respect to per- and postoperative mortality and morbidity, in patients with a moderate to high-predicted preoperative risk. We screened consecutive patients with known ischemic three-vessel heart disease who were >54 years of age, had a EuroSCORE more or equal to 5, and admitted for elective or sub-acute CABG at the Heart Center, Copenhagen University Hospital. We excluded patients with previous heart surgery, ejection fraction less than 30%, those with unstable preoperative condition, i.e., continuous infusion of inotropics on the day of the operation, and patients unable to give informed consent. For the present sub-study, patients were recruited consecutively from the BBS Trial but with the following additional exclusion criteria: Mini Mental State Examination score below 24 points, as a screening test for dementia after randomization and before inclusion in the study, current severe psychiatric disease, i.e., depression, psychosis or alcoholism (patients at referral currently using either antipsychotic or antidepressive medication, or drinking more than 5 units of alcohol per day within the last 3 months), neuropsychological testing within the last year, illiteracy, poor comprehension of Danish, severe visual or auditory disorder, and unwillingness to return to follow-up.

2.2. Procedure

The local Ethics Committee approved the study, subject to journal no. 01-079/02, and all patients provided written informed consent. The patients were centrally randomized to one of the two groups by an external press button telephone voice response system, stratified by the following characteristics: gender, age (55–65 years; >65 years), diabetes mellitus and EuroSCORE (5–8; >8). Patients were randomized in a 1:1 ratio to off-pump or on-pump surgery. The assessors of outcomes and the staff undertaking data analysis were blinded for allocation.

In the off-pump group, the revascularization procedure was performed on the beating heart with a stabilization of the target coronary arteries. When access was needed for posterior coronary arteries a suction device was used to lift the heart. In the on-pump group, the revascularization procedure was performed with the use of a heart-lung machine in normothermia, with aortic cross clamp and cold blood cardioplegic arrest. In both groups, the left internal mammary artery in combination with saphenous vein grafts were standard graft material. The same surgeons performed both procedures. Outcome was assessed the day before bypass surgery or on the day of operation and repeated 3 months after surgery. On both occasions, the patients completed two self-reported questionnaires: the 36-item Medical Outcomes Study Short Form (SF-36) and the Major Depression Inventory (MDI). If a patient was unable to complete the questionnaire, the principal investigator did interview administration. Three months after the operation the same questionnaires were mailed to the patients.

2.3. Assessment of HRQoL

The SF-36 is a self-administered generic questionnaire, which is widely used, reliable, and a valid tool that aims to measure functioning, well-being, and general health status [13]. SF-36 is one of the most commonly used questionnaires for evaluating HRQoL in cardiac surgery and found sensitive to changes within patients undergoing open-heart operation [14]. Besides, it is available in Danish and previously applied in a sample of the general population [15]. The age-matched data are presented in Table 2 for comparison. The instrument measures eight health domains using eight scales with 2–10 items per scale. It reflects the impact of both cardiac and noncardiac diseases on: physical functioning, role limitations due to physical health problems, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems and mental health. The questions relating to each domain is scored on a scale from 0 to 100. The higher the score, the higher the level of functioning, i.e., a score of 100 indicates no impairment of functioning for a given domain. Furthermore, the eight domains can be divided into two distinct groupings summarizing a physical health component and a mental health component. In the current study, the scoring of data was done according to the Danish manual to SF-36 [16] and findings are reported using the eight domains.

The Major Depression Inventory diagnostic scale is a validated 10-item self-rating list containing the 10 ICD-10 symptoms of depression [17]. It can be used both as an instrument measuring the severity of depressive states, and as a screening instrument for the diagnosis of clinical depression. The instrument is available in Danish and previously applied in a sample of the general population [18]. Symptoms are measured on a six-point Likert scale,

indicating whether the symptom has not been present at all (score = 0) to symptom being present all the time (score = 5). Two of the items (8 and 10) are divided into two sub-items (a and b). Only the maximum score for these items were included in the statistical analysis. For this study, we used the MDI as a screening instrument. A mean score for the replied 10 items was calculated in a score range from 0 to 5 with a mean score > 2.5 indicating depression.

2.4. Statistical analysis

All data were analyzed according to randomization on an intention to treat basis. The primary end point was the change in SF-36 score. Differences are presented with 95% confidence intervals (95% CI). The SF-36 and MDI scores are presented with mean and standard deviation (SD) or number and percentage (%). Categorical variables were compared using Pearson's chi-square test or Fisher's exact test as appropriate. For continuous data, changes within the groups were analyzed using paired *t*-test. Groups were compared using unpaired *t*-test (for normally distributed data) or Mann–Whitney's rank sum test (for data not normally distributed). A *P*-value less than .05 were considered statistically significant. No correction for multiple comparisons was applied. All data management and analyzes were performed with Statistical Package for Social Sciences (SPSS) 12.0 software.

3. Results

Between July 2002 and December 2004, 206 consecutive patients who were included for the BBS Trial were evaluated for eligibility. Of these, 56 patients were excluded due to: logistic reasons (35 patients), not meeting inclusion criteria for cognitive testing (13 patients), and refusing to participate (8 patients). As patients were included consecutively, the logistic reasons for the exclusion of 17% can be explained by the absence of a trained surgeon in off-pump technique, the staff collecting data having vacation or day off, or patients not available for baseline information due to inclusion late in the evening or just before operation. Furthermore, 30 of the eligible patients were excluded due to Mini Mental State Examination score of less than 24. Thus, 120 randomized patients were included in the present study. At 30 days, one patient in the off-pump group and three patients in the on-pump group had died. Furthermore, 3 patients in the off-pump group had died beyond 30 days, thus 7 patients (5.8%) were dead by the time of follow-up. Of the remaining 113 patients, response was obtained from 109 (96.5%), i.e., HRQoL could be determined by 54 in the off-pump group and 55 in the on-pump group (Fig. 1). At baseline there were no differences between the groups except for level of education (Table 1).

Table 1
Baseline characteristic of patients undergoing coronary artery bypass grafting with or without cardiopulmonary bypass (off-pump vs on-pump)

Variable	Off-pump ($n = 61$)	On-pump ($n = 59$)
Age, mean (SD) (years)	76 (4.8)	75 (4.2)
Sex, female, *n* (%)	26 (43)	22 (37)
Co-morbidity		
Predisposition for IHD < 55 years of age, *n* (%)	18 (31)	12 (20)
Diabetes, *n* (%)	11 (18)	11 (19)
Hypertension, *n* (%)	40 (66)	33 (56)
Previous myocardial infarction, *n* (%)	42 (69)	46 (78)
Previous neurological complications[a], *n* (%)	12 (20)	15 (25)
History of atrial fibrillation, *n* (%)	3 (5)	6 (10)
Current smoker, *n* (%)	10 (16)	12 (20)
Former smoker, *n* (%)	37 (61)	34 (58)
Basic school		
7 years or less, *n* (%)	31 (51)	34 (58)
8–9 years, *n* (%)	16 (26)	18 (31)
10 years, *n* (%)	9 (15)	5 (9)
High school, *n* (%)	5 (8)	2 (3)
Education level		
None, *n* (%)	17 (28)	30 (51)
Vocational, *n* (%)	35 (57)	28 (48)
University, *n* (%)	9 (15)	1 (2)

[a] Stroke and transient ischemic attack.

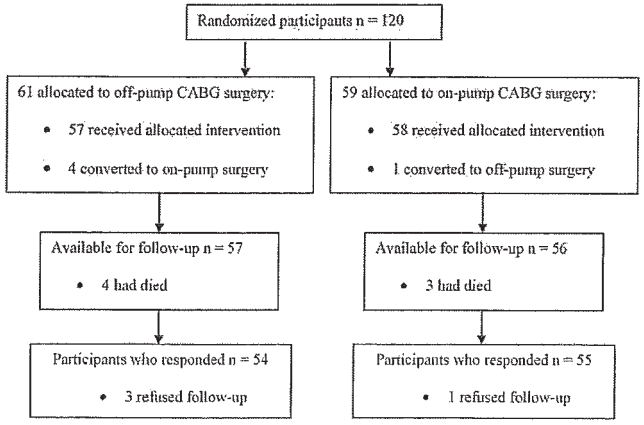

Fig. 1. Flow diagram of patients assigned to off-pump or on-pump coronary artery bypass surgery. CABG: coronary artery bypass grafting.

Table 2
Changes in health-related quality of life (SF-36 scores) in patients undergoing coronary artery bypass grafting with or without cardiopulmonary bypass (off-pump vs on-pump)

Domain	Off-pump					On-pump					National norms[a]
	Baseline	3 months	Difference	95% CI of the difference		Baseline	3 months	Difference	95% CI of the difference		
				Lower	Upper				Lower	Upper	
PF	54.9 (27)	68.4 (23)	11.5 (30)[b]	3.36	19.72	55.5 (24)	64.4 (25)	7.4 (23)	−.81	13.97	61.6
RP	21.2 (34)	43.5 (43)	19.5 (41)[b]	7.73	31.27	15.1 (29)	42.5 (45)	28.9 (45)[b]	15.50	42.28	52.2
BP	62.9 (28)	78.3 (21)	12.1 (29)[b]	4.04	20.19	65.0 (26)	75.2 (23)	10.1 (31)[b]	1.63	18.59	71.0
GH	63.0 (18)	62.7 (21)	.4 (21)	−5.57	6.45	64.3 (19)	64.2 (18)	.4 (24)	−6.67	7.50	62.6
VT	47.0 (23)	57.5 (26)	10.5 (31)[b]	1.52	19.41	51.5 (25)	54.9 (24)	3.7 (27)	−4.00	11.31	60.5
SF	74.8 (28)	88.0 (19)	11.1 (33)[b]	2.03	20.14	79.6 (22)	81.1 (26)	3.4 (30)	−5.12	11.99	81.6
RE	44.8 (43)	54.6 (41)	5.7 (57)	−10.56	21.90	36.4 (38)	59.8 (40)	28.5 (51)[b]	13.67	43.28	64.9
MH	63.0 (19)	75.7 (22)	11.1 (29)[b]	2.87	19.33	68.8 (24)	76.7 (22)	10.5 (24)[b]	3.85	17.09	79.0

Change in groups, with age-matched normative scores included for comparison. PF: physical functioning; RP: role limitations due to physical health problems; BP: bodily pain; GH: general health perceptions; VT: vitality; SF: social functioning; RE: role limitations due to emotional problems; MH: mental health. Values are mean (SD).
[a] General Danish population aged 75+ years ($n = 229$).
[b] Significant difference ($P < .05$) compared with baseline.

Mean duration of operation was 159 (±40) min in the off-pump group and 152 (±30) min in the on-pump group. Duration of cardiopulmonary bypass was 60 (±19) min with 36 (±13) min cross-clamp time. The incidence of postoperative atrial fibrillation was 57% (CI: 43.2–69.4) in the off-pump group and 55% (CI: 41.5–68.3) in the on-pump group. At 3 months, one nonfatal stroke was seen in the off-pump group and two nonfatal strokes occurred in the on-pump group.

3.1. HRQoL

In both groups there was an improvement in HRQoL at 3 months (Table 2). Except for RE favoring on-pump surgery ($P = .04$), no significant difference was found in the change of SF-36 scores between the two groups (Table 3).

The number of patients with depressive symptoms remained unchanged in both groups from baseline to 3 months (Table 4). No significant difference between the groups was found in the change of depressive symptoms (Tables 5 and 6).

Table 3
Changes in health-related quality of life (SF-36 scores) in patients undergoing coronary artery bypass grafting with or without cardiopulmonary bypass (off-pump vs on-pump)

Domain	Off-pump versus on-pump at 3 months			P
	Difference	95% CI of the difference		
		Lower	Upper	
PF	4.15	−6.29	14.60	.43
RP	−9.39	−26.91	8.14	.29
BP	2.00	−9.57	13.57	.73
GH	.020	−9.11	9.15	1.00
VT	6.81	−4.78	18.41	.25
SF	7.65	−4.68	19.98	.22
RE	−22.81	−44.54	−1.07	.04
MT	.63	−9.77	11.03	.91

Difference between groups. PF: physical functioning; RP: role limitations due to physical health problems; BP: bodily pain; GH: general health perceptions; VT: vitality; SF: social functioning; RE: role limitations due to emotional problems; MH: mental health. Values are mean.

Table 4
Changes in depression (based on MDI questionnaire) in patients undergoing coronary artery bypass grafting with or without cardiopulmonary bypass (off-pump vs on-pump)

	Baseline	3 months	Difference	95% CI of the difference	
				Lower	Upper
OPCAB	1.10 (.90)	1.03 (.87)	.05 (.76)	−.16	.26
CCAB	1.03 (.81)	.96 (.91)	−.11 (.92)	−.37	.14

Change in groups. CI: confidence interval.

Table 5
Changes in depression (based on MDI questionnaire) in patients undergoing coronary artery bypass grafting with or without cardiopulmonary bypass (off-pump vs on-pump)

	Off-pump versus on-pump			P
	Difference	95% CI of the difference		
		Lower	Upper	
Baseline	.08	−.24	.39	.64
3 months–baseline	.16	−.16	.49	.33

Difference between groups. CI: confidence interval.

Table 6
Number of patients with depression (based on MDI questionnaire) before and after coronary artery bypass grafting with or without cardiopulmonary bypass (off-pump vs on-pump)

	Baseline	3 months	Changes from baseline to 3 months		
			No → yes	Unchanged	Yes → no
OPCAB	4 (6.9)	4 (7.5)	3 (5.8)	48 (92.3)	1 (1.9)
CCAB	4 (6.9)	4 (7.5)	4 (7.7)	44 (84.6)	4 (7.7)

Values in percentages are shown in parentheses.

4. Discussion

Our objective was to evaluate the effect of off-pump versus on-pump CABG on changes in various aspects of HRQoL in elderly moderate to high-risk patients during the first 3 months after the operation. To our knowledge, this is the first randomized study focusing on that specific topic and, in addition, we assessed depression scores. Generalizations of the findings are further limited by the single-center experience, and should therefore be replicated in larger multi-center trials in order to finally verify whether or not there is an improvement in health-related quality of life among off-pump patients compared to patients undergoing on-pump CABG surgery. This study is characterized by a high degree of internal validity in terms of accounting for patient selection, and a large number of the patients were available for 3 months follow-up, as only 4 out of 113 refused to participate. The study was randomized with a negligible crossover between the groups and the instruments used are based on well-documented valid and reliable questionnaires. The two treatment groups were similar regarding demographic variables at baseline expect for education level which is considered to be incidental (Table 2). We have previously demonstrated a nonsignificant difference in the incidence of cognitive dysfunction between the two surgical procedures (unpublished data); therefore, known consisting confounders related to cognitive function, age and gender, can be excluded. With an incidence of cognitive dysfunction previously found to be 7% in the off-pump group and 10% in the on-pump group, it was not possible to make any reasonable analysis for this study, examining the impact of cognitive dysfunction on specific domains of SF-36 within and between the groups.

In both groups, there was an improvement in SF-36 scores. Baseline scores were clearly below the values in the background population but after surgery, several domains improved to a level equal to or even better than those of a comparable background population. We expected that the improvement would be greater in the off-pump group but, in contrast, a small but significant difference in one SF-36 domain (RE) ($P = .04$) was seen at 3 months, favoring treatment with on-pump. It should, however, be taken into account that we did not correct for multiple comparisons, so we must conclude that no difference could be detected. We are aware that limited statistical power may be important but, on the other hand, the differences in the individual scores between the groups are very small and in different directions. The detection of a difference between scores of RE at 54.6 and 59.8 would require approximately 2000 patients if a type 2 error of 20% is accepted. Besides, the variation in scores of HRQoL may not only reflect variation of the individual person, but suggests consideration of the total surgical treatment and care from admission to completed outpatient rehabilitation. The use of extracorporeal circulation is only one element of this course of the disease [19]. Previously published measurements of HRQoL at 1, 3, 6, and 12 months have been reported in four randomized trials mainly including younger patients at lower risk [19–23]. Additionally, one study obtained data from 328 of 401 randomized patients using a post-test only design with a median follow-up at 3 years [24]. Different instruments such as EuroQOL-6, EuroQOL (original version), EuroQOL-5, SF-36, and the 16-item Quality of Life Scale-Norwegian were used, all showing that HRQoL improved in off-pump and on-pump groups over time, but there were no significant differences between the surgical groups regardless of the instruments used or the design of the study.

It is remarkable that only 6.9% and 7.5% of the patients scored more than 2.5 at the MDI diagnostic scale. For this study, we used the MDI as a screening instrument. A mean score for the replied 10 items was calculated in a score range from 0 to 5 with a mean score >2.5 indicating symptoms of depression. This is in accordance with the reported prevalence of MDI score ≥20 that was 7.1% in the Danish population [18]. In contrast, the prevalence of depression is estimated to be between 27% and 47% of patients scheduled for heart surgery, and between 19% and 61% of patients after the intervention [25]. A plausible explanation might be that the studies up to now, mainly were completed in the mid 90s as criteria for operation were more restrictive and the course of disease from the first signs of symptoms until discharge from hospital has become much shorter now. Another possible explanation could be the age of the study population as younger persons might have a higher degree of anxiety when they are confronted with a life-threatening disease and its emotional consequences.

In conclusion, this is the first randomized trial of self-reported outcomes after on-pump versus off-pump coronary artery bypass surgery in elderly moderate to high-risk patients. We revealed improvement in HRQoL within both surgical groups to the same level as a comparable healthy background population. Depression scores remained unchanged within and between the two surgical groups. No clinically relevant difference between off-pump and on-pump bypass surgery could be demonstrated. Therefore, the method of choice at our center still depends on which of the techniques the individual surgeon prefers and feels most comfortable with.

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