

Peer Review File

Article information: <https://dx.doi.org/10.21037/jtd-21-1731>

Reviewer A:

Comment 1: “Composite grafts are used in over 70% of patients, which is too many. I believe that bilateral internal thoracic arteries should be used *in situ* as much as possible and should not be used as a free graft from the beginning.”

Response 1: We agree with you that it would be ideal if *in situ* RITA is used as a separate blood source. However, as described in the text, when an *in situ* RITA graft is used, it is frequently too short to reach the lateral or inferior wall. Therefore, we adopted the main policy of using free RITA as a composite graft anastomosed to the side of *in situ* LITA in an inverted Y configuration.

Comment 2: “In 15% of patients, sequential anastomosis is performed on LITA grafts. I believe that grafts to LADs should not be subjected to sequential anastomosis.”

Response 2: We agree with this point. We tried to avoid sequential anastomosis using the LITA graft as much as possible, but considering the ideal graft routing, sometimes it was inevitable for us to perform LITA graft sequential anastomosis.

Comment 3: “In your surgery, bilateral internal thoracic artery Y composite is more than 70% of CABG, do you consider bilateral internal thoracic artery Y composite as the first choice?”

Response 3: As described in response 1, our first choice is a LITA-RITA composite graft using *in situ* LITA as a single blood source. In most cases, total revascularization was possible with this configuration.

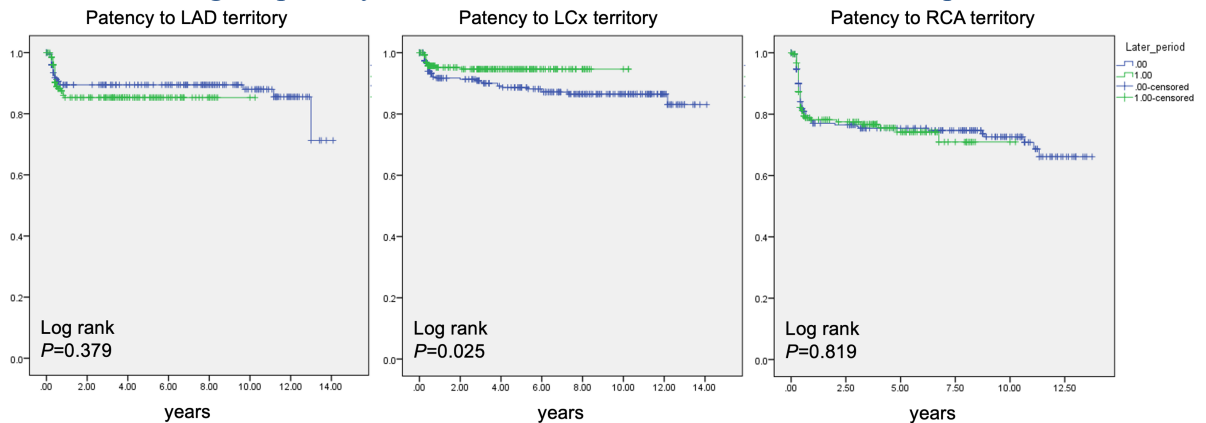
Comment 4: “The “string sign” is an ambiguous expression; please specify a clear definition.”

Response 4: As described in the text, the “string sign” is a concept that originated from findings on conventional coronary angiography. It is defined as “diffuse narrowing of the graft without stenosis in the anastomoses.” There have been articles about the string sign in conventional coronary angiography. The papers that originally used this term were cited in the text.

Comment 5: “It is thought that there is a learning curve in the mastery of beating surgery. It would be interesting to compare the graft patency rates in the LCX and RCA regions between the early and late surgeries in the sample.”

Response 5: Thank you very much for your important point. However, when the 415 total subjects were divided into the first half and the second half, no significant difference in patency was found in the LAD and RCA territories. Although there was a statistically significant difference of patency in the LCx territory, the magnitude of this difference was actually very small. Considering the scope of this

study, we thought that it would not be necessary to include this comparison in the text. However, we present the comparison of graft patency between the first and the second half of the patients.



Reviewer B:

Comment 1: “The fact that only 415 cases have been included over 17 years can induce an important bias that cannot be corrected. Also, there is a mix of comparisons of off pump and on pump, significant and non-significant stenoses that make it impossible in such a small group of patients to draw correct conclusions.”

Response 1: As the reviewer pointed out, it is difficult to interpret the results of various surgical procedures on heterogeneous patients over a long period of time, and it may be unreasonable to draw strong conclusions from these results. However, the results of this study are based on the 17-year-long policy of using bilateral ITA as much as possible, and various problems that occurred while trying to implement this policy are reflected. The following sentence has been added to the Limitations section reflecting the points pointed out by the reviewer.

Added sentence in the Limitations (end of Discussion):

*“...First, we maintained a consistent surgical strategy throughout the study period, but this is a small retrospective study of procedures performed by a single surgeon. **There were conditions that made it difficult to adhere to this strategy, and various adaptations resulting from those conditions were reflected in the study results. Clearly, the existence of such variability in surgical procedures is a weakness in terms of homogeneity. In a future study, an analysis of the results of almost identical surgical procedures without exceptions would be warranted.**”* Page 16 lines 288-292

Comment 2: “Questions rises whether the surgeons were comfortable or forced to perform anastomoses in OPCAB manner. OPCAB requires a mindset where it is feasible even in difficult situations. The numbers are too low and mingled with potential NS stenoses, making all conclusion potentially very dangerous for the scientific world.”

Response 2: We agree with the importance of this point. The surgeon who

performed CABG in this series is an experienced surgeon who was able to perform CABG comfortably, and most of the beating heart CABGs were OPCAB (89%), not on-pump beating CABG. Conventional CABG was chosen in cases where the patient had prominent cardiomegaly or a severely decreased left ventricular ejection fraction. It is well documented that revascularization of target vessels with insignificant stenosis (<75%) results in inferior long-term patency. However, after carefully reviewing the preoperative angiography, the surgeon determined the target vessels to revascularize even if the degree of stenosis was less than 75%, considering the graft routing and the possibility of future disease progression. Rather, a more important comparison would be with the boundary of 90% stenosis. We think that the results of this study provide sufficient information about the comparison between target vessel stenosis of $\geq 90\%$ and $< 90\%$ severity.

Reviewer C:

Comment 1: “The whole text needs to be improved for English language.”

Response 1: Thank you for the comment. This manuscript was reviewed and corrected by a commercial language editing service provider. We checked the manuscript again.

Comment 2: “Please remove statement saying that long-term patency beyond 5 years remains unclear and add more references such as: - Lytle BW, Blackstone EH, Loop FD, Houghtaling PL, Arnold JH, Akhrass R, McCarthy PM, Cosgrove DM. Two internal thoracic artery grafts are better than one. J Thorac Cardiovasc Surg. 1999 May;117(5):855-72.”

Response 2: Thank you for the comment. However, the article you recommended that we cite does not mention graft patency, and only the long-term survival rate is presented. Therefore, it appears to be inappropriate to delete the pointed-out sentence and cite the recommended article instead. We ask for your kind understanding.

Comment 3: “Flow competition phenomena is not the only concern related to BITA technique - please add more references and refer also to: - Sef D, Raja SG. Bilateral internal thoracic artery use in coronary artery bypass grafting in the post-ART era - Perspective. Int J Surg. 2021 Feb;86:1-4.”

Response 3: Thank you for your comment. We have additionally cited the literature you recommended, and also mentioned the results of the Arterial Revascularization Trial (ART).

Added sentences in the Introduction:

“The Arterial Revascularization Trial (ART) results showed no superiority of bilateral ITA over single ITA (5). Other concerns regarding the use of bilateral ITA are an uncertain survival benefit and increased risk of deep sternal wound infection (6). In contrast, even after the publication of the ART results, there have been papers reporting that bilateral ITA use had a survival benefit

compared to single ITA in large patient groups, although they were not randomized controlled trials (7, 8).” Page 5 lines 67 – 72

Comment 4: “Authors report that “the right ITA graft extended with remaining left ITA graft showed the highest freedom from patency events (P=0.045)”. How do they describe this findings? Can they describe how and why did they found to have residual LITA graft in those cases?”

Response 4: Thank you for your comment. As mentioned several times, when the *in situ* right ITA was used, anastomosis to the lateral wall or inferior wall was not easy because of its limited length, and even if right ITA was used as a Y-composite graft from the left ITA, it was sometimes impossible to reach the inferior wall target vessels. In these cases, we used a residual left ITA fragment (if its length was sufficiently long) that was left after the left ITA to LAD anastomosis to extend the right ITA. When the remaining left ITA was too short or absent, a saphenous vein graft was used to extend the right ITA.

Comment 5: “Authors compare two subgroups >90% and <90% stenosis on failed grafts on MDCT. Did they confirm this finding with conventional angiography? MDCT is less precise when comparing to MDCT. I suggest to change “more stenotic target” to more standardized terms such as “high-degree stenosis””

Response 5: Thank you for your comment. The severity of target vessel stenosis was evaluated by conventional angiography in all patients before surgery. Therefore, it can be regarded as relatively accurate data. Meanwhile, graft patency after surgery was mostly evaluated through MDCT. After surgery, unless there is a special reason, conventional angiography was not usually performed, and this is similar to the practice performed in most other hospitals. In accordance with your comment, the term “more stenotic” has been changed to “high-degree stenosis.”

Comment 6: “Authors refer to “decreased risk of patency events”. Please change to “graft failure” as more standardized term.”

Response 6: Thank you for the comment. However, it is somewhat questionable whether it is appropriate to view “patency event” and “graft failure” as the same concept in this study. “Graft failure” traditionally means that the graft is completely occluded. Instead, the concept of a “patency event” in this study includes not only graft failure (occlusion, non-visualization of the whole graft segment) but also the “string sign,” in which it is not clear whether the graft patency is maintained or not.

Comment 7: “Main issue with this study is whether the authors report on how many CT were false positive for graft failure? It would be more reasonable to compare conventional angio “graft failure subgroup” with “patent grafts subgroup””

Response 7: Thank you for this important point. There were 56 patients (13%) in whom conventional angiography was performed at least once after surgery, but only three had an interval of less than 1 month between angiography and MDCT. Therefore, it is difficult to evaluate the false positive rate of MDCT. In addition, since only 38 patients (9%) underwent conventional angiography as the last patency evaluation, it seems difficult to compare the “patency event group” and the “no patency event group” in the patients who had undergone conventional angiography. As the reviewer pointed out, if conventional angiography and MDCT were performed at a reasonably close interval, it could have been very helpful and could have provided very useful information. We ask for your kind understanding regarding our ability to address this point.

Comment 8: “How many patients had conventional angiography during this follow up?”

Response 8: There were 56 patients (13%) in whom conventional angiography was performed at least once after surgery, and 38 patients (9%) underwent conventional angiography as the last patency evaluation. We have added this information to the Results.

Changes in the text (added in the Results):

“...There were 56 patients (13%) who underwent conventional angiography at least once postoperatively, and conventional angiography was the last patency evaluation in 38 patients (9%)...”

Page 10 lines 158 – 160

Responses to Reviewer D:

Comment 1: “A key criticism is based on the method of analysis of graft patency which includes all of 1. per conduit, 2. per coronary territory, and 3. per anastomosis. Further, there appears to be separate consideration of the right versus the left internal thoracic arteries. This inconsistent approach diminishes this manuscript in its current form. It is strongly recommended by this reviewer that only one of these considerations would be used, such as the per anastomosis approach.”

Response 1: Thank you for this insightful point. As pointed out, this study analyzed the patency rates according to the type of grafts, target vessel territory, and each anastomosis. We agree that if only one of these three aspects had been analyzed, the manuscript might have been more concise and clearer. However, the issues in the manuscript are among the most frequently asked questions asked by CABG surgeons. As we have tried to analyze the factors affecting long-term patency of grafts in CABG using bilateral ITA from various aspects, we included these three aspects in the manuscript. In the future, we will conduct a more in-depth study for each issue separately.

Comment 2: “Throughout the manuscript, the first angiogram (and for many the only angiogram) was performed via CT scanning.

This is referred to as <1 year; although according to the protocol this would have been performed 3-4 months post-operative as a matter of routine. Greater precision in the reporting would enhance the manuscript.”

Response 2: Thank you for the comment. As the reviewer pointed out, our postoperative follow-up protocol was to perform initial CT angiography at 3-4 months. However, out of 415 patients, 44 patients (10.6%) underwent initial CT angiography during postoperative 6-12 months for reasons such as patient compliance. Considering this, we used the term ‘<1 year (implemented within one year)’. We have added corresponding sentences to the Results section.

Changes in the text (added in the Results):

“According to the protocol, initial MDCT was scheduled for postoperative 3 to 6 months. However, for reasons such as patient compliance, 44 out of 415 patients (11%) underwent initial MDCT during postoperative 6 to 12 months. ...” Page 10 lines 156-160

Comment 3: **“Further, such early angiographic data is known to have differential results compared to later angiography studies after 12 months, and this differential was reported as early as the 1990s by Calafiore et al. There was no recognition of this consideration in the discussions, which is a significant omission.”**

Response 3: Thank you for the important point. However, when we reviewed the papers published by Dr. Calafiore from 1990 to 2000, we could not find any paper showing significant differences between early and late angiogram. Rather, in one of his articles; *Bilateral internal thoracic artery grafting: long-term clinical and angiographic results of in situ versus Y grafts*. J Thorac Cardiovasc Surg 2000;120:990-8, the authors wrote that "Early and late patency rates were similar in the 2 groups." As the reviewer pointed out, we agree that there may be a fundamental difference between early and late angiograms, but we are not sure if the reference point will be around 12 months. A clearer comparison could have been made if initial MDCT was performed within 1-2 months (the true early period) after surgery. However, in this study, initial MDCT was mostly performed at postoperative 3-6 months. We doubt that the initial MDCT in our series is equivalent to ‘early’ angiogram in previous articles.

Comment 4: **“Equally, the relative accuracy of CT scanning versus conventional angiography should have been discussed. In their manuscript, they did perform conventional angiography when a graft occlusion or string sign had been reported on CT scanning, but they provided no details as to the accuracy of CT scanning as judged by the subsequent conventional angiography, again a significant admission.”**

Response 4: Thank you for this important point. According to the protocol, if the string sign or occlusion of the graft was seen in the MDCT

performed after surgery, conventional angiography was recommended 1 month later. However, there were difficulties in recommending asymptomatic patients to receive conventional angiography, which required hospitalization for at least 1 night. In fact, there were 14 cases where conventional angiography was performed shortly after MDCT. In 10 of these cases, the results of MDCT and conventional angiography were almost identical, but in 4 cases, the results of conventional angiography were less severe than those of MDCT. We ask for your kind understanding.

Changes in the text (added in the Methods):

*“Patients who showed abnormal findings (e.g., no visualization of the left ITA graft to the LAD or the entire right ITA graft) underwent conventional coronary angiography at 1 month after CT **if the patient had angina**. Patients who experienced recurrent angina or major cardiovascular events underwent conventional coronary angiography or MDCT.” Page 8 line 132*

Comment 5: “The inclusion of some patients with this saphenous vein grafting either as independent grafts or as extension grafts complicates the analysis of survival and patency (since saphenous vein grafts are known to have accelerated failure rates) and these patients should have been excluded entirely.”

Response 5: As shown in Figure 1, there are patients in whom saphenous vein grafts (SVGs) were used. However, when conducting the analysis by territory or anastomosis, anastomoses from free SVGs were excluded from the evaluation. The RITA was extended with SVG in 34 out of 415 patients (8.2%). As the reviewer pointed out, this is a weakness that reduces the homogeneity of the surgical procedures analyzed in this study. However, this shows that even with the intention to use bilateral ITA only, this policy may not be implemented in some patients (less than 10%), and the results of the analysis including these patients show real-world data even though there is inadequate homogeneity. Sentences have been added to the Limitations section (at the end of Discussion) to reflect the points made by the reviewer.

Changes in the text (added at the end of Discussion):

*“...First, we maintained a consistent surgical strategy throughout the study period, but this is a small retrospective study of procedures performed by a single surgeon. **There were conditions that made it difficult to adhere to this strategy, and various adaptations resulting from those conditions were reflected in the study results. Clearly, the existence of such variability in surgical procedures is a weakness in terms of homogeneity. In a future study, an analysis of the results of almost identical surgical procedures without exceptions would be warranted.**” Page 15 lines 288-292*

Comment 6: “Subset analysis according to the variables of beating heart, coronary territory, and strings signs, in a single surgeon, single center experience may be overreach and may be significantly underpowered. This did not appear to be considered in the

discussion.”

Response 6: We agree with this point. We think that the first part of the revised limitations (shown in Response 5) reflects the issue you have raised. Although we are not fully sure whether this description will satisfy your concerns, we did our best to address these points.

Comment 7: “With regard to the severity of native coronary stenosis, there is insufficient data listed to reach any meaningful conclusions from their analysis and at the very least greater granularity of this analysis is required.”

Response 7: We agree with you regarding this point. The severity of native coronary artery stenosis in our study was based on cardiologists’ reports of preoperative coronary angiography. As you are well aware, quantitative coronary angiography (QCA) is performed in only a small percentage of patients who are selected for CABG while undergoing coronary angiography. We had no choice but to rely on the cardiologist's report, which is conducted in the same environment as actual clinical practice. The problem pointed out by the reviewer has been reflected in the Discussion section.

Changes in the text (added at the end of Discussion):

*“...For the determination of whether or not to revascularize, assessing the severity of target vessel stenosis with **quantitative coronary analysis (QCA)** and/or fractional flow reserve (FFR) may be more helpful than subjective grading (20). Meanwhile, in real-world practice, **QCA** or FFR assessment are rarely performed in patients in whom CABG is planned...” Page 14 lines 240-244*

Comment 8: “It remains uncertain as to the Key recommendation that is being reached based on these data. If the technique itself is being promoted, there is no comparison group, and the technique used was not uniform or homogeneous. This is because some patients had an extension of the grafts by saphenous vein, or alternatively supplementary aorta to coronary saphenous vein grafts was used. An obvious conclusion from this report is that the technique is not uniformly applicable insofar as the right ITA may not be of sufficient length in all cases, thus requiring these additional vein graft maneuvers. As a technique, therefore, it clearly is not a universal technique, at least in the hands of this single surgeon and single center. Thus the shortcomings from the technical perspective have not been addressed or considered in the discussion.”

Response 8: We agree with you. As the reviewer pointed out, it is difficult to interpret the results of various surgical procedures on heterogeneous patients over a long period of time, and it may be unreasonable to draw strong conclusions from these results. The fact that these results are from single center and single surgeon might also be a weakness. However, the results of this study are based on the 17-year-long policy of using bilateral ITA as much as possible, and various problems that occurred while trying to

implement this policy are reflected. The following sentence has been added to the Limitations, reflecting the points made by the reviewer.

Added sentence in the Limitations (end of Discussion):

*“...First, we maintained a consistent surgical strategy throughout the study period, but this is a small retrospective study of procedures performed by a single surgeon. **There were conditions that made it difficult to adhere to this strategy, and various adaptations resulting from those conditions were reflected in the study results. Clearly, the existence of such variability in surgical procedures is a weakness in terms of homogeneity. In a future study, an analysis of the results of almost identical surgical procedures without exceptions would be warranted.**”* Page 15 lines 288-292

Comment 9: “The discussion of “beating heart” is nonconventional. It would appear that many such cases were in fact “on-pump” rather than “off-pump” which would be the usual connotation of the use of the words “beating heart”. Insofar as the patency was lower with the arrested (non-moving) heart, this would be expected, but there would be considerable reservations about the sample size in the single centre, single surgeon experience to reach important conclusions.”

Response 9: Thank you for this comment. However, 89% of the patients in the beating-heart group received off-pump CABG. In addition, overall patency was better in the arrest heart surgery group. The issue of this study being a single-surgeon, single-center experience was described in detail in the first item of the revised limitations.

Comment 10: “It is recommended that a revision according to stringent and limited analyses (such as an analysis on a per anastomosis basis) be considered from this dataset. Additionally, extraneous considerations (such as the reversal of findings from the early (3-4 month CT scans) to later (>1 year) scans be separately reported rather than acting as a distraction for this current manuscript.”

Response 10: We recognize the validity of your point. As shown in Figure 4, the results of this study included analysis by anastomosis. As the reviewer wrote, we think there will be an advantage to a separate analysis given the fact that abnormal findings of graft patency in the early MDCT may be recovered later. However, this is a long-term study with more than 15 years of follow-up, and along with investigating the factors that can worsen long-term graft patency, we wanted to emphasize that it might be inappropriate to simply accept the results of MDCT. Although the cases reported in this study were operated by a single surgeon due to the consistency of surgical strategy, we are planning a further study including multiple surgeons. Thank you very much, and we ask for your kind understanding regarding these issues of study design.