

Format for ANSWERING REVIEWERS

January 27, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: Revised 7960.docx).

Title: Off-pump Coronary Artery Bypass grafting: misperceptions and misconceptions

Author: Shahzad G. Raja, Umberto Benedetto

Name of Journal: *World Journal of Methodology*

ESPS Manuscript NO: 7960

The manuscript has been improved according to the suggestions of reviewers:

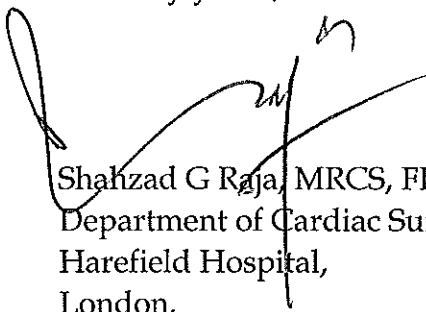
1 Format has been updated

2 Revision has been made according to the suggestions of the reviewers. The point by point response to reviewers comments is uploaded for your attention.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Methodology*.

Sincerely yours,



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Response to Reviewer 02518353

REVIEWER COMMENT The authors may consider summary main findings in the abstract.

RESPONSE: We are grateful to the esteemed reviewer for his/hers supportive comments. As the manuscript is a review article we feel that the current abstract appropriately summarizes the contents of the article. Providing additional material in the abstract will breach the word count as per requirements of WJM.

Response to Reviewer 00214274

REVIEWER COMMENT: Specific comments: You stated that “larger observational studies that are better powered to statistically compare outcomes have shown more favourable in-hospital outcomes and equivalent long-term outcomes with off-pump and on-pump CABG” but there is only one reference. Please give more references or modify your text.

RESPONSE: We thank the learned reviewer for his/hers scholarly critique of our manuscript as well as supportive general comments about off-pump coronary artery bypass grafting. We have provided more references [11-16], highlighted in yellow, in support of the above statement as per suggestions of the learned reviewer.

REVIEWER COMMENT: You stated that “off-pump CABG involves less manipulation of the ascending aorta”, and that is true, but an increase incidence of acute dissection of the ascending aorta has been reported in off-pump CABG (Chavanon O. et al. Ann Thorac Surg 2001; 71:117-21). Could you comment please?

RESPONSE: In the study by Chavanon o et al, iatrogenic acute aortic dissection occurred in 3 patients among 308 operated on without ECC (0.97%) and 1 patient among 2,723 operated on under ECC (0.04%). This difference was statistically significant ($p < 0.00001$). Iatrogenic aortic dissection is a recognised complication of tangential (side) clamping of the aorta. This complication can occur in both on- as well as off-pump CABG if the aorta is side clamped for construction of proximal anastomoses. Chavanon and associates did not attempt to reduce arterial pressure in the first 100 patients and then lowered the pressure to 100 mm Hg for the next 208 patients. They did not mention their technique for screening the aorta, ie, transesophageal echocardiography or epiaortic scanning. Some of the patients who had dissection might have had major atherosclerosis of the aorta. The high aortic pressure during application of the partial occlusion clamp will be a risk factor for injury to the aortic intima especially in the older patient and the patient with a diseased aorta. We reduce the pressure to < 90 mm Hg while applying the clamp and have never witnessed this complication in our practice. Finally, adopting no-

touch aortic technique and using arterial grafts (in-situ BIMAs) and composite grafting can eliminate iatrogenic aortic dissection post off-pump CABG.

REVIEWER COMMENT: You stated that “recent studies have demonstrated improve outcomes in higher-risk patients undergoing off-pump CABG”. In fact it is on short-term outcomes in ref 6, without comparative group in ref 17 and the authors conclusion in ref 19 is “however suboptimal quality of the available studies, particularly the lack of comparability of the study groups prevents conclusive results on this controversial issue”.

RESPONSE: Ref 6 is a randomized controlled trial, ref 17 is representative of majority of studies reporting outcomes for off-pump CABG in high-risk patient groups while ref 19 is the most recent meta-analysis on the subject which provides evidence from all major studies on the subject.

REVIEWER COMMENT: About graft patency, beside your criticism of published studies demonstrating suboptimal graft patency during off-pump CABG, have you any reference demonstrating equivalence in graft patency?

RESPONSE: Ref 26 Raja SG, Dreyfus GD. Impact of off-pump coronary artery bypass surgery on graft patency: current best available evidence. *J Card Surg* 2007;22:165-9. Provides an excellent and comprehensive review of the issue of graft patency after off-pump CABG and has a good bibliography of studies reporting equivalent graft patency. Furthermore, reference 8 & 9 report equivalent graft patency after off- and on-pump CABG.

REVIEWER COMMENT: However, I suggest rewriting this manuscript with an absolute objectivity and with a clear distinction between the facts observed and the expected facts, as well as between results demonstrating something and results suggesting something.

RESPONSE: We humbly tend to disagree with the learned reviewer that there is a lack of objectivity in the manuscript. The manuscript clearly and objectively addresses all the issues highlighting the fine print and flaws of all those studies which are used by skeptics and opponents of off-pump CABG as the evidence against safety and efficacy of off-pump CABG.

Response to Reviewer 00505578

REVIEWER COMMENT: Dr. Raja and colleagues performed a review of literature regarding off-pump and on-pump CABG. The manuscript is written with many bias in favor of off-pump. Several statements are not substantiated by published literature. A large > 60,000 patient observation by Chu, et. al published in *Annals of Thoracic Surgery* did not show any favorable outcome comparing off and on-pump

CABG. Ref 21 by Bakaeen, et. al. showed a decreased long-term survival in Veterans in a large cohort of patients. The appendix of NEJM on the ROOBY trial specifically looked at surgeon's Off-Pump volume experience and their results still holds after adjusting for surgeon volume experience. ROOBY trial EVH is the same in off-pump and on-pump and thus cannot be attributed to decreased SVG patency in off-pump patients. Overall, this manuscript is biased towards off-pump CABG and not substantiated by level I evidence.

RESPONSE: We thank the esteemed reviewer for his/hers scholarly review of our manuscript. Contrary to the perception of the learned reviewer this manuscript is not biased in favour of off-pump CABG instead the authors have attempted to address the misperceptions and misconceptions prevalent in the cardiac surgical community regarding this technique. The authors have made a conscious effort to ensure that all major concerns about off-pump are tackled in light of the published scientific evidence (randomized trials as well as large observational studies) without any personal bias or prejudice. In fact, the final paragraph of this manuscript clearly summarizes the authors' take on the subject. The studies (ROOBY trial & Ref 21) cited by the esteemed reviewer in his comments have all been heavily criticized in numerous peer reviewed publications for different flaws and we feel that there is no need for us to repeat all those comments and views. Finally, the failure of the large > 60,000 patient observational study by Chu, et. al published in Annals of Thoracic Surgery to show any favorable outcome comparing off and on-pump CABG just means that both are acceptable strategies and should be considered on individualized basis.

Response to Reviewer 02445851

REVIEWER COMMENT: Interesting statement pro off-pump CABG surgery. I think that in general the position is understandable and clear. However, it is my opinion that the statements should be softened not to change the content but to focus more on what are the information missing and/or the weak points in the comparative studies (as already done in the manuscript in several points). For instance the lack of MR LV functional assessment pre-post and pre-LGE viability assessment; the graft patency after CABGs with cardiac CT... these are all strong points to highlight in my view. I am personally in favour of off-pump CABG surgery. But the Authors should consider the fact that the poor experience of many centers and the more comfortable environment provided by on-pump CABG surgery are key factors. So maybe it is not a question of science but a question of penetration of the technique within the cardiac surgery community. In addition, we are in times in which PCI plays a major role even in 3-vessel disease. Sometimes PCI is used to complete revascularization, and so forth... - " A more logical way to address the issue of completeness of revascularization is to use the index of

completeness of revascularization (number of grafts performed divided by the number of grafts needed [number of graftable vessels with angiographically significant stenoses]). " This sentence needs a reference.

RESPONSE: We are grateful to the learned reviewer for his supportive comments and scholarly review of our manuscript. As per advice of the esteemed reviewer we have provided a reference in support of the statement. Reference 20 highlighted in yellow.