European Journal of Cardio-Thoracic Surgery Advance Access published April 22, 2016

European Journal of Cardio-Thoracic Surgery (2016) 1–9
doi:10.1093/ejcts/ezw129

REVIEW

Cite this article as: Ueki C, Sakaguchi G, Akimoto T, Ohashi Y, Sato H. On-pump beating-heart technique is associated with lower morbidity and mortality following coronary artery bypass grafting: a meta-analysis. Eur J Cardiothorac Surg 2016; doi:10.1093/ejcts/ezw129.

REVIEW

On-pump beating-heart technique is associated with lower morbidity and mortality following coronary artery bypass grafting: a meta-analysis†

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Received 12 October 2015; received in revised form 13 February 2016; accepted 8 March 2016

Summary

A hybrid procedure of beating-heart coronary artery bypass grafting (CABG) with the concomitant use of cardiopulmonary bypass termed on-pump beating-heart CABG (ON-BH CABG) has emerged as an alternative for high-risk patient populations. Although several studies have reported the advantage of ON-BH CABG in high-risk patients, the clinical benefit of ON-BH CABG is still under discussion. Here, we performed a meta-analysis of the data derived from published studies comparing the clinical outcomes of ON-BH CABG with that of conventional arrested heart CABG. Medline, Embase and Scopus databases were searched for relevant publications up to March 2015. A systematic review of the published literature identified 14 published studies incorporating 2040 patients (884 ON-BH CABG and 1156 conventional CABG). Odds ratios (ORs) for binary variables or weighted mean difference for continuous variables were combined using the inverse variance method in a fixed-effects model. Study heterogeneity was tested using Cochran's *Q* test and the publication bias was assessed using Begg's and Egger's tests. The fixed-effects meta-analysis for early mortality showed that ON-BH CABG provided a 45% lower risk of early mortality compared with conventional CABG (OR 0.553; 95% confidence interval [CI] 0.376–0.815; $P = 0.003$). There was minimal heterogeneity in the included studies ($P = 0.29$) and no evidence of significant publication bias. A sensitivity analysis, including a random-effects meta-analysis (OR 0.552; 95% CI 0.356–0.856; $P = 0.008$) and a one-study-removed meta-analysis, supported the validity of the primary analysis for early mortality. There was significantly lower perioperative morbidity associated with ON-BH CABG, including myocardial infarction (OR 0.294; 95% CI 0.141–0.613; $P = 0.001$), renal failure (OR 0.362; 95% CI 0.209–0.626; $P < 0.001$) and low output syndrome (OR 0.330; 95% CI 0.197–0.551; $P < 0.001$) with no significant heterogeneity. In conclusion, current evidence from comparative studies indicates that ON-BH CABG is associated with significantly lower early morbidity and mortality. The ON-BH CABG could be an attractive planned alternative for high-risk patient populations.

Keywords: Coronary artery bypass graft • On pump • Beating heart • Meta-analysis

INTRODUCTION

The use of less invasive surgery is an important factor in the improvement of clinical outcome following coronary artery bypass grafting (CABG) surgery, especially in the high-risk patient population. Off-pump beating-heart CABG (OPCAB) is a less invasive procedure by eliminating cardiopulmonary bypass (CPB) and avoiding cardioplegic cardiac arrest. Recent large observational studies comparing OPCAB and on-pump CABG have shown that OPCAB is associated with significantly lower morbidity and mortality, especially in patients with a higher predicted clinical risk, low ejection fraction (EF) or impaired renal function [1–3]. In 2012, 61.4% of isolated CABG procedures in Japan were performed by the off-pump technique, with the conversion rate from OPCAB to on-pump CABG of 2.1% [4]. However, especially in the high-risk population, OPCAB has a potential risk of unplanned conversion to on-pump CABG during surgery and unplanned conversion is associated with high morbidity and mortality [5]. Keeling *et al.* [2] reported that 5.2% of OPCAB patients with a low EF underwent unplanned conversion to on-pump CABG, and their in-hospital mortality rate was 9.3%. Thus, the recent 2014 ESC/EACTS guidelines on myocardial revascularization state that OPCAB should be considered for subgroups of high-risk patients in high-volume off-pump centres (Class IIa) [6]. A hybrid procedure of beating-heart CABG with the concomitant use of CPB termed on-pump beating-heart CABG (ON-BH CABG) has emerged as an attractive alternative for those high-risk patient populations.

Previous studies have reported the clinical benefit of ON-BH CABG in high-risk patients [7, 8]. Edgerton *et al.* [7] compared ON-BH CABG and conventional CABG and reported that, in spite of significantly higher predicted risk of mortality in patients

†Presented at the 29th Annual Meeting of the European Association of Cardio-Thoracic Surgery, Amsterdam, Netherlands, 3–7 October 2015.

selected for ON-BH CABG, observed : expected mortality ratios showed no difference between two groups. Furthermore, Mizutani *et al.* [8], in their comparison of ON-BH CABG and conventional CABG using 114 propensity score-matched pairs, reported that ON-BH CABG was associated with a significantly lower in-hospital mortality. However, most previously reported studies have included relatively small numbers of patients and the clinical benefit of ON-BH CABG is still under discussion.

The aim of this study was to assess the impact of ON-BH CABG on early patient morbidity and mortality following CABG by performing a meta-analysis of data derived from published studies comparing ON-BH CABG with conventional arrested heart CABG.

MATERIALS AND METHODS

To identify all studies comparing ON-BH CABG with conventional CABG, the MEDLINE (PubMed), Embase (OVID Interface) and SCOPUS databases were searched for relevant publications up to March 2015. The following keywords were used in the search: 'coronary artery bypass', 'CABG', 'beating-heart', 'cardiopulmonary bypass', 'on-pump' and 'cardioplegia'. Published studies that satisfied the following criteria were included in this meta-analysis: (i) comparing ON-BH versus conventional CABG; (ii) reporting at least one of the major clinical outcomes (early mortality, stroke, myocardial infarction and renal failure requiring haemodialysis); (iii) performing ON-BH CABG on more than 20% of patients undergoing on-pump CABG and (iv) publications in the English language. Conventional CABG was defined as CABG performed with the use of CPB and cardioplegic cardiac arrest. If the same group had reported multiple studies, only the most recent and most comprehensive publication within the group was included. We inspected the references of all studies and performed a manual search using Google Scholar to identify any overlooked studies.

Data regarding detailed patient characteristics and clinical outcomes were abstracted from each study. Continuous variables that were not presented as the mean and standard deviation were excluded from the analysis. In studies reporting clinical outcomes in each subgroup separately, the data were extracted and analysed separately. Odds ratios (ORs) for binary variables or weighted mean difference (WMD) for continuous variables were combined using the inverse variance method in the fixed-effects model. If statistically significant heterogeneity among included studies was found, a pooled analysis using a random-effects model was also performed to assess the sensitivity of primary meta-analysis. Heterogeneity among included studies was tested by using the Cochran's Q test, with the significance level set at a P-value of <0.10, and was quantified by using the I^2 statistic, where a value of 50% or greater indicated substantial heterogeneity. The publication bias was assessed by using the Begg's and Egger's tests with the significance level set at a P-value of <0.05. All analyses were conducted using comprehensive meta-analysis (CMA) software version 2 (Biostat, Englewood, NJ, USA).

RESULTS

Our search identified 18 studies [7–24] that compared clinical outcomes of ON-BH CABG and conventional CABG and met our inclusion criteria. One comparative study was excluded [23] as inclusive data from the same institution were found [9]. One study investigated only patients who developed perioperative myocardial infarction after ON-BH CABG or conventional CABG and, therefore, it was excluded [24]. Two studies were also excluded because ON-BH CABG was performed on <20% of patients undergoing on-pump CABG in these two studies [7, 18]. Finally, our meta-analysis included 14 studies [8–17, 19–22] with 2040 patients undergoing CABG: 884 with ON-BH CABG and 1156 with conventional CABG. The main characteristics of the studies included are illustrated in Table 1. Eight studies focused on high-risk patients; two studies focused on patients with acute coronary syndrome [8, 12], two studies focused on haemodialysis patients [19, 20], two studies focused on patients with low EF [9, 21], one study focused on patients with a high-risk EuroSCORE [16] and one study included patients with one of the following risk factors: severe left main coronary artery stenosis, early post-acute myocardial infarction with ongoing chest pain, unstable angina, intractable ventricular arrhythmia, complicated post-coronary intervention and severe left ventricular dysfunction [22]. The ORs for early morbidity and mortality in patients undergoing ON-BH versus conventional CABG are listed in Table 2.

Early mortality

A total of 2040 patients were included from 14 studies [8–17, 19–22], which reported data on early mortality. After removing one study with no events in two groups [17], 1959 patients from 13 studies were included in this meta-analysis [8–16, 19–22]. A pooled analysis demonstrated that ON-BH CABG was associated with a statistically significant 45% lower rate of early mortality in the fixed-effects model (OR 0.553; 95% confidence interval [CI] 0.373–0.815; P = 0.003; Fig. 1). No significant heterogeneity was observed in included studies (Cochran's Q test = 14.18, I^2 = 15.37%, P = 0.29) and, consequently, there was little difference in the pooled results from random-effects modelling (OR 0.552; 95% CI 0.356–0.856; P = 0.008). Furthermore, a one-study-removed meta-analysis showed that this positive effect of ON-BH CABG was robust even if any single study was removed from the meta-analysis. Begg's and Egger's tests showed no significant potential publication bias in the studies (Begg's test, P = 0.58; Egger's test, P = 0.64).

Stroke

A total of 1528 patients were included from 10 studies [8–11, 13–16, 19, 21], which reported the incidence of stroke. There was no significant difference between the two techniques in the incidence of stroke (OR 0.638; 95% CI 0.380–1.072; P = 0.089; Fig. 2). No significant heterogeneity was observed in included studies (Cochran's Q test = 3.71, I^2 = 0%, P = 0.93). Begg's and Egger's tests showed no significant potential publication bias in studies (Begg's test, P = 0.37; Egger's test, P = 0.083).

Postoperative myocardial infarction

A total of 864 patients were included from six studies [9–11, 16, 17, 21], which reported the incidence of postoperative myocardial infarction. The incidence of postoperative myocardial infarction was significantly lower in ON-BH CABG when compared with conventional CABG in the fixed-effects model (OR 0.294; 95% CI 0.141–0.613; P = 0.001; Fig. 3A). No significant heterogeneity was observed in included studies (Cochran's Q test = 2.38, I^2 = 0%, P = 0.80). Begg's and Egger's tests showed no significant potential publication bias within studies (Begg's test, P = 0.71; Egger's test, P = 0.94).

Table 1: Study design and patient characteristics

Study First author, year	Study population	Study type	Number of patients ON-BH	 C-CABG	Age (year) ON-BH	 C-CABG
Prifti, 2000 [9]	Low EF	RO	107	191	65.8	64.1
Kim, 2001 [10]		RO	19	65	59	63
Uva, 2004 [11]		RO	47	66	66.2	66.2
Izumi, 2006 [12]	ACS (AMI)	RO	15	16	65.5	66.4
Mizutani, 2007 [8]		RO, PS matching	114	114	66.0	64.5
Sabban, 2007 [13]		RO	33	73	63.8	59.1
Pegg, 2008 [14]		Randomized trial	25	25	68	64
Lin, 2010 [15]		RO	132	99	64	64
Munos, 2011[16]	High EuroSCORE	RO	51	106	72.9	75.2
Narayan, 2011 [17]		Randomized trial	40	41	65	67
Tsai, 2012 [19]	HD	RO	48	82	68.3	63.6
Takami, 2012 [20]	HD	RO	31	55	63	
Erkut, 2013 [21]	Low EF	RO	65	66	68.1	65.3
Afrasiabirad, 2015 [22]	High risk	RO, PS matching	157	157	56.8	57.2
	EF (%) ON-BH	 C-CABG	Male (%) ON-BH	 C-CABG	Urgent/emergent (%) ON-BH	 C-CABG
Prifti, 2000 [9]	24.8	26.2	64.5	73.3	NR	NR
Kim, 2001 [10]	47	56	63.2	70.8	31.6	33.9
Uva, 2004 [11]	<50, 25.5%	<50, 19.6%	76.6	69.7	NR	NR
Izumi, 2006 [12]	NR	NR	80.0	68.8	100	100
Mizutani, 2007 [8]	50.2	53.9	77.2	82.5	56.1	56.1
Sabban, 2007 [13]	40.1	46.6	NR	NR	15.2	17.8
Pegg, 2008 [14]	39	39	88	100	44	28
Lin, 2010 [15]	54	53	75	64	4	9
Munos, 2011 [16]	35.0	40.5	68	69	45	45
Narayan, 2011 [17]	≤50, 33%	≤50, 20%	83	78	40	49
Tsai, 2012 [19]	40.9	45.1	64.6	60.9	27.1	24.4
Takami, 2012 [20]	54		77		20	
Erkut, 2013 [21]	27.7	26.6	50.8	60.7	NR	NR
Afrasiabirad, 2015 [22]	38	34	74.4	75.6	NR	NR

ACS: acute coronary syndrome; AMI: acute myocardial infarction; C-CABG: conventional coronary artery bypass grafting; EF: ejection fraction; HD: haemodialysis; NR: not reported; ON-BH: on-pump beating-heart; PS: propensity score; RO: retrospective observational study.

Table 2: Fixed-effects meta-analysis of clinical outcomes

Clinical outcome	Number of studies	Number of patients	OR/WMD [95% CI]	*P*-value	Heterogeneity I^2, *P*-value
Mortality	13	1959	0.553 [0.376–0.815]	0.003	$I^2 = 15.37$, $P = 0.29$
Stroke	10	1528	0.638 [0.380–1.072]	0.089	$I^2 = 0$, $P = 0.93$
Myocardial infarction	6	864	0.294 [0.141–0.613]	0.001	$I^2 = 0$, $P = 0.80$
Renal failure needing HD	6	1076	0.362 [0.209–0.626]	<0.001	$I^2 = 7.20$, $P = 0.37$
Low output syndrome	5	800	0.330 [0.197–0.551]	<0.001	$I^2 = 0$, $P = 0.87$
Reoperation for bleeding	6	1031	0.532 [0.304–0.932]	0.027	$I^2 = 0$, $P = 0.90$
Mediastinitis	5	998	0.676 [0.307–1.491]	0.33	$I^2 = 0$, $P = 0.87$
Atrial fibrillation	4	579	1.511 [0.994–2.298]	0.054	$I^2 = 61.63$, $P = 0.05$
Prolonged ventilation	3	675	0.527 [0.354–0.786]	0.002	$I^2 = 0$, $P = 0.63$
No. of distal anastomosis	9	1604	−0.064 [−0.128–0.001]	0.053	$I^2 = 89.62$, $P < 0.001$
Incomplete revascularization	5	877	2.437 [1.611–3.687]	<0.001	$I^2 = 61.57$, $P = 0.034$

CI: confidence interval; HD: haemodialysis; OR: odds ratio; WMD: weighted mean difference.

Renal failure requiring haemodialysis

A total of 1076 patients were included from eight studies [8, 9, 12, 15, 16, 21], which reported the incidence of postoperative renal failure requiring haemodialysis. The incidence of renal failure was significantly lower in the ON-BH CABG group than in the conventional CABG in the fixed-effects model (OR 0.362; 95% CI 0.209–0.626; $P < 0.001$; Fig. 3B). No significant heterogeneity was observed in included studies (Cochrane $Q = 5.39$, $I^2 = 7.20\%$, $P = 0.37$). Begg's and Egger's tests showed no significant potential

Study or Subgroup	Events / Total		Statistics for each study			
	ON-BH	Conventional	Odds ratio	Lower limit	Upper limit	p-Value
Prifti 2000	7 / 107	19 / 191	0.634	0.257	1.560	0.321
Kim 2001	0 / 19	2 / 65	0.651	0.030	14.149	0.785
Uva 2004	2 / 47	1 / 66	2.889	0.254	32.826	0.392
Izumi 2006	2 / 15	5 / 16	0.338	0.055	2.101	0.245
Mizutani 2007	3 / 114	11 / 114	0.253	0.069	0.933	0.039
Sabban 2007	2 / 33	3 / 73	1.505	0.239	9.464	0.663
Pegg 2008	1 / 25	0 / 25	3.122	0.121	80.391	0.492
Lin 2010	10 / 132	11 / 99	0.656	0.267	1.612	0.358
Munos 2011	1 / 51	6 / 106	0.333	0.039	2.845	0.315
Tsai 2012	2 / 48	7 / 82	0.466	0.093	2.339	0.354
Takami 2012	6 / 31	7 / 55	1.646	0.499	5.425	0.413
Erkut 2013	2 / 65	14 / 66	0.118	0.026	0.543	0.006
Afrasiabirad 2015	5 / 157	14 / 157	0.336	0.118	0.957	0.041
	43 / 844	100 / 1115	0.553	0.376	0.815	0.003

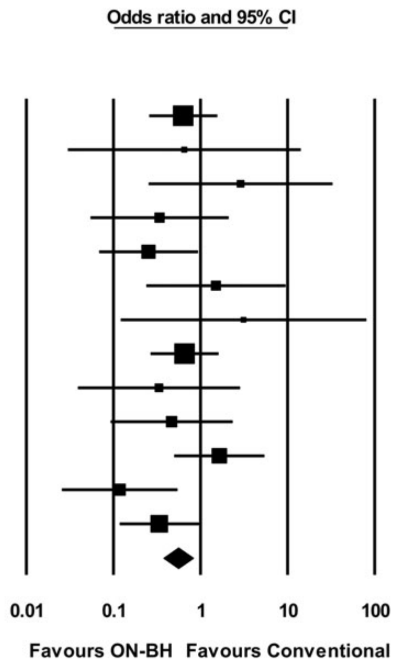

Figure 1: Forest plot of the odds ratios for early mortality in patients undergoing on-pump beating-heart versus conventional coronary artery bypass grafting. CI: confidence interval; ON-BH: on-pump beating-heart.

Study or Subgroup	Events / Total		Statistics for each study			
	ON-BH	Conventional	Odds ratio	Lower limit	Upper limit	p-Value
Erkut 2013	2 / 65	4 / 66	0.492	0.087	2.784	0.423
Kim 2001	0 / 19	2 / 65	0.651	0.030	14.149	0.785
Lin 2010	6 / 132	5 / 99	0.895	0.265	3.022	0.858
Mizutani 2007	3 / 114	8 / 114	0.358	0.093	1.386	0.137
Munos 2011	0 / 51	4 / 106	0.221	0.012	4.187	0.315
Pegg 2008	0 / 25	1 / 25	0.320	0.012	8.245	0.492
Prifti 2000	8 / 107	16 / 191	0.884	0.365	2.139	0.784
Sabban 2007	0 / 33	4 / 73	0.231	0.012	4.407	0.330
Tsai 2012	1 / 48	5 / 82	0.328	0.037	2.891	0.315
Uva 2004	2 / 47	2 / 66	1.422	0.193	10.474	0.730
	22 / 641	51 / 887	0.638	0.380	1.072	0.089

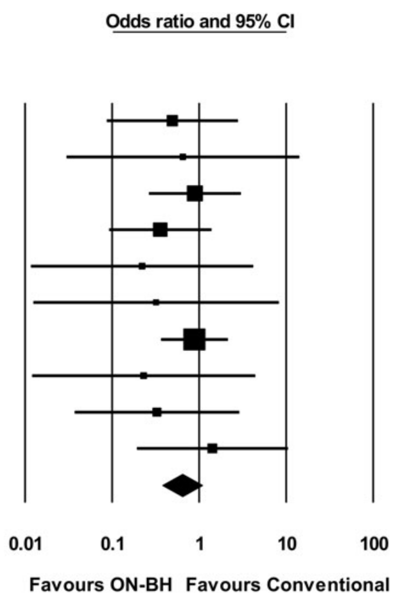

Figure 2: Forest plot of the odds ratios for stroke in patients undergoing on-pump beating-heart versus conventional coronary artery bypass grafting. CI: confidence interval; ON-BH: on-pump beating-heart.

publication bias within studies (Begg's test, $P = 0.26$; Egger's test, $P = 0.17$).

Low output syndrome

A total of 800 patients were included from six studies [9, 10, 16, 19, 21], which reported the incidence of low output syndrome (LOS). The incidence of LOS was significantly lower in ON-BH CABG when compared with conventional CABG in the fixed-effects model (OR 0.330; 95% CI 0.197–0.551; $P < 0.001$; Fig. 3C). No significant heterogeneity was observed in included studies (Cochran's Q test = 1.26, $I^2 = 0\%$, $P = 0.87$). Begg's and Egger's tests showed no significant potential publication bias within studies (Begg's test, $P = 1.00$; Egger's test, $P = 0.50$).

Other complications

There was no significant difference between the two techniques in the incidence of mediastinitis (five studies [8–10, 15, 16], fixed-effects OR 0.676; 95% CI 0.307–1.491; $P = 0.33$) and postoperative atrial fibrillation (four studies [8, 11, 16, 17], fixed-effects OR 1.511; 95% CI 0.994–2.298; $P = 0.054$). The ON-BH CABG technique was

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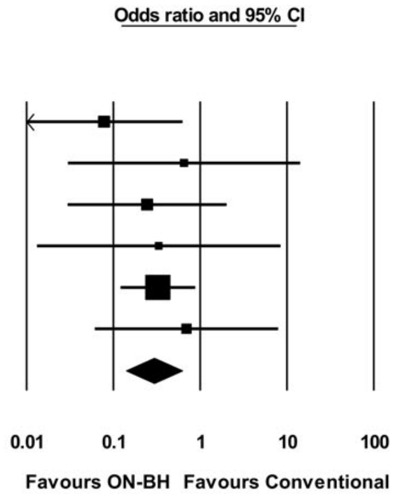
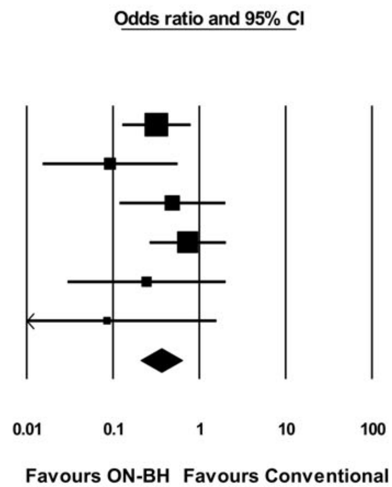
A

Study or Subgroup	Events / Total: ON-BH	Events / Total: Conventional	Odds ratio	Lower limit	Upper limit	p-Value
Erkut 2013	1 / 65	11 / 66	0.078	0.010	0.624	0.016
Kim 2001	0 / 19	2 / 65	0.651	0.030	14.149	0.785
Munos 2011	1 / 51	8 / 106	0.245	0.030	2.014	0.191
Narayan 2011	0 / 40	1 / 41	0.333	0.013	8.427	0.505
Prifti 2000	5 / 107	25 / 191	0.325	0.121	0.877	0.026
Uva 2004	1 / 47	2 / 66	0.696	0.061	7.903	0.770
	8 / 329	49 / 535	0.294	0.141	0.613	0.001



B

Study and Subgroup	Events / Total: ON-BH	Events / Total: Conventional	Odds ratio	Lower limit	Upper limit	p-Value
Prifti 2000	6 / 107	30 / 191	0.319	0.128	0.793	0.014
Izumi 2006	2 / 15	10 / 16	0.092	0.015	0.559	0.009
Mizutani 2007	3 / 114	6 / 114	0.486	0.119	1.995	0.317
Lin 2010	8 / 132	8 / 99	0.734	0.266	2.028	0.551
Munos 2011	1 / 51	8 / 106	0.245	0.030	2.014	0.191
Erkut 2013	0 / 65	5 / 66	0.085	0.005	1.576	0.098
	20 / 484	67 / 592	0.362	0.209	0.626	0.000



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Study or Subgroup	Events / Total: ON-BH	Events / Total: Conventional	Odds ratio	Lower limit	Upper limit	p-Value
Prifti 2000	12 / 107	46 / 191	0.398	0.201	0.791	0.009
Kim 2001	0 / 19	3 / 65	0.458	0.023	9.256	0.611
Munos 2011	1 / 51	10 / 106	0.192	0.024	1.543	0.121
Tsai 2012	3 / 48	13 / 82	0.354	0.095	1.312	0.120
Erkut 2013	4 / 65	16 / 66	0.205	0.064	0.652	0.007
	20 / 290	88 / 510	0.330	0.197	0.551	0.000

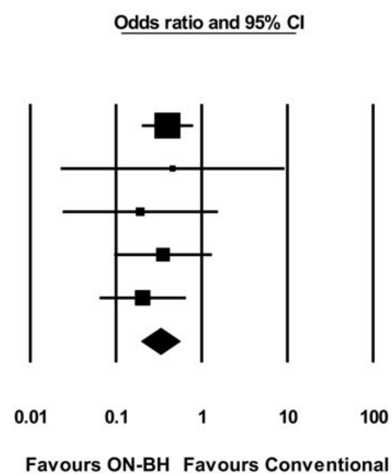


Figure 3: Forest plots of odds ratios for postoperative morbidity in patients undergoing on-pump beating-heart versus conventional coronary artery bypass grafting. (**A**) Myocardial infarction, (**B**) renal failure requiring haemodialysis, (**C**) low output syndrome (LOS). CI: confidence interval; ON-BH: on-pump beating-heart.

associated with significantly lower incidence of prolonged ventilation in the fixed-effects model (three studies [15, 19, 22], OR 0.527; 95% CI 0.354–0.786; $P = 0.002$, Q test = 0.94, $I^2 = 0\%$, P for heterogeneity = 0.63) and reoperation for bleeding (six studies [9, 10, 15, 16, 19, 21], fixed-effects OR 0.532; 95% CI 0.304–0.932; $P = 0.027$, Q test = 1.61, $I^2 = 0\%$, P for heterogeneity = 0.90).

Number of distal anastomoses and incomplete revascularization

The meta-analysis of nine studies that reported the number of distal anastomoses [8–10, 12, 15, 16, 19, 21, 22] showed that the ON-BH CABG technique was not associated with a significantly lower number of distal anastomoses (in fixed-effects model WMD −0.064, 95% CI −0.128 to 0.001, $P = 0.053$; in the random-effects model WMD −0.118, 95% CI −0.341 to 0.105, $P = 0.30$; Fig. 4A). There was significant heterogeneity within studies (Cochran's Q test = 77.10, $I^2 = 89.62\%$, $P < 0.001$). To evaluate the sensitivity of this meta-analysis, a one-study-removed meta-analysis was performed. The analysis showed that several studies [8, 9, 15] had a strong influence on the overall result of the meta-analysis (Fig. 4B).

Five studies reported the incidence of incomplete revascularization [8, 15, 16, 19, 21]. The incidence of incomplete revascularization was significantly greater in the ON-BH CABG group when compared with conventional CABG in the fixed-effects model (OR 2.437; 95% CI 1.611–3.687; $P < 0.001$; Fig. 5A). However, significant heterogeneity was observed in included studies (Cochran's Q test = 10.41, $I^2 = 61.57\%$, $P = 0.034$) and, in the random-effects model, there was no significant difference in the incidence of

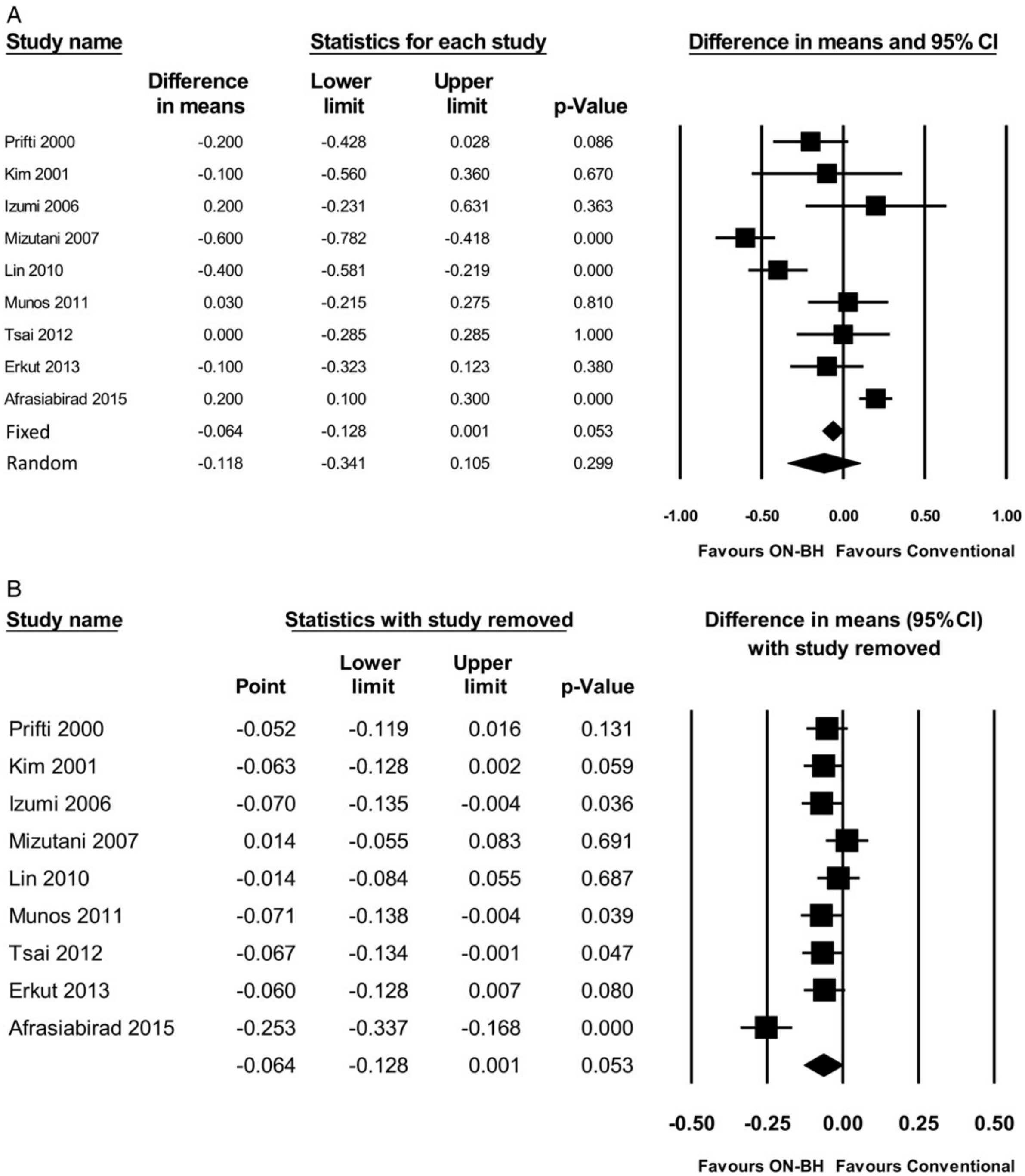
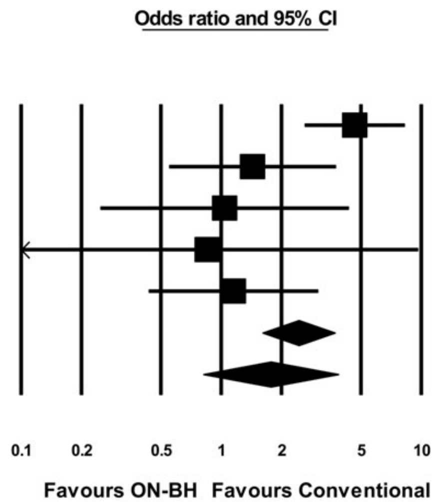


Figure 4: Weighted mean difference in the number of distal anastomoses in patients undergoing on-pump beating-heart versus conventional coronary artery bypass grafting. (**A**) Forest plot of the weighted mean difference in both fixed- and random-effects models. (**B**) One-study-removed meta-analysis. CI: confidence interval; ON-BH: on-pump beating-heart.

A

Study and Subgroup	Events / Total ON-BH	Events / Total Conventional	Odds ratio	Lower limit	Upper limit	p-Value
Mizutani 2007	66 / 114	26 / 114	4.654	2.621	8.263	0.000
Lin 2010	13 / 132	7 / 99	1.436	0.551	3.743	0.459
Munos 2011	3 / 51	6 / 106	1.042	0.250	4.344	0.955
Tsai 2012	1 / 48	2 / 82	0.851	0.075	9.641	0.896
Erkut 2013	10 / 65	9 / 66	1.152	0.435	3.049	0.776
Fixed	93 / 410	50 / 467	2.437	1.611	3.687	0.000
Random	93 / 410	50 / 467	1.768	0.815	3.836	0.150



B

Study and Subgroup	Point	Lower limit	Upper limit	p-Value
Mizutani 2007	1.210	0.666	2.199	0.531
Lin 2010	2.752	1.739	4.354	0.000
Munos 2011	2.635	1.710	4.060	0.000
Tsai 2012	2.515	1.653	3.828	0.000
Erkut 2013	2.875	1.820	4.542	0.000
	2.437	1.611	3.687	0.000

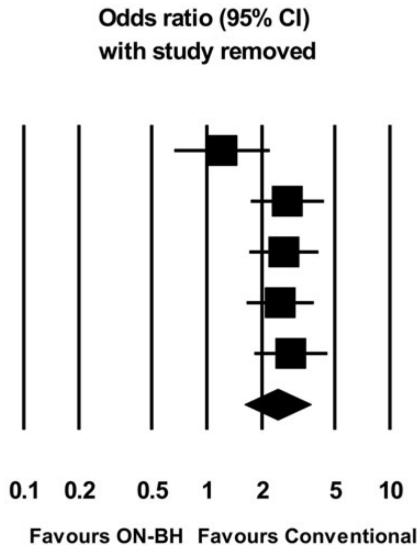


Figure 5: Meta-analysis for the incidence of incomplete revascularization in patients undergoing on-pump beating-heart versus conventional coronary artery bypass grafting. (**A**) Forest plot of the odds ratio in both fixed- and random-effects models. (**B**) One-study-removed meta-analysis. CI: confidence interval; ON-BH: on-pump beating-heart.

incomplete revascularization (OR 1.768; 95% CI 0.815–3.836; $P = 0.15$). The one-study-removed meta-analysis showed that there was one study that reported a very high incidence of incomplete revascularization in the ON-BH CABG group [8] and had a strong influence on the overall result of the meta-analysis (Fig. 5B).

DISCUSSION

This study has shown that an on-pump beating-heart technique provides a significantly lower early morbidity and mortality than conventional arrested heart CABG. In addition, meta-analysis and additional sensitivity analysis have shown that ON-BH CABG involves slightly fewer distal anastomoses, but does not result in a significantly higher incidence of incomplete revascularization.

The fixed-effects meta-analysis for early mortality showed that the risk of early mortality was 45% lower with ON-BH CABG than with conventional CABG (OR 0.553; 95% CI 0.376–0.815; $P = 0.003$). There was minimal heterogeneity in the included studies ($I^2 = 15.37\%$, $P = 0.29$) and no evidence for significant potential publication bias. Also, sensitivity analysis, including random-effects meta-analysis (OR 0.552; 95% CI 0.356–0.856; $P = 0.008$), and a one-study-removed meta-analysis support the validity of the primary analysis for early mortality. Among the included studies, seven studies focused on high-risk populations (patients with low EF, patients with acute coronary syndrome, patients on chronic haemodialysis and patients with other risk factors) [9, 12, 16, 19–22] and another three studies included many emergency patients (40–65.9%) [8, 14, 17]. Consequently, the meta-analysis data demonstrate the clinical benefit of ON-BH CABG particularly in high-risk patients.

Our analysis has also revealed that ON-BH CABG is associated with significantly lower perioperative morbidity. There was a significantly lower incidence of perioperative LOS and myocardial infarction in the ON-BH CABG group. By avoiding cardioplegic cardiac arrest and preserving native coronary artery blood flow, the ON-BH CABG technique could prevent global myocardial ischaemia and reduce myocardial injury [25]. However, to facilitate this advantage of ON-BH CABG, we have to understand the pitfalls of this technique. Pegg *et al.* [14] have reported a higher incidence of irreversible myocardial injury in ON-BH CABG compared with conventional CABG. This result might be explained by the relatively low mean arterial pressure (50–60 mmHg) during ON-BH CABG in their series [14] because another study, with higher mean arterial pressures (70–80 mmHg), reported no significant difference in myocardial injury [17]. Comparison of these two studies may suggest that maintaining a high mean arterial pressure is important in achieving improved myocardial perfusion during ON-BH CABG. Also, Mizutani *et al.* [8] reported that left ventricular venting was associated with high mortality and a high incidence of LOS in their early series. Maintaining adequate cardiac output and systemic perfusion pressure is, therefore, important in preserving cardiac function. ON-BH CABG is more technically demanding than conventional CABG. Therefore, the difference in experience of surgeons should be considered in the comparison of incidence of perioperative morbidity. Fabricius *et al.* [26], in their study performing routine control angiography for patients with perioperative myocardial ischaemia, reported that the majority of perioperative ischaemia was explained by pathomorphological findings, such as incorrect anastomosis, graft stenosis and incomplete revascularization. Thus, the difference in the experience of surgeons should be considered especially in the interpretation of the difference of perioperative myocardial infarction between the two techniques.

In this study, the incidence of prolonged ventilation was significantly lower in patients in the ON-BH CABG group. Massoudy *et al.* [27] reported that the continuous perfusion of the lungs with the Drew technique of bilateral extracorporeal circulation significantly reduced the inflammatory responses from the pulmonary vascular bed. Taking this evidence into consideration, the improved pulmonary function after ON-BH CABG might be explained by the continuous perfusion of the lungs during CPB.

Our analysis has also shown that ON-BH CABG can have a significant renoprotective effect. A previously published meta-analysis that included 22 randomized controlled trials reported a significantly lower incidence of postoperative acute renal injury in off-pump CABG compared with on-pump CABG [28]. In the present study, although ON-BH CABG was performed with CPB support, the incidence of renal failure resulting in haemodialysis was significantly lower in the ON-BH CABG group. This finding may be explained by the renoprotective effect of the preserved systemic perfusion and pulsatility in the ON-BH CABG group.

There has been concern that the ON-BH CABG technique may make it difficult to achieve complete cardiac revascularization. The present study shows that the ON-BH CABG group is not associated with significantly fewer distal anastomoses (WMD −0.064, 95% CI −0.128 to 0.001, $P = 0.053$ in fixed-effects model; WMD −0.118, 95% CI −0.341 to 0.105, $P = 0.30$ in random-effects model). However, there was significant heterogeneity in the included studies, and a one-study-removed meta-analysis suggests that data from a single study, within several studies, may affect the overall result of the meta-analysis. Therefore, the result of this analysis of numbers of distal anastomoses should be interpreted with care. Our fixed-effects meta-analysis for the incidence of incomplete revascularization showed a significantly greater risk of incomplete revascularization in the ON-BH CABG group (OR 2.437; 95% CI 1.611–3.687; $P < 0.001$). However, this analysis showed that significant heterogeneity among included studies and the higher risk of incomplete revascularization in the ON-BH CABG group could not be confirmed in the random-effects model (OR 1.768; 95% CI 0.815–3.836; $P = 0.15$). Our sensitivity analysis with a one-study-removed meta-analysis revealed that the one study reported by Mizutani *et al.* [8] had a strong effect on the overall result of the fixed-effects meta-analysis. Mizutani *et al.* [8] reported that in their early series, the culprit lesion and jeopardized coronary vessel tended to be especially targeted in an emergency setting to reduce surgical intervention, and that the rate of complete revascularization in their later series was much greater. In summary, the current evidence derived from our meta-analysis has not indicated that the ON-BH CABG procedure has an adverse effect on the rate of complete cardiac revascularization.

Recent meta-analysis data have been published that do not support our findings regarding the survival benefits of ON-BH CABG [29]. Between the present study and the previous study by Chaudhry *et al.* [29], there are several differences in study design, which may account for the differences in the study findings. First, we excluded two studies [7, 18], in which ON-BH CABG was performed on <20% of patients undergoing on-pump CABG, because the huge difference between the two groups would make any comparison difficult. Secondly, although the previous study included reports in non-English languages [29], our study focused on English reports. Studies published in languages other than English tend to be more difficult to locate, which would make it more difficult to complete a comprehensive literature review. Even when limiting searches to English reports, it is still challenging to complete a systematic review. In fact, the meta-analysis by Chaudhry failed to include a study reported by Lin *et al.* [15]. Thirdly, the previous meta-analysis includes an inappropriate article investigating only patients who had developed postoperative myocardial infarction [24]. We therefore believe that, at the present time, we have conducted the most extensive and detailed systematic review and meta-analysis of this important cardiac surgical procedure and its early outcomes.

Several limitations exist concerning the present study. First, our analysis included data from observational studies, which have the potential for observer bias. Most of the included studies did not adopt risk-adjustment methods, such as randomization or propensity score matching. Although our sensitivity analyses did not overturn the results of the initial meta-analysis for early patient mortality, the results of this meta-analysis should still be interpreted carefully. Secondly, the present study focuses only on the early patient morbidity and mortality. Consequently, the long-term effect of slightly fewer distal anastomoses in the ON-BH CABG group was not assessed. Further studies are required to assess the effects of the ON-BH CABG technique on long-term clinical outcomes. Finally, the results of the present study may be influenced by publication bias in favour of the ON-BH CABG technique although the statistical tests for publication bias showed no significant evidence of this.

In conclusion, current evidence from comparative studies between ON-BH CABG and conventional CABG indicates that early morbidity and mortality are significantly lower with the ON-BH CABG technique, particularly in high-risk patient populations. The ON-BH CABG could be an attractive planned alternative for high-risk patient populations who are at higher risk of unplanned conversion from off-pump to on-pump CABG.

Conflict of interest: none declared.

REFERENCES

[1] Polomsky M, He X, O'Brien SM, Puskas JD. Outcomes of off-pump versus on-pump coronary artery bypass grafting: impact of preoperative risk. J Thorac Cardiovasc Surg 2013;145:1193–8.

[2] Keeling WB, Williams ML, Slaughter MS, Zhao Y, Puskas JD. Off-pump and on-pump coronary revascularization in patients with low ejection fraction: a report from the Society of Thoracic Surgeons National Database. Ann Thorac Surg 2013;96:83–9.

[3] Chawla LS, Zhao Y, Lough FC, Schroeder E, Seneff MG, Brennan JM. Off-pump versus on-pump coronary artery bypass grafting outcomes stratified by preoperative renal function. J Am Soc Nephrol 2012;23:1389–97.

[4] Masuda M, Kuwano H, Okumura M, Amano J, Arai H, Endo S *et al*. Thoracic and cardiovascular surgery in Japan during 2012. Gen Thorac Cardiovasc Surg 2014;62:734–64.

[5] Mukherjee D, Ashrafian H, Kourliouros A, Ahmed K, Darzi A, Athanasiou T. Intra-operative conversion is a cause of masked mortality in off-pump coronary artery bypass: a meta-analysis. Eur J Cardiothorac Surg 2012;41: 291–9.

[6] Kolh P, Windecker S, Alfonso F, Collet JP, Cremer J, Falk V *et al*. 2014 ESC/ EACTS guidelines on myocardial revascularization. Eur J Cardiothorac Surg 2014;46:517–92.

[7] Edgerton JR, Herbert MA, Jones KK, Prince SL, Acuff T, Carter D *et al*. On-pump beating heart surgery offers an alternative for unstable patients undergoing coronary artery bypass grafting. Heart Surg Forum 2004;7: 8–15.

[8] Mizutani S, Matsuura A, Miyahara K, Eda T, Kawamura A, Yoshioka T *et al*. On-pump beating-heart coronary artery bypass: a propensity matched analysis. Ann Thorac Surg 2007;83:1368–73.

[9] Prifti E, Bonacchi M, Giunti G, Frati G, Proietti P, Leacche M *et al*. Does on-pump/beating-heart coronary artery bypass grafting offer better outcome in end-stage coronary artery disease patients? J Cardiac Surg 2000;15:403–10.

[10] Kim KB, Lim C, Lee C, Chae IH, Oh BH, Lee MM *et al*. Off-pump coronary artery bypass may decrease the patency of saphenous vein grafts. Ann Thorac Surg 2001;72:S1033–37.

[11] Uva MS, Rodrigues V, Monteiro N, Pereira F, Bervens D, Caria R *et al*. Coronary surgery: which method to use? Rev Port Cardiol 2004;23: 517–30.

[12] Izumi Y, Magishi K, Ishikawa N, Kimura F. On-pump beating-heart coronary artery bypass grafting for acute myocardial infarction. Ann Thorac Surg 2006;81:573–6.

[13] Sabban MA, Jalal A, Bakir BM, Alshaer AA, Abbas OA, Abdal-Aal MM *et al*. Comparison of neurological outcomes in patients undergoing conventional coronary artery bypass grafting, on-pump beating heart coronary bypass, and off-pump coronary bypass. Neurosciences (Riyadh) 2007;12: 35–41.

[14] Pegg TJ, Selvanayagam JB, Francis JM, Karamitsos TD, Maunsell Z, Yu LM *et al*. A randomized trial of on-pump beating heart and conventional cardioplegic arrest in coronary artery bypass surgery patients with impaired left ventricular function using cardiac magnetic resonance imaging and biochemical markers. Circulation 2008;118:2130–8.

[15] Lin CC, Wu MY, Tsai FC, Chu JJ, Chang YS, Haung YK *et al*. Prediction of major complications after isolated coronary artery bypass grafting: the CGMH experience. Chang Gung Med J 2010;33:370–9.

[16] Munos E, Calderon J, Pillois X, Lafitte S, Ouattara A, Labrousse L *et al*. Beating-heart coronary artery bypass surgery with the help of mini extracorporeal circulation for very high-risk patients. Perfusion 2011;26: 123–31.

[17] Narayan P, Rogers CA, Bayliss KM, Rahaman NC, Panayiotou N, Angelini GD *et al*. On-pump coronary surgery with and without cardioplegic arrest: comparison of inflammation, myocardial, cerebral and renal injury and early and late health outcome in a single-centre randomised controlled trial. Eur J Cardiothorac Surg 2011;39:675–83.

[18] Tarakji KG, Sabik JF, Bhudia SK, Batizy LH, Blackstone EH. Temporal onset, risk factors, and outcomes associated with stroke after coronary artery bypass grafting. JAMA 2011;305:381–90.

[19] Tsai YT, Lin FY, Lai CH, Lin YC, Lin CY, Tsai CS. On-pump beating-heart coronary artery bypass provides efficacious short-and long-term outcomes in hemodialysis patients. Nephrol Dial Transplant 2012;27:2059–65.

[20] Takami Y, Tajima K, Kato W, Fujii K, Hibino M, Munakata H *et al*. Predictors for early and late outcomes after coronary artery bypass grafting in hemodialysis patients. Ann Thorac Surg 2012;94:1940–5.

[21] Erkut B, Dag O, Kaygin MA, Senocak M, Limandal HK, Arslan U *et al*. On-pump beating-heart versus conventional coronary artery bypass grafting for revascularization in patients with severe left ventricular dysfunction: early outcomes. Can J Surg 2013;56:398–404.

[22] Afrasiabirad A, Safaie N, Montazergaem H. On-pump beating coronary artery bypass in high risk coronary patients. Iran J Med Sci 2015;40:40–4.

[23] Miyahara K, Matsuura A, Takemura H, Saito S, Sawaki S, Yoshioka T *et al*. On-pump beating-heart coronary artery bypass grafting after acute myocardial infarction has lower mortality and morbidity. J Thorac Cardiovasc Surg 2008;135:521–6.

[24] Borowski A, Korb H. Myocardial infarction in coronary bypass surgery using on-pump, beating heart technique with pressure-and volume-controlled coronary perfusion. J Cardiac Surg 2002;17:272–8.

[25] Perrault LP, Menasché P, Peynet J, Faris B, Bel A, de Chaumaray T *et al*. On-pump, beating-heart coronary artery operations in high-risk patients: an acceptable trade-off? Ann Thorac Surg 1997;64:1368–73.

[26] Fabricius AM, Gerber W, Hanke M, Garbade J, Autschbach R, Mohr FW. Early angiographic control of perioperative ischemia after coronary artery bypass grafting. Eur J Cardiothorac Surg 2001;19:853–8.

[27] Massoudy P, Zahler S, Tassani P, Becker BF, Richter JA, Pfauder M *et al*. Reduction of pro-inflammatory cytokine levels and cellular adhesion in CABG procedures with separated pulmonary and systemic extracorporeal circulation without an oxygenator. Eur J Cardiothorac Surg 2000;17: 729–36.

[28] Seabra VF, Alobaidi S, Balk EM, Poon AH, Jaber BL. Off-pump coronary artery bypass surgery and acute kidney injury: a meta-analysis of randomized controlled trials. Clin J Am Soc Nephrol 2010;5:1734–44.

[29] Chaudhry UAR, Harling L, Sepehripour AH, Stavridis G, Kokotsakis J, Ashrafian H *et al*. Beating-heart versus conventional on-pump coronary artery bypass grafting: a meta-analysis of clinical outcomes. Ann Thorac Surg 2015;100:2251–60.