Outcomes after off-pump coronary bypass surgery

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Outcomes after off-pump coronary bypass surgery

Effecten van coronaire bypass chirurgie zonder hart-longmachine

(met een samenvatting in het Nederlands)

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voor Toon

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Chapter 1

General introduction

Coronary artery bypass surgery (CABG) effectively relieves angina, but is associated with significant morbidity.[1-3] The potential benefits gained by avoiding cardiopulmonary bypass (CPB) have led to a renewed interest in bypass surgery on the beating heart.[4-6] The Octopus Stabilizer is one of the recently developed devices that can immobilize and present all sides of the beating heart, thus facilitating coronary bypass surgery without the use of CPB (off-pump CABG).[7]

Predominantly observational studies have claimed advantages of off-pump CABG, including less morbidity,[8] faster recovery,[9] shorter hospitalization[8,10,11] and a reduction of costs.[10,12] While sternotomy is virtually always required when CPB is used, off-pump CABG may be performed via smaller incisions.[13,14] The most important potential advantage of off-pump CABG, however, is improved cerebral outcome. A substantial number of studies indicate that conventional coronary bypass surgery using CPB (on-pump CABG) is associated with postoperative cognitive decline, which has been attributed to the use of CPB.[3,15-20] These studies are systematically reviewed in *chapter 2* of this thesis. It is assumed that cardiac outcome after off-pump CABG is similar to conventional procedures.[4,9] Off-pump CABG, however, is technically more demanding and no proof is yet available that off-pump surgery can match the long-term cardiac benefits of the on-pump operation.[21] It is conceivable that grafting vessels in the depth of the thoracic cavity on a slightly moving target might compromise the quality of the distal anastomoses and result in more late cardiac complications.[22]

The Octopus Study was designed to compare off-pump CABG to intracoronary stent implantation, and to conventional CABG with use of CPB. The Octopus Study therefore consists of two randomized trials: one directly comparing off-pump CABG and intracoronary stent implantation (OctoStent Trial) and one directly comparing off-pump CABG and on-pump CABG (OctoPump Trial).[23] In this thesis, the rationale, design, and principal results of the OctoPump Trial are presented. The term Octopus Study therefore refers here to the OctoPump Trial, i.e. the randomized comparison of off-pump and on-pump CABG.

The primary objective of the study was to compare cognitive outcome between patients randomized to off-pump or on-pump

CABG. As it was assumed, but not established that off-pump and on-pump CABG are equally effective in terms of myocardial revascularization, an important secondary objective of the trial was to compare cardiac outcome. An extensive description of the objectives and methods of the Octopus Study is given in *chapter 3*. The principal results of the study, i.e. the effect of CPB on cognitive outcome, are described in *chapter 4*. In addition, the effects of CPB on quality of life are presented. We constructed multivariate models in order to identify predictors of cognitive decline after CABG. These multivariate analyses are presented in *chapter 5*. The clinical outcomes are the focus of the following two chapters. In *chapter 6*, the in-hospital and early postoperative course of the patients are described. This includes the completeness of revascularization, transfusion rate, and perioperative complications. *Chapter 7* presents cardiac outcome at one year after surgery, including the occurrence of cardiovascular events, recurrence of angina, exercise testing, and coronary angiography. In this chapter, we also present a cost-effectiveness analysis. Finally, *chapter 8* discusses explanations for some unexpected results of the study, together with its methodological limitations. Suggestions for future research are provided.

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Chapter 2

Neurocognitive dysfunction after coronary artery bypass surgery: a systematic review

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Abstract

Objective Substantial, albeit scattered, evidence suggests that coronary artery bypass grafting may impair cognitive function. As methods and definitions differ greatly across studies, the reported incidence of cognitive decline after coronary bypass surgery varies widely as well. The aim of the present study was to systematically review those studies on cognitive decline that are relatively comparable and meet with certain quality criteria.

Methods Four electronic databases and the references of several abstract books and earlier reviews were used to identify relevant literature. Stringent criteria, based in part on the 1994 consensus meeting on assessment of neurobehavioral outcomes after cardiac surgery, were used to assess the studies that were found. In total, 256 different titles were found, of which 23 met with the formulated selection criteria.

Results Twelve cohort studies and eleven intervention studies were evaluated. A pooled analysis of six highly comparable studies yielded a proportion of 22.5% (95% confidence interval, 18.7%-26.4%) of patients with a cognitive deficit (a decrease of at least 1 standard deviation in at least two of nine or ten tests) 2 months after the operation.

Conclusions Neurocognitive dysfunction is a frequently occurring complication of coronary artery bypass grafting. The etiologic contribution of cardiopulmonary bypass to this complication will remain unclear until a randomized trial that directly compares off-pump and on-pump bypass surgery is carried out.

Introduction

Coronary artery bypass grafting (CABG) with the use of cardiopulmonary bypass (CPB) is associated with significant cerebral morbidity.[1] The two main clinical manifestations of brain injury after CABG are stroke and cognitive decline.[1] The incidence of postoperative stroke is consistently reported to be around 3%[1,2] and as high as 9% in patients older than 75 years.[3,4] However, the reported incidence of cognitive decline varies widely.[5] This variability is partly caused by methodologic problems: a multitude of definitions of cognitive decline are used, and a large number of neuropsychologic tests exist to assess the various cognitive domains.[6] Moreover, the interval between operation and administration of the neuropsychologic tests may range from a few days to several years. Some literature reviews on cognitive deficits after CPB have been published,[7-10] but the methodologic variability of the studies hampers comparison of the results.

At a consensus meeting in 1994, several guidelines for the assessment of neuropsychologic deficits after CPB were established.[11] It was recommended that the neurologic and neuropsychologic state be assessed before the operation to provide accurate baseline information. A second important recommendation was that the analysis should be based on the individual change in performance from baseline to a particular time after the operation. In general, practice effects cause the overall group performance to improve after the operation. Accordingly, when the overall postoperative mean is compared with the preoperative mean, the decline of some individuals is overshadowed by the improvement of others. Also, it was agreed that a late assessment (ideally after 3 months) should be included in the study design, because the patients' performances are unstable in the immediate postoperative period.

Although these consensus guidelines were developed for the design of new research protocols, we found some of them also suitable to interpret studies carried out in the past. This systematic review is restricted to studies on cognitive decline 1 to 12 months after CABG, which were considered methodologically homogeneous according to well-defined and strict criteria. Both the primary selection of studies and the assessment and comparison of the studies that were included were largely based on rec-

ommendations of the 1994 consensus.[11] As a result of the technical improvements of CPB and the alterations in anesthetic management, studies published before 1980 were considered less relevant and therefore were excluded.

Methods

Literature search

For the literature search, four electronic databases (MEDLINE, PsychLit, PubMed, and Current Contents) and references of four earlier published (abstract) books and three reviews were used. The precise search strategy is described in Table 1. To assess the quality of the search strategy, we sampled ten studies that we already had on file and considered relevant. The search strategy was able to identify these articles. The total number of different titles found was 256 (Table 1).

Selection of the literature

The studies were independently judged by a clinician and a psychologist using the following selection criteria:

Inclusion criteria:

- Primary research on cognitive decline after CABG, including a preoperative neuropsychologic assessment to provide baseline information
- Postoperative neuropsychologic assessment between 1 and 12 months after the operation
- Data analysis based on the individual change in performance from baseline to a time after the operation

Exclusion criteria:

- Studies published before 1980
- Studies including open chamber or valvular procedures
- Studies with unclear timing of test administration
- Articles describing the same or an overlapping patient sample as other articles already included in the review

These selection criteria were applied on the 256 titles found. Thirty-four articles could be excluded on the basis of the title only and 111 articles were excluded on the basis of the abstract. For the remaining 111 titles, the complete article was studied.

Table 1: Literature search: sources and results

Source	No. of titles found
• MEDLINE electronic database 1980-1999: Medical Subject Heading (MeSH) standard terms: *(heart surgery or coronary artery bypass or extracorporeal circulation or cardio-pulmonary bypass) and (cognition disorders or cognitive symptoms or neuropsychology or neuropsychological tests)*	161
• Psychlit electronic database 1980-1999: standard terms: *(heart surgery) and (neuro-psychological assessment or cognitive assessment or cognition or concentration or attention)*	10
• Book: 'cardiac surgery and the brain' by Smith and Taylor12: relevant references of relevant chapters	67
• Abstract books of the conferences on cardiac surgery and the brain ('Outcomes - The Key West Meeting' '97, '98, '99): relevant references of relevant chapters	69
• The references of three recent reviews on cardiac surgery and cognitive decline[9,10,13]	91
• Current Contents and PubMed 1999: January - September	18
Total number of different titles	256

In the numbers of titles found, articles published before 1980 and books are not included

The majority of these publications were written in English. Many articles were excluded because data of patients undergoing CABG were mixed with data of patients having valve replacement, because data analysis was based on comparison of mean group performance before and after the operation, or because only an early postoperative neuropsychologic assessment (ie, less than 1 month) was performed. Seven studies were excluded[14-20] because the same patient series had (partly) been used in other studies already included in the review and their inclusion would have overemphasized the results of these series. Finally, one article published in Japanese was rejected because a translation could not be obtained. Only 23 articles matched all the selection criteria.[5,21-42]

Literature processing

The 23 articles meeting the selection criteria were processed independently by a psychologist and a clinician using a three-page standard form. This form was filled out to systematically assess the research question, study design, neuropsychologic tests used, statistics, main conclusions, and other items. The forms were the basis for Tables 2 and 3 in the "Results" section.

The neuropsychologic sections were independently judged by two trained neuropsychologists, blinded for author and journal

Table 2: Cohort studies

First author	Year of publication	No. of patients	Mean age, y	NP-test timing, mo	Lost to follow-up, %
Ellis[21]	1980	30	55	1	0
Shaw[22]	1987	259	54	6	17
Treasure[23]	1989	76	55	2	12
Harrison[24]	1989	78	55	2	40
Mahanna[5]	1996	232	61	1,5 / 6	60 / 61
Toner[25]	1996	61	60	2	0
Tardiff[26]	1997	65	62	1,5	12
McKhann[27]	1997	172	63	1 / 12	26
Braekken[28]	1998	14	64	2	0
Vanninen[29]	1998	38	64	3	3
Browne[30]	1999	120	?	3	0
Rasmussen[31]	1999	35	70	3	17

NP-test timing indicates time between CABG and postoperative neuropsychologic test administration; Definition of cognitive deficit: 1 (>=1 SD in >=1 test); 2 (>=1 SD in >=2 tests); 3 (>=1 SD in >=3 tests); 4 (>=0.5 SD in a domain); 5 (>=20% in >=2 tests); 6 (>=20% in >=20%); 7 (other); Comparability: ++: tests of 'core battery' are used (Rey auditory verbal learning task, Trailmaking Tests A and B, Grooved Pegboard); +: comparable tests were used; -: tests were not comparable with core battery.

* Five different definitions were used. The percentages given are for 1 SD decline in one or more tests.

† Analyzed per domain.

‡ Three different definitions were used on two tests. Proportions of patients with deficit varied from 7% to 33 %.

names. Again, several recommendations of the Statement of Consensus 11 were taken into account. Neuropsychologic test batteries were rated with respect to (1) the cognitive domain of the tests, (2) the sensitivity of the tests, (3) the availability of parallel forms of the tests, and (4) the overall balance of the cognitive domains assessed in the battery. So that the comparability of the studies could be further improved, (5) a recommended core battery was taken as the basis for our assessment of quality of the test batteries used. This core battery minimally includes the Rey Auditory Verbal Learning Task, the Trail Making Tests A and B, and the Grooved Pegboard. These tests are widely used, easy to conduct, well-normalized, and sensitive to cerebral damage.

Analysis

Studies were classified as (1) cohort studies, aiming to determine the incidence of cognitive decline at a certain moment after the operation and/or to identify determinants of cognitive decline, or

Table 2: (continued)

No. of tests used	Definition cognitive deficit	Compar-ability	Proportion patients with cognitive deficit, %
3	7	-	17
10	2	-	22
10	2	++	37
10	2	++	36
5	7*	-	14* / 4*
10	2	++	38
7	6	-	47
8	4	+	†
10	2	+	14
8	3	-	22
2	7‡	-	‡
5	7	-	14

(2) intervention (controlled) studies, investigating the cerebral protective effect of intraoperative interventions.
To determine whether a pooled analysis could be carried out, we assessed the comparability of the studies entered into the review in terms of precise timing of neuropsychologic testing, comparability of tests, and definition of decline.

Results

Cohort studies

The twelve cohort studies meeting the selection criteria are presented in Table 2. Some of these studies exclusively aimed to determine the incidence of neuropsychologic decline, whereas others were designed to identify determinants of cognitive decline. The studies in Table 2 are ordered by year of publication. The mean age of the patients studied increased over time,

Table 3: Intervention studies

First author	Year of public	No. of patients	Mean age, y	NP-test iming, tmo	Lost to follow-up, %	No. of tests used	Definition cognitive deficit
Fish[32]	1987	2 x 50	58	2	26	10	7
Arrow smith[33]	1998	87 + 84	59	2	7	9	2
Sellman[34]	1993	3 x 20	59	1 / 6	10	13	2
Pugsley[35]	1994	53 + 52	55	2	5	10	2
Murkin[36]	1995	4 x 79	61	2	24	5	7
Patel[37]	1996	2 x 35	57	1,5	0	10	2
Gold[38]	1995	2 x 124	66	6	9	11	7
Mora[39]	1996	54 + 55	63	1,5	23	5	1
Regragui[40]	1996	31+36+29	59	1,5	27	7	7
Heyer[41]	1997	46 + 53	64	1,5	74	5	7
Hammon[42]	1997	192 + 203	61	1,5	?	11	5

NP-test timing indicates time between CABG and postoperative neuropsychologic test administration; Definition of cognitive deficit: 1 (>=1 SD in >=1 test); 2 (>=1 SD in >=2 tests); 3 (>=1 SD in >=3 tests); 4 (>=0.5 SD in a domain); 5 (>=20% in >=2 tests); 6 (>=20% in >=20%); 7 (other); Comparability: ++: tests of 'core battery' are used (Rey auditory verbal learning task, Trailmaking Tests A and B, Grooved Pegboard); +: comparable tests were used; -: tests were not comparable with core battery.

Table 3: (continued)

Comparability	Intervention studied	Results
-	prostacyclin during CPB	0% cognitive decline in intervention group and control group
+	remacemide vs placebo	remacemide group: 9% decline; placebo group 12% decline (p=0.6)
-	membrane vs bubble oxygenator and use of arterial line filter	bubble ox - no filter: 24% / 12% decline; bubble ox - with filter: 12% / 6% decline; membrane ox - no filter: 15% / 5% decline. All differences NS
++	use of arterial filter	filter-group: 8.2% decline; control-group: 26.7% decline (p<0.03)
-	alpha-stat vs pH-stat blood gas management and pulsatile vs non-pulsatile CPB	alpha-stat group: 30% cognitive dysfunction; pH-stat group: 36% cognitive dysfunction (NS); pulsatility has no effect on outcome
++	alpha-stat vs pH-stat blood gas management	alpha-stat group: 45.7% np deficit; pH-stat group: 68.6% np deficit (NS)
-	bloodpressure during CPB: 50-60 mmHg vs 80-100 mmHg	low pressure group: 12% deteriorated; high pressure group: 11% deteriorated (NS)
-	perfusion temperature <28 °C vs >35 °C	15% deterioration in both treatment groups
-	perfusion temperature 28 °C vs 32 °C vs 37 °C	significantly more deterioration in 37 °C group, compared to 32 °C group (p=0.015)
+	perfusion temperature 28 °C vs 34 °C	15% decline in 28 °C group; 39% decline in 34 °C group; difference NS
++	combination of epi-aortic scanning, more use of single cross clamp and more ventricular venting versus standard treatment	intervention group: 18% decline; standard treatment group: 29% decline (p=0.01) (nonrandomized study)

Table 4: The four cohort studies and two intervention studies that were comparable

First author	Year of publication	No. of patients	Mean age, y	NP-test timing, mo	No. of tests used
Treasure[23]	1989	76	55	2	10
Harrison[24]	1989	78	55	2	10
Pugsley[35*]	1994	105	55	2	10
Toner[25]	1996	61	60	2	10
Arrowsmith[33*]	1998	171	59	2	9
Braekken[28]	1998	14	64	2	10
Total		505			
Weighted average					

The four cohort studies and two intervention studies that were comparable in definition of cognitive decline (a decline in performance at least 1 standard deviation in at least two tests), use of the core-battery (Rey Auditory Verbal Learning Task, the Trailmaking Tests A and B, and the Grooved Pegboard) or comparable neuropsychological tests, and timing of test-administration (2 months after operation). These six studies include 505 patients, of whom 448 completed two months follow-up. To calculate a weighted average, the proportion of patients with cognitive decline per study was multiplied with the number of patients per study who completed follow-up. The sum of the multiplications was then divided by the total number of patients who completed follow-up. On average, the proportion of patients with cognitive decline was 22.5% ($p < 0.0001$; 95% confidence interval 18.7 % - 26.4 %).

* Intervention studies, in which the weighted mean of the proportions of patients with a deficit in the two treatment groups was used.

but no clear time trend could be observed in the incidences of cognitive deficits, which varied from 4% to 47%.

None of the studies designed as a correlation study[21,25,26,28,31] was able to identify determinants of cognitive decline in the primary analysis. However, in a multivariate analysis, Tardiff and associates[26] found a significant association between short-term memory dysfunction after CABG and a variant form of the apolipoprotein E gene, especially in patients with lower educational levels. This gene encodes the APOE protein, which is responsible for repair of neuronal injury and probably involved in the development of Alzheimer disease.

Intervention studies

The eleven intervention studies included are shown in Table 3. Ten of them were randomized trials. In two studies, the initial data analysis demonstrated that the intervention studied led to a statistically significantly ($p<0.05$) decreased risk of cognitive decline. Hammon and colleagues[42] compared the results in

Table 4: (continued)

No. of patients who completed follow-up	Proportion of patients with cognitive deficit, %
67	37
47	36
100	17.45*
61	38
159	10.45*
14	14
448	
	22.5

patients operated on in 1991 and 1992 with results in patients operated on in the next 2 years. In the second time period, the surgical team had adopted the use of epiaortic scanning and had increased the use of the single crossclamp technique and left ventricular venting. This combined strategy reduced the incidence of cognitive decline by 11% (p=0.01). The other study with a significant result in the initial analysis showed a beneficial effect of the use of an arterial line filter.[35]

Many intervention studies had insufficient statistical power to detect clinically meaningful differences. In some of these studies, post hoc use of another definition of cognitive decline led to significant results. One example is the remacemide trial by Arrowsmith and coworkers.[33] Individual cognitive decline was less frequent in the treated group, but the study lacked power to reach statistical significance. Redefining cognitive decline as "overall postoperative change" made the favorable effect of remacemide statistically significant.

Pulsatile blood flow during CPB did not improve neurocognitive outcome in 316 patients,[36] but in the same series, alpha-stat blood gas management reduced the incidence of cognitive deficits. This reduction was significant in patients with a bypass time of more than 90 minutes. The protective effect of alpha-stat blood gas management was also found by Patel and associates.[37] The observed difference became statistically significant when a more stringent definition of neuropsychologic deficit (decline on three tests instead of two tests) was used.

The three studies on the influence of perfusion temperature[39-41] failed to demonstrate a clear advantage of hypothermia compared with normothermia, but the sample sizes of the studies were relatively small, and in the study of Heyer and colleagues[41] only 26% of the study patients were available for follow-up.

Neuropsychology

The selected studies included neuropsychologic tests as the measure of cognitive decline. Of the 23 selected studies, six included the core battery as recommended by the Statement of Consensus.[11] In addition, four studies used tests similar to the recommended core battery (see Tables 2 and 3). Accordingly, ten studies were at least partially comparable and met with widely accepted quality criteria.

Four study groups[5,22,30,37] used several definitions of cognitive decline in their samples. The definition used most frequently (in nine studies) was a postoperative deterioration of at least 1 standard deviation (of the population's performance at baseline) compared with preoperative testing in at least two tests. In one study the same definition was used with a minimum of three tests showing deterioration, whereas one other study took deterioration in one test as criterion. Comparability in terms of definition of cognitive decline was thus limited to nine studies.

Pooled analysis

Four cohort studies[23-25,28] and two intervention studies[33,35] were comparable not only in definition of decline and use of the core battery or comparable tests, but also in timing of test administration. These six studies in total included 505 patients, of whom 448 completed 2 months of follow-up (Table 4). We combined the results of these studies in a weighted average (the sum of the proportions of patients with cognitive decline per study times number of patients per study, divided by the total number of patients). For the two intervention studies, the weighted mean of the two treatment groups was used. On average, 22.5% of the CABG patients had a decline of at least 1 standard deviation in at least two of a total of nine or ten tests 2 months after their operation ($p<0.0001$; 95% confidence interval, 18.7%-26.4%).

Discussion

This study systematically reviewed reports on cognitive decline after CABG. The literature search was extensive. In an attempt to select studies that could be compared, we formulated stringent selection criteria. A limitation of using these selection criteria is that some informative aspects of research were rejected. The relatively small number of the studies that could be included in the review underlines the lack of comparability of studies carried out until now.

The reported incidences of cognitive deficits varied widely. At least in part, this can be explained by the differences in timing of test administration and definitions of cognitive deficit. A high loss to follow-up in 3 studies[5,24,41] may also have influenced the incidences found, as loss to follow-up is seldom random.[6] Most of the included studies were comparable in terms of neuropsychologic tests used, which is probably encouraged by the Statement of Consensus that was held in 1994.[11]

Within the six studies used for the pooled analysis, there was still a considerable variation in the reported incidence of cognitive decline (10%–38% 2 months after the operation). It is not possible to conclude from these studies that the incidence of cognitive deficits has decreased in the past 10 years. Improved outcome as a result of better anesthesiologic and perfusion management may be offset by the increasing age of the patients, which in itself is associated with an increased risk for cerebral complications.[36,42] With the six selected studies, we calculated an average incidence of cognitive deficits of 22.5% 2 months after CABG. This figure must be interpreted with caution because, even within these six studies, methodologic differences were present. For example, the cutoff value of 1 standard deviation, used to define a deficit, varied per study, because the baseline performances of the six patient series are inevitably not the same. A formal meta-analysis, which is typically performed with a series of methodologically comparable randomized trials, includes the use of more advanced weighing factors, testing of homogeneity of the effect estimates of the different studies, and a sensitivity analysis. However, the methodology of meta-analysis of uncontrolled observational studies is

subject to debate,[43] and its use in this review would have unjustly suggested a high level of objectiveness and precision.

The clinical meaning of a decline of 1 standard deviation in two tests is relative, because the figure calculated, 22.5%, does not indicate the percentage of patients who are significantly disabled after CABG. Several authors emphasize that, in most patients, the deficit does not matter to the patient in functional terms. Apparently, many activities of daily life do not require the level of performance called for during neuropsychologic testing. However, a small proportion of patients with intellectual dysfunction or memory deficits become sufficiently disabled to prevent return to employment.[1,22]

The discrepancy between decline in test performance and functional decline is also expressed by the methodologic difficulties of defining a cognitive deficit. Mahanna and colleagues[5] demonstrated the enormous influence of the definition of cognitive deficit that is chosen by applying five different definitions on the same patient sample. Depending on the definition used, the incidence of cognitive deficit ranged from 1.1% to 34% at 6 weeks and from 3.4% to 19.4% at 6 months postoperatively.

Most authors defined deficit as a certain deterioration in one or more tests, which may seem accurate. However, some tests comprise more than one test variable, and from most studies it was not clear whether test deficit meant deterioration in one or all of the variables of one test. This obviously creates a multitude of possible outcomes and is therefore a factor complicating the interpretation of the incidence data. A deterioration of 1 standard deviation in postoperative functioning compared with preoperative functioning was the most frequently used cutoff value. This is arbitrary and does not necessarily reveal real cognitive change, since it does not take into account the reliability of the change scores. Practice effects were almost always mentioned but not included in analyses, which may have resulted in an underestimation of incidence figures. There is emerging recognition of the importance of defining real change in test-retest scores as opposed to artifactual change resulting from low test reliability and susceptibility to practice effects. Recent research is increasingly focused on the use of reliable change indices. These indices define the range in which an individual score is likely to fluctuate

because of the imprecision of the measure, providing statistically based cut-off scores for cognitive change on each measure.[44,45] For example, a 90% reliable change interval is calculated on the basis of the correlation and the standard error of the difference between baseline and follow-up scores of control subjects. When the difference between an individual patient's postoperative and preoperative scores falls outside this interval, he or she is considered to have a statistically significant change in performance on this particular neuropsychologic measure.[44]

The single-case analysis technique, recommended in the consensus statements,[11,46] uses the patient as his or her own control and defines a cognitive deficit as a 20% decrease in at least 20% of the tests. This method also has some drawbacks. In the first place, reducing the continuous test scores to a dichotomous outcome measure (presence of a 20% decrease or not) is a "costly" way of data handling that reduces statistical power and may have made several randomized studies fail to reach statistically significant results. The 20% decrease rule is as arbitrary as the 1 standard deviation decrease rule. The problem may be overcome by refraining from "dichotomizing" data and just calculating how much the patient's performance deviates from the expected (baseline or control group) performance. Second, due to floor effects it may be difficult to demonstrate a deficit in patients with a low preoperative test performance. In the third place, as demonstrated by Browne and colleagues,[30] "regression toward the mean" may strongly influence single-case definitions of cognitive deterioration. High baseline performers may be wrongly classified as impaired and low baseline performers may not show a deficit although deterioration had actually occurred. This problem can be overcome by using group mean analysis, which is free from the influence of regression to the mean (in contrast to analysis by single-case definitions). As discussed before, comparison of mean group performance before and after surgery does have disadvantages, especially if large practice effects are present. However, if a suitable control group is available (randomized trial), comparison of group means allows for the control of both practice effects and regression to the mean.

Conclusions

A pooled analysis of six highly comparable studies yielded a proportion of 22.5% of patients with a cognitive deficit 2 months after CABG. Although this percentage is partly determined by the definition of cognitive deficit that was used, it demonstrates that cognitive dysfunction is a frequently occurring complication of CABG. The etiologic contribution of CPB to this complication will remain unclear until a randomized trial that directly compares off-pump CABG with on-pump CABG is carried out. To improve comparability of future studies, we advocate that researchers use the guidelines of the 1994 consensus meeting. However, the recommended single-case analysis technique has some drawbacks and may be replaced by other analysis techniques, especially when a control group is included in the study design.

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Chapter 3

The Octopus Study: rationale and design of two randomized trials on medical effectiveness, safety, and cost-effectiveness of bypass surgery on the beating heart

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Abstract

The Octopus Study consists of two multicenter randomized clinical trials in which coronary artery bypass grafting on the beating heart (off-pump CABG) using the Utrecht Octopus Method is compared to intracoronary stent implantation and conventional CABG. The primary endpoint in the comparison of off-pump CABG versus stent implantation (OctoStent Trial) is medical effectiveness (i.e., absence of reintervention and major adverse cardiac and cerebrovascular events at 1 year after treatment). The primary endpoint in the comparison of off-pump CABG versus conventional CABG (OctoPump Trial) is cerebral safety (i.e., absence of cognitive deficits and cerebrovascular events at 3 months after treatment). Secondary endpoints in both trials include presence and severity of angina, quality of life, exercise capacity, and cost-effectiveness. A total of 560 patients will be enrolled. A random sample of 210 patients will undergo repeat angiography at 1 year to assess angiographic restenosis rate and graft patency. Including 1-year follow-up, the study will last for 3 years.

Introduction

Ischemic heart disease is the leading cause of morbidity and mortality in the industrialized world.[1] Treatment is basically aimed at palliation and consists of either pharmacologic intervention or revascularization. The latter may be performed by percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass surgery (CABG). PTCA is increasingly being combined with intracoronary stent implantation, which expands the pool of candidates for nonsurgical treatment to patients with more advanced disease.[2] Concurrently, the conventional bypass operation during which cardiopulmonary bypass is used (on-pump CABG) is being challenged by bypass surgery on the beating heart (off-pump CABG).[3-7] The latter obviates the need for cardiopulmonary bypass (CPB) and aortic cross-clamping, which are held responsible for major complications following CABG, in particular neurological and cognitive dysfunction.[8,9]
Recently, in the Heart Lung Institute of Utrecht University Hospital, the Octopus Tissue Stabilizer® for local cardiac wall stabilization has been developed.[10] This device offers immobilization and presentation of all sides of the heart and therefore allows three-vessel revascularization without the use of CPB.[7] The feasibility of off-pump CABG using the Octopus method has been demonstrated in animal studies[10-14] and clinical practice.[7] The early clinical outcome and graft patency rates in the first 100 patients stimulated us to initiate randomized trials to compare this new technique with other revascularization strategies.[7]

Objectives
The aim of the Octopus Study is twofold: first, to compare medical effectiveness between off-pump CABG and PTCA with intracoronary stent implantation in patients referred for PTCA in whom off-pump CABG is feasible (OctoStent Trial); second, to assess the cerebral safety of off-pump CABG compared to the cerebral safety of conventional CABG in patients referred for CABG in whom off-pump CABG is feasible (OctoPump Trial). In addition, in both trials the cost-effectiveness of off-pump CABG will be estimated relative to the reference treatment.

Rationale

PTCA and CABG play an important role in the treatment and management of ischemic heart disease. Both treatment modalities have their intrinsic advantages and disadvantages. A limitation of PTCA is the risk for restenosis. Approximately 20 - 40% of the patients who underwent a first successful PTCA will undergo another revascularization procedure within the first year after the procedure.[15,16] Intracoronary stent placement leads to a reduction of restenosis rate and repeat interventions, especially with improved implantation techniques.[17] Other advantages of stent implantation are a highly predictable and complete restoration of the coronary anatomy immediately after implantation and a reduced risk of (sub)acute vessel closure, which improves the safety of the procedure.[18,19]

CABG provides more complete revascularization and requires fewer repeat interventions in comparison with PTCA. However, the procedure is more invasive and is associated with cardiac as well as noncardiac morbidity.[20,21] Major neurologic complications after conventional cardiac surgery have recently been reported to occur in 3.1% of the patients.[8] In addition, neuropsychological dysfunction is increasingly being recognized as a complication of on-pump CABG. Currently, cognitive deficits can be documented accurately[22,23] and may occur in up to 38% of the patients.[8,9,24,25]

The increasing awareness of the cerebral complications following CABG, especially in the elderly[9], has led to a renewed interest in bypass surgery on the beating heart. The Utrecht Octopus method is a recent technique developed to avoid CPB and the complications associated with its use.[7,10-14] A feasibility study in the first 100 patients operated on with the Octopus Method showed angiographic results comparable with historical controls. There was no mortality at 30 days, and the myocardial infarction (MI) rate was 4%. The patients had a fast recovery and quickly resumed normal socioeconomic activities.[7]

The role of off-pump CABG, however, is subject to debate. Opponents emphasize the excellent results of conventional CABG and express their concerns about the safety, early anastomotic failure, and eventual incomplete revascularization related to off-pump CABG.[26] Moreover, although widely accepted, the suspected deleterious role of cardiopulmonary bypass in the gene-

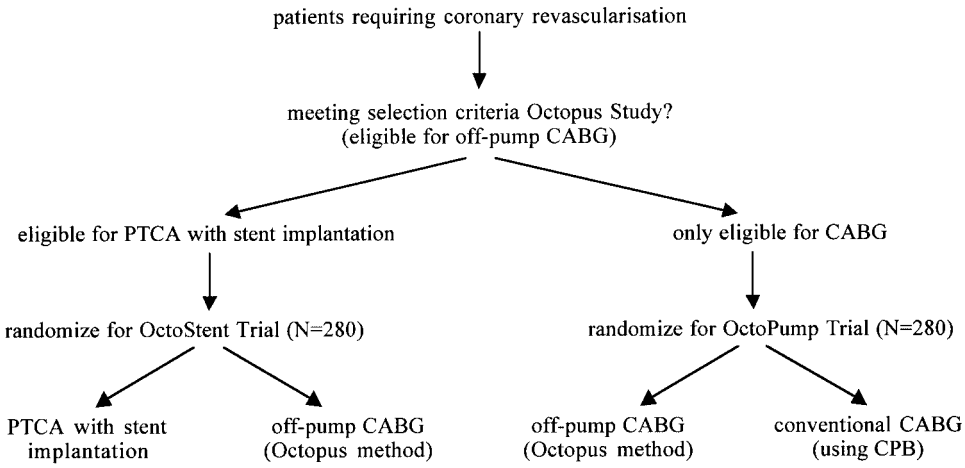

Figure 1: Flow-chart Octopus Study

Only patients eligible for offpump CABG can enter the study. CABG = coronary artery bypass grafting; PTCA = percutaneous transluminal coronary angioplasty; CPB = cardiopulmonary bypass.

sis of adverse cerebral outcome has never been proved, simply because an appropriate control group has never been available. A limited number of randomized clinical trials have directly compared PTCA to CABG.[15, 20, 27-29] There are no randomized clinical trials comparing off-pump CABG to stent implantation or conventional CABG. Therefore, we initiated the Octopus Study to assess the postulated benefits of off-pump CABG.

Methods

The Octopus Study comprises two multicenter randomized clinical trials, of which the design, timing of investigations, and definitions of main outcome events are presented in Figure 1, Table 1, and Table 2, respectively.

Table 1: Timing of investigations

	S	P	D	1m	3m	6m	12m
Angiography		X[†]					X[‡]
History/events	X	X	X	X		X	X
Anginal assessment	X	X	X	X		X	X
Medications	X		X	X		X	X
Physical examination	X		X	X			X
Electrocardiography	X		X	X			X
Neuropsychological tests[*]	X		X		X		X
Blood analysis							
Cardiac enzymes	X	X					
Routine laboratory	X		X	X			
Total, HDL, HDL, cholesterol	X						X
Resource utilization	X	X	X	X		X	X
Quality of life	X			X		X	X
Working status	X			X		X	X
ECG stress test							X

Abbreviations: S = preprocedural screening; P = procedure; D = discharge; 1m = 1 month after intervention; 3 m = 3 months after intervention; 6 m = 6 months after intervention; 12 m = 12 months after intervention.

[*] Only for patients in the comparison of off-pump CABG and conventional CABG (OctoPump Trial).

[†] Only for patients undergoing PTCA with stent implantation.

[‡] Coronary angiography will be performed in a sample of 210 patients.

Primary endpoints

The OctoStent Trial

It is expected that the need for repeat revascularization after off-pump CABG and conventional CABG is similar. PTCA with stent implantation is less invasive than CABG, but is associated with a higher need for repeat interventions.[16] Although repeat interventions can be seen as part of the angioplasty procedure, they have major clinical impact and are considered as failure of treatment in this study, which aims to compare the medical effectiveness of two revascularization procedures. Therefore, the primary endpoint in comparing off-pump CABG with PTCA with stent implantation incorporates revascularization as part of the combined primary endpoint, which is the proportion of patients free of cardiovascular death, nonfatal myocardial infarction, nonfatal cerebrovascular accident (CVA), or revascularization by means of CABG or PTCA, whichever occurs first, at 1 year (± 1 month) after the index treatment.

Table 2: Definitions of main outcome events.

Cardiovascular death	All deaths are considered cardiovascular unless an unequivocal non-cardiovascular cause can be established. Cardiovascular death includes fatal myocardial infarction, sudden death, terminal heart failure, fatal cerebral infarction and hemorrhage and procedure-related fatal bleeding (e.g. tamponade, access site bleeding).
Cerebral infarction and hemorrhage	Patients with relevant clinical features (focal injury persisting for more than 24 hours, preferably confirmed by computed tomography scan) combined with an increase in handicap of at least one grade on the Rankin Scale.
Cognitive dysfunction	A decrease of 20% or more between the baseline and post-treatment assessment of an individual's score in three or more tests of a battery of eleven neuropsychological tests (Appendix 1).
Myocardial infarction	Elevation of specific cardiac enzymes or the development of specific abnormalities in the ECG specified in Appendix 2.
Repeat revascularization	The initial PTCA procedure is considered completed at the time when the guiding catheter is removed from the arterial sheath. The initial CABG is considered comple-ted when the patient is transferred from the operating table into his/her bed.

The OctoPump Trial

As mentioned above, off-pump CABG and conventional CABG are assumed to be equally effective in terms of myocardial revascularization (i.e., have similar medical effectiveness). However, the use of cardiopulmonary bypass in conventional CABG is associated with considerable cerebral morbidity, in particular neuropsychological deficits.[8,9] Therefore, the primary endpoint in the comparison of off-pump CABG to conventional CABG is cerebral safety. This is defined as the proportion of patients free of the combined event of fatal and nonfatal CVA and cognitive dysfunction, whichever occurs first, to be determined at 3 months (± 3 weeks) after the index treatment. The occurrence of cognitive dysfunction is determined using a neuropsychological test procedure (Appendix 1).

Secondary endpoints

The secondary endpoints in both trials include all cause mortality, presence and severity of angina, quality of life using SF-36[30,31] and EuroQol[32,33] questionnaires, and cost/effectiveness at 1 (± 1 week), 6 (± 1 month), and 12 months (± 1 month) after the index treatment. Exercise capacity is assessed at 1 year. Finally, angiographic restenosis rate and graft patency are evaluated in a

random subgroup of 210 patients undergoing repeat angiography at 1 year (70 patients having undergone PTCA; 70 patients having undergone off-pump CABG, equally split between the two substudies; 70 patients having undergone conventional CABG).
In the OctoPump Trial no difference is expected in cardiac outcome; nevertheless, cardiac death, myocardial infarction, and repeat revascularization procedures will be assessed at 1, 6, and 12 months. Cognitive function will also be assessed 4 days after operation. It is expected that most patients will show a decline in this early postoperative stage. However, the fast recovery and short hospital stay of the first 100 patients operated on in our hospital with the use of the Octopus Method suggest that the benefits of off-pump CABG may be especially reflected in a reduction of neuropsychological deficits in the first week after operation.

Patients

Patients with coronary lesions technically suitable for angioplasty and off-pump CABG are selected for the OctoStent Trial. Patients with coronary lesions suitable for off-pump CABG and on-pump CABG are selected for the OctoPump Trial. This selection predominantly depends on the precise location of the stenoses, the anticipated capacity of the heart to endure temporary occlusion of the involved coronary arteries, and hemodynamic consequences of local immobilization of the ventricular wall. In particular, bypass grafting of posterior coronary arteries may result in a significant drop in left ventricular stroke volume upon presentation of these vessels.[12,13] The selection criteria for the Octopus Study are presented in Table 3.

Randomization procedure

Patients eligible for the OctoStent or OctoPump Trial are invited to the outpatient clinic to receive additional information. Candidates for either trial admitted to a referring hospital are visited by one of the trial monitors. After obtaining informed consent, patients are randomized by a telephone call from the trial monitor of the participating hospital to the randomization center of the Julius Center for General Practice and Patient Oriented Research, Utrecht, The Netherlands. To ensure a reasonable bal-

Table 3: Inclusion and exclusion criteria of the Octopus Study

INCLUSION CRITERIA
1. Patients with stable or unstable angina pectoris (Braunwald Class I-II, b) and/or documented ischemia due to single or multivessel disease and a normal or moderately impaired global left ventricular function.
2. Patients who are considered candidate for PTCA (OctoStent Trial) or CABG (OctoPump Trial).
3. Patients who are eligible for off-pump CABG: Patients with single and multivessel disease in which one or more significant stenosis(es) in at least one major epicardial coronary artery (left anterior descending srtery, left circumflex artery, right coronary artery or the combination of one of the former and a side branch providing different myocardial territories) are to be treated. With respect to the left circumflex artery, only patients in whom one graft needs to be inserted to provide sufficient revascularization are candidates. In addition, only patients without a hemodynamic significant left main stem stenosis can be included.
4. Written informed consent.

EXCLUSION CRITERIA
General exclusion criteria
1. Age under 18.
2. History of CABG.
3. History of PTCA < 6 months before.
4. Need for concomitant major surgery (e.g. valve replacement, resection ventricular aneurysm, congenital heart disease, vascular surgery of the carotid artery, or thoracic-abdominal aorta).
5. Concomitant medical disorders making clinical follow-up of at least 1 year unlikely or impossible (e.g. neoplastic disease, hepatic failure).
6. Q-wave myocardial infarction in the last 6 weeks.
7. Overt congestive heart failure.
8. Hemorrhagic diathesis or hypercoagulability.
9. Thoracic deformations technically precluding off-pump CABG.
10. Unable to give informed consent.

Criteria specifically related to PTCA/stent implantation (only for OctoStent Trial)
1. Totally occluded coronary arteries supplying documented viable myocardium. Patients with a totally occluded coronary artery may be included provided this artery does not need to be revascularized because it supplies an akinetic segment of the left ventricle as documented on the diagnostic ventriculogram in combination with pathologic Q-wave on the ECG.
2. Balloon angioplasty without stent implantation is permitted as a complementary treatment provided that at least one other target lesion is amenable to stenting.
3. Intolerance or contraindication to acetylsalicylic acid or ticlopidine.
4. Leucopenia (< 3.5×10^9/liter).
5. Neutropenia (< 1000 neutrophils/mm^3).
6. Thrombocytopenia (< 100.000 platelets per mm^3).
7. Documented peptic ulcer or gastro-intestinal bleeding in the last 6 months.
8. In-stent restenosis.

ance, assignment is performed according to computer-generated lists of random permuted blocks that are unknown by the investigators. After randomization patients are scheduled for the allotted treatment.

Number of patients required

All sample size calculations are based on a two-sided alpha error of 0.05 and 90% power.

The OctoStent Trial

Meta-analysis of randomized trials comparing coronary angioplasty with bypass surgery have disclosed no difference between PTCA and CABG in the survival free from myocardial infarction (92% at 1 year and 90% at 3 years after PTCA and CABG). However, event-free survival (free from myocardial infarction, repeat bypass surgery, or PTCA) was approximately 60% and 90% at 1 year after PTCA and CABG, respectively.[16] Additional stent implantation is expected to improve vessel patency and 1-year event-free survival as compared to simple balloon angioplasty.[2,19] Off-pump CABG is expected to result in similar medical effectiveness as conventional CABG. Accordingly, an event-free survival at 1 year of 75% after stent implantation and of 90% after off-pump CABG is assumed. To detect the resulting absolute difference of 15% in event rate, just over 125 patients are required in each group.

The OctoPump Trial

No difference in medical effectiveness in terms of mortality, myocardial infarction, and repeat revascularization at 1 year is expected between off-pump CABG and standard CABG. However, a significant difference in morbidity is expected in favor of off-pump CABG owing to a reduction in major neurologic and neuropsychological complications. Assuming an incidence of cerebral complications, including neuropsychological deficits, of 21% after on-pump CABG[8,9] and a two-thirds reduction of complications resulting from off-pump CABG, a total of 125 patients is again required in each group.

Taking into account a loss to follow-up of 10%, 140 patients will be randomized to each group. Therefore, the total study population will be 4 x 140 = 560 patients.

Inclusion rate and generalizibility

Eligibility for study participation is evaluated by filling out a standard checklist encompassing the inclusion and exclusion criteria

of the study for all patients referred for coronary revascularization (PTCA or CABG). These checklists, or "screening logs," have shown that off-pump CABG may currently be an alternative for conventional CABG in approximately 15% of cases and for PTCA with stent implantation in approximately 30% of cases. To allow inclusion of 560 patients within 2 years (six per week) and to improve the generalizibility of the results, two other cardiac centers in the Netherlands are participating in the trial and are expected to enroll 125 patients each.

Analytical plan

The aim of the main analysis is to compare the incidence of the primary outcome events in either trial. Kaplan Meier curves will be used for graphic comparison. The occurrence of outcome events will be compared by means of Cox's proportional hazards model yielding a hazard ratio. For the Octostent Trial, in addition to the combined endpoint of cardiovascular death, nonfatal myocardial infarction, CVA, or revascularization by means of CABG or PTCA, each component of this primary outcome will be assessed. The precision of the hazard ratio estimates will be described by means of 95% confidence intervals. The primary data analysis will be based on the intention-to-treat principle.

For all treatment modalities the costs of diagnostic procedures, treatment procedures, complications, and short- and long-term differences in effects will be estimated. Marginal costs in monetary terms will be calculated by multiplying unit costs and marginal medical consumption as recorded for each patient. Subsequently, marginal cost-effectiveness ratios will be estimated from the perspective of health-care insurance (tariffs) and from a societal perspective (actual costs). A theoretical decision model (i.e., an arithmetical model taking into account all relevant outcomes of interest such as efficacy, complications, quality of life, and costs) will be used to estimate long-term cost-effectiveness.

Study organization

The departments involved each delegate one or two staff members not directly in charge of the treatment of the patients to the Steering Committee. This is the main policy- and decision-making committee of the study and has final responsibility for the

administrative, clinical, and scientific conduct of the study. A cardiopulmonary surgeon, a cardiologist, a cardioanesthesiologist, and a neurologist form the Critical Event Committee and confirm and classify the major adverse cardiac and cerebrovascular events, blinded to the treatment if possible (in the OctoStent Trial, blinding is sometimes impossible). To verify whether important differences in the incidence of major adverse cardiac events and cerebrovascular events exist between the treatment groups, the Data Monitoring Committee performed an interim analysis after the first 190 patients had entered each arm of the study. The three members of this committee are experienced in patient-oriented research, are independent of the study, and may also offer unsolicited recommendations. A stopping rule was not specified prior to the start of the study.
The Data Coordinating Center is located at the Julius Center for General Practice and Patient Oriented Research, University Hospital Utrecht, and is responsible for data acquisition, data entry, data processing, and data and statistical analysis of the study. Defined vital parameters will be double-entered. The data will be queried at the coordinating center. An independent Angiographic Core Laboratory is responsible for confirming all angiographic components of the revascularization procedure and for quantitative analysis of the angiograms before and immediately after intracoronary stent implantation or other angioplasty technique. In addition, it will perform the analysis of the 12-month repeat angiography performed in the predefined group of patients who were assigned to establish the 12-month angiographic restenosis rate and graft patency. All electrocardiograms (ECGs) and stress tests will be centrally collected and analyzed by the ECG Core Laboratory located in the Department of Cardiology, University Hospital Utrecht. The execution of the study, including data acquisition, data analysis, and reporting, is the responsibility of the four Principal Investigators and two Trial Coordinators.

Ethical aspects

This study is conducted in accordance with the principles of the Declaration of Helsinki and with the laws and regulations of the Netherlands. The study protocol has been approved by the local

Ethics Committee of each participating hospital. Written informed consent is obtained by the attending physician. It is explained to the patient that if he or she is randomized to off-pump CABG, eventually conventional CABG may have to be performed due to technical difficulties.

Implementation issues

As in most patient-oriented research, the logistic implications of the study are considerable and change the daily routines on the wards and require flexibility of doctors, nurses, and secretaries. The implementation of the study therefore was accompanied by a large number of presentations for the hospital personnel. A constant supply of letters, news bulletins, and presentations about the goals and progress of the study appears to be necessary to keep everyone motivated.

The waiting list for bypass surgery is longer than it is for angioplasty. The latter is more easy to plan, especially when a patient is admitted to a referring hospital. The difference in waiting time to the intervention can be a reason for patients to refuse participation in the study, and much effort was made to harmonize it.

Referring cardiologists and cardiopulmonary surgeons have varying degrees of belief with regard to the effectiveness of the treatment modalities; it was difficult for them to accept a new treatment and allow their patients to participate in the trial. Not all cardiopulmonary surgeons of the participating hospitals were trained to use the Octopus immobilization device for the new treatment and therefore did not participate in the study.

To keep our independence we chose not to approach an industrial sponsor, so only costs are refunded. Other running trials can create a conflict of interest for patients and physicians, and it was recommended to take these into account with regard to the inclusion rate.

Initially the study was hampered by these problems. Due to combined ongoing efforts of the Steering Committee, especially its chairman, the trial monitors, and principle investigators, patient enrollment was on schedule.

Table 4: Baseline characteristics of the first 360 randomized patients

	OctoStent Trial		OctoPump Trial	
	Randomized to PTCA with stenting (n=89)	Randomized to off-pump CABG (n=91)	Randomized to off-pump CABG (n=89)	Randomized to conventional CABG (n=91)
Mean age (years)	60	59	61	61
Males	73%	74%	67%	71%
One–vessel disease	63%	78%	29%	22%
Two–vessel disease	34%	20%	51%	50%
Three–vessel disease	2%	2%	20%	27%
History of myocardial infarction	27%	21%	24%	29%
History of PTCA	3%	2%	17%	22%
Peripheral vascular disease	7%	3%	8%	13%
Diabetes	6%	16%	11%	14%
History of smoking	71%	81%	70%	77%
Hypertension	35%	32%	41%	40%
Hypercholesterolemia	58%	56%	66%	67%
Familial history of CAD	67%	65%	55%	60%
COPD	12%	12%	9%	13%

PTCA = percutaneous transluminal angioplasty; CABG = coronary artery bypass grafting; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease.

Epilogue

The Octopus Study is designed to include patients who need coronary revascularization and for whom several treatment strategies are feasible. Currently, it represents the only randomized study comparing off-pump CABG to conventional CABG and PTCA with stent implantation. The results of the study may facilitate selection of the most appropriate therapy for individual patients and foster the appropriate use of available resources. Randomization of patients started in April 1998 and was completed in June 2000. The baseline characteristics of the first 360 randomized patients are presented in Table 4. Including 1-year follow-up, the study will last for 3 years. The results will be reported in 2001.

Participating hospitals Utrecht University Hospital, Utrecht, The Netherlands; Isala Klinieken, Zwolle, The Netherlands; Antonius Ziekenhuis, Nieuwegein, The Netherlands.

Steering committee **P.P.Th. de Jaegere, E.O. Robles de Medina, J.J. Bredée, D.E. Grobbee, C. Borst, J.T.A. Knape, R.S. Kahn, J.C. Diephuis, F.A.M. Spijkers, H.W.M. Plokker.**

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Appendix 1: Neuropsychological tests

The neuropsychological tests consist of the following:

1. Motor Choice Reaction Test (MCRT). A computer test in which reaction time is studied as a function of the complexity of the task requirements. Dependent variables are movement time and initiation time.

2. Grooved Pegboard. A test for manual dexterity, it is a highly sensitive test for studying improvement in motor functions following stroke. Time to completion is scored.

3. Trail Making Test Part A and B. A test procedure in which shifting between concepts is operationalized. Time to completion of both tests is scored.

4. Symbol Digit Modalities Test. The subject has to fill in blanks that correspond to a key in which a symbol corresponds to a digit. The test measures speed of simple information processing. The number of filled blanks in a fixed time is scored.

5. Stroop Color Word Test. This test consists of subtasks that measure, first, the speed at which color names are read; second, the speed at which colors are named; third, the speed at which the color of the printing ink is named when there is interference from the printed color name. An interference score is calculated by subtracting the time scores for subtasks 3 and 2. The test measures selective attention.

6. Continuous Performance Task. A computerized test for sustained attention. The test requires the subject to react to a visual target. The median of reaction time is recorded.

7. Rey Auditory Verbal Learning Test. The learning list consists of 15 meaningful monosyllabic words that are presented in five trials. Each trial ends with a free recall of the words. After a period of 20 minutes following the fifth trial, the subject is requested to recall as many words as possible (delayed recall), immediately followed by a recognition trial. Main variables consist of (a) the total number of correct words in the five trials, (b) the total number of correct words on delayed recall, and (c) the total number of correct words on delayed recognition.

8. Self-Ordering Tasks. The procedure consists of three tasks: digit span, missing item scan, and randomization task. The tasks measure immediate memory and verbal working memory.

9. Visual/spatial Working Memory Test (DOT test). The procedure consists of 20 trials. Trials 1 through 8 have no delay; the other trials have a timed interval of 10, 20, and 30 seconds. The subject has to fill in as accurately as possible a visuospatial target on a sheet of paper. The average distance is determined by subtracting the average no-delay distance from the average delayed recall distance.

10. Sternberg Memory Comparison Task. The subject is asked to cancel out digits or letters between letters, while the memory load is expanded. Two variables are of relevance: the memory comparison stage (expressed in the slope) and the stage of motor organization and response execution (the intercept).

11. Line Orientation Test. This test measures spatial perception ability by requiring subjects to match angled lines to an array of lines with varying slopes. The task is administered as a control task to ensure that any correlations that were found on neuropsychological testing could not be attributed to global neuropsychological dysfunction.

One to two weeks preoperatively tests 2, 3, 7, and 11 are administered to control for practice effects. Duration of administration is 45 minutes. The whole test battery is administered 1 day before the operation, and 4 days and 3 and 12 months postoperatively. The whole battery takes 100 minutes.

According to the guidelines of the 1994 meeting on this subject, cognitive dysfunction is defined as > 20% decrease in a patient's individual performance from baseline (1 day before operation) to a postoperative assessment in three or more tests.[22]

Appendix 2: Definition of myocardial infarction

Definition 1: Within 7 days after intervention

A. Q-wave infarction

See ECG-criteria new Q-wave infarction

and

Enzyme elevation as follows:

- After PTCA: CKMB elevation 3 _ upper limit of normal
- After CABG or MI-CABG: CKMB elevation 5 _ upper limit of normal
- If CKMB is not available: use CK

or in absence of Q-wave infarction (see definition 1A)

B. Enzymatic/non-Q-wave infarction

Enzyme elevation as follows:

- After PTCA: CKMB elevation 3 _ upper limit of normal
- After CABG or MI-CABG: CKMB elevation 5 _ upper limit of normal
- If CKMB is not available: use CK

Definition 2: At least 7 days after any intervention (PTCA, CABG, or MI-CABG)

A. Q-wave infarction

See ECG criteria new Q-wave infarction, or in absence of Q-wave infarction (see definition 1A)

B. Enzymatic/non-Q-wave infarction

Enzyme elevation as follows:

* Peak CKMB/CK ratio > 10%

* If no ratio available: CKMB elevation 2 _ upper limit of normal after any intervention

ECG criteria new Q-wave infarction

1. New QS in two associated leads in absence of left bundle branche block (LBBB)/Wolff-Parkinson-White Syndrome (WPW)

or

2. New Q-wave in two associated leads, defined as 0.04 seconds broad and/or Q/R ratio 1/4

or

3. Posterior wall infarction: new broad R-wave (0,04 seconds) and tall R-wave (R/S ratio > 1 or R-wave 0.5 mv) in lead V1 and V2, in absence of right bundle branche block (RBBB)/right ventricular hypertrophy (RVH)

or

4. New permanent LBBB and enzyme elevation (see definition 1B and 2B)

or

5. Reversed R-wave progression precordial: decrement R-wave 0.2 mv in two consecutive precordial leads and enzyme elevation (see definition 1B and 2B)

or

6. Any new Q-wave in lead V2 and V3 and enzyme elevation (see definitions 1B and 2B)

Chapter 4

Cognitive outcome after off-pump and on-pump coronary artery bypass graft surgery: a randomized trial

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Abstract

Context Coronary artery bypass graft (CABG) surgery is associated with a decline in cognitive function, which has largely been attributed to the use of cardiopulmonary bypass (on-pump procedures). Cardiac stabilizers facilitate CABG surgery without use of cardiopulmonary bypass (off-pump procedures) and should reduce the cognitive decline associated with on-pump procedures.

Objective To compare the effect of CABG surgery with (on-pump) and without (off-pump) cardiopulmonary bypass on cognitive outcome.

Design and setting Randomized controlled trial conducted in the Netherlands of CABG surgery patients enrolled from March 1998 through August 2000, with 3- and 12-month follow-up.

Participants and intervention Patients scheduled for their first CABG surgery (mean age, 61 years; n = 281) were randomly assigned to off-pump surgery (n = 142) or on-pump surgery (n = 139).

Main outcome measures Cognitive outcome at 3 and 12 months, which was determined by psychologists (blinded for randomization) who administered 10 neuropsychological tests before and after surgery. Quality of life, stroke rate, and all-cause mortality at 3 and 12 months were secondary outcome measures.

Results Cognitive outcome could be determined at 3 months in 248 patients. Cognitive decline occurred in 21% in the off-pump group and 29% in the on-pump group (relative risk [RR], 0.65; 95% confidence interval [CI], 0.36-1.16; p=0.15). The overall standardized change score (ie, improvement of cognitive performance) was 0.19 in the off-pump vs 0.13 in the on-pump group (p=0.03). At 12 months, cognitive decline occurred in 31% in the off-pump group and 34% in the on-pump group (RR, 0.88; 95% CI, 0.52-1.49; p= 0.69). The overall standardized change score was 0.19 in the off-pump vs 0.12 in the on-pump group (p=0.09). No statistically significant differences were observed between the on-pump and off-pump groups in quality of life, stroke rate, or all-cause mortality at 3 and 12 months.

Conclusion Patients who received their first CABG surgery without cardiopulmonary bypass had improved cognitive outcomes 3 months after the procedure, but the effects were limited and became negligible at 12 months.

Introduction

Coronary artery bypass graft (CABG) surgery with the use of cardiopulmonary bypass (CPB) is associated with significant cerebral morbidity, usually manifested as cognitive decline or stroke.[1] The incidence of cognitive decline ranges from 3% to 50%, depending on patient characteristics, definition of decline, and timing of neuropsychologic assessment.[1,2] A recent pooled analysis of 6 comparable studies yielded a proportion of 23% of patients with cognitive decline 2 months after surgery.[3] Although this degree of cognitive decline does not affect most patients in functional terms, a small proportion of patients with cognitive decline becomes sufficiently disabled to prevent return to employment.[1] Perioperative stroke occurs in approximately 3% of the patients undergoing CABG surgery.[1,4]

Cerebral morbidity after CABG surgery has largely been attributed to the use of CPB.[1] Cardiopulmonary bypass increases the permeability of the blood-brain barrier and generates microemboli, which may affect cognitive function,[5-7] and also requires cannulation and cross-clamping of the ascending aorta, which may induce atheromatous macroemboli causing stroke.[8] Factors increasing the risk of cerebral morbidity include advanced age and prolonged time undergoing CPB.[1,4] However, the assumption that CPB is the main cause of cerebral morbidity after CABG surgery has not been quantified in randomized trials of sufficient size. Two small trials showed conflicting results. One study (n = 40) demonstrated a marked improvement of cognitive outcome by using off-pump CABG surgery,[5] while the other study (n = 60) showed no improvement.[6]

Recently, cardiac stabilization devices were developed to facilitate CABG surgery on the beating heart (off-pump CABG), which allow immobilization and presentation of all sides of the beating heart,[9,10] and for many patients complete revascularization can now be achieved without the use of CPB.[10-12] In a previous article,[12] we reported the clinical outcomes at 1 month after on-pump vs off-pump CABG surgery for patients in this clinical trial. In this study, we compared the effect of CABG surgery with and without CPB on cognitive outcome.

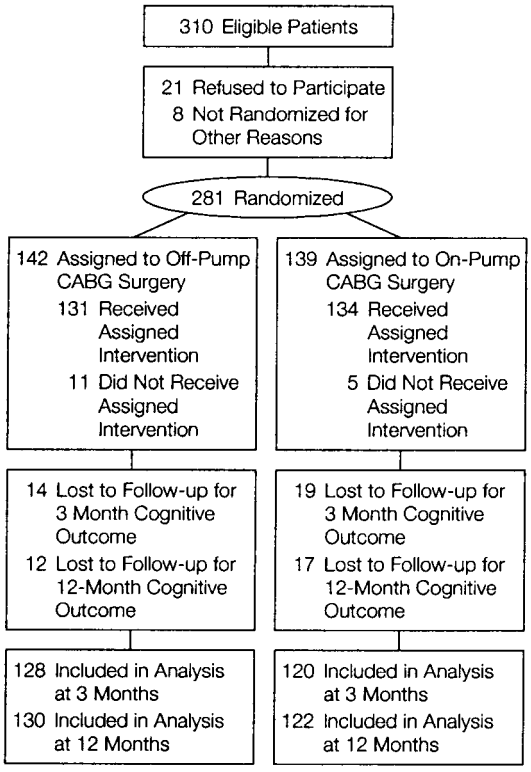

Figure: Flow of patients throughout the trial

Methods

Design and patients

The design and methods of the Octopus trial have been described in detail.[13] In brief, patients were eligible if referred for first-time isolated coronary bypass surgery and an off-pump procedure was deemed technically feasible. Patients were excluded in case of emergency or concomitant major surgery, Q-wave myocardial infarction in the last 6 weeks, or poor left ventricular function. Patients who were unlikely to complete 1-year follow-up, unable to give informed consent, or undergo neuropsychologic testing were excluded. There were no restrictions to age. Eligible patients were informed with a letter and invited to the outpatient clinic to receive additional information. After written informed consent was obtained, patients were randomly assigned by computerized block-randomization, over the telephone, to off-pump or on-pump CABG surgery. The block size varied from 8 to 20 patients and was unknown by the physicians who randomized the patients. The study was approved by the ethics committees of the 3 participating centers.

Between March 1998 and August 2000, 281 patients were enrolled, of whom 265 were treated according to randomization (Figure and Table 1). Ten patients randomized to off-pump surgery underwent CABG with CPB because progression of symptoms required emergency surgery or because technical problems

Table 1: Patients characteristics at baseline

Characteristics, %	Off-pump (n=142)	On-pump (n=139)
Age, mean (SD), y	61.7 (9.2)	60.8 (8.8)
Education, mean (SD), y	9.3 (2.4)	9.7 (2.8)
Sex, male	66	71
Coronary artery disease		
1-vessel disease	30	22
2-vessel disease	50	50
3-vessel disease	20	27
Peripheral vascular disease	7	13
Diabetes	9	17
History of stroke	4	3
Hypertension	40	44
Pulmonary disease	9	10

were encountered during the procedure. One other off-pump patient underwent coronary angioplasty. In 5 patients assigned to on-pump CABG surgery, an off-pump procedure was performed.

Outcome

The primary end point of the study was cognitive outcome at 3 months after surgery. Patients underwent a battery of 10 neuropsychologic tests 1 day before and 3 and 12 months after operation. The tests were administered in the participating hospitals by trained psychologists who were blinded to treatment allocation. Administration of the tests lasted approximately 100 minutes.

In accordance with the Statement of Consensus on Assessment of Neurobehavioral Outcomes after Cardiac Surgery,[14] the battery included tests for motor skills, verbal memory capacity, and attention. In addition, tests were included to assess speed and capacity of working memory, visuospatial capacity, selective and sustained attention, and information processing. Each test yielded 1 or more variables, with different ranges per variable. Eleven main variables were chosen a priori to be used in the analyses. The cognitive domains that were covered, the tests, and the main variables[13] are listed in Table 2. Cognitive decline was defined as a decrease in an individual's performance of at least 20% from

Table 2: Cognitive domains and neuropsychologic tests at pretesting and baseline*

Domain	Test	Main variable
Verbal memory, learning	Rey Auditory Verbal Learning	total score trial 1-5
Verbal memory, retrieval	Rey Auditory Verbal Learning	delayed recall score
Motor capacity	Grooved Pegboard	time dominant hand, s
Divided attention	Trail Making Test Part A and B	time trail B, s
Working memory speed	Sternberg Memory Comparison	time 4 character chart, s
Visuospatial capacity	Line Orientation Test	total score
Selective attention	Stroop Color Word Test	time C – time B, s
Sustained attention	Continuous Performance Task	mean reaction time, ms
Working memory	Self Ordering Tasks	sum score
Visual working memory	Visuospatial Working Memory	average distance, cm
Information processing	Symbol Digit Modalities Test	total score

* Ellipses indicate not applicable. All values are raw data and presented as medians, with 10th and 90th percentiles in parentheses. Pretest denotes cognitive performance two weeks before baseline assessment.

baseline, in at least 20% (3) of the main variables.[15] Patients who sustained a stroke were considered to have cognitive decline. To limit practice effects, 6 of the 10 tests were also administered 2 weeks before baseline assessment (pretest, Table 2) and, wherever possible, parallel forms of the tests were used in the consecutive assessments.

In addition to the primary analysis based on a dichotomous cognitive outcome, 2 additional analyses were performed, both including continuous cognitive outcome measures. The first consisted of a direct comparison of the continuous test scores. To estimate the change in performance from baseline to 3 months after operation, a standardized change score (SCS) was calculated for each main variable in each patient by subtracting the preoperative score from the postoperative score and dividing the difference by the preoperative SD of that variable. If improved performance

Table 2: (continued)

Off-pump		On-pump	
pretest	baseline	pretest	baseline
37	36	35	36
(25-49)	(25-48)	(24-48)	(26-48)
7	6	7	6
(4-11)	(3-9)	(3-10)	(3-10)
107	106	107	104
(91-147)	(88-137)	(91-157)	(91-141)
97	83	91	84
(56-176)	(49-153)	(61-165)	(52-154)
62	59	60	57
(42-89)	(43-88)	(45-86)	(43-87)
25	24	24	24
(17-29)	(17-29)	(17-29)	(18-28)
48	43	46	40
(29-98)	(23-76)	(29-85)	(23-77)
...	544	...	544
	(460-711)		(476-738)
...	9	...	10
	(5-16)		(6-17)
...	0.4	...	0.5
	(-0.3-1.5)		(-0.1-1.1)
...	41	...	39
	(25-55)		(26-53)

was reflected by a lower score (eg, in timed tasks), the directional data were reversed so that all improvements gave positive change scores. Per subject, the mean of the 11 SCSs was taken as a quantitative measure of the overall postoperative change in performance.[16,17]

The second additional analysis of cognitive outcome included a factor analysis with orthogonal rotation, which was performed to minimize the overlap between the 11 main test variables and to facilitate interpretation.[2,18] This reduced the data set to 4 independent factor scores, each representing a separate domain of cognitive function: (1) attention and visuospatial capacity; (2) verbal memory; (3) selective attention and motor capacity; and (4) working memory. The factor coefficients needed to calculate the factor scores at the various time points were derived using the factor loadings and weights from the baseline cognitive data.

Factor change scores were obtained by subtracting the baseline factor scores from the postoperative factor scores.
Secondary end points included identical measures of cognitive outcome at 12 months, differences in quality of life at 3 and 12 months, and stroke rate and all-cause mortality at 3 and 12 months. Health-related quality of life was assessed using 2 generic questionnaires. The EuroQol questionnaire generates a single index, ranging from -1 to +1, with -1 reflecting the worst imaginable quality of life and +1 reflecting the best imaginable quality of life.[19] The Short Form-36 questionnaire comprises 8 different domains all ranging from 0 to 100. Higher scores indicate higher levels of functioning or well-being.[20] Stroke was defined as focal brain injury, detected by standard neurologic examination, persisting for more than 24 hours, and combined with an increase in functional deficit of at least 1 grade on the Rankin Scale.[21]

Treatment and procedures
The goal of surgery was to obtain complete arterial revascularization. With the exception of 2 emergency procedures, all operations were performed by cardiac surgeons experienced in both off-pump and on-pump bypass surgery. During off-pump procedures, the Octopus method[9] (Octopus Device, Medtronic, Minneapolis, Minn) was used for stabilization of the target coronary artery.
The use of CPB requires full heparinization, which influenced the selection of anaesthetic technique. In the on-pump group, 99% of the patients received total intravenous anesthesia including high dose opioids, whereas in the off-pump group, 54% of the patients received thoracic epidural anesthesia combined with low-dose opioids. Cardiopulmonary bypass was managed according to the alpha-stat principle,[22] with a minimal nasopharyngeal temperature of 32°C and a nonpulsatile perfusion of 2.0 to 2.4 L/m^2 per minute. The pump was primed with a crystalloid-colloid mixture. During rewarming, the maximal gradient between blood and water in the heat exchanger was 5°C with a maximal water temperature of 39°C. To reduce blood loss in the CPB group, blood was recollected using a suction cardiotomy reservoir, without filter or processing. In the off-pump group, a cell-saver was used.

Data analysis

The sample size calculation was based on the assumptions that the incidence of cognitive decline at 3 months is 21% after on-pump CABG surgery[3] and that a two-thirds reduction could be achieved using an off-pump technique. With the alpha-error set at 0.05 and beta-error set at 0.10 (power of 90%), a total of 125 patients in each group were required, which was increased to 140 patients per group because a 10% loss to follow-up was anticipated.

Data were analyzed according to randomization. Incidences of cognitive decline and mortality were compared using Fisher exact test and the relative risk (RR) estimate with 95% confidence interval (CI). Odds ratios were used as a measure of RR. Continuous outcome measures were compared using the Wilcoxon nonparametric test. Differences in quality of life are presented as means with 95% CIs. For the cognitive outcome measures, multivariable regression models were used to adjust for possible baseline differences.

Missing data

At 3 months, cognitive outcome and quality of life could be determined in 128 patients in the off-pump group and 120 patients in the on-pump group (Figure). Within these groups, 4 patients completed fewer neuropsychologic tests during postoperative assessment than at baseline. In the primary analysis (dichotomous cognitive outcome), these patients were considered to have a decreased performance of at least 20% on the missing tests (worst-case score).[23] To assess the effect of loss to follow-up, several additional analyses were performed. The baseline characteristics of the patients who completed cognitive follow-up were compared. A sensitivity analysis was performed in which the outcome, cognitive decline, was first assigned to the 19 on-pump CABG surgery patients without 3-month neuropsychologic testing, and then to the 14 off-pump patients without 3-month neuropsychologic testing. Finally, missing cognitive data were imputed by means of linear regression modeling using SPSS version 10.0 (SPSS Inc, Chicago, Ill). Such modeling predicts the value of a missing variable by using all available cognitive and

Table 3: Neuropsychologic tests and standardized change scores (SCSs) at 3 and 12 months after surgery *

	Off-pump			
	3 months		12 months	
Test	raw	change	raw	change
Rey, total score	38 (24-49)	0.00	41 (27-53)	0.33
Rey, delayed recall	7 (3-11)	0.40	8 (5-12)	0.79
Grooved Pegboard	100 (86-134)	0.07	99 (85-130)	0.03
Trail Making Test part B	75 (50-137)	0.13	77 (45-137)	0.16
Sternberg Memory Comparison	56 (39-86)	0.18	57 (38-82)	0.12
Line Orientation Test	26 (19-29)	0.23	25 (19-30)	0.23
Stroop Color Word Test	39 (26-73)	0.41	43 (22-71)	0.08
Continuous Performance Task	536 (452-735)	0.11	544 (444-726)	0.04
Self Ordering Tasks	11 (6-17)	0.12	11 (6-17)	0.25
Visuospatial Working Memory	0.3 (-0.3-10.3)	0.08	0.5 (-0.3-10.5)	0.11
Symbol Digit Modalities Test	45 (28-60)	0.27	42 (26-59)	0.09
Overall postoperative change (mean of the change scores)	...	0.19	...	0.19

* Values are medians, with 10th and 90th percentiles in parentheses. Change denotes standardized change score and reflects improved performance from baseline to 3 or 12 months after surgery. Ellipses indicate not applicable.

clinical data of that patient. Analyses were repeated with the completed data set.

Results

Patient population and operation

Baseline characteristics of the patients, including preoperative cognitive test performance, were well balanced between the 2 groups (Table 1 and Table 2). Patients in the off-pump group were on average 1 year older than the on-pump group and comprised slightly fewer men and patients with diabetes, peripheral

Table 3: (continued)

On-pump				p-value of off-pump vs on-pump	
3 months		12 months			
raw	change	raw	change	3 months	12 months
37 (23-51)	0.11	37 (28-53)	0.22	0.59	0.26
7 (2-11)	0.00	7 (3-11)	0.40	0.13	0.01
102 (88-124)	0.14	102 (90-135)	0.07	0.78	0.85
79 (50-137)	0.11	76 (50-134)	0.09	0.33	0.51
59 (44-88)	0.06	58 (45-81)	0.03	0.28	0.19
25 (19-29)	0.12	25 (19-29)	0.23	0.31	0.57
37 (21-69)	0.12	40 (24-69)	0.00	0.69	0.50
521 (467-737)	0.09	526 (451-717)	0.08	0.59	0.25
S11 (6-17)	0.12	11 (5-16)	0.12	0.61	0.18
0.4 (-0.4-10.2)	0.23	0.4 (-0.4-10.2	-0.04	0.71	0.56
42 (29-55)	0.18	41 (26-56)	0.18	0.23	0.64
...	0.13	...	0.12	0.03	0.09

vascular disease, and 3-vessel disease. The latter is reflected by the mean number of distal anastomoses, which was 2.4 in the off-pump and 2.6 in the on-pump group. For proximal anastomoses, aortic side clamps were used in 36% of the off-pump patients and 50% of the on-pump patients. In the on-pump group, time undergoing CPB averaged 66 minutes with 44 minutes cross-clamp time.

To assess the theoretical possibility of selection bias, the likelihood of the participants randomized to the off-pump group, which was influenced by the assignments of the previous patients, was entered in a logistic regression model. This variable appeared to be no determinant of cognitive outcome (p=0.99). We also

Table 4. Factor change score analysis of cognitive function at 3 and 12 months*

	off-pump		on-pump	
Cognitive score	**3 months**	**12 months**	**3 months**	**12 months**
Change in factor 1	0.21 (-0.46-0.80)	-0.02 (-0.67-0.75)	0.18 (-0.61-0.86)	0.14 (-0.58-0.71)
Change in factor 2	0.19 (-0.92-10.55)	0.53 (-0.64-10.70)	0.09 (-10.31-10.05)	0.18 (-0.79-10.40)
Change in factor 3	0.08 (-0.47-0.80)	-0.03 (-0.59-0.81)	0.08 (-0.49-0.71)	0.01 (-0.52-0.67)
Change in factor 4	0.08 (-0.67-0.73)	-0.04 (-0.67-0.84)	0.09 (-0.71-0.89)	-0.04 (-0.68-0.75)

* Values are medians, with 10th and 90th percentiles in parentheses. Positive values reflect improved performance from baseline to 3 or 12 months after surgery. Factor 1 denotes attention and visuospatial capacity; factor 2, verbal memory; factor 3, selective attention and motor capacity; and factor 4, working memory.

compared 21 baseline characteristics from off-pump patients who had a high likelihood of being randomized to off-pump with the baseline characteristics from on-pump patients with a low likelihood. No significant differences were observed in all the comparisons on the 21 baseline characteristics. Both analyses indicate that there was no selection bias (ie, the randomization sequence was well concealed).[24]

Cognitive outcome

The mean interval between operation and 3-month follow-up was 92 (SD, 17) days in the off-pump group and 96 (SD, 12) days in the on-pump group (p=0.06). At 3 months after surgery, cognitive decline occurred in 21.1% of patients after off-pump CABG surgery and 29.2% after on-pump CABG surgery (RR, 0.65; 95% CI, 0.36-1.16; p=0.15). The RR did not change after adjusting for baseline differences in age, sex, diabetes, peripheral vascular disease, and number of diseased vessels (RR, 0.65; 95% CI, 0.36-1.17; p=0.15) or with adjustment for anesthetic technique (data not shown). Within the off-pump group, cognitive decline occurred in 22.7% of patients who received epidural anesthesia with low-dose opioids and 18.9% of patients who received high-dose opioids without epidural anesthesia (p=0.67).

Table 4. (continued)

p-value	
3 months	12 months
0.76	0.19
0.19	0.01
0.94	0.97
0.85	0.67

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The results per neuropsychologic test variable are presented in Table 3. At 3 months, the patients in both groups improved on all 11 main variables. The overall postoperative change in performance (ie, overall improvement; mean of the 11 SCSs) was 0.19 SCS in the off-pump and 0.13 SCS in the on-pump group (p=0.03). Adjustment for baseline differences did not change the difference between the groups.

The change in performance per cognitive domain, as calculated with factor analysis, is presented in Table 4. Patients improved on all domains from baseline to 3 months after surgery, but no statistically significant differences between the groups were present.

At 12 months, cognitive decline occurred in 30.8% of patients after off-pump CABG surgery and 33.6% after on-pump CABG surgery (RR, 0.88; 95% CI, 0.52–1.49; p=0.69). The other analyses (Table 3 and Table 4) also showed nonsignificant differences between the groups. An exception was the domain verbal memo-

Table 5. Reasons for missing neuropsychologic assessment

Reason	3-month analysis		12-month analysis	
	Off-pump	On-pump	Off-pump	On-pump
Patient appeared to be unsuitable for neuropsychologic testing	1	1	1	1
Withdrawal immediately after randomization	0	3	0	3
Withdrawal after baseline assessment, but before surgery	2	4	2	4
Failure to administer baseline tests (logistic)	2	1	2	1
(Noncerebral) mortality at time of cognitive follow-up	1	1	2	1
Readmission to hospital or too ill for postoperative assessment	3	2	1	1
Failure to administer tests at time of cognitive follow-up (logistic)	1	0	1	0
Unable to come for follow-up (holiday or care for ill partners)	1	4	0	0
Not motivated for follow-up/withdrawal	3	3	3	6
Total No. of patients with failed neuropsychologic assessment	**14**	**19**	**12**	**17**

Table 6: Comparison of quality of life, within and between the treatment groups*

	Off-pump†			On-pump†		
Domain	**baseline**	**3 months**	**12 months**	**baseline**	**3 months**	**12 months**
Overall	0.64 (0.27)	0.86 (0.17)	0.82 (0.23)	0.65 (0.27)	0.83 (0.20)	0.86 (0.19)
PF	52 (25)	82 (17)	80 (20)	52 (25)	81 (18)	81 (21)
RP	23 (36)	62 (43)	69 (41)	23 (38)	56 (44)	74 (39)
BP	62 (26)	80 (20)	82 (23)	61 (26)	77 (21)	84 (21)
GH	56 (17)	71 (18)	67 (20)	54 (20)	68 (18)	66 (20)
VT	49 (23)	69 (19)	68 (20)	49 (24)	65 (20)	67 (18)
SF	61 (30)	83 (22)	83 (22)	61 (30)	77 (24)	82 (21)
RE	51 (46)	79 (37)	79 (36)	53 (47)	76 (37)	84 (32)
MH	66 (20)	80 (16)	78 (18)	67 (22)	78 (18)	78 (16)

* Values are means with standard deviation in parentheses. Overall denotes overall quality of life; 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; and MH, general mental health.

† All differences within the groups between baseline and 3 months, and baseline and 12 months: $p < 0.01$ by the Wilcoxon signed ranks test.

ry (factor 2), which had improved twice as much in the off-pump group (p=0.01). At 12 months, the overall change in cognitive performance was 0.19 SCS in the off-pump group and 0.12 SCS in the on-pump group (p=0.09).

Missing data

At 3 months, the cognitive outcome of 33 (12%) patients could not be determined and at 12 months the cognitive data of 29 (10%) patients were not obtained. Reasons for not obtaining neuropsychological test data testing are summarized in Table 5. The 3-month sensitivity analysis yielded an RR of 0.37 (95% CI, 0.22-0.63) and 1.21 (95% CI, 0.71-2.05), which are the extremes that could be obtained if all patients had been available for 3-month follow-up. The baseline characteristics of the patients who were available for analysis of cognitive outcome were comparable to the baseline characteristics of the entire patient sample. Imputation of all missing data by means of linear regression increased the differences in cognitive decline between the 2 groups at 3 months. After imputation, the rate of cognitive

Table 6: (continued)

Difference between off-pump and on-pump (95% CI)	
3 months	**12 months**
0.03 (-0.02 – 0.07)	-0.04 (-0.09 – 0.02)
1 (-4 – 6)	-1 (-6 – 4)
6 (-5 – 17)	-5 (-15 – 5)
3 (-2 – 8)	-2 (-7 – 3)
3 (-2 – 8)	2 (-3 – 7)
4 (-1 – 9)	1 (-4 – 6)
5 (-1 – 11)	0 (-5 – 6)
3 (-7 – 13)	-5 (-13 – 4)
2 (-2 – 6)	0 (-4 – 4)

decline at 3 months was 19.0% in the off-pump group and 28.8% in the on-pump group (RR, 0.58; 95% CI, 0.33-1.02; p=0.07), and the overall postoperative change in performance became 0.18 SCS and 0.13 SCS in the off-pump and on-pump groups, respectively (p=0.25). After imputation, the RR for cognitive decline at 12 months was 0.90 (95% CI, 0.53-1.54; p=0.79) and the overall postoperative change in performance became 0.20 SCS and 0.12 SCS in the off-pump and on-pump groups, respectively (p=0.05).

Quality of life

Both groups reported a marked improvement in overall quality of life at 3 months as well as each of the 8 subdomains (Table 6). Within these domains, only bodily pain and general health perceptions improved further from 3 to 12 months. Direct comparison between the groups of the overall scores and scores per domain at 3 and 12 months revealed only nonsignificant differences.

Mortality and stroke

At 3 months, 1 nonfatal stroke (perioperative) occurred in the off-pump group and 2 nonfatal strokes (1 perioperative) in the on-pump group. One off-pump patient died from gastrointestinal bleeding 49 days after CABG surgery and 1 on-pump patient died 58 days after perioperative myocardial infarction.

At 12 months, the mortality was 2 per group. In the off-pump group, 1 patient died from hepatic cancer 153 days after CABG surgery and in the on-pump group, 1 patient (who had had a pre-

vious stroke just prior to CABG surgery) died after a second 232 days after CABG surgery. The number of patients who had experienced stroke at 12 months remained 1 in the off-pump group and 2 in the on-pump group.

Comment

The use of CPB is generally regarded as the main cause of cognitive decline following heart surgery.[1] The present study demonstrates limited improvement of cognitive outcome at 3 months in patients undergoing off-pump CABG surgery. The 29% incidence of cognitive decline after on-pump CABG surgery is consistent with previous, uncontrolled studies[2,3] but the benefit of avoiding CPB was smaller than was anticipated. Moreover, at 12 months, the small differences between the groups had become negligible.

The present study is to our knowledge the largest randomized trial on cognitive outcome after off-pump and on-pump CABG surgery. Two other randomized studies on cognitive outcome after CABG surgery were published recently. Age and extent of coronary disease of the participants of both studies were comparable with the present study. Diegeler et al[5] administered the Syndrom Kurz Test to 40 patients and demonstrated a marked improvement of cognitive outcome after 7 days by using off-pump CABG surgery. Lloyd et al,[6] in contrast, administered 7 tests from the Wechsler Memory Scale and Wechsler Adult Intelligence Scale to 60 patients and found no difference in cognitive function after 3 months.

Several reasons may be considered to explain the limited difference in cognitive outcome between the treatment groups observed in the present study. First, factors other than CPB may cause cognitive decline after CABG surgery. It is conceivable that undergoing anesthesia affects cognitive function, though in the present study no association was found between cognitive decline and type of anesthetic technique. Moller et al[25] demonstrated a 10% incidence of cognitive decline after noncardiac surgery, independent of regional or general anesthesia. These observations suggest that surgical trauma could be a source of cognitive decline.

Second, to minimize crossovers from off-pump to on-pump groups, stringent patient selection criteria were used. This has resulted in a relatively young group of patients (mean, 61 years) with less advanced coronary artery disease and limited comorbidity. The effects of an off-pump technique may be more marked in older patients, patients with more extensive coronary artery and aortic disease, and patients with substantial comorbidity.[1,4,26]

Third, the off-pump technique may be a new source of cognitive decline. Exposure of the posterior cardiac wall frequently leads to transient episodes of elevated central venous pressure and concurrent decreased systemic blood pressure, resulting in a decreased cerebral perfusion pressure.[27]

Fourth, improved cognitive outcome by using an off-pump technique may only become more clear in the long term. In a recent long-term follow-up study by Newman et al,[2] cognitive decline was found in 24% of the patients 6 months after on-pump CABG surgery, which increased to 42% after 5 years. The present study demonstrated an increasing incidence of cognitive decline from 3 to 12 months, but the difference in cognitive decline observed earlier between patients in the on-pump group and the off-pump group decreased.

A final explanation involves the definition of cognitive decline (20% decrease in performance in 20% of the variables), which appears to have limited precision. Although this definition has been reported to be sensitive and reliable,[15,28,29] the cut-off value may be within the range of an individual's natural fluctuations in performance. Recently, the International Study of Post-Operative Cognitive Dysfunction group applied an almost similar definition to 176 volunteers undergoing 5 neuropsychologic tests.[30] After 3 months, 25% of the volunteers were identified as having cognitive decline. Therefore, it is likely that the true incidence of cognitive decline after CABG surgery is lower than generally assumed.[30] Moreover, measurement errors may have diluted the difference in cognitive decline found in the present study. Because of the methodological difficulties associated with defining cognitive outcome at the individual patient level, we regard the analysis based on comparison of the continuous neuropsychologic test scores more reliable than the analysis based on the dichotomous outcome measure.

The present study has several limitations, including single blinding and a 12% loss to follow-up. It is unlikely, however, that the differences in cognitive outcome found between the groups were caused by loss to follow-up. Both the drop-out rate and the baseline characteristics of the remaining patients were largely similar across the groups. Adjustments for small inequalities in baseline characteristics did not affect the results. Imputation of cognitive data for the patients that were lost to follow-up increased the difference in cognitive decline between the groups. Only a small number of the patients in whom cognitive outcome could not be determined lost motivation for cognitive follow-up after their surgery. A relation between loss to follow-up and cognitive outcome may therefore be present in only a very small proportion of the patients. In addition, the sample size calculation was based on achieving a two-thirds reduction in cognitive decline at 3 months. Thus, a more modest benefit in reducing cognitive decline cannot be excluded and would need to be evaluated in larger randomized trials.

We conclude that patients who received their first CABG surgery without CPB had improved cognitive outcomes 3 months after the procedure, but the effects were limited and became negligible at 12 months.

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Chapter 5

Predictors of cognitive outcome after coronary bypass surgery

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Abstract

Objective Coronary artery bypass surgery is associated with postoperative cognitive decline, which has generally been attributed to the use of cardiopulmonary bypass. In a recently conducted trial that compared off-pump and conventional bypass surgery, avoiding cardiopulmonary bypass only slightly improved cognitive outcome. The aim of the present study was to identify other determinants of cognitive outcome after bypass surgery.

Methods Ten neuropsychologic tests were repeatedly administered to 248 first time coronary bypass surgery patients (mean age 61 y). A dichotomous and a continuous measure of cognitive outcome were established by comparing test performance before and 3 months after surgery. Thirteen possible clinical predictors of cognitive outcome and 2 measures of early cognitive performance (4th day after surgery), were entered into logistic and linear regression models.

Results Variables identified in previous studies as determinants of cognitive outcome were no predictor of cognitive outcome in the present patient sample. As was demonstrated before, the use of cardiopulmonary bypass was not a major determinant of cognitive decline either. The only variables that were significantly associated with cognitive outcome after 3 months, were measures of cognitive outcome 4 days after surgery. This association was stronger in patients operated with cardiopulmonary bypass (odds ratio 4.72; $p<0.01$) than in patients operated without cardiopulmonary bypass (odds ratio 2.00; $p=0.16$).

Conclusions Cognitive outcome four days after coronary bypass surgery predicted cognitive outcome after three months. Previously reported associations between patient variables or perioperative variables and cognitive outcome could not be confirmed in the present study.

Introduction

Coronary artery bypass surgery (CABG) effectively relieves angina but may affect cognitive function.[1] This may occur in up to 50 percent of the patients, depending on the type of patient, and timing and methodology of neuropsychologic assessment.[1-3] Cognitive decline after CABG has largely been attributed to the use of CPB.[4] We conducted the Octopus trial to directly compare the effect of CABG with and without CPB on cognitive outcome.[5,6] At three months, the incidence of cognitive decline was 29 percent after on-pump CABG and 21 percent after off-pump CABG.[6] The improvement of cognitive outcome when avoiding CPB was smaller than anticipated, suggesting that other factors determine cognitive outcome after coronary bypass surgery as well. It would be helpful for both the patient and the physician to know the determinants of postoperative cognitive decline, because this may guide decisions such as the choice between surgical and non-surgical treatment, or between off-pump and on-pump surgery.

In previous studies, advanced age,[1,7-9] female sex,[10] diabetes,[10] history of stroke,[11] manipulation of the ascending aorta,[7,10] CPB-rewarming rate,[12] prolonged perfusion time,[8] postoperative hyperthermia,[13] and postoperative time to awakening,[11] were identified as predictors of cognitive decline. In other studies, cognitive decline in the first week after surgery predicted late cognitive decline (six months and five years after surgery).[1,14]

The aim of the present study was to determine which demographic and peri-operative variables predict cognitive outcome three months after surgery, using the data obtained from the Octopus study. We also evaluated whether the predictors and their predictive value differed between patients operated with and without CPB.

Methods

Patients

The present prognostic analyses are based on data of the Octopus multicenter trial, in which 281 patients were randomized to off-

Table 1: Cognitive test battery and raw data

Test	Cognitive domain	Main variable
Rey Auditory Verbal Learning	verbal memory, learning	total score trial 1-5
Rey Auditory Verbal Learning	verbal memory, retrieval	delayed recall score
Grooved Pegboard	motor capacity	time dominant hand, s
Trail Making Test Part A and B	divided attention	time trail B, s
Sternberg Memory Comparison	working memory speed	time 4 character chart, s
Line Orientation Test	visuospatial capacity	total score
Stroop Color Word Test	selective attention	time C – time B, s
Continuous Performance Task	sustained attention	mean reaction time, ms
Self Ordering Tasks	working memory	sum score
Visuospatial Working Memory	visual working memory	average distance, cm
Symbol Digit Modalities Test	information processing	total score

All values are means, with standard deviations in parentheses.

pump or on-pump CABG. The methods of this trial have been described elsewhere.[5,6] In brief, patients were included if referred for first time isolated CABG and eligible for both off-pump and on-pump surgery. Patients were excluded from the trial in case of emergency or concomitant major surgery, Q-wave myocardial infarction in the last six weeks or poor left ventricular function. Also patients that were unlikely to complete one year follow-up or undergo neuropsychologic testing, were excluded. There were no restrictions to age. The study was approved by the local Ethics Committee of each participating hospital and written informed consent was obtained from all patients.

Operative procedure

Goal of surgery was to obtain complete, arterial revascularization. During off-pump procedures, the Octopus method[15] was used for stabilization of the target coronary artery. During on-pump procedures, CPB was managed according to the alpha-stat principle, with a minimal nasopharyngeal temperature of 32 °C and a non-pulsatile perfusion of 2.0 to 2.4 l/m2/min. During rewarming, the maximal gradient between blood and water in the heat exchanger was 5 °C, with a maximal water temperature of 39 °C.

Outcome

To establish cognitive outcome at three months, patients underwent a battery of ten neuropsychologic tests, comprising eleven

Table 1: (continued)

Baseline	Day 4	3 months
37 (9)	35 (8)	37 (10)
6 (3)	6 (3)	7 (3)
112 (29)	114 (27)	105 (21)
95 (46)	97 (46)	85 (37)
61 (16)	60 (22)	60 (16)
24 (4)	24 (4)	25 (4)
47 (25)	45 (25)	44 (26)
544 (117)	-	559 (114)
10 (4)	-	11 (4)
0.53 (0.79)	-	0.42 (0.63)
40 (11)	-	43 (11)

main variables, one day before and three months after operation. The battery included tests for motor skills, verbal memory capacity, speed of working memory, visuospatial capacity, selective and sustained attention and information processing (Table 1). Two outcome measures of cognitive outcome were used. Both were based on a comparison of the test results after three months with those at baseline (preoperatively). As a dichotomous measure, we defined 'cognitive decline', conform commonly used criteria, as a decrease in an individual's performance of at least 20 percent from baseline, in at least 20 percent (i.e. three) of the main variables.[16] Patients who had suffered a stroke were considered to have cognitive decline. To establish a continuous cognitive outcome measure, the relative cognitive performance (RCP) was calculated for each main variable in each patient by subtracting the preoperative score from the postoperative score and dividing the difference by the preoperative standard deviation (SD) of that variable. If improved performance was reflected by a lower score (e.g. in timed tasks), the directional data were reversed so that all improvements gave rise to a positive RCP. 'Overall RCP' at three months was defined as the mean of the RCPs that were calculated per test.[17,18]

Three months after surgery, the cognitive outcome could be determined in 248 patients (88%). Reasons for loss to follow-up were withdrawal before surgery (9 patients), failure to administer the pre-operative or postoperative tests (6 patients), mortality at the time of follow-up (2 patients), patients being too ill at the time of follow-up (5 patients), patients unable to appear for follow-up (5 patients), and a lack of motivation for follow-up (6 patients).

Potential predictors

Fifteen potential predictors of cognitive outcome at three months were evaluated. Preoperative patient characteristics included age, sex, diabetes, peripheral vascular disease, history of stroke or transient ischaemic attack, and the number of diseased coronary arteries. Intra-operative characteristics included sternotomy (versus anterolateral thoracotomy), milligrams of opioids (sufentanil) used during anesthesia (which influences the postoperative awake time), off-pump or on-pump treatment, perfusion time (in patients operated with CPB), use of aortic side clamps, and transfusion of blood products. Postoperative characteristics included number of days in hospital, and two overall measures of cognitive performance on the fourth day after surgery. Analogous to the measures of cognitive outcome at three months, we obtained a dichotomous measure of cognitive outcome at the fourth day ('cognitive decline at day four'), as well as a continuous outcome measure ('overall RCP at day four'). Cognitive performance at day four was determined with a battery of six tests, including seven main variables. Thirty-eight patients refused or were unable to undergo neuropsychologic assessment on the fourth day. Of the remaining 210 patients 28 actually underwent the assessment on the fifth postoperative day, but their test results were not excluded from the analyses.

Data analysis

All analyses were performed using SPSS version 10.0 software. We used logistic regression analysis to determine which characteristics predicted 'cognitive decline' at three months (dichotomous outcome) and to what extent, and linear regression analysis to determine which characteristics predicted 'overall RCP' at three months (continuous outcome). Both models were obtained following the same procedure. First, for explorative reasons, the association between cognitive outcome at three months and each of the possible predictors was quantified using univariable analysis. Continuous variables were initially included as continuous terms as a linear relation was plausible, but logical transformations (e.g. squared and log) were evaluated as well.[19] As the aim of this study was to obtain optimal prediction of cognitive outcome after three months, all predictors contributing prognostic

information should preferably be included in a multivariable model.[20] Therefore, as is common in prediction research, we included all predictors with p-value 0.25 in the univariable analysis in a multivariable model.[20]

This overall multivariable model was then reduced by excluding predictors one by one and comparing each reduced model to the overall model using the LR-test in case of logistic regression and the partial F-test in case of linear regression. If the p-value of these tests became < 0.15 the variable was retained in the final (reduced) model. Then all previously excluded predictors were one by one re-entered in the final model to evaluate whether they indeed did not contain any additional prognostic information. Finally, if previously excluded, the final model was extended with the variables, age, sex and surgery with or without CPB, regardless their p-value. We assumed that these three variables are important predictors of cognitive function anyhow and should be left in the model to enhance comparison with the literature.

In the prediction of 'cognitive decline' at three months (logistic model), the odds ratio (OR) and 95% confidence interval (95% CI) were used as measures of association. Of the overall and the reduced multivariable model, the ability to discriminate between patients with and without cognitive decline at three months was estimated using the area under the Receiver Operating Characteristic curve (ROC area).[20,21] The ROC area is a suitable parameter to summarize the predictive or discriminative ability of a model and can range from 0.5 (useless model, like a coin flip) to 1.0 (perfect discrimination). A value over 0.7 is often interpreted as reasonable and over 0.8 as good.[20,21]

In the prediction of 'overall RCP' at three months (linear model), the linear regression coefficient with 95% CI was used as the measure of association. This coefficient reflects the amount of improvement (positive value) or decrease (negative value) in cognitive performance. The ability of the linear model to explain the variation in the outcome was estimated by using R^2, which represents the proportion of 'overall relative cognitive performance' at three months that can be explained by the model.

Of all 248 cases, 38 had no neuropsychologic assessment on the fourth (or fifth) postoperative day. Perfusion time was known only in patients operated with CPB. The other predictors were

Table 2: Characteristics of patients and results of univariable analyses for both measures of three-month cognitive outcome

		Logistic regression			
Predictor	All patients (n=248)	Decline absent (n=185)	Decline present (n=63)	Odds ratio*	p-value
Age, y‡	61	61	61	1.02‡	0.90
Female sex, %	29	29	29	1.00	1.00
Diabetes, %	12	12	13	1.10	0.82
Peripheral vascular disease,%	8	8	8	1.00	1.00
Previous stroke or TIA, %	4	4	3	0.74	0.71
No. of diseased coronary arteries	2.0	2.0	2.0	1.06	0.79
Sternotomy, %	96	96	94	0.57	0.37
Sufentanil dose, mg	0.23	0.23	0.24	1.00	0.75
Off-pump treatment, %	49	52	42	0.68	0.19
Perfusion time, min §	66	65	68	1.04§	0.61
Use of sideclamp(s), %	42	40	48	1.42	0.24
Blood transfusion, %	30	31	29	0.91	0.78
Days in hospital	8.5	7.6	9.3	1.02	0.21
Cognitive decline at day 4, %	52	46	72	3.07	<0.01
Overall RCP at day 4	-0.13	-0.10	-0.22	0.47	0.07
Individual cognitive tests day 4:					
-RCP Rey test-totalscore day 4	-0.25	-0.18	-0.45	0.72	0.08
-RCP Rey test-recallscore day 4	-0.20	-0.16	-0.23	0.94	0.68
-RCP Grooved Pegboard day 4	-0.22	-0.21	-0.27	0.87	0.59
-RCP Trailmaking test day 4	-0.17	-0.15	-0.25	0.76	0.32
-RCP Sternberg test day 4	0.11	0.16	-0.08	0.81	0.18
-RCP Line Orientation test day 4	-0.12	-0.17	-0.03	1.28	0.30
-RCP Stroop test day 4	-0.01	0.00	-0.06	0.86	0.58

TIA denotes transient ischaemic attack, RCP denotes relative cognitive performance

* odds ratio > 1.0 predicts cognitive decline at three months (< 1.0 absence)

† positive coefficient predicts better cognitive outcome at three months (negative coefficient predicts worse outcome)

‡ odds ratio and coefficient per 10 years

§ applies only to the on-pump patients; odds ratio and coefficient per 10 minutes

known in at least 98 percent of the patients. To decrease bias and increase statistical efficiency we filled in (imputed) the missing values using the linear regression method.[22] Such imputation is based on the correlation between each variable with missing values and all other variables. The results of the analyses based on the complete subjects and on all subjects after imputation were compared. Since this yielded no different results (i.e. the same independent predictors were selected with similar regression coefficients) only the analyses based on observed (i.e. unimputed) data are presented.

Table 2: (continued)

Linear regression	
Coefficient‡	p-value
0.011‡	0.54
0.039	0.30
0.046	0.38
0.038	0.55
-0.066	0.45
0.025	0.31
-0.068	0.41
-0.21	0.05
0.061	0.08
0.0098§	0.36
-0.013	0.70
0.024	0.53
-0.0020	0.33
-0.038	0.31
0.16	<0.01
0.050	0.01
0.053	<0.01
0.0035	0.90
0.11	<0.01
-0.0038	0.83
0.035	0.17
0.019	0.51

To examine whether the determinants of cognitive outcome after off-pump CABG differed from those after on-pump CABG, all analyses were repeated in exclusively the patients who underwent off-pump CABG (n=122), and then in those who underwent on-pump CABG (n=126).

Results

The raw data of the neuropsychologic tests are presented in Table 1. Table 2 shows the distribution of the predictors in all patients (first column).

Dichotomous outcome

Table 2 shows the results of the univariable logistic regression analysis (2nd to 5th column). At three months, 63 of the 248 patients had 'cognitive decline'. Three clinical variables were weakly associated with cognitive decline: on-pump versus off-pump treatment (p=0.19), use of sideclamps (p=0.24), and days in hospital (p=0.21). Cognitive decline at day four (p<0.01) and overall RCP at day four (p=0.07) were stronger associated. To distinguish which of the component tests were responsible for this, we analyzed the association of the individual tests at day 4 with the outcome. It appeared that the Rey Auditory Verbal Learning Test (total score) was mainly associated with the outcome (p=0.08).

We fitted a multivariable model including the use of side clamps, cognitive decline at day four plus off-pump surgery, age and sex. In this model, decline at day four was the only important predictor of cognitive decline at 3 months (OR 3.11; p<0.01). The OR

Table 3: Univariable logistic regression analysis: off-pump versus on-pump

	Off-pump treatment (n=122)		On-pump treatment (n=126)	
Predictor	**Odds ratio***	**p-value**	**Odds ratio***	**p-value**
Cognitive decline at day 4	2.00	0.16	4.72	<0.01
Age, y	1.12†	0.64	0.94†	0.79
Female sex	0.93	0.88	1.12	0.80

* odds ratio > 1.0 predicts cognitive decline at three months (< 1.0 absence)

† odds ratio per 10 years

of off-pump treatment was 0.96 (p=0.91). The ROC area of this model was 0.68 (95% CI 0.59 - 0.76).

Continuous outcome

'Overall relative cognitive performance' had a normal distribution, with mean 0.139; standard deviation 0.268; and median 0.164. The last two columns of Table 2 show that the dose of sufentanil (p=0.05), off-pump surgery (p=0.08), and overall relative cognitive performance at day four (p<0.01) were associated with 'overall relative cognitive performance' at three months. Further analysis of the individual neuropsychologic tests at day four showed that performance on the Trail Making Test and Rey Auditory Verbal Memory Test were mainly associated with the outcome (p-values < 0.01).

We fitted a multivariable model including overall RCP at day four, off-pump treatment, age and sex. Overall RCP at day four (coefficient 0.16; p<0.01) and off-pump treatment (coefficient 0.071; p=0.05) predicted 'overall relative cognitive performance' at three months. The R-square was 0.08, i.e. the model explained only 8% of the variance in cognitive performance at three months.

Off-pump versus on-pump treatment

The incidence of cognitive decline at day four was 46% in patients operated off-pump, and 59% in patients operated on-pump (p=0.07). Within the group of 122 patients that was operated without CPB, cognitive decline (dichotomous) on day four

Table 4: Univariable linear regression analysis: off-pump versus on-pump

	Off-pump treatment (n=122)		On-pump treatment (n=126)	
Predictor	**Coefficient***	**p-value**	**Coefficient***	**p-value**
Overall RCP at day 4	0.12	0.02	0.21	0.02
Age, y	-0.011†	0.64	0.037†	0.20
Female sex	-0.007	0.88	0.081	0.16

RCP denotes relative cognitive performance

* positive coefficient predicts better cognitive outcome at three months (negative coefficient predicts worse outcome)

† coefficient per 10 years

was the only predictor of cognitive decline after three months (OR 2.00; 95% CI 0.77 - 5.20). Within the group of 126 on-pump patients, the association between early and late cognitive decline was considerably stronger (OR 4.72; 95% CI 1.63 - 13.66) (Table 3). Comparable results were found when cognitive outcome was analyzed as a continuous variable (Table 4).

Discussion

This study aimed to identify predictors of cognitive outcome after CABG. The study was conducted in a sample of 248 patients, of whom 63 suffered cognitive decline at three months, but in whom the use of CPB appeared not to be the major determinant of this outcome. The principal result of the present study, which was based on multivariable analyses, is that previously reported predictors of cognitive decline, including age and sex, were not associated with this outcome in the present patient sample. The only peri-operative variable that was significantly associated with cognitive outcome at three months was early cognitive outcome, measured on the fourth day after surgery. The effect of CPB on cognitive outcome in the present study differs slightly from what was described in the trial report,[6] because the trial analyses were based on assigned treatment ('intention to treat'), while the present analyses were based on actually undergone treatment (i.e. cross-overs were taken into account).

Several aspects need to be discussed. First, in prediction research, the number of subjects with the outcome of interest (i.e. cognitive decline) determine the ability to identify relevant predictors of that outcome (statistical power).[23-25] The sample may have been too small to find relatively weak predictors such as diabetes and perfusion time, which have been found in other studies.[8,10] A rule of thumb for prediction studies with a dichotomous outcome, is that the number of candidate predictor variables (in our case 15) does not exceed the number of patients in the smallest group divided by 10 (in our case this would be 6.3).[23-25] We did exceed this ratio. However, this rule of thumb was introduced to prevent overfitting, i.e. to prevent the selection of predictors which in fact are spurious (or 'noise') predictors. In this study we did hardly detect any predictors of cognitive outcome. The problem of overfitting may therefore be less applicable.

We may have selected the wrong candidate predictors. A vast body of literature indicates that CABG with CPB affects cognitive outcome.[1-4,6-13,17] However, in the first randomized study of substantial sample size, we only found slight improvement of cognitive outcome when avoiding CPB.[6] This suggests other variables may play a role in the development and therefore in the prediction of cognitive decline. Advanced age represents the least controversial demographic risk factor for cognitive decline,[1,7-9] but even this association could not be confirmed in the present patient sample. Many other previously reported predictors were considered in our study as well, with exception of rewarming rate and postoperative hyperthermia. The present study was conducted in relatively young patients with limited co-morbidity, but they were comparable to the patients included in previous studies.[1,7-13] The fact that previously reported associations could not be confirmed suggests that new determinants of cognitive injury are yet to be identified and unknown mechanisms are to be elucidated.

An alternative explanation for our inability to predict cognitive decline is that modern CPB management, with use of membrane oxygenators, mild rather than moderate hypothermia, relatively slow rewarming rates, and prevention of postoperative hyperthermia, has reduced the incidence of cognitive decline. This would imply that the > 20% incidence of decline found in our patient

sample is an overestimation of the true size of the problem. The instrument used to measure cognitive decline (i.e. the repeated administration of a battery of neuropsychologic tests) is not very accurate. It was recently suggested that the current definitions of cognitive decline after CABG have limited precision and may overestimate its true incidence.[26] The definitions are based on a particular degree of decline in test performance, for example postoperatively 20 percent or one SD worse than preoperatively. These cut-off values may be within the range of an individual's natural fluctuations in performance. Recently, the ISPOCD group determined cognitive status using five neuropsychologic tests in 176 volunteers, not undergoing surgery.[26] After three months, 25 percent of the volunteers was identified as having cognitive decline, which suggests a considerable degree of measurement error. Incorrect identification of patients with and without cognitive decline, and/or a severe overestimation of the number of patients with cognitive decline, may both explain our inability to find predictors of cognitive decline in a sample of 248 patients.

The data from volunteer studies emphasize our inability to reliably dichotomize patients into 'normal' and 'declined' by means of repeated administration of neuropsychologic tests. This raised the question whether our neuropsychologic test battery measures cognitive performance sufficiently accurately, which is a prerequisite for capturing subtle decreases in performance from before to after surgery. These observations prompted us to quantify the association between the patient's baseline characteristics and cognitive performance at baseline. Cognitive performance at baseline was defined as the mean of the standardized neuropsychologic test scores before surgery. A multivariable linear regression model identified advanced age ($p<0.001$) and female sex ($p=0.01$) as independent predictors of a low cognitive performance at baseline. The presence of these associations suggests that the neuropsychologic tests are able to determine cognitive performance.

We did find an association between cognitive decline in the first week and after three months. Several authors have described comparable associations.[1,3,14] However, since all definitions of cognitive decline are based on a comparison between postoperative and preoperative test performance, this association may be explained by regression to the mean.[27] Patients who perform well

-according to their own standards- on their preoperative assessment, have a greater risk to perform worse on all future (postoperative) assessments, and therefore might repeatedly meet the criteria of cognitive decline. Nevertheless, it is a remarkable finding that in the present study, the association between early and late cognitive decline was stronger in patients operated with CPB than in those operated without CPB.

In conclusion, cognitive outcome four days after coronary bypass surgery predicted cognitive outcome after three months. Previously reported associations between patient variables or perioperative variables and cognitive outcome could not be confirmed in the present study.

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Chapter 6

Early outcome after off-pump versus on-pump coronary bypass surgery: results from a randomized study

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Abstract

Background The use of cardiopulmonary bypass during coronary artery bypass surgery (CABG) has been associated with substantial morbidity. The recent introduction of cardiac stabilizers facilitates CABG without cardiopulmonary bypass (off-pump CABG), but it is unknown whether cardiac outcome after off-pump surgery is similar to that for the on-pump procedure.

Methods and Results In a multicenter trial, 281 patients (mean age 61 years, SD 9 years) were randomly assigned to off-pump or on-pump CABG. In-hospital results and cardiac outcome and quality of life after 1 month are presented. Cardiac outcome was defined as survival free of stroke, myocardial infarction, and coronary reintervention. The mean numbers of distal anastomoses per patient were 2.4 (SD 1.0) and 2.6 (SD 1.1) in the off-pump and on-pump groups, respectively. Completeness of revascularization was similar in both groups. Blood products were needed during 3% of the off-pump procedures and 13% of the on-pump procedures ($p<0.01$). Release of creatine kinase muscle-brain isoenzyme was 41% less in the off-pump group ($p<0.01$). Otherwise, no differences in complications were found postoperatively. Off-pump patients were discharged 1 day earlier. At 1 month, operative mortality was zero in both groups, and quality of life had improved similarly. In both groups, 4% of the patients had recurrent angina. The proportions of patients surviving free of cardiovascular events were 93.0% in the off-pump group and 94.2% in the on-pump group ($p=0.66$).

Conclusions In selected patients, off-pump CABG is safe and yields a short-term cardiac outcome comparable to that of on-pump CABG.

Introduction

Coronary artery bypass surgery (CABG) using cardiopulmonary bypass (CPB) relieves angina but is associated with substantial morbidity.[1,2] CPB requires full heparinization, induces a whole-body inflammatory response, and generates microemboli.[3–5] It also requires cannulation and cross-clamping of the ascending aorta, which may lead to atheromatous macroemboli.[6] Procedures that do not use CPB are likely to prevent these unwanted effects. Moreover, in selected patients, the operation may be performed via a left anterior thoracotomy or a substernal incision, which makes sternotomy unnecessary.[7] Avoiding full heparinization allows safe use of a thoracic epidural catheter. Apart from thoracic sympatholysis, this may lead to improved postoperative pain relief and reduced mechanical ventilation time.[8] Consequently, if CPB can be avoided (off-pump CABG), a reduction in perioperative morbidity and mortality is anticipated, with faster recovery, shorter hospitalization, and less need of medical facilities and materials.[9,10]

Recently, cardiac stabilization techniques were developed to facilitate bypass surgery on the beating heart (off-pump CABG). The Octopus[11] is one of the devices that can immobilize and present all sides of the beating heart. This allows off-pump CABG in patients with 3-vessel disease.[9,12] The feasibility of off-pump CABG depends primarily on the coronary anatomy and the hemodynamic consequences of exposure of the posterior ventricular wall.[9,13,14] The procedure is technically more demanding, and it is unknown whether cardiac outcome is comparable to on-pump procedures.[9]

This randomized trial compared off-pump and on-pump CABG. We present in-hospital results and cardiac outcome and quality of life after 1 month.

Methods

Study design and patients

Design and methods of the Octopus multicenter trial have been described in detail.[15] In brief, after they had given written

informed consent, patients were randomly assigned to off-pump or on-pump CABG. Patients were eligible if referred for first-time isolated coronary bypass surgery and an off-pump procedure was deemed technically feasible. Patients were excluded in case of emergency or concomitant major surgery, Q-wave myocardial infarction in the previous 6 weeks, or poor left ventricular function or if they were unlikely to complete 1 year of follow-up or unable to give informed consent. There were no restrictions as to age. The study was approved by the ethics committees of the participating centers.

Between March 1998 and August 2000, 281 patients were enrolled in 3 hospitals in the Netherlands, of whom 265 underwent treatment according to randomization. In 10 patients randomized to off-pump surgery, CPB was used during the procedure. One other patient randomized to off-pump surgery underwent coronary angioplasty because of infection. In 5 patients assigned to on-pump CABG, an off-pump procedure was performed.

Treatment and procedures

Before randomization, the treatment plan was recorded on dedicated forms. The goal of surgery was to obtain complete arterial revascularization. With the exception of 2 emergency procedures, all operations were performed by cardiac surgeons experienced in both off-pump and on-pump bypass surgery. During off-pump procedures, the Octopus method[11] was used for stabilization of the target coronary artery.

Anesthetic technique varied according to the treatment allocation. In the on-pump group, 99% of the patients received total intravenous anesthesia, including high-dose opioids, whereas in the off-pump group, 54% of the patients received thoracic epidural anesthesia combined with low-dose opioids. The CPB was primed with a crystalloid-colloid mixture, and the minimal nasopharyngeal temperature was 32°C. During aortic cross-clamping, cold crystalloid cardioplegia (St Thomas solution) was used for myocardial protection. To reduce blood loss, blood was recollected with a suction cardiotomy reservoir in the CPB group, whereas a cell saver was used in the off-pump group. In an attempt to reduce the incidence of postoperative atrial fibrilla-

tion, all patients were given sotalol 40 mg twice daily from the first day to 1 month after surgery.

Data collection and outcome measures

During surgery, the following parameters were recorded: access to the heart, number of distal anastomoses, type of graft (arterial versus venous), completeness of revascularization (the agreement between treatment plan and actual number of distal anastomoses), switch to CPB for the off-pump group, time on CPB and cross-clamp time for the on-pump group, use of blood products, and time between arrival in the operating room and transfer to the intensive care unit (ICU).

After surgery, the following were measured: serum creatine kinase muscle-brain isoenzymes (CK-MB) (mean area under the curve, based on 5 measurements within the first 20 hours), incidence of atrial fibrillation, use of inotropes, blood loss during the first 12 hours, use of blood products, overall postoperative complication rate (cardiac arrest, cardiac failure, repeat thoracotomy, infection requiring antibiotics or surgical treatment, pneumothorax, time to extubation >24 hours, or renal failure requiring dialysis), weight changes, time to extubation, time spent in the ICU, number of days until discharge, pain during the first 3 days (visual analog score, with 0 reflecting no pain and 10 reflecting the worst imaginable pain), hemoglobin at discharge, and creatinine at discharge.

As part of a formal long-term cost-effectiveness analysis, all material and resources used during the hospital stay were recorded. Also, in parallel, a cost study on the unit costs was performed. Actual costs were estimated by multiplying resource use by unit costs.

Cardiac outcome 1 month after surgery was defined as survival free of cardiovascular events, which included stroke, myocardial infarction, and coronary reintervention (CABG or coronary angioplasty). These events were evaluated by an independent committee blinded to treatment allocation. Stroke was defined as focal brain injury persisting for >24 hours, combined with an increase in handicap of 1 grade on the Rankin scale.[16] During the first 7 days after surgery, myocardial infarction was defined by elevation of serum CK-MB to >5 times the upper limit of nor-

mal.17 After 7 days, it was considered present when 2 of the following criteria were met: chest discomfort lasting 30 minutes, CK-MB/CK ratio >0.1, and the development of abnormal new Q waves on the ECG. The latter distinguished Q-wave and non-Q-wave myocardial infarction at any time.[15] Recurrence of stable or unstable angina after 1 month was defined according to the Canadian Cardiovascular Society[18] and Braunwald classifications,[19] respectively.

Health-related quality of life was assessed 1 week before and 1 month after surgery by use of 2 generic questionnaires. The EuroQol questionnaire generates a single index, ranging from -1 to +1, with -1 reflecting the worst imaginable quality of life and +1 reflecting the best imaginable quality of life.[20] The ShortForm-36 questionnaire comprises 8 different domains, all ranging from 0 to 100. Higher scores indicate higher levels of functioning or well-being.[21]

Data analysis

All data were analyzed on an intention-to-treat basis, ie, based on randomization. Differences are presented with 95% CIs. Dichotomous data were compared by the Chi^2 statistic. Means are presented with SD and were compared by a 2-sample t test. Nonnormally distributed continuous variables are presented as medians and were compared by a Mann-Whitney test.

Results

Patient population and in-hospital results

Baseline characteristics were well balanced across the randomized groups (Table 1). The small difference between the 2 groups in patients with 3-vessel disease is reflected by the mean number of grafts per patient (Table 2), which was 2.4 in the off-pump group and 2.6 in the on-pump group. There was no difference in completeness of revascularization. Use of vein grafts was avoided in 84.4% of the off-pump patients and 75.7% of the on-pump patients. In 8% of the off-pump patients, access to the heart was obtained via left anterior thoracotomy instead of sternotomy. Two patients randomized to off-pump CABG were operated on

Table 1: Baseline Characteristics

Variable	Off-pump (n=142)	On-pump (n=139)
Age, y	61.7 (9.2)	60.8 (8.8)
Male sex, %	66	71
One-vessel disease, %	30	22
Two-vessel disease, %	50	50
Three-vessel disease, %	20	27
Normal left ventricular function, %	77	79
Moderate left ventricular function, %	23	21
Angina CCS class I or II, %	32	26
Angina CCS class III or IV, %	45	49
Unstable angina, Braunwald I to IIB, %	22	21
Previous myocardial infarction, %	34	26
History of coronary angioplasty, %	17	20
Currently smoking, %	14	14
Hypertension, %	40	44
Hypercholesterolaemia, %	68	68
Family history of coronary disease, %	59	58
Obesity (quetelet index >30 kg/m2), %	18	22
Peripheral vascular disease, %	7	13
Diabetes, %	9	17
History of stroke, %	4	3
Pulmonary disease, %	9	10
Hemoglobin, g/dl	14.25 (1.24)	14.20 (1.11)
Serum creatinine, mg/dl	1.01 (0.17)	1.04 (0.22)

CCS indicates Canadian Cardiovascular society. Values are percentage or mean (SD).

Table 2: Intraoperative data

Variable	Off-pump	On-pump	Difference	95% CI	p-value
Access to the heart via sternotomy, %	92	100	8	4 – 13	<0.01
Number of distal anastomoses	2.4 (1.0)	2.6 (1.1)	0.3	0.0 – 0.5	0.05
Graft left anterior descending artery, %	98	96	-2	-6 – 2	0.44
Graft right coronary artery, %	53	64	11	-1 – 22	0.07
Graft ramus circumflexus, %	40	45	5	-7 – 17	0.39
Exclusive use of arterial grafts, %	84	76	-9	-18 – 1	0.07
Grafting according to treatment plan, %	83	83	0	-9 – 9	0.98
Switch to cardiopulmonary bypass, %	7.7				
Time on cardiopulmonary bypass, min		66 (23)			
Cross-clamp time, min		44 (18)			
Use of blood products, %	3	13	10	4 – 17	<0.01
Time in operating room, hours	4.2 (1.1)	3.8 (0.7)	-0.4	-0.6 – -0.1	<0.01

Values are percentage or mean (SD).

Table 3: Postoperative data

Variable	Off-pump	On-pump	Difference	95% CI	p-value
Release of CK-MB, AUC (median)	164	277	113		<0.01
CK-MB, 2 h after surgery, U/l (median)	7.0	16.0	9.0		<0.01
CK-MB, 4 h after surgery, U/l (median)	7.0	15.0	8.0		<0.01
CK-MB, 8 h after surgery, U/l (median)	8.0	14.5	6.5		<0.01
CK-MB, 12 h after surgery, U/l (median)	8.5	13.0	4.5		<0.01
CK-MB, 20 h after surgery, U/l (median)	10.0	13.5	3.5		<0.01
Atrial fibrillation, %	20	21	1	-8 – 11	0.79
Use of inotropes, %	27	28	1	-10 – 11	0.88
Blood loss first 12 h, L	0.5 (0.4)	0.4 (0.2)	-0.1	-0.2 – 0.0	0.02
Use of blood products, %	28	29	1	-10 – 12	0.85
Overall postoperative complication rate, %	14	11	-3	-10 – 5	0.52
cardiac arrest, %	1	0	-1	-2 – 1	0.32
cardiac failure, %	2	2	-1	-4 – 2	0.68
repeat thoracotomy, %	4	2	-2	-6 – 2	0.33
infection, %	5	5	0	-5 – 5	0.96
pneumothorax, %	2	2	0	-3 – 4	0.97
time to extubation > 24 h, %	1	2	0	-3 – 3	0.98
renal failure, %	0	1	1	-1 – 2	0.31
Weight day 4 – preoperative weight, kg	0.1 (2.1)	-0.8 (2.2)	-0.9	-1.5 – -0.4	<0.01
Time to extubation, h (median)	3	9	6		<0.01
Time in intensive care, h (median)	22	22	0		0.88
Time before discharge, days (median)	6	7	1		<0.01
Pain, mean visual analog score day 1 - 3	2.6 (1.7)	2.6 (1.8)	0.1	-0.4 – 0.5	0.84
Hemoglobin at discharge, g/dl	11.5 (1.5)	11.5 (1.5)	0.0	-0.2 – 0.2	0.88
Serum creatinine at discharge, mg/dl	0.94 (0.18)	0.98 (0.26)	0.04	-0.02 – 0.09	0.16

AUC indicates area under the curve (h x U/L).Values are percentage, median, or mean (SD).

with CPB because progression of symptoms necessitated emergency surgery. In 4 off-pump patients, CPB was used because of persistent arrhythmias, myocardial ischemia, and hypotension during the procedure. In 4 others, CPB was used because the coronary anatomy turned out to be unsuitable for a beating-heart approach. The proportion of patients in whom blood products were used during surgery was 4 times lower in the off-pump group.

Detailed data of the postoperative period are presented in Table 3. The release of CK-MB, expressed as area under the curve, was 41% less in the off-pump group ($p<0.01$). There was no difference in frequency of postoperative atrial fibrillation, overall complication rate, or pain. After surgery, the proportion of patients receiving blood products was similar. After 4 days, on-

Table 4: Cardiac outcome after 1 month

Event	Off-pump (n=142)	On-pump (n=139)
All-cause mortality	0 (0%)	0 (0%)
Stroke	1 (0.7%)	2 (1.4%)*
Myocardial infarction	7 (4.9%)†	6 (4.3%)*
PTCA	2 (1.4%)	0 (0%)
Repeat CABG	0 (0%)	0 (0%)
Survival free of cardiovascular events	132 (93.0%)	131 (94.2%)

* One occurred before surgery.

† Two occurred before surgery.

pump patients had lost weight, whereas off-pump patients had gained weight. Off-pump patients were discharged 1 day earlier than on-pump patients.

The costs of the surgical procedure were slightly lower for the off-pump group, ie, US $3112 versus $3535 ($p<0.01$). The overall costs associated with hospitalization and the procedure, however, were not significantly different for the off-pump and on-pump groups, ie, US $8796 and $9118, respectively ($p=0.75$).

Cardiac outcome at 1 month

The mean follow-up period was 37 days (SD 8 days) in both groups. None of the patients died. In the off-pump group, 93.0% of the patients had survived free of cardiovascular events, compared with 94.2% in the on-pump group (difference 1.2%; 95% CI -4.4 to 7.0%; P=0.66) (Table 4). In the off-pump group, 4 patients suffered a Q-wave and 3 patients a non-Q-wave myocardial infarction. In the on-pump group, 4 Q-wave and 2 non-Q-wave myocardial infarctions occurred. One patient had supplementary angioplasty after off-pump surgery because the deep intramural course of the left anterior descending coronary artery prevented grafting of this vessel without cardioplegia. In both groups, 5 patients had recurrent, stable angina. One on-pump patient had unstable angina.

Table 5: Comparison of quality of life within and between the treatment groups

	Off-pump*			On-pump*		
Domain	**Baseline**	**1 month**	**p-value**	**Baseline**	**1 month**	**p-value**
Overall	0.64 (0.27)	0.69 (0.26)	0.03	0.65 (0.27)	0.71 (0.22)	0.05
PF	52 (25)	66 (20)	<0.01	52 (25)	69 (20)	<0.01
RP	23 (36)	21 (34)	0.86	23 (38)	19 (31)	0.45
BP	62 (26)	57 (21)	0.24	61 (26)	59 (21)	0.61
GH	56 (17)	67 (18)	<0.01	54 (20)	69 (19)	<0.01
VT	49 (23)	58 (20)	<0.01	49 (24)	57 (22)	<0.01
SF	61 (30)	60 (26)	0.95	61 (30)	59 (26)	0.40
RE	51 (46)	60 (46)	0.04	53 (47)	69 (43)	<0.01
MH	66 (20)	76 (18)	<0.01	67 (22)	76 (18)	<0.01

Overall denotes overall quality of life; 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; and MH, general mental health. Values are mean (SD).

* Differences within the groups between baseline and 1 month were compared by the paired t-test.

Quality of life

In both groups, there was a marked improvement in self-reported quality of life at 1 month (Table 5). This improvement was statistically significant for overall quality of life, as well as for the domains "physical functioning," "general health," "vitality," "role limitations due to emotional problems," and "general mental health." No differences in quality of life were observed between the off-pump and on-pump CABG group.

Discussion

The results of this randomized trial indicate that there is no difference between off-pump and on-pump CABG in completeness of revascularization and cardiac outcome after 1 month. Off-pump CABG, however, resulted in reduced CK-MB release, reduced use of blood products, and shorter hospital stay.

To appreciate these results, certain features of the study need to be addressed. Although the difference in survival free of cardiovascular events at 1 month was negligible, the 95% CI was wide, ranging from -4% to +7%, owing to the low number of clinical

Table 5: (continued)

Off-pump versus on-pump after one month		
Difference	**95% CI**	**p-value**
-0.01	-0.08 – 0.05	0.57
-3	-9 – 3	0.28
3	-6 – 11	0.58
-2	-8 – 4	0.49
-2	-7 – 3	0.41
1	-5 – 6	0.82
2	-5 – 9	0.66
-9	-21 – 4	0.17
0	-5 – 5	0.99

events in this trial. Another limitation is that, although the cardiovascular events were judged by an independent blinded committee, the patients and their attending physicians were not blinded for randomization. This may have influenced the timing of hospital discharge, self-reported quality of life, and anginal assessment.

In several respects, the present study could not show benefits that were anticipated from off-pump CABG.[1,3,12,22] The perioperative complication rate, however, was already quite low in the patients undergoing on-pump CABG. The incidence of postoperative atrial fibrillation was similar in both groups. This deviates from the results of Ascione et al,[22] who did not administer a prophylactic ß-blocker after surgery and found an absolute difference of 39% in favor of off-pump CABG. The shorter mechanical ventilation in off-pump patients has been caused at least partially by differences in anesthetic technique. This did not shorten ICU stay, because all patients stayed 1 night. Off-pump patients were discharged from hospital 1 day earlier, but the presumed faster recovery after off-pump CABG[9,12] was not reflected in better scores in health-related quality of life after 1 month. Overall hospital costs were not significantly different, although costs of the surgical procedure were slightly lower for the off-pump group. This was caused primarily by the materials used, i.e. stabilizer versus CPB. The current cost difference, however, should be interpreted cautiously, because long-term clinical outcomes will determine actual cost-effectiveness.

Two findings favor off-pump CABG. First, the intraoperative use of blood products was reduced in the off-pump group. This may be because dilution of the patient's blood with 2 L of CPB priming solution was avoided. Second, the 41% reduction in postoper-

ative CK-MB release suggests that avoiding CPB reduced the degree of myocardial necrosis. This is supported by the strong (up to 22-fold) reduction in maximum cardiac troponin I release in off-pump patients that was reported previously.[23,24] Apparently, local ischemia during clamping of the coronary arteries is less harmful than global cardiac ischemia. The clinical significance of this finding is uncertain. In patients undergoing PTCA, elevation of CK-MB was associated with higher risk of subsequent cardiac events and mortality.[17]

Completeness of revascularization was similar in both groups, but the study was conducted in relatively young patients with predominantly 1- or 2-vessel disease and normal left ventricular function. Old patients with generalized vascular disease and poor left ventricular function may benefit more from an off-pump technique,[25] because the risk of adverse outcomes after on-pump CABG in these patients is much higher.[2,26,27] Conversely, off-pump procedures in these patients carry a greater risk of hemodynamic instability or inadequate revascularization.

In conclusion, the results of this randomized trial in 281 patients suggest that in selected patients, off-pump CABG is safe and yields a short-term cardiac outcome comparable to that with on-pump CABG. In addition, omitting CPB leads to reduced cardiac enzyme release, reduced use of blood products, and a slightly shorter hospital stay.

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Chapter 7

Cardiac outcome and cost-effectiveness at one year after off-pump and on-pump coronary artery bypass surgery: results from a randomized study

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Submitted

Abstract

Background Avoiding cardiopulmonary bypass during coronary artery bypass surgery may reduce perioperative morbidity and costs. It is, however, unknown whether cardiac outcome is similar to bypass surgery using cardiopulmonary bypass. The purpose of this study was to compare cardiac outcome and cost-effectiveness at one year between bypass surgery on the beating heart (off-pump surgery) and conventional bypass surgery with the use of cardiopulmonary bypass (on-pump surgery).

Methods In a multicenter randomized clinical trial, 142 patients were randomly assigned to off-pump surgery and 139 patients to on-pump surgery. Cardiac outcome, cost-effectiveness and graft patency were determined at one year after surgery.

Results At one year, survival free from stroke, myocardial infarction and coronary re-intervention was 88.0% after off-pump and 90.6% after on-pump surgery ($p=0.48$). Survival free from angina was 89.3% vs 89.0% ($p=0.93$), respectively. Graft patency determined in a randomized subset of patients, was 91% in the off-pump and 93% in the on-pump group ($p=0.65$). Off-pump surgery reduced costs by $ 2,329 (13.1%) per patient ($ 15,479 vs $ 17,808 $p<0.01$). Quality adjusted life expectancy after off-pump and on-pump surgery was 0.82 vs 0.83 year ($p=0.70$). The cost-effectiveness ratio for off-pump compared with on-pump surgery as estimated by bootstrapping, remained in 98% of estimates below the conservative 'willingness to pay' threshold of $20,000 per quality adjusted life year.

Conclusions At one year, off-pump surgery was more cost-effective than on-pump surgery, while maintaining comparable cardiac outcome. In selected patients, off-pump surgery as an alternative for on-pump surgery is justified from an economic perspective.

Introduction

Coronary artery bypass graft surgery (CABG) plays an important role in the management of patients with ischemic heart disease.[1-3] Although excellent clinical results have been reported in a wide range of patients, the safety of CABG is being questioned.[4,5] Data from the National Cardiac Surgery Database of the Society of Thoracic Surgeons (January 1998) encompassing 170,895 patients, show that the proportion of patients without complications is only 65.4%.[6] In addition, health insurance data from 101,812 patients show that 10.2% of the patients do not leave the hospital within 14 days after the operation and 3.6% are discharged to a non-acute-care facility.[7]

Cardiopulmonary bypass (CPB) with cardiac arrest offers a still and bloodless surgical field allowing safe construction of the anastomoses. Yet, the use of CPB is believed to be a major determinant of perioperative morbidity,[4,5] hospital stay and costs.[8] As a result, bypass surgery on the beating heart without the use of CPB (off-pump surgery) has been reintroduced in clinical practice[9] and was stimulated by the introduction of cardiac stabilizers in the mid-nineties.[10] By immobilizing local areas of the beating heart, cardiac stabilizers facilitate the construction of the anastomoses.[11,12]

Off-pump surgery is expected to lower costs by reducing perioperative morbidity and recovery time. Nevertheless, the procedure is technically more demanding and it is unknown whether off-pump surgery can match the long-term benefits of on-pump surgery. The purpose of this randomized multicenter trial was to compare cardiac outcome and cost-effectiveness between off-pump and on-pump surgery at one year after the operation.

Methods

Study design and patients

The design and methods of the trial have been described in detail elsewhere.[13] In brief, patients with stable or unstable angina (Braunwald class I-II, B) with normal or moderately impaired ventricular function were randomly assigned to off-pump or on-

pump surgery. Patients were eligible if referred for first time isolated coronary bypass surgery and an off-pump procedure was deemed technically feasible. Patients were excluded in case of emergency or concomitant major surgery, Q-wave myocardial infarction in the last six weeks or poor left ventricular function. The study was carried out according to the principles of the declaration of Helsinki. Written informed consent was obtained in all patients. The ethics committees of the three participating centers approved the study protocol.

Treatment and procedures

The goal of surgery was to obtain complete, arterial revascularization. Surgeons experienced in both off-pump and on-pump surgery performed all operations. In the off-pump group, the 'Octopus' suction stabilizer was used for stabilization of the target coronary arteries.[11] In the CPB-group, cold crystalloid cardioplegia was used for myocardial protection.

Cardiac outcome

Cardiac outcome was defined as the composite of the following events: all-cause mortality, stroke, myocardial infarction and coronary re-intervention (CABG or angioplasty). Stroke was defined as focal brain injury persisting for more than 24 hours, combined with an increase in handicap of at least one grade on the Rankin Scale.[14] Within seven days of surgery, a myocardial infarction was diagnosed if serum creatine kinase (CK-MB) exceeded 5 times the upper limit of the normal value (non-Q-wave) and if concomitantly new pathological Q-waves appeared (Q-wave).[15] Seven days after surgery, a Q-wave infarction was documented in the presence of new pathological Q-waves and a non-Q-wave infarction in case of isolated CK-MB elevation with a CK-MB/CK ratio > 0.1. An independent committee blinded to the treatment allocation evaluated all events.

Additional endpoints were survival free of angina, anti-anginal medication (Beta-blockers, calcium entry-blockers or nitrates) and of exercise induced ischaemia. Stable and unstable angina were defined according to the Canadian Cardiovascular Society[16] and Braunwald classification, respectively.[17]

At the time of inclusion a subset of 110 patients was randomly assigned to control angiography at one year after surgery. A cardiologist and a cardiac surgeon independently examined the quality of the grafts using the Fitzgibbon criteria.[18] Also the flow was graded using the Thrombolysis In Myocardial Infarction (TIMI) classification.[19]

Costs and Cost-effectiveness

Costs were assessed in 1999 Dutch florins (DFL) and were converted in US dollars using an exchange rate of 1$=2.5DFL. Direct medical costs were assessed separately during initial hospitalization and subsequent follow-up until one year. Costs per patient were calculated by multiplying resource use by the cost per unit. Costs of myocardial infarction[20] and stroke[21-23] after the initial hospitalization were calculated using unit costs, as assessed by other investigators in the Netherlands. The direct in-hospital costs of on-pump surgery from the present study, were used as an estimate of costs of repeat CABG during follow-up. The unit costs of coronary angioplasty were previously determined at the University Medical Center Utrecht. Indirect costs concern losses of productivity and were calculated over a period of 4 weeks at baseline and prior to every 1, 3, 6 and 12 months follow-up by the 'friction cost' method.[24]

Health related quality of life was assessed using the Euroqol and its summary score (EQ-5D)[25] at baseline and 1, 3, 6 and 12 months after surgery. Using linear extrapolation for the periods in between measurements, quality adjusted survival time was estimated by calculating the individual area under the curve of the EQ-5D. Event-free survival was defined as the average time-interval in years between the randomization and first event, or one year follow-up if no event occurred. Effectiveness was expressed in terms of quality adjusted life year (QALY) and event free survival year (EFSY). Efficiency was addressed by calculating cost-effectiveness ratios by dividing the difference in costs by the difference in effects (QALY and EFSY). The uncertainty surrounding the obtained costs and effects was evaluated by standard bootstrap techniques.[26]

Data analysis

The sample size calculation was based on neurocognitive outcome after bypass surgery and has been described elsewhere.[27] All data were analyzed on an intention to treat basis. The risk of an event after off-pump surgery was compared with on-pump surgery and is presented as relative risk (RR) with 95% confidence intervals (CI). Dichotomous data were compared using the chi-square statistic. Means are presented with standard deviation (SD) and were compared using a two-sample t-test. Non-normally distributed continuous variables were compared by a Mann Whitney test. Event-free survival was graphically compared using Kaplan-Meier curves. Overall change from baseline of the EQ-5D was analyzed by repeated measures anova.[28]

Results

Patient characteristics and treatment allocation

Between March 1998 and August 2000, 281 patients were randomly assigned to off-pump (142 patients) and on-pump surgery (139 patients) in three hospitals in the Netherlands. Their baseline characteristics are summarized in Table 1. Ten patients randomized to off-pump surgery were intra-operatively converted to an on-pump procedure. One other patient randomized to off-pump surgery underwent coronary angioplasty. Five patients randomized to on-pump surgery underwent off-pump surgery. Therefore, a total of 265 patients (94%) were treated according to the randomization protocol.

The mean number of grafts per patient was 2.4 in the off-pump and 2.6 in the on-pump group. Complete arterial revascularization was achieved in 84% and 76% of the patients in the off-pump and on-pump group, respectively. In both treatment groups, 83% of patients were revascularized according to the surgical treatment plan which was defined before the randomization. The mean interval between operation and one year follow-up was 375 (SD 29) days in the off-pump and 378 (SD 33) days in the on-pump group (p=0.42).

Table 1: Baseline characteristics*

Variable	Off-pump (n=142)	On-pump (n=139)
Age, years	61.7 (9.2)	60.8 (8.8)
Male sex, %	66	71
One-vessel disease, %	30	22
Two-vessel disease, %	50	50
Three-vessel disease, %	20	27
Normal left ventricular function, %	77	79
Moderate left ventricular function, %	23	21
Angina CCS class I or II, %	32	26
Angina CCS class III or IV, %	45	49
Unstable angina, Braunwald I-II, B, %	22	21
Previous myocardial infarction, %	34	26
History of coronary angioplasty, %	17	20
Currently smoking, %	14	14
Hypertension, %	40	44
Hypercholesterolaemia, %	68	68
Family history of coronary disease, %	59	58
Obesity (quetelet index >30 kg/m^2), %	18	22
Peripheral vascular disease, %	7	13
Diabetes, %	9	17
History of stroke, %	4	3
Pulmonary disease, %	9	10

* Values are percentages or means with standard deviation in parentheses.

CCS denotes Canadian Cardiovascular Society.

Cardiac outcome at one year

The frequency of events is shown in Table 2 and illustrated by the Kaplan-Meier curve (Figure 1). In the off-pump group, two patients died from a non-cardiac cause and in the on-pump group two patients from a cardiac cause. One patient in the off-pump group and two patients in the on-pump group suffered a stroke (one patient who experienced a stroke just before

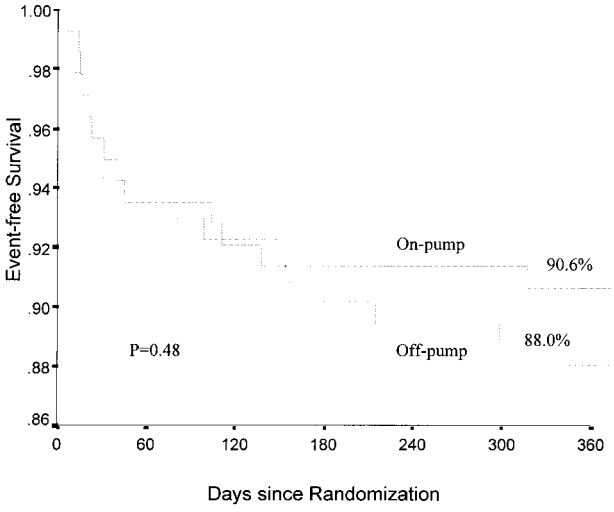

Figure 1: Kaplan-Meier estimates of survival free from stroke, myocardial infarction and coronary reintervention, (p=0.48 by the log rank test).

Table 2: Clinical events at one year, in descending order of severity*

Variable	Worst event†		All events‡	
	Off-pump (n=142)	On-pump (n=139)	Off-pump (n=142)	On-pump (n=139)
In-hospital events ¶				
All cause mortality	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.7)
Stroke	1 (0.7)	2 (1.4)	1 (0.7)	2 (1.4)
Myocardial infarction	7 (4.9)	6 (4.3)	7 (4.9)	7 (5.0)
Repeated CABG	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PTCA	2 (1.4)	0 (0.0)	2 (1.4)	0 (0.0)
Any event occurred	10 (7.0)	9 (6.5)	10 (7.0)	10 (7.2)
Events at 1 year‖				
All cause mortality	2 (1.4)	2 (1.4)	2 (1.4)	2 (1.4)
Stroke	1 (0.7)	1 (0.7)	1 (0.7)	3 (2.2)
Myocardial infarction	7 (4.9)	8 (5.8)	7 (4.9)	9 (6.5)
Repeated CABG	1 (0.7)	1 (0.7)	1 (0.7)	1 (0.7)
PTCA	6 (4.2)	1 (0.7)	6 (4.2)	4 (2.9)
Any event occurred	17 (12.0)	13 (9.4)	17 (12.0)	19 (13.7)
Event-free survival	125 (88.0)	126 (90.6)	-- --	-- --

* Values are numbers of patients, with percentages in parentheses.

† If a patient died after myocardial infarction or stroke, only the worst event (mortality) was counted.

‡ If a patient died after myocardial infarction or stroke, both events were counted.

§ Relative risk ratios and p-values concern the worst event.

¶ Between randomization and discharge.
In the off-pump group, one patient underwent PTCA while waiting for surgery. In the on-pump group, one patient suffered a myocardial infarction and another patient a minor stroke while waiting for surgery.

‖ Between randomization and 1 year follow-up.

CABG denotes coronary artery bypass grafting and PTCA percutaneous transluminal coronary angioplasty.

CABG, died 8 months after surgery from a second stroke). Seven patients in the off-pump group (Q-wave 4, non Q-wave 3) and 9 patients in the on-pump group (Q-wave 6 and non Q-wave 3) had sustained a myocardial infarction (p=0.60). Six patients in the off-pump group and 3 patients in the on-pump group (one patient twice), underwent percutaneous coronary angioplasty (p=0.33). Repeat CABG was performed in one patient in each group. At least one event occurred in 17 patients (12.0%) in the off-pump group and in 13 patients (9.4%) in the on-pump group, resulting in event-free survival of 88.0% and 90.6%, respectively (p=0.48). Survival free of stroke and myocardial infarction was 93.0% after off-pump and 92.1% after on-pump surgery (p=0.78). Freedom of angina at one year was 89.3% in the off-pump and

Table 2: (continued)

Worst event†	
Relative Risk§ (95% CI)	**p-value§**
--	0.31
0.49 (0.05 – 5.38)	0.55
1.14 (0.39 – 3.31)	0.80
--	--
--	0.16
1.09 (0.46 – 2.60)	0.85
0.98 (0.14 – 6.85)	0.98
0.98 (0.06 – 15.50)	0.99
0.86 (0.32 – 2.30)	0.76
0.98 (0.06 – 15.50)	0.99
5.87 (0.72 – 48.16)	0.06
1.28 (0.65 – 2.54)	0.48
0.97 (0.90 – 1.05)	0.48

89.0% in the on-pump group (p=0.93).

Exercise testing was performed in 246 patients (88%) at one year after surgery. The test was inconclusive in 7.1 % of the off-pump group and in 8.4% of the on-pump group. Myocardial ischaemia was documented in 16.9 % and 20.2 % of the remaining 227 patients, respectively (p=0.53). The exercise capacity expressed by metabolic equivalents (METS) was 9.0 METS in the off-pump and 9.5 METS in the on-pump group (p=0.28).

Forty of the 110 selected patients refused to undergo control angiography. Angiography was performed in 28 patients randomized to off-pump surgery and in 42 patients randomized to on-pump surgery. The angiographic results are shown in Table 3. The overall patency rate (Fitzgibbon grade A+B) was 91% in the off-pump and 93% in the on-pump group (p=0.65).

Costs and Cost-effectiveness

Average costs per patient per treatment are presented in Table 4. Off-pump surgery reduced the direct in-hospital costs by $1,375 (13.6%) per patient ($8,720 vs $10,095; p<0.01). The overall costs at one year were $2,329 (13.1%) per patient lower after off-pump surgery ($15,479 vs $17,808; p<0.01). The direct follow-up costs and the indirect costs at one year were comparable between treatment groups. Medication accounted for more than 50% of the one year direct follow-up costs.

Table 3: Angiographic results at one year*

	Off-pump (69 grafts)	On-pump (89 grafts)	Difference	(95% CI)	p-value
Patency†					
grade A (excellent)	53 (77%)	71 (80%)	3%	(-10% – 16%)	0.65
grade B	10 (14%)	12 (13%)	-1%	(-12% – 10%)	0.86
grade A + B	63 (91%)	83 (93%)	2%	(-7% – 10%)	0.65
grade O (occlusion)	6 (9%)	6 (7%)	-2%	(-10% – 7%)	0.65
Disease†					
I (smooth)	54 (78%)	75 (84%)	6%	(-6% – 18%)	0.33
II (<50%)	5 (7%)	3 (3%)	-4%	(-11% – 3%)	0.27
III (>50%)	1 (1%)	0 (0%)	-1%	(-4% – 1%)	0.25
Inconclusive	9 (13%)	11 (12%)	-1%	(-11% – 10%)	0.90
Flow‡					
TIMI III (normal)	58 (84%)	70 (79%)	-5%	(-18% – 7%)	0.39
TIMI I or II	3 (4%)	7 (8%)	4%	(-4% – 11%)	0.37
TIMI 0 (no flow)	3 (4%)	4 (4%)	0%	(-6% – 7%)	0.97
Inconclusive	5 (7%)	8 (9%)	2%	(-7% – 10%)	0.69

* Values are numbers of grafts, with percentages in parentheses.
Every distal anastomosis was counted as a separate graft.

† Graft patency and graft disease were determined by the Fitzgibbon criteria.[18]

‡ Flow was determined by the TIMI (Thrombolysis In Myocardial Infarction) criteria.[19]

Quality of life as assessed by the EQ-5D increased significantly after surgery (Figure 2: overall change $p<0.01$)[28] and, moreover, fell within normal limits at 3 months.[29] There was, however, no difference between treatment groups. The QALYs after off-pump and on-pump surgery were 0.82 vs 0.83 ($p=0.70$) and the EFSYs 1.02 vs 1.03 ($p=0.72$), respectively. The cost-effectiveness ratio for off-pump surgery compared with on-pump surgery was $232,900 for one QALY gained (i.e. difference in overall costs divided by the difference in QALYs: -$2,329/-0.01). The ratio for EFSY was also $232,900. Note that cost savings were realized at the expense of a marginal difference in effects.

The bootstrap estimates in terms of incremental costs per QALY are illustrated by Figure 3. The solid lines in this figure indicate a conservative threshold of $20,000 society is 'willing to pay' per QALY gained, and a more stringent threshold of $40,000 society is 'willing to accept' per QALY lost.[30] The cost-effectiveness ratios were below the defined thresholds in 95% of estimates, indicating better cost-effectiveness of off-pump surgery. In case the stringent 'willingness to accept' threshold per QALY lost is

replaced by a conservative one of $20,000, even 98% of estimates would indicate better cost-effectiveness.

Discussion

The results of this randomized trial at one year indicate that cardiac outcome, symptomatic status and quality of life were comparable between off-pump and on-pump surgery. However, off-pump surgery was less expensive and more cost-effective than on-pump surgery. Therefore, from an economic perspective, off-pump surgery can be justified as an alternative treatment for 'conventional' CABG. To appreciate these results certain features of the study need to be addressed.

By nature of the study design and the fact that it concerns the first multicenter randomized clinical trial comparing a novel surgical strategy with 'conventional' on-pump surgery, a low to moderate risk population was treated. The mean age of

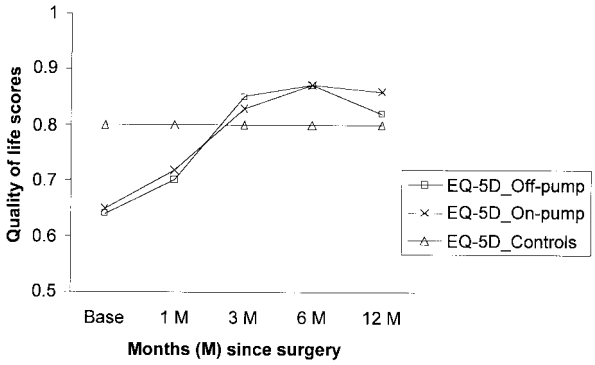

Figure 2: Quality of life after off-pump and on-pump coronary bypass surgery, as expressed by the summary score of the Euroqol (EQ-5D).25 The EQ-5D increased significantly from baseline (overall p<0.01), without differences between treatment groups. Controls: EQ-5D scores of age matched controls.[29]

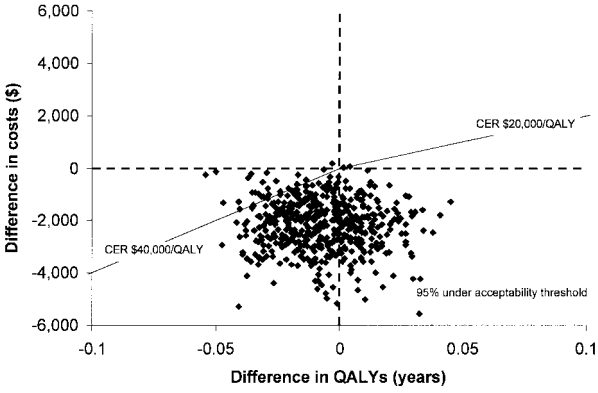

Figure 3: Bootstrap estimates of expected costs and quality adjusted life years (QALYs) after off-pump and on-pump coronary bypass surgery. The solid lines indicate threshold values society is 'willing to pay' for one QALY gained ($ 20,000) or 'willing to accept' for one QALY lost ($ 40,000).[30] This figure demonstrates that off-pump surgery is more cost-effective from a societal perspective, as 95% of all 500 estimates were under acceptability threshold values (♦ under solid lines). CER denotes cost-effectiveness ratio.

Table 4: Average resource use and costs per patient at one year*

Resource	Average resource use: Off-pump (n=142)	Average resource use: On-pump (n=139)	Costs ($) per unit
Direct in-hospital costs			
Staff: operating time (hours)†	4.17	3.82	338
Intra-operative material use:			
Off-pump CABG	0.99	0.04	1235
Cardiac stabilizer	0.99	0.04	438
On-pump CABG	0.08	0.96	2092
Cardio-pulmonary bypass	0.08	0.96	902
Intensive care unit (days)	1.43	1.62	1057
Ward (days)	8.11	8.65	247
Transfusion blood products ‡	0.85	1.07	--
Additional investigations §	--	--	--
Total direct in-hospital costs	--	--	--
Direct follow-up costs (discharge – 1 year)			
Stroke	--	0.01	6818
Myocardial infarction	--	0.01	10908
CABG, on-pump	0.01	0.01	10095
Percutaneous coronary angioplasty	0.03	0.02	3740
Angiography (not study-protocol)	0.06	0.05	809
Hospitalization, other cardiac (days) ¶	2.46	2.17	--
Rehabilitation, intramural (days)‖	0.68	2.20	--
Outpatient health care #	--	--	--
Medication use	--	--	--
Total direct follow-up costs	--	--	--
Total direct costs at 1 year	--	--	--
Total indirect costs at 1 year	--	--	--
Total direct and indirect costs at 1 year	--	--	--

* The costs per unit have been rounded in the calculation of the average.

† Costs of all staff: Surgeon, Anesthesiologist, Perfusionist and Nurse.

‡ Costs of all transfusions: erythrocyte, platelets and fresh frozen plasma.

§ Costs of blood tests, radiology, electrocardiography, intra-aortic balloon pump, pulmonary artery catheter, angiography, coronary angioplasty, myocardial infarction, consulting pysicians and in-hospital rehabilitation.

¶ Costs of hospitalizations: intensive care unit , coronary care unit and ward.

‖ Costs of intramural rehabilitation: rehabilitation center and nursing home.

\# Costs of outpatient care: rehabilitation, consulting Physician and Nurse.

CABG denotes coronary artery bypass graft surgery.

Table 4: (continued)

Average costs ($)		
Off-pump) (n=142)	**On-pump (n=139)**	**p-value**
1411	1290	<0.01
1226	44	<0.01
435	16	<0.01
162	2017	<0.01
70	870	<0.01
1512	1712	0.98
2002	2134	0.06
35	44	0.38
1867	1968	0.02
8720	*10095*	*< 0.01*
--	49	0.31
--	157	0.15
71	71	0.98
96	91	0.73
46	41	0.62
736	827	0.47
81	322	0.05
564	555	0.63
2755	2700	0.16
4349	*4813*	*0.32*
13069	**14908**	**<0.01**
2410	**2900**	**0.23**
15479	**17808**	**<0.01**

the patients was 61 years and the majority had single or double vessel disease with preserved ventricular function and limited co-morbidity. The low risk profile may explain the lower in-hospital mortality (off-pump 0% and on-pump 0.7%) than the mortality after first time elective CABG reported by the Society of Thoracic Surgeons (1.8%).[6] It may also explain the lower one year mortality of the present population (off-pump and on-pump surgery both 1.4%) in comparison to the mortality in patients who underwent conventional CABG in the recently conducted ARTS study (2.8%).[31]

The characteristics of the present population may also explain the low incidence of perioperative stroke after off-pump and on-pump surgery (both 0.7%). It was lower than the one reported by Roach et al (3.1%)[5] and by the Society of Thoracic Surgeons (1.7%)[6] but is comparable to the incidence reported in a review of observational studies on off-pump surgery, encompassing 1,582 patients (0.6%).[12] The use of CPB is considered a major determinant of perioperative stroke during on-pump surgery.[4,5] In contrast to a decade ago, patients undergoing CABG nowadays are older and have more comorbid conditions.[3] These patients are at higher risk of perioperative mortality and stroke, and may particularly benefit from off-pump surgery.[32] This in turn may have a pronounced effect on costs and cost-effectiveness. A retrospective analysis of high risk patients from the database of the Society of Thoracic Surgeons showed, indeed, a lower incidence of stroke after off-pump surgery.[33] The possible benefits and role of off-pump surgery in patients known to be at increased risk of stroke needs to be addressed in appropriately designed trials.

The incidence of perioperative myocardial infarction in the present study was comparable between treatment groups. The incidence of perioperative Q-wave infarction after off-pump surgery however, was higher (2.8%) than the one reported from a recent randomized trial (0.5%).[34] Differences in the definition of infarction may explain this discrepancy. In a series of observational studies, myocardial infarction after off-pump surgery was reported in 0.0%[32] to 4.0% of the patients.[10]

We have previously reported that off-pump as compared with on-pump surgery, reduced the release of CKMB postoperatively by 41% ($p<0.01$).[35] Troponin-I release after off-pump surgery was

also significantly lower in one other randomized trial.[36] This may have important clinical implications since a lower CKMB release after CABG[37] and coronary angioplasty is associated with a better prognosis.[38]

Both surgical approaches resulted in a comparable improvement of angina, quality of life and exercise capacity. It is unlikely that the small difference in repeat revascularization after off-pump (4.9%) and on-pump surgery (3.6%) contributed to this observation. The angiographic data showed no difference in graft patency and quality of the anastomoses. Unfortunately, a substantial number of patients refused to undergo control angiography because of absence of symptoms. Although not proven, it suggests the existence of patent grafts in these patients. Graft patency may, therefore, have been underestimated. It precludes, anyway, the precise interpretation and comparison of the angiographic data of the present study with those of other series. Nevertheless, graft patency after off-pump surgery at one year in the present study (91%) was comparable to the early graft patency reported in a review of non-randomized studies (91%-99%).[39]

In the present population, cardiac outcome was comparable between treatment groups. Yet, off-pump surgery was associated with cost savings and, therefore, was more cost-effective than on-pump surgery. One might consider 13% cost savings irrelevant. Yet, considering the 571,000 bypass operations performed in 1999 in the United States (American Heart Association, 2002), and much more worldwide, the saving of money may be substantial. Our findings are in concordance with a recently conducted single-center randomized trial.[40] In this trial, off-pump surgery lowered hospital costs by 30%, mainly because perioperative morbidity was reduced.[40]

The main limitations of the present study are the sample size and the risk profile of the population. As a result, the point estimates of the (cost-)effectiveness lack precision. The difference in effects in a high risk population may be more pronounced. Also, the open design of the trial may have affected the assessment of the outcome measures such as the need of repeat revascularization, angina and quality of life. Finally one could question the limited time horizon of the (cost-)effectiveness analysis of one year. Yet, it is reasonable to assume that beyond one year, cardiac events

because of graft failure and progression of atherosclerosis will occur to a similar degree in both groups.
We conclude that at one year, off-pump surgery was more cost-effective than on-pump surgery, while maintaining comparable cardiac outcome. In selected patients, off-pump surgery as an alternative for on-pump surgery is justified from an economic perspective.

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Chapter 8

General discussion

The Octopus Trial: hypotheses and findings

The aim of the Octopus Trial was to directly compare off-pump and on-pump coronary artery bypass surgery (CABG).[1] We assumed that both strategies would have similar cardiac outcome, but that cognitive outcome would be better in patients operated without cardiopulmonary bypass (CPB).

Two hundred eighty-one patients were included in the study, and randomly assigned to off-pump and on-pump coronary bypass surgery.[2] Cognitive performance of the participants was assessed at four days and three and twelve months after surgery. At three months, a slightly better cognitive outcome in the off-pump group was demonstrated, but the effect was smaller than anticipated and became negligible at twelve months.[3] Twelve months after surgery, the incidence of cardiovascular events, and other measures of cardiac outcome including anginal status, exercise testing and coronary angiography, were similar between the two groups.[4] The confidence intervals of the point estimates, however, were wide. Off-pump surgery was more cost-effective because quality of life across the groups was similar, while the costs of off-pump procedures were lower.[4]

The Octopus Study was largely unable to substantiate the anticipated benefits of off-pump CABG. Several explanations are possible. We may have overestimated the potential advantages of off-pump surgery. Perhaps we also overestimated the complications of conventional bypass surgery. Finally, we may have underestimated some methodological limitations of the trial. In the following paragraphs, these possible explanations will be discussed in detail.

Overestimation of the potential advantages of off-pump surgery

It was expected that avoiding CPB would improve cognitive outcome.[5,6] Cognitive decline after CABG is well documented.[5] However, data from our study suggest that CPB is not the only cause of cognitive decline.[3,7] Undergoing major surgery and anesthesia may also be responsible for cognitive decline.[8]

Alternatively, the off-pump technique may be a new source of cognitive decline. Manipulation of the beating heart, especially exposure of the posterior cardiac wall, might dislocate aortic atheromas. Moreover, such manipulations cause a drop in cerebral perfusion pressure due to an elevated central venous pressure and a concurrent decreased systemic blood pressure.[9] Together, this may be equally harmful to the brain as CPB.[10,11]

One of the most reported advantages of off-pump CABG is shorter hospitalization.[2,12-15] This outcome, however, is sensitive to bias. In studies where the doctors responsible for discharge of the patients are not blinded (including our own), we cannot exclude that enthusiasm for the new technique caused earlier discharge. A possible faster recovery of the patients should translate to improved short-term quality of life. In the Octopus Study, quality of life had significantly improved from before to one month after surgery, but no difference was observed between the off-pump and on-pump group.[2] Altogether, there is little proof of faster recovery after off-pump surgery.

While sternotomy is virtually always required when CPB is used, off-pump CABG may in selected cases be performed via left lateral thoracotomy, mini-incisions or 'port-access'.[16,17] It is difficult to argue against attempts to decrease the invasiveness of a surgical procedure. However, a lateral thoracotomy seems to be equally invasive as sternotomy. Patients report more pain in the first postoperative days and a substantial proportion of the patients may develop chronic intercostal neuralgia (unpublished results). The term 'minimally invasive CABG' is therefore misleading and should be reserved for true keyhole surgery, which is currently at an experimental stage.[18] Off-pump CABG as currently practiced is still major surgery, with all the possible complications that are associated with conventional CABG.[19]

Overestimation of the disadvantages of conventional bypass surgery

CABG may lead to perioperative mortality, stroke, myocardial infarction, and prolonged hospital stay.[20,21] Age and co-morbidity largely determine the risk of these complications.[20-22] In the ini-

tial case series of relatively young and healthy patients, off-pump surgery was associated with a low complication rate.[12,13] However, it appears that patients of comparable age and with a similar degree of co-morbidity undergoing conventional on-pump CABG do also well.[23] As several authors have suggested, it may not be the off-pump procedure, but the selection of young and relatively healthy patients that generates favorable outcomes.[24,25]

It is beyond doubt that CABG may cause serious cognitive impairment, even to such an extent that it prevents patients from return to work and normal social activities.[20,26] Previous studies have demonstrated that advanced age increases the risk of postoperative cognitive decline,[6,27-29] but this association could not be confirmed in the Octopus Study.[7] Moreover, high incidences of subtle brain injury have also been reported in younger patients.[27,30-33] Therefore, the inclusion of relatively young patients in the Octopus Study does not entirely explain its inability to demonstrate a marked difference in cognitive outcome between the groups.

An alternative explanation is that, due to methodological limitations, the true incidence of cognitive decline after CABG is lower than has been reported.[30,34] There is evidence that the instrument used to measure cognitive status (a series of neuropsychological tests) is not very accurate. Both patients and healthy controls have natural fluctuations in their performance on neuropsychological tests.[34] To identify patients with cognitive decline these natural fluctuations must be taken into account, which requires a control group.[8] However, most studies reporting high incidences of cognitive decline after CABG are without non-surgical controls. At least three commonly used definitions of cognitive decline (an arbitrary decrease of 20% or 1 SD in cognitive performance in an arbitrary proportion of the tests or cognitive domains)[6,35,36] are therefore without empirical basis. The cut-off values for abnormal performance may be well within the range of an individual's natural fluctuations in performance. Current definitions of cognitive decline may therefore generate false positive outcomes, as was recently demonstrated in two studies. We administered a battery of cognitive tests to 110 volunteers (mean age 60.5 y) with a time interval of three months. More than 20% of the volunteers had 'cognitive decline' after three months,

according to the definition that was also used in the Octopus Study.[37] The ISPOCD group found similar results.[34] A virtually identical definition was applied to 176 volunteers undergoing five neuropsychologic tests. After three months, 25% of the volunteers was identified as having cognitive decline.
Misclassification of patients with and without cognitive decline, and an overestimation overestimation of the number of patients with cognitive decline, may both explain our inability to show improvement after off-pump procedures and to identify other determinants of cognitive decline. It would also imply that the proportion of 22.5% found in the pooled analysis in Chapter 2 of this thesis[5] overestimates the true incidence of cognitive decline after CABG.

Methodological limitations

A lower incidence of cognitive decline after conventional CABG and a smaller potential benefit of off-pump CABG both have consequences for the statistical power of the trial.[38] In retrospect, we must conclude that the power calculation may have been too optimistic. More subtle benefits of off-pump surgery might have become clear with a larger sample size. Moreover, the claim of equivalence in cardiac outcome would have been more precise. Comparable problems were encountered in the recently published BHACAS studies. Pooled analysis of two randomized trials, in total including 2 x 200 patients, demonstrated lower mortality and less cardiac related events 25 months after off-pump surgery, but the confidence intervals were wide.[39]
A major restriction of the study is the unreliability of the neuropsychologic tests. When conducting a trial on cognitive outcome, we have to rely on these tests because we are lacking better instruments. The test battery applied in the Octopus Study evaluated a broad spectrum of cognitive functions,[1] but was not targeted to assess tasks of daily life, i.e. to measure outcomes that matter to the patients. More important, a high level of noise (previous paragraph) may have diluted the difference in cognitive outcome between the groups.

The Octopus Study was designed as a pragmatic trial, i.e. as a trial comparing two *strategies*.[1] This seemed logical, as the parallel OctoStent Trial evaluated two completely different treatments of coronary artery disease (intracoronary stenting versus off-pump bypass surgery). Such a study obviously can not be conducted as an explanatory trial, which aims to quantify the effect of one specific treatment feature, keeping all other medical procedures similar.[40] When designing the present study (the OctoPump Trial), off-pump and on-pump CABG were also perceived as two different strategies. After all, off-pump CABG could be performed via small incisions,[16,17] allowed the use of epidural anesthesia,[41] and was performed without high dose steroids, which attenuate the inflammatory reaction on CPB.[42] However, the *strategies* of conventional CABG and off-pump CABG appeared not to be as different as perhaps anticipated. In the trial, only 8% of the off-pump patients were operated via another incision than sternotomy.[2] In several hospitals, epidural anesthesia is now also applied in on-pump procedures, because a short period of complete heparinization is not considered an absolute contra-indication for epidural anesthesia anymore.[43,44] In addition only some, but not all centers administer high dose steroids before commencing CPB.[42]

A more explanatory design of the study, in which the use of CPB is the only difference between the two treatment groups, would have avoided a number of problems.[40] Only around 50% of the off-pump patients in the trial received epidural anesthesia, because this depended on the preference of the attending anesthesiologist. This complicated the interpretation of the early outcomes. The selective use of steroids in the on-pump group may have prevented postoperative hyperthermia. A recent study by Grocott et al. found an association between postoperative hyperthermia and cognitive decline,[45] which is again a possible explanation for the Octopus Study failing to demonstrate a difference in cognitive outcome. The most important disadvantage of the pragmatic study design, however, is that it lacks blinding. It was assumed that a substantial proportion of the off-pump patients would be operated on via left lateral thoracotomy. Therefore, the patients were not blinded. This, however, decreased their motivation for neuropsychologic testing and caused withdrawals from

the study if they were assigned to conventional treatment. The physicians discharging the patients were also not blinded and may have been tempted to discharge the off-pump patients sooner than the on-pump patients. The doctors who determined postoperative anginal status were not blinded either because they also inspected the surgical wound. It turned out, however, that only a very small proportion of the patients could be operated via alternative incisions. If sternotomy had been applied to all participants of the study, a completely blinded design would have been possible.

Future studies

It is currently still unknown whether off-pump CABG, compared to on-pump CABG, leads to long-standing better cerebral outcome. The participants of the Octopus Study will be reassessed five years after surgery, but the limited statistical power of the study may again preclude a precise estimate of the effect of CPB on cardiac and cognitive outcome.[38] Retrospective cohort studies suggest a lower risk-adjusted perioperative complication rate after off-pump CABG, but the question whether long-term graft patency and freedom from reintervention is comparable to on-pump CABG remains unanswered.[14,15]

A new randomized study evaluating cognitive outcome needs an even larger sample size and a more reliable definition of cognitive decline. Such a definition is currently being developed at Utrecht University. It is based on indices, derived from non-surgical controls, which reflect the normal range in which an individual's performance on cognitive tests may fluctuate.[37] Alternatively, we may have to accept that we are presently unable to reliably identify patients with subtle cognitive decline. Direct comparison of the mean cognitive performances of two randomized groups, at some time after surgery, is sufficient to identify the better treatment. No pre-surgery assessments are necessary and less sources of noise may dilute the difference between the groups. The only prerequisite is that randomization is performed adequately so that the groups are really comparable at baseline. And then of course cognitive decline after CABG really needs to exist.

The advantages of off-pump surgery may be more apparent in older patients. Cohort studies have described an association between age and the risk of cognitive decline.[6,27-29] Within the patients of the Octopus Study, however, age was not a predictor of cognitive outcome. The association between age and the risk of peri-operative stroke, on the other hand, is well established. A Stroke Risk Index, derived from over 2000 patients, identified age as a major determinant of peri-operative stroke[22] and Tuman found that in CABG patients older than 80 years, the risk of stroke is 9%.[21] The most probable mechanism is that aortic atherosclerosis is more pronounced in older people and that atheromas may be dislocated by cannulation and clamping of the aorta.[46]
The Octopus Study could be repeated in older patients. The applicability of cognitive tests, however, is even lower in older patients. As the results of the studies in volunteers suggest that cognitive decline is less common than was assumed, the premise that cognitive decline is a 'surrogate endpoint' for more severe cerebral injury is no longer valid. Because the diagnosis of stroke, in contrast to the diagnosis of cognitive decline, is relatively uncomplicated, the occurrence of stroke could be chosen as an alternative endpoint. Stroke, however, only occurs in a minority of the patients and this has consequences for the power of a future study. For instance, to demonstrate a reduction in stroke rate in elderly patients from 5% to 2.5% by avoiding CPB, with the alpha error set at 0.05 and a power of 80%, a sample size of 1000 patients per group is needed. The large number of study subjects that is required to obtain sufficient power is offset by several advantages. Neuropsychologic testing can be avoided, which circumvents the need for intensive patient cooperation and the availability of neuropsychologists and testing rooms. Loss to follow-up will be uncommon. Because determining the primary outcome measure is straightforward, the logistics of a multicenter trial are less complicated. The large sample size also allows reliable inference with respect to cardiac outcome after off- and on-pump surgery. If the one-month survival free from cardiovascular events again would be 93% in the off-pump group and 94% in the on-pump group (like it was in the Octopus Study), the risk difference is again 1%, but if studied in 2 x 1000 patients, this esti-

mate has a high level of precision, e.g. a narrow 95% confidence interval ranging from -1% to 3%.
Because establishing cognitive outcome is difficult and not performed in routine patient care, it cannot be studied in a retrospective study. In contrast, the occurrence of stroke is routinely recorded in patient files, and made available in databases, such as those maintained by the Society of Thoracic Surgeons (STS: National Adult Cardiac Surgery Database), or the Department of Veterans Affairs (Continuous Improvement in Cardiac Surgery Program Records). Because ten thousands of off-pump procedures are now performed annually, retrospective multivariate studies can be carried out to quantify the effect of off-pump surgery on stroke rate. A first study of this design has been performed recently. Cleveland et al. retrospectively studied 118,140 CABG procedures from the STS database, of which 10% was performed off-pump. The use of an off-pump procedure decreased the risk-adjusted operative mortality from 2.9% to 2.3% ($p<0.001$) and in patients with known cerebrovascular disease, the risk-adjusted peri-operative stroke rate decreased from 4.6% to 2.5% if CPB was avoided ($p<0.001$).[14] These results are encouraging, but because retrospective observational studies are prone to confounding, randomized data are still needed to confirm better cerebral outcome after off-pump CABG.

Conclusions

In selected patients, off-pump CABG is safe and yields a cardiac outcome that is comparable to that of on-pump CABG. Avoiding CPB is more cost-effective. It slightly decreases the need for blood transfusion, but other clinically relevant benefits of off-pump CABG are not established yet. Patients undergoing off-pump CABG have better cognitive outcome at 3 months after surgery, but the effect is of limited size. This may be caused by an overestimation of the incidence of cognitive decline after bypass surgery. Off-pump CABG still has significant potential advantages compared to on-pump surgery. Future randomized studies are essential and should focus on clinically relevant out-

comes such as stroke, which is a common complication of CABG in elderly patients.

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Summary

The complications associated with coronary artery bypass surgery (CABG) using cardiopulmonary bypass (CPB) have led to a renewed interest in coronary bypass surgery on the beating heart. The Octopus Stabilizer is one of the recently developed devices that facilitate CABG without CPB (off-pump CABG) by immobilizing the target coronary arteries. CABG may lead to a decline in cognitive function, which has largely been attributed to the use of CPB. Therefore, CABG without CPB should improve cognitive outcome. It is assumed that cardiac outcome after off-pump CABG is similar to conventional procedures using CPB (on-pump CABG). Nevertheless, bypass surgery on the beating heart is technically more demanding and no proof is yet available that off-pump CABG can match the long-term cardiac benefits of the on-pump operation.

The primary objective of the Octopus Study was to compare cognitive outcome between patients randomized to off-pump or on-pump CABG. As it was assumed, but not established that off-pump and on-pump CABG are equally effective in terms of myocardial revascularization, an important secondary objective of the trial was to compare cardiac outcome.

In *chapter 2*, the literature suggesting that CABG may impair cognitive function is systematically reviewed. As methods and definitions differ greatly across studies, the reported incidence of cognitive decline after coronary bypass surgery varies widely as well. Only those studies on cognitive decline that were relatively comparable and met with certain quality criteria were included in the review. Four electronic databases and the references of several abstract books and earlier reviews were used to identify relevant literature. Stringent criteria, based in part on the 1994 consensus meeting on assessment of neurobehavioral outcomes after cardiac surgery, were used to assess the studies that were found. In total, 256 different titles were found, of which twelve cohort studies and eleven intervention studies met with the formulated selection criteria. A pooled analysis of six highly comparable studies yielded a proportion of 22.5% (95% confidence interval [CI] 18.7%-26.4%) of patients with a cognitive deficit (a decrease of at least 1 standard deviation in at least two of nine or ten tests) 2 months after the operation. This suggested that cognitive dysfunction is a frequently occurring complication of coro-

nary artery bypass grafting. A randomized trial directly comparing off-pump and on-pump bypass surgery could reveal the etiologic contribution of cardiopulmonary bypass to this complication.

Chapter 3 describes in detail the rationale and design of the Octopus Study. The Octopus Study comprised two randomized trials: one directly comparing off-pump CABG and intracoronary stent implantation (OctoStent Trial) and one directly comparing off-pump CABG and on-pump CABG (OctoPump Trial). In both trials, the Utrecht Octopus Method was used for the off-pump CABG procedures.

In this thesis, the results of the OctoPump Trial are presented. The term Octopus Study therefore refers here to the OctoPump Trial, i.e. the randomized comparison of off-pump and on-pump CABG. Patients were eligible for this trial if they were referred for first-time isolated coronary bypass surgery and an off-pump procedure was deemed technically feasible. Patients were excluded in case of emergency surgery, Q-wave myocardial infarction in the last 6 weeks, or poor left ventricular function. Patients who were unlikely to complete 1-year follow-up, unable to give informed consent, or undergo neuropsychologic testing were also excluded. There were no restrictions to age. The primary endpoint of the trial was the presence or absence of cognitive decline and/or stroke, at 3 months after surgery. Secondary endpoints included cognitive outcome at 12 months, occurrence of cardiovascular events, recurrence angina, presence of cardiac ischaemia during exercise testing, quality of life, and cost-effectiveness. Stable and unstable angina were classified according to the Canadian Cardiovascular Society and Braunwald classification, respectively. Quality of life was assessed using the EuroQol and ShortForm-36 questionnaires. Per treatment group, 140 patients were to be enrolled. A subsample of the patients was randomized to undergo repeat coronary angiography at 1 year to assess graft patency.

In *chapter 4*, the cerebral outcome and quality of life after off-pump and on-pump CABG is presented. From March 1998 through August 2000, 281 patients were enrolled. At 3 and 12 months after surgery, there was no difference in quality of life between the two groups. Psychologists, blinded for randomization, repeatedly administered 10 neuropsychological tests to

determine cognitive outcome at 3 and 12 months. At 3 months, cognitive outcome could be determined in 248 patients. Cognitive decline (or stroke) occurred in 21% in the off-pump group and 29% in the on-pump group (relative risk 0.65; 95% CI 0.36-1.16; p=0.15). The overall standardized change score (i.e. improvement of cognitive performance from before to 3 months after surgery) was 0.19 in the off-pump vs 0.13 in the on-pump group (p=0.03). At 12 months, cognitive decline occurred in 31% in the off-pump group and 34% in the on-pump group (relative risk 0.88; 95% CI 0.52-1.49; p=0.69). The overall standardized change score was 0.19 in the off-pump vs 0.12 in the on-pump group (p=0.09). These results indicate that patients undergoing first-time CABG without cardiopulmonary bypass have improved cognitive outcomes 3 months after the procedure, but the effects are limited and become negligible at 12 months.

Chapter 5 is a prediction study on cognitive outcome. Because avoiding cardiopulmonary bypass only slightly improved cognitive outcome, an effort was made to identify other determinants of cognitive outcome after bypass surgery. In previous studies, advanced age, female sex, diabetes, history of stroke, manipulation of the ascending aorta, prolonged perfusion time, and postoperative time to awakening were identified as predictors of cognitive decline. The dichotomous and the continuous measure of 3-month cognitive outcome, used before in the analyses of the randomized trial (chapter 4), were applied again as dependent variables. Thirteen possible clinical predictors of 3-month cognitive outcome and two measures of early cognitive performance (4th day after surgery), were entered into logistic and linear regression models. The previously identified determinants of cognitive outcome were no predictor of cognitive outcome in the present patient sample. The only variables that were significantly associated with cognitive outcome after 3 months, were measures of cognitive outcome 4 days after surgery. This association was stronger in patients operated with cardiopulmonary bypass (odds ratio 4.72; 95% CI 1.63 - 13.66; p<0.01) than in patients operated without cardiopulmonary bypass (odds ratio 2.00; 95% CI 0.77 - 5.20; p=0.16).

In *chapter 6* measures of early clinical outcome after off-pump and on-pump CABG are compared. In-hospital results and cardiac

outcome and quality of life after 1 month are presented. Cardiac outcome was defined as survival free of cardiovascular events (stroke, myocardial infarction, and coronary reintervention). The mean numbers of distal anastomoses per patient were 2.4 and 2.6 in the off-pump and on-pump group, respectively. Completeness of revascularization was similar in both groups. Blood products were needed during 3% of the off-pump procedures and 13% of the on-pump procedures ($p<0.01$). Release of creatine kinase muscle-brain isoenzyme was 41% less in the off-pump group ($p<0.01$). Off-pump patients were discharged 1 day earlier. Otherwise, no differences in complications were found postoperatively. At 1 month, operative mortality was zero in both groups, and quality of life had improved similarly. In both groups, 4% of the patients had recurrent angina. The proportions of patients surviving free of cardiovascular events were 93.0% in the off-pump group and 94.2% in the on-pump group (difference 1.2%; 95% CI -4.4 to 7.0%; $p=0.66$). These results suggest that in selected patients, off-pump CABG is safe and yields a short-term cardiac outcome comparable to that of on-pump CABG.

In *chapter 7*, a comparison of cardiac outcome and cost-effectiveness one year after off-pump and on-pump CABG is reported. One year survival free from stroke, myocardial infarction and coronary re-intervention was 88.0% after off-pump surgery and 90.6% after on-pump surgery ($p=0.48$). Survival free from angina was 89.3% vs 89.0% ($p=0.93$). Graft patency, determined in a randomized subset of patients, was 91% after off-pump and 93% after on-pump surgery ($p=0.65$). Off-pump surgery reduced costs by $2,329 (13.1%) per patient ($ 15,479 vs $ 17,808; $p<0.01$). Quality adjusted life years (0.82 vs 0.83; $p=0.74$) and event free survival years (1.02 vs 1.03; $p=0.23$) did not differ. Consequently, off-pump bypass surgery was more cost-effective than on-pump surgery, with comparable cardiac outcome and graft patency. In selected patients, the application of off-pump bypass surgery as an alternative for on-pump surgery is therefore justified from an economic perspective.

Finally, *Chapter 8* comprises a general discussion of the Octopus Study. The discussion focuses on the inability of the study to demonstrate several of the anticipated benefits of off-pump CABG. Several explanations are possible.

First, the potential advantages of off-pump surgery may have been overestimated. The Octopus Study suggests that CPB is not the only cause of cognitive decline. Undergoing major surgery and anesthesia may also be responsible for cognitive decline or, alternatively, the off-pump technique may be a new source of cognitive decline. The reports that off-pump CABG shortens hospitalization may be biased due to a lack of blinding. Even when access to the heart is achieved via left lateral thoracotomy, the procedure may lead to most of the complications that are associated with conventional CABG.

Second, the complications of conventional bypass surgery may have been overestimated. Off-pump surgery is generally associated with a low complication rate, but it appears that patients with a similar (usually low) risk profile undergoing conventional on-pump CABG do also well. The incidence of cognitive decline after CABG may have been overestimated, because the currently used definitions of cognitive decline may generate false positive outcomes. Misclassification of patients with and without cognitive decline, and an overestimation of the number of patients with cognitive decline, may both explain our inability to show substantial improvement when avoiding CPB.

Third, methodological limitations of the trial may have been underestimated. More subtle benefits of off-pump surgery might have become clear with a larger sample size. The high level of noise associated with neuropsychologic testing and defining cognitive decline, may have diluted the difference in cognitive outcome that was found. Too little attention was paid to blinding.

Future studies evaluating the cerebral effects of CPB should be carried out in elderly patients, because in these patients improved cerebral outcome after off-pump surgery may be more apparent. A new study needs a more reliable definition of cognitive decline. With a larger sample size, stroke could be chosen as an alternative endpoint. The diagnosis of stroke, in contrast to the diagnosis of cognitive decline, is relatively straightforward. In older patients, the risk of stroke after CABG is up to 9%, and there is no doubt that this is an outcome that matters to the patient.

It is concluded that in selected patients, off-pump CABG is safe and yields a cardiac outcome that is comparable to that of on-pump CABG. Avoiding CPB is cost-effective and slightly

decreases the need for blood transfusion, but other clinically relevant benefits of off-pump CABG are not established yet. Patients undergoing off-pump CABG have better cognitive outcome at 3 months after surgery, but the effect is of limited size.

Samenvatting

De complicaties die kunnen optreden bij coronaire bypass chirurgie (CABG) met gebruik van de hart-longmachine, hebben tot een hernieuwde aandacht geleid voor bypass chirurgie op het kloppende hart. De Octopus Methode is één van de recentelijk ontwikkelde technieken die CABG zònder hart-longmachine (off-pump CABG) vereenvoudigen door het kloppende hart gedeeltelijk te immobiliseren. Coronaire bypass chirurgie kan tot een achteruitgang van cognitieve functies leiden, die wordt toegeschreven aan het gebruik van de hart-longmachine. Daarom zou CABG zònder hart-longmachine gepaard moeten gaan met minder cognitieve schade. Verondersteld wordt dat off-pump CABG en conventionele CABG met gebruik van de hart-longmachine (on-pump CABG) tot een vergelijkbare cardiale uitkomst leiden. Chirurgie op het kloppende hart is echter technisch lastiger en er bestaat nog geen bewijs dat off-pump CABG op lange termijn even succesvol de cardiale klachten wegneemt als on-pump CABG.
Het primaire doel van de Octopus Studie was om een vergelijking te maken tussen patiënten die door loting (randomisatie) ofwel off-pump CABG, ofwel on-pump CABG kregen toegewezen. Omdat het nog niet aangetoond is dat beide operatietechnieken tot een even goed cardiaal resultaat leiden, was een belangrijk secundair doel om de cardiale uitkomsten van beide operatie methodes te vergelijken.
In *hoofdstuk 2* van dit proefschrift wordt de literatuur samengevat die suggereert dat CABG samengaat met cognitieve schade (systematisch review). Omdat er grote verschillen bestaan tussen de diverse studies met betrekking tot methodologie en definiëring van cognitieve schade, bestaat er eveneens een groot verschil in de gerapporteerde incidenties. Uitsluitend studies die in enige mate onderling vergelijkbaar waren en die aan bepaalde kwaliteits criteria voldeden werden betrokken in het literatuuroverzicht. Vier elektronische bibliografieën en de referenties van een aantal boeken werden gebruikt om relevante literatuur op te sporen. Bij de beoordeling van de gevonden literatuur werd gebruik gemaakt van criteria, die gedeeltelijk ontleend waren aan een consensus bijeenkomst over onderzoek naar cognitieve schade na hartchirurgie. In totaal werden 256 verschillende artikelen gevonden, waarvan 12 cohort studies en 11 interventie studies voldeden aan

de opgestelde criteria. In een gepoolde analyse van 6 sterk vergelijkbare studies werd een incidentie van cognitieve beschadiging berekend van 22,5%, 2 maanden na CABG (95% betrouwbaarheids interval [BTI] 18,7%-26,4%). Cognitieve beschadiging was hier gedefinieerd als een achteruitgang in cognitieve prestaties van minimaal 1 standaarddeviatie, in minimaal 2 uit 9 of 10 neuropsychologische tests. Dit resultaat suggereert dat cognitieve beschadiging een frequent voorkomende complicatie van coronaire bypass chirurgie is. In hoeverre dit veroorzaakt wordt door de hart-longmachine, kan worden onderzocht in een gerandomiseerde studie, waarin off-pump CABG en on-pump CABG direct met elkaar vergeleken worden.

Hoofdstuk 3 beschrijft in detail de opzet van de Octopus Studie. De studie bestaat feitelijk uit twee gerandomiseerde onderzoeken. In het ene onderzoek wordt een vergelijking gemaakt tussen off-pump CABG en dotterbehandeling (PTCA) met stentimplantatie (OctoStent Trial). In het andere onderzoek wordt een vergelijking gemaakt tussen off-pump CABG en on-pump CABG (OctoPump Trial). In beide studies werd voor de off-pump operaties de Octopus Methode toegepast.

In dit proefschrift worden de resultaten van de OctoPump Trial gepresenteerd. Met Octopus Studie wordt daarom hier steeds de OctoPump Trial bedoeld, de gerandomiseerde vergelijking tussen off-pump en on-pump CABG. In deze studie werden patiënten opgenomen die verwezen werden voor een eerste CABG, zonder bijkomende interventies als klepchirurgie en bij wie een off-pump operatie technisch mogelijk werd geacht. Patiënten werden van de studie uitgesloten indien een spoedoperatie noodzakelijk was, indien zij de afgelopen 6 weken een Q-wave myocardinfarct hadden doorgemaakt, of indien zij een slechte linker hartkamer functie hadden. Ook patiënten bij wie het voltooien van 1 jaar follow-up onwaarschijnlijk geacht werd, patiënten die niet geschikt waren voor neuropsychologisch onderzoek en patiënten die geen schriftelijke toestemming gaven werden uitgesloten van het onderzoek. Er bestonden geen restricties met betrekking tot de leeftijd van de patiënten. De primaire uitkomstmaat van de studie was de aanwezigheid of afwezigheid van cognitieve beschadiging en/of beroerte, 3 maanden na de operatie. Secundaire eindpunten waren onder meer de cerebrale uitkomst

na 12 maanden, het optreden van cardiovasculaire complicaties, het opnieuw ontstaan van angina pectoris, het optreden van cardiale ischemie tijdens ergometrie, kwaliteit van leven en kosteneffectiviteit. Stabiele angina pectoris werd geclassificeerd volgens de indeling van de Canadian Cardiovascular Society en instabiele angina pectoris volgens de indeling van Braunwald. Kwaliteit van leven werd gemeten met behulp van de EuroQol en de ShortForm-36 vragenlijsten. De benodigde omvang van de studie (power calculatie) was 140 patiënten per groep. Een deel van de patiënten werd bovendien gerandomiseerd om een jaar na de operatie coronair-angiografie te ondergaan, teneinde de doorgankelijkheid van de aangelegde omleidingen te beoordelen.

In *hoofdstuk 4* worden de cerebrale uitkomsten en de kwaliteit van leven na off-pump en on-pump CABG gepresenteerd. Tussen maart 1998 en Augustus 2000 werden 281 patiënten geïncludeerd in de studie. Zowel 3 als 12 maanden na chirurgie bestond er geen verschil in kwaliteit van leven tussen de beide groepen. Psychologen, die geblindeerd waren voor de soort operatie die aan de patiënten was toegewezen, namen herhaaldelijk een serie van 10 neuropsychologische tests af om de cognitieve uitkomst na 3 en 12 maanden te kunnen bepalen. Na 3 maanden kon de cognitieve uitkomst in 248 patiënten worden vastgesteld. Cognitieve beschadiging (of een beroerte) was aanwezig bij 21% van de off-pump patiënten en 29% van de on-pump patiënten (relatief risico 0,65; 95% BTI 0,36-1,16; p=0,15). De gemiddelde, gestandaardiseerde cognitieve verbetering (van pre-operatief naar 3 maanden post-operatief) was 0,19 in de off-pump groep versus 0,13 in de on-pump groep (p=0,03). Twaalf maanden na de operatie was cognitieve beschadiging aanwezig bij 31% van de off-pump patiënten en 34% van de on-pump patiënten (relatief risico 0,88; 95% BTI 0,52-1,49; p=0,69). De gemiddelde gestandaardiseerde cognitieve verbetering bedroeg 0,19 in de off-pump groep en 0,12 in de on-pump groep (p=0,09). Deze resultaten suggereren dat patiënten die voor het eerst een CABG ondergaan na 3 maanden een betere cognitieve uitkomst hebben als deze zonder hart-longmachine wordt uitgevoerd. Het effect is echter klein en wordt na 12 maanden verwaarloosbaar.

Hoofdstuk 5 bestaat uit een predictie-studie. Omdat het vermijden van de hart-longmachine slechts tot een kleine verbetering van

de cognitieve uitkomsten leidde, werd getracht om andere determinanten te identificeren. In eerder uitgevoerde studies werden gevorderde leeftijd, vrouwelijk geslacht, diabetes, een beroerte in de voorgeschiedenis, manipulatie van de aorta ascendens, een lange tijd aan de hart-longmachine en een lange tijd voor ontwaken na de operatie, gevonden als voorspellers (predictoren) van cognitieve beschadiging. De dichotome en continue maat voor cognitieve uitkomst na 3 maanden die in de analyse van de gerandomiseerde studie gehanteerd werden (hoofdstuk 4), werden opnieuw toegepast als afhankelijke variabelen. Dertien klinische potentiële predictoren van de cognitieve uitkomst na 3 maanden en 2 maten van vroege cognitieve uitkomst (4 dagen na de operatie) werden opgenomen in logistische en lineaire regressiemodellen. De eerder gevonden determinanten van cognitieve uitkomst hadden in de huidige patiënten groep geen predictieve waarde. De enige variabelen die geassocieerd waren met de cognitieve uitkomst na 3 maanden waren maten voor cognitieve uitkomst na 4 dagen. Dit verband was sterker aanwezig in patiënten die geopereerd waren met hart-longmachine (odds ratio 4,72; 95% BTI 1,63 - 13,66; $p<0,01$) dan in patiënten die geopereerd waren zònder hart-longmachine (odds ratio 2,00; 95% BTI 0,77 - 5,20; $p=0,16$).

In *hoofdstuk 6* worden de vroege klinische uitkomsten van off-pump en on-pump CABG met elkaar vergeleken. Zowel het beloop tijdens de ziekenhuisopname als de cardiale uitkomst en kwaliteit van leven na 1 maand worden gerapporteerd. De cardiale uitkomst werd gedefinieerd als overleving zonder cardiovasculaire complicaties (beroerte, hartinfarct, of coronaire re-interventie). Het gemiddelde aantal distale anastomoses was 2,4 in de off-pump groep en 2, 6 in de on-pump groep, maar het percentage patiënten waarin sprake was van volledige revascularisatie was in beide groepen gelijk. Tijdens 3% van de off-pump operaties en 13% van de on-pump operaties moesten bloedproducten getransfundeerd worden ($p<0,01$). De post-operatieve stijging van een enzym dat duidt op hartspierschade (CK-MB) was in de off-pump groep 41% minder dan in de on-pump groep. De off-pump patiënten werden gemiddeld 1 dag eerder uit het ziekenhuis ontslagen. Voor het overige werden tijdens de ziekenhuisopname geen verschillen waargenomen. Na 1 maand was er

geen mortaliteit opgetreden en de kwaliteit van leven was in de 2 groepen in gelijke mate verbeterd. In beide groepen had 4% van de patiënten opnieuw angina pectoris. Het aandeel patiënten dat overleefde zonder cardiovasculaire complicaties was 93,0% in de off-pump groep en 94.2% in de on-pump groep (verschil 1,2%; 95% BTI -4,4 tot 7,0%; p=0,66). Dit suggereert dat in geselecteerde patiënten off-pump chirurgie veilig is en gepaard gaat met een cardiale uitkomst die vergelijkbaar is met on-pump CABG.

In *hoofdstuk 7* wordt een vergelijking gerapporteerd van cardiale uitkomsten en kosten-effectiviteit, 1 jaar na de operatie. De overleving zonder cardiovasculaire complicaties was 88.0% na off-pump chirurgie en 90.6% na on-pump chirurgie (p=0,48). Overleving zonder dat opnieuw angina pectoris optrad was eveneens vergelijkbaar (respectievelijk 89,3% en 89,0%; p=0,93). In de off-pump groep was 91% van de aangelegde omleidingen nog doorgankelijk; in de on-pump groep was dat 93% (p=0,65). De totale kosten na 1 jaar waren na een off-pump operatie $ 2.329 lager dan na een on-pump operatie ($ 15.479 versus $ 17.808; p<0,01). 'Quality adjusted life years' (respectievelijk 0.82 en 0.83; p=0,74) and 'event free survival years' (respectievelijk 1,02 en 1,03; p=0,23), waren echter gelijk. Daardoor was off-pump chirurgie kosten-effectiever dan on-pump chirurgie, terwijl de cardiale uitkomsten na beide behandelingen gelijk waren. De toepassing van off-pump CABG lijkt daarom vanuit economisch perspectief gerechtvaardigd.

Hoofdstuk 8 tenslotte omvat een algemene bespreking van het uitgevoerde onderzoek. Deze is met name gericht op het feit dat een aantal van de verwachte voordelen van off-pump CABG niet kon worden aangetoond. Hiervoor worden mogelijke verklaringen aangedragen.

Allereerst is het mogelijk dat de potentiële voordelen van off-pump CABG zijn overschat. De resultaten van de Octopus Studie suggereren dat de hart-longmachine niet de enige oorzaak van cognitieve schade na hartchirurgie is. Het ondergaan van chirurgie en narcose zouden eveneens oorzaken kunnen zijn. Ook is het voorstelbaar dat de off-pump techniek zelf een nieuwe bron van cognitieve schade is. De waarneming dat off-pump chirurgie tot een korter ziekenhuis verblijf leidt kan voortkomen uit een gebrekkige blindering van de artsen die de patiënten uit het zie-

kenhuis ontsloegen. Ook indien in plaats van een sternotomie een laterale thoracotomie wordt toegepast, blijft de kans op serieuze chirurgische complicaties bestaan.
Ten tweede is het mogelijk dat de schadelijke gevolgen van conventionele bypass chirurgie zijn overschat. Off-pump CABG gaat gepaard met weinig complicaties, maar het blijkt dat patiënten met een vergelijkbaar (doorgaans laag) risicoprofiel, die een conventionele operatie ondergaan, het eveneens goed doen. De incidentie van cognitieve beschadiging na bypass chirurgie is mogelijk overschat omdat de thans gebruikelijke definities van cognitieve beschadiging tot vals-positieve uitkomsten kunnen leiden. Misclassificatie van patiënten met en zonder cognitieve beschadiging en een overschatting van het aantal patiënten met dergelijke schade vormen beide een verklaring voor de slechts beperkte verbetering die in de Ocopus Studie kon worden aangetoond na off-pump chirurgie.
Een derde verklaring wordt gevormd door de methodologische beperkingen van de studie. Een kleine verbetering in cognitieve uitkomsten was mogelijk overtuigender aangetoond met een groter aantal patienten. Het hoge ruis-niveau van de neuropsychologische tests en de definitie van cognitieve schade kan het waargenomen verschil in cognitieve uitkomsten tussen de groepen hebben verkleind. Ook werd in de studie te weinig aandacht aan blindering geschonken.
Een toekomstige studie zou moeten worden uitgevoerd in oudere patiënten. Hier zou het effect van off-pump chirurgie op cognitieve uitkomst groter kunnen zijn. In een nieuwe studie dient een betrouwbaarder definitie van cognitieve beschadiging te worden gehanteerd. Indien besloten wordt een beduidend groter aantal patiënten in een nieuwe studie op te nemen, kan ook het optreden van een beroerte worden gekozen als primaire uitkomstmaat. De diagnose van een beroerte is, in tegenstelling tot die van cognitieve beschadiging, relatief eenvoudig. In oudere patiënten is de kans op een beroerte na CABG bijna 9% en het lijdt geen twijfel dat een dergelijke complicatie voor de patiënt verstrekkende gevolgen heeft.
Geconcludeerd wordt dat binnen een geselecteerde patiëntenpopulatie de off-pump operatie veilig is en tot een cardiale uitkomst leidt die vergelijkbaar is met on-pump CABG. Het

vermijden van de hart-longmachine is kosten-effectief en vermindert in geringe mate de bloedtransfusie-behoefte, maar andere klinisch relevante voordelen van off-pump CABG zijn nog niet aangetoond. Patiënten die zonder hart-longmachine geopereerd worden hebben na 3 maanden een betere cognitieve uitkomst, maar de verbetering is slechts beperkt.

Dankwoord

Wetenschappelijk onderzoek kent vele verschijningsvormen. Eénzame opsluiting in het lab behoort tot de mogelijkheden. Maar het kan ook uitpakken als een wervelend circus vol medeonderzoekers, patiënten, hoogleraren en andere artiesten. De Octopus Studie behoort ongetwijfeld tot de laatste soort. De disciplines thoraxchirurgie, cardiologie, anesthesiologie, epidemiologie en psychiatrie hebben ieder belangrijke bijdragen geleverd aan het ontwerp en de uitvoering van dit onderzoek. Bij het schrijven van dit proefschrift heb ik dan ook kunnen profiteren van een overvloed aan begeleiding en hulp. Enkelen wil ik hierbij bijzonder danken voor hun inbreng.

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Annemieke Keizer. Een psycholoog waarmee ik praten kan, en niet alleen over het werk. Voorzien van ferme doses humor en relativeringsvermogen. Katten-aanbidster ook, wat wil een mens

nog meer. Ik hoop dat we onze aangename analyse-aanvaringen nog lang voort kunnen zetten.
Karl Moons. Je verspreidt effectief het epidemiologie-evangelie door de afdeling anesthesiologie. Ambitieus, maar vooral ook enthousiast en hartelijk. Jij bent iemand die het saaiste van het saaiste kan brengen als een spannend jongensboek.
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Ron Hijman. Leverancier van neuropsychologische tests, gedegen kritiek op manuscripten en natuurlijk de test-psychologen:
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The Octopump Study: rationale and design of a randomized clinical trial evaluating cerebral outcome after coronary bypass surgery on the beating heart. Presented at: Outcomes 99: Conference on cardiac surgery and the brain, Key West, Florida, USA, May 1999.

The Octopus Trial: limited effect of off-pump bypass surgery on cognitive outcome. Presented at: Outcomes 02: Conference on cardiac surgery and the brain, Key West, Florida, USA, May 2002.

Curriculum vitae

Diederik van Dijk was born on October 27, 1968 in Maarn, The Netherlands. After graduating high school at the 'Revius Lyceum' in Doorn in 1987, he took colleges in history during one year and then started medical studies at Utrecht University. During and after his medical studies, he was involved in the organization of three opera productions: 1990 *Suor Angelica*; 1992 *Tosca*; and 1998 *Pagliacci*.

In 1996 Diederik began working as a resident in Anesthesiology at Utrecht University Hospital. One year later he started the work described in this thesis at the Department of Perioperative care, Anesthesia and Pain therapy and the Julius Center for General Practice and Patient Oriented Research at Utrecht University (promotores: Prof. dr. C.J. Kalkman and Prof. dr. D.E. Grobbee; co-promotor: Dr. P.P.Th. de Jaegere). Simultaneously, he started specialist training in Anesthesiology (supervisor: Prof. dr. J.T.A. Knape). In 2000, he obtained the Master of Science degree in Clinical Epidemiology at the Netherlands Institute for Health Sciences in Rotterdam.