Review Article

Should I change to OPCAB?

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Summary

Much is written about the benefits of off-pump coronary artery bypass surgery (OPCAB). Is it applicable to all practices? Does that mean we all need to change to OPCAB? The surgical literature appears to have flaws with regard to providing answers. In striving for evidence-based medicine, one could integrate clinical data with external best evidence or do proper power calculations to determine study sizes. In a local, retrospective, observational study, 535 patients had a CABG done with the aid of cardiopulmonary bypass and cardiac arrest. Five hundred and seven patients were considered appropriate for analysis. Mortality was seven (1.4%), the prevalence of myocardial infarction four (0.8%), renal dialysis was four (0.8%) and stroke six (1.2%). Eighty (16%) patients required homologous blood transfusions. The median length of hospital stay was five days.

If a local, randomised, controlled study was to be conducted to confirm an improvement with OPCAB, a large number of patients would be needed. For a 12.5% reduction in an event rate presently at 0.8%, 262 000 patients would be necessary. For a 50% reduction in an event rate presently at 4.0%, 2 300 patients should be recruited. The local prevalence rate is very low and the number of patients required for a series is too high. The supremacy of OPCAB for this practice is therefore not established.

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It is only the wisest and stupidest that cannot change.

Confucius

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Coronary artery bypass graft surgery (CABG) is the most intensively described surgical procedure.[1] At present the debate is whether to do it on cardiopulmonary bypass (CPB) with or without cardiac arrest (ONCAB), or to do it while the beating heart supports the circulation (OPCAB). Each technique has its antagonists and protagonists and arguments are used such as the detrimental effect of the associated systemic inflammatory response related to the unphysiological cardiopulmonary bypass on one hand or incomplete revascularisation on the other. Unfortunately it becomes a 'yes' or 'no' kind of argument. This form of debate is familiar: warm versus cold surgery, blood versus crystalloid cardioplegia and antegrade versus retrograde cardioplegic infusion. As long as the debate is limited to scientific journals and meetings, surgeons' views are not exposed to the public. However, once it gets in the lay press, readers who are the patients could ask questions.

In the *Volksblad* of 23 November 2002, an article appeared under the heading 'New technology of great aid to heart patients' (freely translated). This article was based on the work presented by Harris *et al*. at the meeting of the South African Heart Association at Sun City in October 2002. With OPCAB they managed to reduce the mortality from 7.7 to 4.8% and shorten the hospital stay from 9.1 to 7.2 days. The writer of the newspaper article used statements such as 'some people are connected to a breathing machine for weeks' or 'a patient walked out of hospital three days after his operation'. It therefore becomes important to evaluate one's way of practising surgery. One does not want to fall victim to John Steinbeck's quote 'it is the nature of man, as he grows older to protest against change, particularly changes that are for the better'.[2]

Greco and Eisenberg wrote on six reasons that might influence physicians to change their way of practice.[3] According to them, a combination of interventions should have the best result in bringing about change, but although the manner of practising may change, it does not necessarily improve patient outcome. To seek answers, one could obviously consult the surgical literature. It is educational, it is a form of feedback, and it does involve the surgeon in the decision-making process, to name three of the methods Greco and Eisenberg described.

However Richard Horton was very outspoken about surgical research in an issue of *Lancet* in 1996.[4] In a given month he collected 175 original research articles from nine

general surgical journals. Only 12 (7%) were randomised, controlled trials (RCTs) and 46% were case studies, which, according to epidemiologists is not a valid way of obtaining answers. RCTs are considered the best approach to solve issues.[5] Blindness is not an option in surgical trials, although patients might be randomised. Unlike drugs that are blinded and exactly reproducible, surgery differs from patient to patient and surgeon to surgeon.

Tom Treasure, however, is not convinced that RCTs are the alpha and the omega of surgical research.[6] He and his co-author analysed 119 series over two years from three major cardiothoracic journals and concluded, 'Many RCTs in surgery by virtue of their design, sample size and insufficient power are incapable of answering the questions researchers seek to address'. His argument was based on the fact that the median score of these 119 studies, according to the consolidated standards of reporting trials (CONSORT[7]), was only eight out of a maximum of 20. He admits that blinding and standardisation is difficult in surgical trials. He suggests that power calculations and clinical rather than surrogate end-points should be part of any surgical trial design. The development and refinement of methods to compare non-randomised study arms should be encouraged.

If the surgical literature is suspect, how does one still practise evidence-based medicine (EBM)? 'Evidence-based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients'.[8] Fortunately, according to the authors, EBM is not limited to randomised trials and meta-analyses. It is also about integrating individual clinical expertise with the best external evidence. This was done in order to answer the title question, as well as taking the advice from Tom Treasure to use clinical endpoints, and for a possible local trial to do proper power calculations.

Methods

This was a retrospective, observational study. All the patients who had had coronary artery bypass graft surgery done by one surgeon (MJS) at Bloemfontein Medi-Clinic were included. Patients who had had an additional procedure that required open-heart surgery and those who had had their CABG done with OPCAB were excluded. All operations were done with cardiopulmonary bypass, moderate hypothermia and cardiac arrest with cold-blood cardioplegia. Major outcomes are given with 95% confidence intervals (CIs).

Outcomes that were selected based on the literature, included mortality, myocardial infarction (MI), renal failure requiring dialysis, stroke, a compilation of major adverse events (MAE), homogeneous blood transfusion, and length of stay in hospital (LOS). Mortality was defined as in-hospital death within 30 days, while myocardial infarction was defined as a new Q-wave and/or raised cardiac enzymes. Renal failure was diagnosed when a consulting physician decided to dialyse and stroke was seen as a new focal cerebral lesion. The prevalence of these events as it occurred in the literature was only used as a reference and was not compared statistically.

Five studies were selected from a personal collection of articles. These studies had the highest number of patients. The ultimate answer, however, should come from a randomised, controlled study including local patients, done in a local unit. To demonstrate a reduction in prevalence of 50, 25 and 12.5% in the existing major outcomes between two arms of ONCAB and OPCAB respectively, sample sizes were calculated with a power of 80% and an alpha value of 0.05.

Results

A total number of 535 patients had had a CABG done. Fifteen patients who had had either a combined valve procedure or left ventricular reconstruction done simultaneously were excluded. Thirteen patients had had their CABG done with OPCAB and were also not included. Therefore, 507 patients formed part of this study. The majority (398) were males and 109 patients were females. Their average age was 59.2 years. Their risk for mortality was according to the additive EuroSCORE 3.7% (range 0–14). Thirty-eight per cent of patients fell in the low-risk group (EuroSCORE 1–2), 40% in the moderate-risk group (3–5), and 22% were considered high-risk patients (≥ 6). Seven (1.4%) patients died while in hospital. The prevalence of morbidity was calculated from the 500 patients who survived. Results are depicted in Table I. Sixteen per cent of patients required homologous blood. The average length of stay was 5.9 days, with a median of five days. Two-thirds of the patients did not stay longer than five days in the hospital.

For a prospective, randomised trial with two arms, namely an ONCAB and an OPCAB group, one requires a

TABLE I. PREVALENCE OF OUTCOMES, BLOEMFONTEIN MEDI-CLINIC

Event	n	*Prevalence*	*%*	*CI (%)*
Mortality	507	7	1 4	(0 6; 2 8)
Myocardial infarction	500	4	0 8	(0 2; 2 0)
Renal dialysis	500	4	0 8	(0 2; 2 0)
Stroke	500	6	1 2	(0 4; 2 6)
MAE	500	20	4 0	(2 5; 6 1)
Blood transfusion	500	80	16 0	(12 8; 19 2)

MAE (major adverse events): myocardial infarction, renal dialysis, stroke, ARDS, septicaemia.

TABLE II: TOTAL SAMPLE SIZE REQUIRED FOR THE STATED PERCENTAGE REDUCTION WITH A POWER OF 80% AND ALPHA OF 0.05

Event	*50% reduction (patients)*	*25% reduction (patients)*	*12.5% reduction (patients)*
Mortality (1 4%)	6 656	31 014	132 810
Myocardial infarction (0 8%)	11 702	54 566	233 742
Renal dialysis (0 8%)	11 702	54 566	233 742
Stroke (1 2%)	7 778	36 248	155 238
MAE (4 0%)	2 282	10 604	45 334

MAE (major adverse events): myocardial infarction, renal dialysis, stroke, ARDS, septicaemia.

large number of patients. The total number of patients for the two groups to show a statistically important reduction is seen in Table II. For a reduction of 12.5% in the myocardial infarction or renal dialysis prevalence, one would need a total of 233 742 patients, divided between the two arms of the trial. At the other end of the spectrum, for a reduction of 50% in the combined number of major adverse events to be statistically significant, one would require 2 282 patients. The smaller the difference that has to be detected as statistically significant, the larger the sample size needed.[9]

Discussion

It seems that cardiothoracic surgery is not necessarily an example of EBM. When James Lee investigated 50 major general thoracic surgical procedures, he found that only seven procedures were backed up by RCTs.[10] The same conclusion was made when Claus Bartels and his co-workers investigated 48 chosen principles applied in cardiopulmonary bypass.[11] Many (33 000) articles related to the various subjects were found. Ultimately, 225 articles were identified as providing the best possible evidence, but it was still considered insufficient to serve as evidence-based medicine.

By comparing data, one can get some idea of performance. The difficulty, however, is which studies to use as references. Studies vary in size. Thirty-six patients randomly assigned to two groups of eighteen each seem like a small study.[12] Contrary to this, four centres in the USA combined figures and could match patients with propensity scores from a source of 11 548 patients.[13] These studies were not necessarily randomised, while in others, patients were retrospectively matched. The study by Al-Ruzzeh included only high-risk patients, i.e. patients with a EuroSCORE of ≥ 5.[14] Studies may be multi-centred, from a single institution, or a meta-analysis. Series have different outcomes as is clearly seen in Table III. An outcome that has improved in one study is not necessarily better in another.

Mortality is the one outcome that is universally described. It might be a crude way of assessing success, but it is a definite endpoint and leaves no room for interpretation. In Table III, the various studies have different results (i.e. a statistically important *p*-value or not), and the answer to whether OPCAB is better than ONCAB is not clear from the literature.

The prevalence of myocardial infarction appears to improve with OPCAB (Table III), but comparing on face value with the local prevalence of 0.8%, there is not much difference between OPCAB in the literature and the local ONCAB technique. As far as renal failure for dialysis is concerned Al-Ruzzeh could not demonstrate a statistically different outcome in high-risk patients.[14] The 4.2% in the ONCAB seems higher than the 0.8% (four patients) in the local series, but those patients were of a higher risk. Sabik from the Cleveland Clinic Foundation was successful in improving renal failure to zero with the aid of OPCAB.[15] In their series, OPCAB made no difference in the outcome of mortality, myocardial infarction, or stroke. This is a common pattern. Units differ in terms of the outcome. What is important in one study is not necessarily the case in another.

Stroke occurred in six (1.2%) of the Bloemfontein Medi-Clinic patients. It was only in the large series of Mack that a difference in the incidence of stroke was seen between the two surgical approaches.[13] None of the others (Table III) could obtain a different outcome with the aid of OPCAB. However, Athanasiou concluded from a meta-analysis which included nine studies and 4 475 patients (28% OPCAB) that OPCAB was associated with a lower incidence of stroke in patients older than 70 years (3 vs 1%).[16] At the Medi-Clinic, the prevalence of stroke in the septuagenarians was two out of 89 (2.4%) patients.

Stroke is a basic assessment of cerebral injury. Taggart classifies cerebral injury as stroke, delirium (encephalopathy) and cognitive dysfunction.[17] In a retrospective, non-randomised study of 16 184 patients (12% OPCAB) by Bucerius at the Heart Centre in Leipzig, the incidence of delirium was improved from 7.9 to 2.3% when patients had their operation done with OPCAB.[18] This study raised two questions by Taggart.[17] Firstly, the two groups were not matched, and secondly other evidence was conflicting. Taggart's own unit could not demonstrate a difference in cognitive function.[19] In a small, prospectively randomised study by Keizer from Utrecht, patients completed a 'cognitive failures' questionnaire.[20] Both the ONCAB and OPCAB groups were compared to a healthy age-matched control group. There was no difference between before, and one year after surgery, or between the ONCAB and the OPCAB groups. In fact, the control group reported more cognitive failures!

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TABLE III: PREVALENCE OF ADVERSE EVENTS (AS PERCENTAGES), BLOOD TRANSFUSIONS AND LENGTH OF STAY FROM FIVE LARGE TRIALS FOR REFERENCE WITH THE BLOEMFONTEIN MEDI-CLINIC SERIES (MJS)

Trial	*MJS*	*Mack*[13]	*Hernandez*[25]	*Califiorie*[24]	*Al-Ruzzeh*[14]	*Sabik*[15]
Number of patients	507	11548	7867	1843	1398	812
Age	59			64 & 63	63 & 68	66 & 66
Mortality (%)	1.4	3.7	2.6	3.0	7.0	1.0
		2.8*	2.5	1.4*	3.5*	0.5
MI (%)	0.8			2.6	3.4	1.2
				1.1*	0.7*	0.7
Renal dialysis (%)	0.8				4.2	1.5
					2.8	0.0*
Stroke (%)	1.2	2.1	1.8	1.0	1.3	1.2
		1.4*	1.3	0.8	0.0	0.7
MAE (MI, dialysis, stroke, ARDS, septicaemia) (%)	4.0				14.0	
					7.0*	
Blood transfusion (number of patients as %)	16	40		30		53
		32*		22*		42*
LOS (average number of days)	5.9			4.9	11	
				4.2*	10	
LOS (median number of days)	5		6			
			5*			

ONCAB given in first line, OPCAB given in second line
*$p < 0\ 05$

confirmed this with his work.[21] Patients who had had CABG, and a similar group with coronary artery disease but without surgery completed a neuropsychological assessment before and after surgery. At three and 12 months, there was no difference. On the other hand, to add to the confusion, Zimpfer concluded differently when he compared CABG patients who had had CPB to non-surgical patients.[22]

The prevalence of so-called delirium in the Bloemfontein Medi-Clinic series was 14 new patients (2.8%). This was not accurate as no standardised neuropsychological objective test was completed before or at any time after the operation. A mere bedside impression of confusion or disorientation was used as a criterion.

The incidence rate of adverse events is generally low, so it makes sense to combine the MAE. Al-Ruzzeh combined myocardial infarction, dialysis, stroke, adult respiratory distress syndrome (ARDS) and septicaemia.[14] He demonstrated a decrease in the combined event rate from 14 to 7% in favour of OPCAB. Jansen from Utrecht achieved the same when he combined mortality, myocardial infarction and stroke in his meta-analyses of 18 trials and 1 584 patients.[23] However, the three adverse advents did not reach statistical significance on their own, and he concluded that OPCAB is equivalent to ONCAB. At Bloemfontein Medi-Clinic MAE occurred in 20 and 17 different patients, respectively, depending on which adverse events were included – as in Al-Ruzzeh's or Jansen's study. (Some patients had more than one adverse event.)

Blood transfusion is also a categorical endpoint. Blood is either given or withheld, however, the indications might differ. Mack,[13] Califiorie[24] and Sabik[15] reduced the usage of homologous blood in the OPCAB patients (Table III). These improved figures were still higher than the 16% of local patients who required homologous blood. However, the patients might not be comparable as body mass index, pre-operative hematocrit and the availability of cell saving could differ from institution to institution.

Length of hospital stay (LOS) is reported as average number of days, or a median length of stay. In a multi-centre study, Hernandez reduced median stay from six to five days.[25] Califiorie reduced the average from 4.9 to 4.2 days.[24] Almost one-third of patients in the Califiorie series were first discharged to a rehabilitation centre and not directly home. The Bloemfontein Medi-Clinic patients, however, were often kept an extra day due to the fact that most were from beyond Bloemfontein. Nevertheless, the median length of stay was five days (average 5.9 days), but 29% were discharged in four days or less. Two-thirds of the patients did not stay longer than five days. These patients all had their CABG done as ONCAB.

Is it possible to reduce event rates further? One sure way is to be more selective and exclude high-risk patients, but usually those are the patients who benefit most. The question remains whether one should change to OPCAB. The literature does not offer a clear answer. The local data appear to be on a par with the improved published figures of OPCAB. The ultimate answer would come from a prospectively randomised trial with two arms done by one surgeon with local patients at the specific unit. With proper power calculations, the size of the series could be determined. In such a study all patients should be fit for either technique, but that may not be possible since there are established contra-indications for OPCAB.[24] Table II shows the number of patients required for such a study and the average cardiothoracic career is too short to operate on the number of patients necessary to demonstrate a 25% reduction of any event rate from the local series.

In the literature, ONCAB and OPCAB are seen as opposing techniques. Should I change to OPCAB? I do not find enough evidence to justify such a change. However, with that point of view, I too, might become part of the simplistic 'yes/no' debate. The question is which individual patient will benefit from which specific CABG procedure or, for that matter, any other modification of technique.

I salute the pioneers and am grateful to those who are prepared to dare in the search for answers. Our discipline depends on them. I still need to do what is best for my patients and with a technique that I am comfortable with. Maybe the title of Paul Sergeant's paper presented at the 17th annual meeting of the EACTS in Vienna, October 2003 is appropriate: 'OPCAB versus early mortality and morbidity: an issue between clinical relevance and statistical significance'.[26]

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