Author's response to reviews

Title: Radial Artery vs Saphenous Vein Graft Used as the Second Conduit for Surgical Myocardial Revascularization: Long-term Clinical Follow-up

Authors:

Ivana Petrovic (petrovicivana@gmail.com)
Dusko Nezic (nezic@ikvbd.com)
Miodrag Peric (mperic2009@hotmail.com)
Predrag Milojovic (pedja@ikvbd.com)
Olivera Djokic (oljaisara@gmail.com)
Dragana Kosevic (otasp@yahoo.com)
Nebojsa Tasic (nebtasa@yahoo.com)
Bosko Djukanovic (doktor@ikvbd.com)
Petar Otasevic (potasevic@yahoo.com)

Version: 3 Date: 7 June 2015

Author's response to reviews: see over
Reviewer 1

Thank you for your thoughtful analysis of our paper. We tried to answer to all of your comments, as it is described below.

General comments

Comment 1. Where were the radial artery grafts deployed to? Were they deployed to the next most significant artery with a tight stenoses (> 80%) or were they deployed to whatever artery the surgeon chose at that time?
Answer: To clarify this important issue we added the following in the Methods: "... All RA grafts were deployed to the artery with at least 80% stenosis, providing that it is considered an important coronary artery (smaller, same territory arteries or arteries supplying heavily infarcted areas were not grafted with radial artery)."

Comment 2. The authors should include a table of the distribution of radial artery grafts to make it easy for the reader to follow.
Answer: We have included the Table 2 and renumbered the other tables consecutively.

Table 2. Distribution of radial artery graft placement.

<table>
<thead>
<tr>
<th></th>
<th>Radial artery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagonal branch</td>
<td>9/100 (9%)</td>
</tr>
<tr>
<td>Ramus intermedius</td>
<td>9/100 (9%)</td>
</tr>
<tr>
<td>First obtuse marginal branch</td>
<td>50/100 (50%)</td>
</tr>
<tr>
<td>Second obtuse marginal branch</td>
<td>15/100 (15%)</td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>17/100 (17%)</td>
</tr>
</tbody>
</table>

Comment 3. If the radial artery as a second arterial graft was placed to the diagonal or intermediate arteries in addition to the LITA to LAD, how would this affect (or not) the long term outcome? Could the authors comment on this, as such a combination would essentially be revascularizing the one and same territory.
Answer: As it can be appreciated from the Table 2 radial grafts were placed in 9 patients to diagonal branch and ramus interemdius, each. We do agree with the reviewer that revascularizing those vessels might be interpreted as revascularization of the same
territory, but the vessels that were revascularized were big in diameter and supplied large amount of myocardium. We also agree that it would be interesting to analyze possible effects of the revascularization of those vessels on long-term outcome, but such analysis in the present data set would probably be misleading due to low number of patients (18 in total). We still performed exploratory mortality analysis, and it turned out that there was no difference in total mortality between the groups in which RA graft was placed to Dg/RI and other territories (11.1% vs 12.2%, p=0.88). We will address this important issue in the future studies.

Comment 4. How were the radial arteries harvested? Open?, endoharvest? Could the authors comment on the possible influence of the different types of harvest on radial artery graft patency and the subsequent effect on clinical outcomes.

Answer: We added the following sentence to the Methods: “... Open harvest of the RA was used in all patients ...” To further comment on this issue the following was added to the Discussion: “... When the type of harvest of the radial artery is concerned, recent prospective, randomized, open-controlled trial that included 119 patients demonstrated that following 5 years of the initial operation both RA harvesting techniques (open and endoscopic harvest) are safe, effective and result in excellent patency rates. (Burns DJP, Swinamer SA, Fox SA et al. Long term patency of endoscopically harvested radial arteries from a randomized controlled trial. Innovations 2015;10(2)77-84.)

Comment 5. The authors should describe the spasm prophylaxis for the radial arteries, as this may be an important aspect in both the short and long term performance of these arteries and the effect on the long term clinical results.

Answer: This is particularly important issue, since spasm of the radial artery graft leads to a significant reduction in blood flow through the graft and, consequently, to a number of undesired further complications. Our patients were given oral preparations Ca channel blockers during one year after surgery. We added the following sentence to the Methods: “... All of our patients were given oral preparations of the calcium channel blockers during one year after surgery to prevent RA spasm ...”

Comment 6. If a radial artery was used to a coronary which was 100% occluded (to avoid competitive flow), it would seem likely that the territory distal to the 100% occluded may well have some or an extensive degree of infarction. Could the authors comment on the usefulness of an arterial graft supplying an infarcted area on the left ventricle. Continuing on this point, there are reports that where there is prior RCA/posterior descending artery occlusion with inferior infarction, then the choice of graft to this area (if grafted at all) may well be irrelevant and of no long term benefit. Can the authors comment on this and weave it in their discussion.

Answer: Radial artery was rarely used to the RCA anyway (only in 17% of cases in this study), and we never used it if the RCA was occluded before (as well as a diagonal branch). Regarding other territories, radial artery was used to totally occluded vessels, but only if it was RCx, OM or big RI, regardless of the echo findings of the segmental kinetics of the left ventricular wall. However, radial artery was preferentially used to
another big vessel with at least 80% stenosis, if there was one available. In other words, RA was used to the 100% occluded vessel only if it was the only one available. We added the following to the Results: "... RA graft was never placed to the right coronary artery or diagonal branch if they were previously occluded...

Comment 7. The authors are to be complimented on the fact there were no intra nor peri-operative deaths in these 200 patients. The authors should provide a description of their myocardial protection techniques.

Answer: In the vast majority of the patients 600-1000 ml of cold antegrade modified St. Thomas cardioplegic solution was given to initially arrest the heart. Topical cooling of the heart was used during procedure (ice slash) and cardioplegia was never repeated unless cross-clamp time exceeded 90-100 minutes. Retrograde cardioplegia was never used, as well as warm blood cardioplegia, or the “warm shut” by the end of the procedure before cross-clamp was removed. We used cold blood cardioplegia only for the patients with a EF<30%. We added the following sentence to the Methods: "... For the myocardial protection purposes we used 600-1000 ml of cold antegrade modified St. Thomas cardioplegic solution to initially arrest the heart. Topical cooling of the heart was used during procedure (ice slash). Cardioplegia was repeated only if cross-clamp time exceeded 90 minutes. Cold blood cardioplegia was used only in patients with a EF<30%. ..."

Comment 8. 2% to 3% of patients had a TIA or stroke in the peri-operative period. For a group of 56 years median age, this was relatively high. Where side biting clamps used? Could the authors include the proximal anastomotic techniques in their methods description to better inform the reader?

Answer: TIA or stroke was the joint name of the complication that occurred. Actually, there were no strokes in the entire group, but there were 3 and 2 pts respectively with minor cerebrovascular symptoms: one pt in LITA/RA/SVG group had TIA on the 3rd postoperative day (pt also had bilateral carotid plaques of 40% and 55%). Two other pts had difficulties waking up immediately postop, which resolved by itself, however was classified as a cerebral complication. In the LITA/SVG group both patients had short lasting mental confusion which we (for technical reasons) classified to this group of complication.

Side-biting clamps are used routinely for performing proximal anastomosis. We found it safe over the period of the last 37 years and over 50000 procedures performed at our Institution. Overall incidence of TIA/stroke for the elective isolated myocardial revascularization during this period was 0.84% (unpublished data, reported in the PhD thesis done at our Institution). Performing the proximals during the cross-clamp on was reserved only for the known heavily diseased ascending aorta. We added the following sentence to the Methods: "... Side-biting clamps were used for performing proximal anastomoses in all patients..."
Comment 9. Were LITA – radial artery Y or T grafts performed, which again may influence the long term results?

**Answer:** LITA-radial Y-graft was performed only once in our series (in the case of the heavily diseased ascending aorta, to avoid proximal anastomosis), so we cannot comment on the influence of this technique on the long-term results.

Comment 10. Was there a philosophy or strategy of using the two arterial grafts to the left coronary system preferentially? Do the authors have a view on this which could be incorporated into the discussion.

**Answer:** This is one of the reasons why radial artery (at our Institution at least) is not used routinely as a second arterial graft. First of all, there is no solid proof in the available literature that using radial artery to the RCA territory will result in any significant improvement over the long term. Using a vein graft will give pretty much the same outcome. So, if we limit using radial artery to the left coronary system, we are left with not so many options – diagonal or even smaller size ramus is probably a waist of a good graft (unless RCx is very small or not graftable). Then we are left with OM’s that should be reasonable size (preferably over 1.5 mm) and at least 80% occluded. And if they are 100% occluded, than we should be sure that the territory they supply is still viable. In other words, all of this should fit together in order to expect long term benefit for the patient. However, using a radial artery in a well suited patient will also enable the surgeon to take the best parts of the vein for the remaining grafts, which probably will result in a better long-term results.

We added the following to the Discussion: "... It is very difficult to develop an algorithm for the use of RA as a second conduit for surgical myocardial revascularization. Since it appears that RA is not superior in terms of clinical outcome to the vein grafts for the revascularization of the right coronary artery, we usually use RA for revascularization of the left side system. The main target for RA graft is reasonably sized (≥1.5mm) obtuse marginal artery with at least 80% stenosis. However, decision about use of RA graft should be tailored individually in order to achieve greatest clinical benefit for the patient. ...

Comments and queries design to enhance and further validate the scientific aspects of the paper

Comment 11. 100 patients in each group of this randomized study seems rather small. Did the authors perform a sample size estimate to ensure they had adequate statistical power to show a difference between the two techniques? Could the authors provide their statistical power calculations?

**Answer:** You are quite right about the sample size, and we acknowledged this fact in Study limitations. No specific sample size calculations was performed, but our sample size was estimated based on previous studies and the fact that all patients were operated in a single tertiary care center which minimises variability in terms of patient selection, operative technique and postoperative management.
Comment 12. In the studies showing benefit for BITA over a single ITA, or two arterial grafts over one arterial graft (published over 15 years ago), a follow up period of 10 years or more was required. Do the authors feel that they have a sufficiently long follow up to determine such a difference or not in their study? Could they please comment on this.

Answer: We are aware that follow-up of 8 years+ is pretty modest regarding the long term results for myocardial revascularization using one or more arterial grafts. Improvement achieved using only LITA graft is so great that further improvement is difficult to achieve, unless the follow-up is close to (or more) then 15 years. Hopefully, we’ll be able to prove significant improvement in this rather small group of patients with radial artery compared to the vein graft group, after we complete the longer follow-up (now already approaching 15 years). Attrition rate for the vein grafts is known, particularly after 8 years, while it looks (from the numerous studies published so far) that radial artery patency rate remains pretty stable after 8 years. The stress this issue, we added the following sentence to the Study limitations: “... Additionally, the follow-up duration in our study group was relatively short (8 years), which may lead to the underestimation of net clinical benefit in patients in whom RA graft was used ...”

Comment 13. The mean age of the patients was 56 years, 56% to 61% had double vessel disease, and conversely only 22% to 27% had triple vessel disease. Did the authors expect to see any difference at 8 years? In the late 1970s and early 1980s, the Veterans Administration Co-Operative Study, the Coronary Artery Surgery Study, and the European Coronary Surgery Study showed no difference between medical treatment and CABG in patients with double vessel disease. Could the authors comment on the possible parallels between these results from 30 years ago and their own results in predominantly double vessel disease patients.

Answer: Unfortunately, significant mistake occurred in the construction of the Table 1. Namely, it was stated that there were 17 and 16 patients in the group with a single vessel disease, and 61 and 56 patients with double vessel disease, respectively. Actually there were no patients with single vessel disease, but 17 and 16 patients, respectively, had double vessel. The rest of the patients had triple vessel disease. The reason why patients with double vessel disease were operated was mainly unfavourable anatomy for the PCI in a highly symptomatic patient. We believe that functional capacity of the patients is the same (if not more) important as the longevity, particularly in a group of patients with a mean age being in the late 50’s. We made changes in the Table 1 accordingly.

Comment 15. Was the follow up complete? It is implied but not stated.

Answer: Follow-up was complete, and this is already explicitly stated in the Results (All patients were followed for 8 years or until death).

Comment 16. The authors should show the P values in Table 1 (baseline characteristics).

Answer: P values added in the Table 1.

Comment 17. Additionally for completeness, they should show the P values on the comparisons for Table 2 (adverse events after index surgery).

Answer: P values added in the Table 2.