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REVIEW ARTICLE

Off-pump coronary revascularization: A potential benefit for female patients?

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Abstract Coronary artery disease is one of the leading causes of illness for both men and women. However, women are 3 times more likely to die for coronary artery disease as they are of breast cancer. There are an increasing prevalence of coronary artery disease in women and thus facing the need for surgical revascularization. It has long being accepted that women carry a high risk of coronary surgery than men. Many investigators have suggested that female itself is predictive of poor outcome after on pump coronary surgery. We thought to search the litlature to investigate whether women who undergo off-pump surgery receive any benefits compared with women undergoing on-pump surgery.

Contents

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1. Introduction

Coronary artery disease (CAD) is one of the leading causes of morbidity and mortality for both men and women. It is a costly disease in terms of both health care resources and patient lives. Approximately 250,000 women die each year in the United States alone, and women are 3 times as likely to die of CAD as they are to die of breast cancer (American Heart Association). This reflects the increasing prevalence of women having ischemic heart disease, and thus facing the need of surgical intervention. Revascularization is one of the most effective tools in the management of symptomatic CAD refractory to medical therapy, however, the issue of whether there are disparities in the outcome of coronary revascularization between women and men, in particular coronary artery bypass graft (CABG) surgery, has been the object of intense debate in the past 10–15 years. Surgical literature since 1970s has cited higher mortality rates among women undergoing CABG using cardiopulmonary bypass (CPB) than men Edwards et al., 1998; Jacobs et al., 1998; O'Rourke et al., 2001; Vaccarino et al., 2002, 2003; O'Connor et al., 2002; Koch et al., 2003; Christakis et al., 1995; Woods et al., 2003; Lawton et al., 2003. Explanations for this observation vary widely. Many investigators have suggested that female gender itself is predictive of poor peri-operative results, whereas many other researchers argue that once co-morbid conditions and smaller body surface area (BSA) or body mass index, surrogates for smaller coronary arteries, are taken into account, female gender ceases to be an independent predictor of outcome. Virtually all investigators, however, agree that women, when compared with men, present at a more acute and symptomatic stage of their disease, are older at presentation, have more severe co-morbidities (diabetes, renal insufficiency, hypertension, and left ventricular dysfunction), and worse functional status at the time of operation (O'Rourke et al., 2001; Vaccarino et al., 2002, 2003; O'Connor et al., 2002). Not only immediate postoperative mortality is increased in women, but also postoperative morbidity is higher. The rate of postoperative acute myocardial infarction is also higher in women as compared with men (Woodfield et al., 1997; Edmund, 1996; Loop et al., 1983).

Over the last decade, cardiac surgeons advocated the development of minimally invasive CABG surgery and modified the techniques of CPB by introducing off-pump CABG (OPCAB). This technique is widely used and has reduced morbidity and complication rates (King et al., 1997). OPCAB has also been shown to reduce postoperative morbidity and mortality in selected high-risk patient groups including those with renal disease, poor ventricular function, previous CABG and in the elderly (Wan et al., 2004). Women are considered a high-risk group in conventional CABG as compared with equally matched male patients (Edwards et al., 1998; O'Connor et al., 1993). Therefore, it is important to investigate whether women who undergo off-pump surgery receive any benefits compared with women who undergo on-pump surgery. In this review, the findings of the most recent studies are being compared and are interpreted in an attempt to define the effectiveness of OPCAB in female patients.

2. Study analysis and comments

Only recently have women been included in sufficient numbers in clinical trials and databases (Yusuf et al., 1994; Solomon and Gersh, 1998; American Heart Association, 2002), in addition to the fact that only 30% of all CABG operations are performed on women, and fewer women than men are referred for operation, resulting in small sample sizes (STS National Database Committee et al., 2002). Therefore, a few articles have been published. By searching the Medline, Embase, Cochrane database of systematic reviews, three articles which focused specifically on the comparison of peri-operative outcomes in the female population were identified.

3. Study design

The three articles were published in 2002, 2004, and 2005, respectively (Table 1). They were all retrospective studies on comparing the short-term and long-term safety, benefits and efficacy of OPCAB surgery with on-pump CABG in women. Jan et al. included 2182 consecutive female patients undergoing CABG either with or without CPB in the Toronto General

Table 1 Characteristics of studies comparing OPCAB and CABG in female patients.

Authors	Study design	Patients	OPCAB (%)	CABG (%)
Philip et al. (2002)	Retrospective (January 1998–June 2001)	16,871	14,240 (84.4)	2631 (15.6)
Michael et al. (2004)	Retrospective with propensity score computer-matching (January 1998–March 2002)	7376	3688 (50)	3688 (50)
Jan et al. (2005)	Retrospective (April 1996–August 2001)	2182	2030 (93)	152 (7)

Hospital. Philip et al. and Michael et al. recruited the patients in the HCA Case mix Database which is a comprehensive database containing patient, clinical, and outcome data on all cardiovascular patients at all HCA hospitals. These two studies based on the same database, but Michael et al. analyzed the data with the technique of propensity score computer-matching of pre-operative risk factors (Mack et al., 2004) in order to obtain a valid comparison between the two treatment groups by minimizing the effect of selection bias on outcomes.

Retrospective analysis of large databases has shown a statistically significant benefit in operative mortality with the use of OPCAB (Mack, 2004; Mack et al., 2004; Society of Thoracic Surgeons, 2003). However, all these analyses are subject to the selection bias that cannot be accounted for in any retrospective series. In an attempt to control for selection bias propensity score comparisons were used to create cohorts with equal pre-operative risk factors.

In comparing females receiving on-pump vs. off-pump CABG, one group is chosen as the treatment group (on-pump), and the other is the control, then the propensity score is simply the probability that a patient given her particular set of characteristics received on-pump CABG. A group of patients with the same propensity score are thus equally likely to have been assigned to OPCAB. The effect is the same as if they had been randomly allocated to either treatment regardless of which treatment they actually received. This matching technique has been described as ''randomization after the fact''. Thus, the comment made by Michael et al. attained comparatively higher level of evidence.

4. Comparison of study characteristics

4.1. Pre-operative variables

Because no randomized trial of OPCAB vs. on-pump CABG in women exists, these three studies retrospectively reviewed CABG outcomes in women in the hospital database. Compared with randomized trials, which aim at minimizing the confounding factors by strictly controlling variables between the test group and the control group, retrospective studies are weak in comparability as confounding factors may skew the true effect of the intervention being tested.

Table 2 shows the pre-operative characteristics of the patients undergoing either OPCAB or off-pump CABG. In Philip et al., significant differences (<0.05) were established by comparing the underlying characteristics between the two groups. These factors influence eventual outcomes of the patients, and they must be taken into account when evaluating the OPCAB vs. CABG in women. In many previous articles, individual factors, including age, smoking history, pre-operative medical conditions, ventricular function, or intra-operative variables, such as the number of vessels bypassed, are previously found to be important determinants in the peri-operative outcomes of the patients (Hoff et al., 2002; Hirose et al., 2001; Arom et al., 2000; Vassiliades et al., 2002; Mishra et al., 2003; Fiore et al., 2005).

One of the most debatable confounders is the age of the patient. Patients of advanced age are known to be at increased risk for morbidity and mortality after bypass surgery (Hirose et al., 2001; Hoff et al., 2002; Stamou et al., 2000; Curtis et al., 1994; Yim et al., 2000).

The use of propensity analysis by Michael et al. eliminated this age bias in that study. By chance Jan et al. had no statistically significant difference in age in their cohort, Philip et al., however, reported that their percentage of patients >65 years undergoing CABG was significantly higher (70.49 vs. 65.22).

In recent few years, OPCAB is becoming increasingly popular, as in most patients it allows complete myocardial revascularization with excellent short-term results. The hemodynamic modifications induced by heart displacement are usually transient and reversible, and the technique seems to be safe even in patients with poor left ventricular function, improving myocardial preservation and leading to successful results (Fiore et al., 2005). However, some patients develop significant intra-operative hemodynamic instability requiring intra-aortic balloon counter pulsation (IABP) or cardiopulmonary bypass (CPB) Vassiliades et al., 2002. Recently Mishra

Table 2 Comparative patient pre-operative characteristics.

STUDY	Philip et al.			Michael et al.			Jan et al.		
Patient characteristic	OPCAB	CABG	*p* value	OPCAB	CABG	*p* value	OPCAB	CABG	*p* value
Age	68.59	69.47	<0.001	68.62	68.90	<0.001	67.90	68.10	0.72
% Age $>$ 65	65.22	70.49	<0.001	33.95 ($>$75 y.o.)	35.44 ($>$75 y.o.)	0.179	43.4 (70–80 y.o.)	44.0 (70–80 y.o.)	0.933
% Smoker	14.37	12.78	0.026	13.72	12.61	0.158	NIL	NIL	NIL
% Insulin-dependent diabetes	7.41	9.05	0.006	6.81	8.16	0.027	55.3	55.9	0.798
% Non-insulin-dependent diabetes	27.52	30.74	0.001	27.7	26.0	0.093			
% Hypertension	68.08	71.06	0.019	66.6	69.5	0.009	82.2	78.3	0.353
% Acute MI	21.4	27.1	<0.001	22.8	22.5	0.76	45.1	42.1	0.035
% CHF	17.56	20.68	<0.001	16.43	16.13	0.729	NIL	NIL	NIL
% S/P CABG	2.62	1.96	0.028	2.01	2.09	0.805	NIL	NIL	NIL
% S/P PTCA	15.66	11.34	<0.001	13.91	12.28	0.038	NIL	NIL	NIL
% PVD	11.21	12.89	0.018	11.50	10.17	0.066	19.1	19.7	0.831
% Conduction disorder	33.18	35.72	0.012	33.03	34.52	0.176	NIL	NIL	NIL
LVEF	NIL	NIL	NIL	NIL	NIL	NIL	0.527	0.584	<0.0001
Urgent operation	NIL	NIL	NIL	NIL	NIL	NIL	24.5	17.1	0.039
Pre-operative cardiogenic shock	1.14	1.69	0.041	1.27	1.41	0.613	8.1	13.1	0.048

Table 3 Comparative peri-operative adverse outcomes in off-pump vs. on-pump CABG female patients.

STUDY	Philip et al.			Michael et al.			Jan et al.		
Outcomes	OPCAB	CABG	*p* value	OPCAB	CABG	*p* value	OPCAB	CABG	*p* value
Mortality (%)	3.12	3.9	0.052	3.17	3.88	0.101	0.7	5.5	0.004
Procedure variables									
% Veins utilized	77.69	96.97	<0.001	87.47	90.75	<0.001	NIL	NIL	NIL
% Arteries utilized	83.01	76.00	<0.001	81.05	72.29	<0.001	NIL	NIL	NIL
No. of vessels bypassed	2.44	3.28	<0.001	2.7	2.7	0.973	1.6	2.5	<0.0001
Procedure complications									
Major									
% Shock (hemorrhage)	2.62	3.92	0.001	2.68	3.61	0.023	77	54.8	<0.0001
% Neurologic complications	1.52	1.73	0.43	1.03	1.79	0.006	1.3 (stroke)	3.4 (stroke)	0.233 (stroke)
Minor									
% Respiratory complications	2.28	3.55	0.001	2.47	3.61	0.004	3.3	8.7	0.015
% ARDS	3.31	5.05	0.000	3.31	4.64	0.003	NIL	NIL	NIL
% Renal complications	0.8	0.95	0.434	NIL	NIL	NIL	2.6	8.0	0.011
% Dialysis	NIL	NIL	NIL	NIL	NIL	NIL	0.7	4.8	0.013
% RBC transfusion > 1000 ml	NIL	NIL	NIL	NIL	NIL	NIL	0.7	3.8	0.04
Hospital characteristics									
Admission-surgery LOS	2.36	2.32	0.478	2.35	2.15	0.001	NIL	NIL	NIL
Surgery-discharge LOS	6.45	7.28	<0.001	6.72	6.89	0.230	NIL	NIL	NIL
Admission-discharge	8.78	9.56	<0.001	9.06	8.93	0.310	NIL	NIL	NIL
Mean hospital CABG volume	34.62	182.56	<0.001	45.53	46.68	0.892	NIL	NIL	NIL

et al. Mishra et al. (2003) identified very low ejection fraction (<25%), recent myocardial infarction (<1 month), congestive heart failure and pre-operative hemodynamic instability as risk factors for cardio circulatory collapse during OPCAB.

Other significant differences in pre-operative characteristics of the two groups are the percentage of patients with prior acute myocardial infarction and cardiogenic shock. These two pre-operative events are conspicuously adverse to the hemodynamic stability of the patients who then underwent major cardiac operation. This predisposes any form of surgery to technical difficulty and poorer operative outcomes.

Despite the propensity-score matching, some of the patients' variables were significantly different in the study of Michael et al. Proportion of patients with the history of insulin-dependent diabetes (IDDM) was significantly higher in on-pump CABG than that in OPCAB (8.16% vs. 6.81%), $p = 0.027$ Similar differences were found by Philp et al. with the percentage of IDDM patient undergoing CABG being higher (9.05% vs. 7.41%) $p = 0.006$.

A recent study showed that insulin-dependent diabetes has a significant impact on in-hospital morbidity after on-pump CABG. Although diabetic patients are not at increased risk of in-hospital mortality, longevity is significantly decreased during a five-year follow-up period (Kubal et al., 2005). Long-term surgical outcomes may be affected by this factor.

4.2. Intra-operative variables

Regarding the intra-operative characteristics which are presented in Table 3, Hravnak and his colleagues have proposed that the predictors of new-onset atrial fibrillation included age ($p = 0.0004$), number of vessels bypassed ($p = 0.013$), vessel location (diagonal [$p < 0.003$] or posterior descending artery [$p < 0.001$]), and net fluid balance on the operative day ($p = 0.015$) Hravnak et al., 2002.

The number of vessels bypassed in the on-pump CABG group was significantly higher than that in the OPCAB group in the studies of Philip et al. (3.28:2.44, $p < 0.001$) and Jan et al. (2.5:1.6, $p < 0.0001$). Obviously, it would also play a role in the final outcomes of the operation. On the other hand, the patients in both groups in the study of Michael et al. have the equal number of vessels bypassed (2.7 vessels). This would make the comparison of operative outcomes of the two groups fairer as two groups are equal in baseline characteristics. This is the art that "randomization after the fact" yields a better controlled study than the retrospective studies.

4.3. Postoperative outcomes

4.3.1. Mortality rates

According to the postoperative outcomes given in Table 3, both Philip et al. and Michael et al. have reported decreased, but not statistically significant, mortality differences in women undergoing CABG by off-pump compared with women undergoing CABG by on-pump.

Women consistently have a higher operative mortality than men undergoing CABG surgery. In the Society of Thoracic Surgeons National Cardiac Database, since 1994, women who comprised 28% of the entrants had a significantly higher operative mortality than men (4.5% vs. 2.6%, $p < 0.001$) (Society of Thoracic Surgeons, 2003). It has been an ongoing debate on whether female gender is an independent risk factor of adverse outcome or whether there are other cofactors more commonly associated with women that raise the risk. Edwards et al. reported from huge STS database ($n = 344{,}913$, 28% women) that female gender was an independent predictor of operative mortality except in very high-risk patients (Edwards et al., 1998), and in another analysis from the same database ($n = 416{,}347$, 32% women), Hogue et al. reported higher mortality and other complications in women (Edwards et al., 1998).

On the other hand, female gender was not a predictor of mortality in the studies from Hogue et al. (2001) (n = 4820, 19% women) and Abramov et al. (2000) (n = 1487, 24% women) after adjustment for other factors. Other possible reasons include women having a higher incidence of diabetes leading to increased complications (Mickleborough et al., 1995). Younger women have been demonstrated to have higher hospital mortality rates than men, especially when younger than 50 years of age (Vaccarino et al., 2002). Later presentation with urgent or emergent status is also a variable occurring more common in women, leading to higher complication rates (O'Rourke et al., 2001; O'Connor et al., 2002).

Although debate still exists, the European System for Cardiac Operative Risk Evaluation (Euro SCORE) has considered female gender as one of the risk factors in the patient-related factors in the evaluation of the operative risk of cardiac surgery. By elimination of CPB and its associated systemic inflammatory response, it was expected that early adverse outcomes could be decreased in OPCAB. Many retrospective studies have shown significant benefit in operative mortality with the use of OPCAB (Mack, 2004; Mack et al., 2004; Society of Thoracic Surgeons, 2003). However, these studies that supported the benefit of off-pump strategy were retrospective analysis which would inevitably lead to selection bias. With regard to this shortcoming, Michael et al. have utilized propensity-score matching to obtain comparable groups, thus the standards of randomized trial can be partially achieved.

4.3.2. Major procedure complications

Among the major complications of CABG, shock due to hemorrhage is relatively common. Patients who had off-pump CABG suffered from shock less frequently in the studies of Philip et al. (2.62 vs. 3.92, 0.001) and Michael et al. (2.68 vs. 3.61, 0.023). Szabo et al. (2002) have shown that there were no significant differences in the amount of blood loss among three risk groups of on-pump and off-pump patients, but overall blood loss per patient was higher in the on-pump patients. Arom and his colleagues suggested that these results were related to extracorporeal circulation and possibly to less heparin use in the OPCAB patients. Ascione and his coworkers (Arom et al., 2000) demonstrated increased red blood cell loss and higher red blood cell, platelet, and fresh frozen plasma transfusions in on-pump patients. Clinically adverse effects include lowered intravascular colloid oncotic pressure, release of vasoactive substances into plasma and platelet damage. CPB also causes systemic inflammatory through the activation of blood constituents. The vasoactive substances, enzymes, and micro emboli produced by the activation of these protein systems and the cells are the cause of morbidity associated with CPB. The activation of platelets reduced platelet numbers and this causes prolonged postoperative bleeding times (Ascione et al., 2001). O'Connor et al. (1993) reported that one of the primary causes of in-patient mortality is hemorrhage which significantly affected more women than men (female:male = 0.85% vs. 0.22%, p = 0.014).

Secondly, the devastating neurological outcomes associated with conventional CABG with CPB have always been a matter of concern. Neuro-cognitive impairment after CPB is believed to be due to micro emboli, non-physiological perfusion, and the inflammatory response (Reed and Stafford, 1985). Anderson and his colleagues (Czerny et al., 2001) in another publication suggested that these cellular changes result in neuronal injury, increased permeability of blood–brain barrier, and cerebral edema. Some studies think that these neuro-cognitive deficits might be transient and resolve several months after the operation (Anderson et al., 1999; Westaby et al., 1996; Taggart et al., 1999; Vingerhoets et al., 1996), whereas a recent study by Newman and colleagues (Toner et al., 1998) suggested that patients are at high risk of long-term neuro-cognitive dysfunction if they developed neurological deficit after CPB.

In a review of more than 24,000 patients undergoing CABG procedures, a considerable increase in patient deaths causally related to adverse neurological events was observed in the decade between 1970 and 1980 (Newman et al., 2001). The reported incidence of neurological complications after on-pump CABG is 3–7% (John and Murkin, 1995). Neurological complication is another common issue that has been all along attributed to consequence of inflammatory cascade arisen by the CPB. Among the three articles being compared, only Michael et al. demonstrated significantly lower occurrence rate of neurological complications in patients having CABG without CPB (1.03 vs. 1.79, 0.006). Jan et al. have found that the complication rates of delirium and stroke in the off pump were lower, but the results were insignificant. Trehan et al. in a study on CABG involving both men and women have also found that OPCAB significantly reduces the incidence of stroke after CABG especially in high-risk group of patients (Van Dijk et al., 2001). On the other hand, Hammer et al. have compared the sex difference in the rate of neurological complications and found that the percentage of women, who died from stroke, is higher than that of men (female:male = 9%:4%) (Trehan et al., 2001). Thus, OPCAB would be more advisable in women, who are known to have a higher risk of neurological dysfunction in conventional CABG.

4.3.3. Minor procedure complications

Organ failure is common in CABG with CPB. First, it has been associated with significant pulmonary complications and functional changes. Increases in lung vascular permeability (Hammer et al., 1997) occur after CPB and can result in the development of ARDS in 0.4–2.5% of patients (Messent et al., 1997). Atelectasis (Asimakopoulos et al., 1999), alterations of lung function (Tenling et al., 1998; Nicholson et al., 2002; Vargas et al., 1997), and reduction in lung compliance (Macguire et al., 2000; Auler et al., 2000) and gas exchange (Ranieri et al., 1999) are also seen. Systemic inflammation (Macnaughton et al., 1992) as well as imbalance of oxidant/antioxidant (Hammer et al., 1997; Paparella et al., 2002) and protease/antiprotease status (Quinlan et al., 2000) induced by CPB have been implicated in producing these patho-physiologic abnormalities.

However, Frass et al. (2001) indicated in a prospective clinical study that off-pump CABG does not confer major protection from postoperative pulmonary dysfunction compared with CABG surgery with CPB. This single study is relatively less reliable as it recruited only 39 patients.

Compared to CABG with CPB, Gerald and his colleagues in another randomized trial of 200 patients suggested that OPCAB was associated with a greater reduction in postoperative respiratory compliance associated with increased fluid administration and rotation of the heart into the right chest to perform posterolateral grafts. OPCAB yielded better gas

exchange and earlier extubation but no difference in chest radiographs, spirometry, or rates of death, pneumonia, pleural effusion, or pulmonary edema (Montes et al., 2004).

Compared with men, Staton et al. (2005) and Edwards et al. (1994) found that women have higher chance of having severe pulmonary complications after on-pump CABG even though the prevalence of smokers and chronic obstructive pulmonary disease (COPD) is higher in male patients. Women seem to be a risk group of having pulmonary complications, hence, off pump technique was thought to be more beneficial to female.

In the current article, the three studies being reviewed, showed a significantly lower incidence of respiratory dysfunction in women having off-pump than women having CPB (2.28% vs. 3.55%, $p = 0.001$, Philip et al.; 2.47% vs. 3.61%, $p = 0.004$, Michael et al.; 3.3% vs. 8.7%, $p = 0.015$, Jan et al.). This supports the hypothesis that respiratory function is protected by avoiding cardiopulmonary bypass.

Another organ commonly compromised by the extracorporeal circulation is the kidneys.

Similar to previous studies (Woods et al., 2003; Brudney et al., 2005), the incidence of new renal failure developed more in on-pump CABG in both male and female patients. To compare the effect of CPB on female patients undergoing CABG solely, Jan et al. indicated that the patients who had off-pump CABG, had a lower risk of renal complications (off vs. on = 2.6 vs. 8.0, 0.011), and subsequent need of dialysis (off vs. on: 0.7 vs. 4.8 = 0.013). Michael et al. also showed higher risk of renal complications in on-pump CABG though without statistical significance (0.8 vs. 0.95, $p = 0.434$). Organ damage is a possibility due to the use of CPB. Postoperative renal function is depressed during CPB time as a result of reduced flow rate, decreased blood pressure and continuous instead of palatial pumping. Since renal arterial pressure is reduced, there is reduced urine output as well. Hemolysis results in hemoglobinuria which also leads to renal dysfunction (Sellke et al., 2005). If bypass duration is extremely long, renal complications are common.

According to the studies on the gender effect on the incidence of renal complications of on-pump CABG, women were more prone to have adverse renal outcome (Vaccarino et al., 2002; Woods et al., 2003). This may be due to older age at presentation and associated co-morbid conditions, such as higher prevalence of pre-operative diabetes, in female patients (female:male = 42%:27%, $p = 0.001$, Gabriel et al.) (Vaccarino et al., 2002). In a recent study by Sabik et al. (2002), the off-pump method was advocated as a way to improve postoperative renal outcomes. Given this background OPCAB should be considered for all females, especially in those patients with pre-operative history of diabetes or pre-operative dialysis-dependent renal insufficiency.

Thirdly, it was mentioned previously that the crystalloid solutions needed to prime the pump led to hemodilution, and the turbulence, cavitations, and osmotic stresses during CPB result in red blood cell membrane injury and hemolysis (Celik et al., 2005; Kawahito et al., 1999). As a result of red blood cell dysfunction, Jan et al. indicated that the patients who had on-pump CABG would have a higher chance of red blood cell transfusion $\geqslant$ 1000 ml (off vs. on = 0.7 vs. 3.8, $p = 0.04$) as one of the minor complications of conventional CABG. In addition, women had a significantly higher incidence (67% vs. 26.1%, $p < 0.001$) and magnitude (3.3 vs. 1.5, $p < 0.0001$) of allogeneic transfusion (Vaccarino et al., 2002). It is then hypothesized if OPCAB could reduce the rate of red blood cell transfusion, women would be more indicative than men to undergo OPCAB which leads to lower red blood cell transfusion rate.

5. Conclusions

This current review helps define where research efforts should be directed to give surgeons better direction as to when and where to use the OPCAB approach. It is hoped to frame the important questions that have yet to be answered, which is one of the goals of any good review of the evidence.

Coronary artery bypass grafting (CABG) continues to be one of the most commonly performed a procedure that has a significant impact on overall health care resources. However, the influence of on-pump or off-pump CABG on female and male remains a question awaiting some answers. Female gender was previously shown to be associated with increased operative mortality, morbidity, and delayed recovery after coronary revascularization with CPB (Murphy et al., 2004; Ott et al., 2001). Capdeville and associates recently evaluated the impact of gender in patients undergoing OPCAB, comparing 61 female with 126 male patients (Brandrup-Wognsen et al., 1996). They demonstrated that female patients having OPCAB surgery should be considered as a high-risk group, compared with men, due to the increased co-morbidity and older age at the time of the operation; and also, the elimination of CPB did not improve the recovery time, a finding that was identified in male patients. This contradiction of clinical findings regarding the effectiveness of off-pump technique may be explained by its relatively steep learning curve (Caputo et al., 2001). The operative success depends on the experience and innate ability of a surgeon. In addition to the intrinsic merits of beating-heart surgery, the improved outcomes observed with OPCAB should also be contributed by the more experienced surgeons with better established outcomes preferentially adopting OPCAB (Caputo et al., 2001).

Another mystery of OPCAB lies on whether its mid-term and long-term outcomes can take over the conventional CABG. Most previous studies that have proved benefit of the OPCAB were limited to the short-term follow-up. A few reports have suggested it may be less durable than on-pump revascularization. Fewer bypass grafts, more incomplete revascularization, increased recurrence of angina and increased reinterventions have been described in OPCAB patients (Arom et al., 2000; Puskas et al., 1998; Parsons, 2001; Contini et al., 1999). When comparing the gender difference in operative outcomes, the female gender is associated with increased mortality and morbidity early but not late, after CABG (Brandrup-Wognsen et al., 1996). No substantial differences in the long-term survival of men and women after CABG have also demonstrated by some large studies taking major risk factors into account (Brandrup-Wognsen et al., 1996; Rahimtoola et al., 1993; Babir et al., 1994; Johnson et al., 1989). The role of OPCAB in long-term survival has not yet been ascertained and awaits further randomized trials to evaluate.

Operative mortality after CABG appears to be considerably higher in women as compared with men (O'Connor et al., 1993; Fisher et al., 1982; Carey et al., 1995; Khan et al., 1990; Richardson and Cyrus, 1986; Edwards et al., 1994). However, many investigators agreed that women pres-

ent at a more acute and symptomatic stage of their disease, and at the time of presentation are older, have a higher incidence of diabetes, renal insufficiency, hypertension and congestive heart failure, thus poorer ventricular function. Aldea et al. reported that there is a significantly higher proportion of diabetes (42.1% vs. 26.7%), hypertension (82% vs. 73.9%) and congestive heart failure (22.6% vs. 17.6%) ($p < 0.001$) in women (Aldea et al., 1999). Some researchers, however, advocate that indications of OPCAB include elderly patients, renal insufficiency, and poor left ventricular function.

There is now a large body of experimental and clinical evidence that supports the wider application of off-pump surgical revascularization. The chief advantage over conventional CABG is the avoidance of the morbidity associated with CPB. As the female patients referred for surgical revascularization are older with more co-morbid medical conditions, OPCAB presents a surgical technique with good short and mid-term outcomes, equivalent graft patency, and reduced cost. Evaluation of long-term outcomes and graft patency and the future provision of training in OPCAB techniques will determine, ultimately, whether its indication would be extended to wider scope possibly replacing conventional on-pump revascularization for women in the future.

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