Author’s response to reviews

Title: Ratio of Preoperative Atrial Natriuretic Peptide to Brain Natriuretic Peptide Predicts the Outcome of the Maze Procedure in Mitral Valve Disease

Authors:

Masafumi Sato (msato@tokuchuhp.jp)
Akihito Mikamo (mikamo@yamaguchi-u.ac.jp)
Hiroshi Kurazumi (kurazumi@yamaguchi-u.ac.jp)
Ryo Suzuki (ryos@yamaguchi-u.ac.jp)
Masanori Murakami (muraka3@yamaguchi-u.ac.jp)
Toshiro Kobayashi (tkobayashi@yamaguchi.saiseikai.or.jp)
Koich Yoshimura (yoshimko@gmail.com)
Kimikazu Hamano (kimikazu@yamaguchi-u.ac.jp)

Version: 2 Date: 5 February 2013

Author’s response to reviews: see over
Authors’ response to the reviewers

Title: Ratio of Preoperative Atrial Natriuretic Peptide to Brain Natriuretic Peptide Predicts the Outcome of the Maze Procedure in Mitral Valve Disease (MS: 5683961938612722)

Authors:
Masafumi Sato (msato@tokuchuhp.jp)
Akihito Mikamo (mikamo@yamaguchi-u.ac.jp)
Hiroshi Kurazumi (kurazumi@yamaguchi-u.ac.jp)
Ryo Suzuki (ryos@yamaguchi-u.ac.jp)
Masanori Murakami (muraka3@yamaguchi-u.ac.jp)
Toshiro Kobayashi (tkobayashi@yamaguchi.saiseikai.or.jp)
Koich Yoshimura (yoshimko@gmail.com)
Kimita Hamano (kimikazu@yamaguchi-u.ac.jp)

Version: 2 Date: January 13, 2013

Authors’ response to the reviews: see attached
Dear Dr. Vipin Zamvar:

We thank the reviewers for their careful reading of our manuscript and for providing many helpful comments. In response to the reviewers’ comments, we have revised the manuscript (no. 5683961938612722).

We would be honored to have our manuscript published in The Journal of Cardiothoracic Surgery

Sincerely,

Our responses to the referees’ comments are as follows:

**Reviewer 1: Takashi Nojiri**

Comment:

Minor Essential Revisions: It is necessary to revise the part of methods and discussion.

Response: We revised the methods and discussion sections (p. 4, lines 13-14; p. 10, line 25; p. 11, line 5).

**Reviewer 2: Hitoshi Yaku**

Comment:

The authors described that the preoperative ANP-to-BNP ratio was closely correlated to the outcome of the Maze procedure and to the fibrosis of the left atrium. This study would provide us with important information in the field of arrhythmia surgery. I would like to raise only one question regarding this index.

General Comments:

I believe that the ANP value basically reflects the loading condition of the atrium, and the BNP value reflects the loading condition of the ventricle. In
the present study, they included patients who had a disease which cause overloading of the left atrium and then atrial fibrillation. The loading condition of the left ventricle, however, was not in the same direction among those patients. The left ventricle of the patients with mitral stenosis might be unloaded, and the left ventricle of the patients with mitral regurgitation should be overloaded. Therefore, the physiological meaning of the preoperative ANP-to-BNP ratio must be different between the two pathophysiological conditions. I suggest that they should analyze the importance of the ratio in those two categories separately.

Specific Comments: □ They should put a label on each panel in Fig. 3.

Response: As noted in the reviewer’s comment, we also thought that the loading condition for the left ventricle was not the same among the patients. Therefore, as described in the discussion (p. 10, lines 4-7), we argue that mitral regurgitation causes left ventricular overload and induces BNP production in the left ventricle and that mitral stenosis causes right ventricular overload and induces BNP production in the right ventricle.

Patients need to be separated into these two categories to improve our understanding of this physiological phenomenon. Unfortunately, the number of cases of mitral stenosis was small (n=4) in this study Therefore, we could not divide the mitral stenosis cases into a sinus group and an AF group. Instead, we compared the preoperative ANP level, preoperative BNP level and preoperative ANP/BNP ratio among the following three groups: a mitral regurgitation group (n=13), a mitral regurgitation and stenosis group (n=6) and a mitral stenosis group (n=4). An analysis of variance (ANOVA) test showed no statistically significant difference in the preoperative ANP level, preoperative BNP level and preoperative ANP/BNP ratio among the three groups.

Reviewer 3: Young Keun On

Comment:
In this manuscript, Sato et al performed an interesting study and demonstrated that preoperative ANP/BNP ratio is related with the restoration rate of sinus rhythm after maze operation in patients with mitral valve disease. This is an interesting study and the manuscript is well written. However, there remain several limitations beyond what the authors have already acknowledged.

1. The authors assessed the maze procedure outcome based upon the cardiac rhythm after the procedure by electrocardiography or 24 hour Holter 6 months after surgery. However, the criteria of AF recurrence is not clear. Detection rate must be different between 12-lead ECG (representing rhythm status for only 10-20 seconds) and 24hr holter. Therefore, any patient with paroxysmal AF could be classified into AF or sinus group depending on the rhythm status when they underwent especially only 12-lead ECG. The authors should clarify at least how many patients underwent holter and 12-lead ECG alone, respectively, and acknowledge this limitation as well.

2. Is there independent association between maze success and the preoperative ANP/BNP ration on multivariate analysis?

3. In a study from Saito et al (Circ J 2007; 71:70-78), interstitial fibrosis between LA appendage and left atrial free wall showed no significant difference. What is the biologic rationale on the difference shown in especially Figure 3 a. and Figure 3b.

4. As the authors have mentioned, the plasma BNP level can be altered by renal function. It would be interesting if the authors give some data on the CCr or Cr level between the two groups.

5. Consider to use LA volume index instead of LA diameter.

Response:
1. Thank you for these important comments. Compared to 24-hour Holter monitoring, Ad et al. suggest that ECGs overestimate the success rate by 5.5% after Cox-Maze III operations (Ad N, Henry L, Hunt S, Barnett S,
Stone L: The Cox-Maze III procedure success rate: comparison by electrocardiogram, 24-hour Holter monitoring and long-term monitoring. *Ann Thorac Surg* 2009, 88(1):101-105. Therefore, we have added the following sentences to describe an additional limitation of the study (p. 10, line 25; p. 11, line 5): “We assessed the cardiac rhythm by electrocardiography in 21 patients and by 24-hour electrocardio-monitoring in the remaining 2 patients. Therefore, the success rate after the maze procedure may be overestimated. In a previous study, when the use of electrocardiography was compared with 24-hour electrocardio-monitoring, the detection rate of AF recurrence differed by 5.5%. However, the difference was not statistically significant [24].” We have also added the number of patients in the methods section (p. 4, lines 13-14).

2. Although we used a multivariate analysis in a logistic regression model, the preoperative ANP/BNP ratio was not identified as an independent factor (preoperative ANP/BNP: p=0.059; LAD: p=0.096; CTR: p=0.525). We have added the following text in the results section (p. 6, line 13): “The preoperative ANP-to-BNP ratio was not identified as an independent factor by the multivariate analysis (p=0.059), but compared to the other factors, the ANP-to-BNP ratio demonstrated the most significant difference (Table 1).”

3. In autopsy cases with a history of regular sinus rhythm and no heart disease, Saito et al. compared interstitial fibrosis between the left atrial appendage and left atrial free wall. The authors found no significant difference in interstitial fibrosis between the left atrial appendage and left atrial free wall. We compared the left atrial appendage with the left atrial free wall in patients with mitral disease. There was a significant difference between the percent of cases with fibrosis in the left atrial appendage and the left atrial free wall (5.37+/−0.45% vs. 7.00+/−0.499%, p=0.022). This result suggests that in mitral disease, left atrial overload may have a stronger effect on the left atrium than on the left atrial appendage. Therefore, ANP secretion from the left atrium decreases and BNP secretion increases according to the severity of mitral disease.

4. We have revised table 1. We now describe the preoperative creatinine level between the two groups.
5. Several previous studies have reported the relationship between the left atrial diameter and the sinus rhythm restoration rate after a maze operation. In this study, we compared the left atrial diameter with the preoperative ANP/BNP ratio. We believe that data on the left atrial volume would be useful, but these data are unavailable.

Reviewer 4: Taijiro Sueda
Comment:
The author must continue this work until the number of patients will become over 40 cases. Because the number of patients is too small.

Response: Thank you for this important comment. We agree that this study should be continued until the sample size is larger, and we would like to report the results from a larger group of patients in the near future.