Author’s response to reviews

Title: Long-term results of radical pericardiectomy for constrictive pericarditis in Korean population

Authors:

Min Suk Choi (cvsurgeonchoi@gmail.com)
Dong Seop Jeong (opheart1@gmail.com)
Jae K. Oh (oh.jae@mayo.edu)
Sung-A Chang (elisabet.chang@gmail.com)
Sung-Ji Park (tyche.park@gmail.com)
Suryeun Chung (suryeun.chung@gmail.com)

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<< Response to the comments of Tsuneo Ariyoshi >>

Comment 1: In this series, CVP level is significantly higher in the patients underwent conventional pericardiectomy than in radical group.

Response:

Yes, you are right. As you pointed out the difference of preoperative CVP, the conventional group had a higher CVP (18.5mmHg) than the radical group had (16.2mmHg) statistically.

However, the postoperative CVP were not different between two groups when they were compared with Chi-Squared test (P = .381, 11.68±5.29 in the conventional group and 10.81±3.25 in the radical group)

We performed univariate and multivariate analyses to verify if the preoperative or postoperative CVP is one of factors associated with long-term mortality. Univariate analyses revealed that the preoperative CVP was not significant (P = .482) and the postoperative CVP was significant (P = .144) However, the postoperative CVP was not associated with long-term mortality in the multivariate analysis (P = .927).

Therefore, we are still careful but we think that the preoperative CVP would not affect the long-term mortality in our study even though they were different between the groups.
Comment 2: In addition, which surgical procedure should be chosen was determined during the operation, however I think severity of constrictive pericarditis should have greatly influenced the choice.

Response:

Another factor which was different preoperatively between groups was pericardial thickening. The radical group had more pericardial thickening than the conventional group had (P < .001). Therefore we think that the severity of constrictive pericarditis was not the only factor which influenced the extent of pericardiectomy.

Comment 3: From these facts, the patients who underwent conventional pericardiectiony may be severer condition than radical group. It does not seem to be preferable to compare the long-term survival of these two groups.

Response:

We sincerely understand your opinion. The patients in the conventional group might have poorer general condition preoperatively and the poor condition could affect the late mortality as well as the early mortality.

We have contemplated carefully solving such bias. Four early mortalities were only in the conventional group.

Late mortalities were composed of 11 cases in the conventional group and 8 cased in the radial group. Therefore, we analyzed 86 patients except the 4 early mortalities to find out the factors associated with long-term mortality. Frankly speaking, the idea was recommended by the other reviewer. You can see the results in Table 4. We hope to reach a less biased conclusion in this way.

Please, let us know if we should revise anything else to make a better article. Thank you for your advice.
The authors evaluated the impact of conventional pericardiectomy (CP) versus radical pericardiectomy (RP) at long term in a retrospective cohort of patients undergoing surgery between 1995 and 2015. They concluded that RP provided better outcome at long term. This is a very interesting topic, rarely assessed but their results and conclusion need to be considered with caution for several reasons that will be detailed as following.

Comment 1: The rate of patients with radiation-induced pericarditis was very low (5.6%), and could explain why the mortality was low. This feature does not fit with the current practices of most cardiac surgery centers. It is therefore difficult to generalize the conclusion presented hereby.

Response:

We totally agree with you. The mortality of patients with radiation-induced pericarditis would have increased if the ratio of such patients had been higher. Therefore we should be careful not to interpret our result to mean the mortality of patients with radiation-induced pericarditis is low.

In Korea, the ratio of radiation-induced pericarditis is low while that of tuberculous pericarditis is high. Therefore our title was decided by 'Long term-results of radical pericardiectomy for constrictive pericarditis in Korean population' in the light of such unique Korean patient population.

The other Korean article which studied the constrictive pericarditis (‘Prognostic predictors in pericardiectomy for chronic constrictive pericarditis’ written by Kang et al.) also expressed their limitation as follows. ‘Finally, our results may be mainly applied to patients with CP caused by idiopathic and tuberculous pericarditis, and may not be extrapolated to patients with CP due to other causes, such as postirradiation, postsurgical, and collagen vascular disease.’

According to your advice, we also added the following sentence in the limitation paragraph.

# In the last paragraph of the DISCUSSION

The survival rate of radiation-induced constrictive pericarditis is known to be low [20] but it was not in this study. We think the ratio of radiation-induced pericarditis was too low in Korean patient population. The other Korean authors also reported such unique Korean environment could be a limitation in their article [6].
Comment 2: The most important result of this study is depicted by the figure 2. According to the KM survival curves, it is easy to consider that differences between the two surgical approaches were mainly observed during immediate postoperative course. For this reason, I would suggest a two-step statistical approach using a logistic regression at first (during early postoperative period) and a Cox model for the long-term outcome. But the difference between the two groups was unlikely due to a better recovery at long term since the two curves seem to follow a similar evolution, once the postoperative period was accomplished.

Response:

Thank you for your exact analysis of our KM survival curves. We analyzed the data in a two-step statistical approach according to your suggestion.

We could not use the logistic regression analysis to compare the early mortalities because there was no event of early mortality in the radical group. Alternatively we demonstrated the difference with Fisher’s exact test and added the P value (=.026) in the paragraph of ‘Early result’.

# Early results in the RESULTS

The early mortality rate was 4.4% (4/90). They all belonged to the conventional group (P=.026) and died of low cardiac output syndrome (LCOS), which was related to early mortality (P<.001).

We found factors associated with long-term survival among 86 patient except the 4 in-hospital mortalities as you recommend. We included the MELD score, which was a rational scoring system, in the analyses. The univariate analyses were done again (Supplementary Material 2). You can see the results of the multivariate analysis in Table 4.

Comment 3: The surgical technique must be detailed more extensively, as well as cardiopulmonary bypass (CPB) management.

Response:

We revised the operative techniques in detail as follows.

# The second paragraph in the Operation

The surgical sequence of the radial pericardiectomy is as follows. Median sternotomy is performed after general anesthesia. If cardiopulmonary bypass is being planned, then initial dissection is performed over the aorta. Dissection around the right atrial auricle is performed for
venous cannulation. After cannulation, normothermic bypass is initiated and the dissection proceeds. The anterior pericardium is initially divided in the midline or wherever a nonadhesive pericardial space is present. The dissection of the pericardium off the heart is usually done with metzenbaum scissors or electrocautery. A cardiac positioner which is used during off-pump coronary bypass grafting is useful to retract the heart [11]. The dissection proceeds laterally on the right side to remove the pericardium surrounding the right atrium until it extends to about 1cm anterior to the right phrenic nerve. The dissection proceeds to the left side until it ends approximately 1 cm anterior to the left phrenic nerve. The anterior pericardium is then removed. Dissection proceeds between the pericardium and the posteroinferior ventricular wall until the inferior vena cava, coronary sinus and pulmonary veins are seen and then the diaphragmatic and posterior pericardia are resected. If cardiopulmonary bypass is not being planned, the initial pericardiectomy is done around the left heart because the pericardiectomy around the right heart without full release of the left heart can cause right heart failure.

Comment 4: Whether CP removed pericardium in the vicinity of the inferior vena cava was obtained is not clear although it's an important step of the surgical procedure to restore adequate right atrium and ventricular filling, whatever the degree of pericardiectomy. CP was indicated by poor operative feasibility according to the authors.

Response:

We think you are telling us an important surgical tip which is easy to miss. We reviewed the operative records again. We found that radical pericardiectomies have released enough around IVC. We added our picture (Figure 2) which shows the complete pericardiectomy posterior to phrenic nerves including the circumference of IVC.

However, the circumference of IVC could not be released completely during the conventional pericardiectomy because IVC is next to or posterior to the right phrenic nerve anatomically.

Comment 5: Therefore it may be argued that patients undergoing CP were sicker than those having RP, or had they a more extensive disease. It may be supposed because higher NT-proBNP levels, pericardial thickening, CVP differences and more frequent preoperative anemia were seen in patients of the CP group.

Response:

The median of NT-proBNP was higher in the conventional group but there was no statistical difference (P = .066). The Hb level was lower in the conventional group but the difference was not significant, either (P = .052). On the other hand, pericardial thickening was severer in the radical group than the conventional group. However, as you pointed out the difference of
preoperative CVP, conventional group had a higher CVP (18.5mmHg) than radical group had (16.2mmHg) statistically. However, the difference did not affect long-term survival in the univariate analysis (P = .0482).

Comment 6: The vast majority of patients were operated on CPB, which is unusual for such an operation that is generally considered needing to be conducted as much as possible without the use of CPB, to limit the risk of bleeding during and after surgery, especially in the patients having liver dysfunction or cirrhosis.

Response:

Bleeding risk is known to be one of complications of CPB. On the other hand, we think that CPB is necessary to retract the heart safely during pericardiectomy posterior to phrenic nerves until coronary sinus and pulmonary veins are seen. Some surgeons say posterior pericardiectomy without CPB through left thoracotomy is useful but we wonder if circumferential dissection of IVC which you point out is possible through left thoracotomy [14, 18].

Therefore we think CPB is necessary for the radical pericardiectomy.

The correlation between CPB and postoperative bleeding especially when patients had liver cirrhosis was analyzed in the next two answers.

Comment 7: How was this latter diagnosis made? What was the severity of the cirrhosis when present? The MELD score of this nearly one third of the patient population must be associated in the data reported in the table 2.

Response:

We are sorry but we could not verify the exact diagnostic criteria of liver cirrhosis because the diagnosis of liver cirrhosis had done by physicians in the medical department when we did pericardiectomy. However, we thought that MELD (Model for End-stage Liver Disease) score which you recommended could be an alternative and would be a more objective parameter. So we calculated the scores of all patients.

There was no intergroup difference of MELD scores, which was demonstrated by Mann Mann-Whitney test (Table 2).

Comment 8: Postoperative blood loss and transfusion rate must be reported since they are important data to explain the quality of the postoperative course. Generally, the patients having
liver cirrhosis are considered to be at high risk after surgery using CPB, which seems to be different in this study. Why?

Response:

Yes, we reviewed medical records of all patients and counted the amount of postoperative transfusions and chest tube drainage. There was no difference between two groups when they were compared by Mann-Whitney test. We added these results in Table 3.

We also found that MELD score was correlated with the amount of postoperative chest tube drainage. (P < .001, Correlation Coefficient = .470, analyzed by Spearman correlation analysis).

However, the correlation between CPB time and the amount of postoperative chest tube drainage was not significantly correlated. (P = .222, Correlation Coefficient = .130, analyzed by Spearman correlation analysis)

We inserted these results in the paragraph of ‘Early results’ and in the ‘DISCUSSION’ as follows.

# In ‘Early results’ in the RESULTS

MELD (Model for End-stage Liver Disease) score was correlated with the amount of postoperative chest tube drainage. (P<0.001, Correlation Coefficient=.470) However, the correlation between CPB time and the amount of postoperative chest tube drainage was not significantly correlated. (P=.222, Correlation Coefficient=.130).

# In the DISCUSSION

Bleeding risk is one of the complications of CPB especially if a patient has liver cirrhosis. In our results, the MELD score was correlated with the amount of postoperative chest tube drainage. (P<0.001, Correlation Coefficient=.470) However, the correlation between CPB time and the amount of postoperative chest tube drainage was not significantly correlated. (P=.222, Correlation Coefficient=.130).

Comment 9: On the other hand, more concomitant operations in RP group were performed. Could the better results in RP group just be explained by a better and more comprehensive surgical approach?

Response:
We reviewed preoperative echocardiographies or coronary angiographies of patients in the conventional group again. However, we could not find any other cardiac disease which should be operated concomitantly during pericardiectomy except 4 patients. A patient who underwent tricuspid valve repair six years after pericardectomy is belong to the radical group, not the conventional group and he is still alive for 11 years after pericardiectomy.

Comment 10: Some sentences are confusing. The authors must clarify the text since it is more or less mentioned that RP increased mortality (page 8/27)

Response:

We are sincerely sorry but we could not find where we said radical pericardiectomy increased mortality. Would you mind if tell us where such sentences are? Then we will express them more clearly. Please.

Comment 11: Considering tricuspid regurgitation (TR), the tricuspid annulus diameter is the most convenient parameter, more than the preoperative degree of TR, to predict the postoperative occurrence of TR. This data should be reported in table 5. I consider that in the current manuscript the impact of the surgical approach on TR at long term is highly speculative.

Response:

We are sorry but we could not find tricuspid annular size in the preoperative echocardiographic reports or operative records. We almost select 26 or 28mm tricuspid annuloplasty ring regardless of TR grade.

We totally agree that it is very speculative that TR repair influences long-term results. Therefore it is dangerous to conclude that tricuspid valve repair affects prognosis. That is the reason why we wrote the next sentence in the discussion. ‘We should be careful not to interpret it to mean tricuspid valve repair would improve late survival.’ The only conclusion which we reached was the grade of preoperative TR was associated with long-term mortality.

Comment 12: The table 4 should mention the statistical methods briefly to ensure quick better understanding. It needs also to be more precise in order to clarify the message, which is sometimes flawed (survival or mortality for hazard ratio of LCOS)

Response:
We have already introduced the revised Table 4 in the response of Comment 2. The statistical methods are explained in the ‘Statistics’. The univariate analyses were done by log-rank test for categorical variables or Cox proportional hazard model for continuous variables. Then the multivariate analysis was done by Cox proportional hazard model. We added these explanations briefly in the title of Table 4.

You said that the previous results were ambiguous if the factors were associated with mortality or survival. We reconfirmed the directivity towards mortality or survival with comparative assays such as two-sample T test or Mann-Whitney test for continuous variables and Chi-square test or Fisher’s exact test for categorical variables. All the above factors except immediate postoperative LOCS and the amount of PC transfusion demonstrated significant differences and directivities. We changed the title from ‘Factors associated with survival’ to ‘Factors associated with long-term mortality’ and ‘the extent of pericardiectomy’ to ‘conventional pericardiectomy’ to clarify the direction. LOCS and the amount of PC transfusion were not significant factors in the multivariate analysis, either.

Please, let us know if we should revise anything else to make a better article. Thank you for your careful reading.