Author's response to reviews

Title: Rare Early Prosthesis Obstruction after Mitral Valve Replacement: A Case Report and Literature Review

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Author's response to reviews: see over
Dear Editors and Reviewers:

Thank you very much for your comments concerning our manuscript entitled “Rare Early Prosthesis Obstruction after Mitral Valve Replacement: A Case Report and Literature Review”. Those comments are valuable and are very helpful for us to improve the quality of our paper. We have read the comments carefully and made modifications accordingly.

Responds to the reviewer’ comments:

Reviewer Dr. Kitamura

Comments:

1. The operative findings in the initial MVR;

Was TEE performed?

Response: Yes, TEE is performed during operation in our institute routinely. In the initial MVR, the patient recovered uneventful. Moreover, we performed the TTE one week after surgery. The mitral prosthesis functions well, EMVmax=1.5m/s, EOA=3.4cm²

How severe was the annular calcification?

Response: the mitral leaflets and chordae were heavily thickened, but no annular calcification was found.

How tight was the 25-mm prosthesis?

Response: the patient was 156cm height, 49kg weight. We implanted a
25-mm mitral mechanical valve without any difficulty and the valve fitted well.

Was posterior mitral leaflet and its subvalvular apparatus resected as well?

Response: Yes, we resected both the anterior and posterior leaflet and the subvalvular apparatus.

Was there any technical difficulty in valve implantation?

Response: the operation went smoothly; there was no technical difficulty in the valve implantation.

In which position was the prosthesis implanted, para- or supra-annular?

Response: the prosthesis was implanted in the para-annular position.

In which position was the prosthesis implanted, antianatomical or anatomical?

Response: Anatomical

2. The strategy of the reoperation;

Why did the authors choose a larger prosthesis?

Response: Some studies suggested that the prosthesis in larger size (27 mm diameter) was potentially effective in reducing the pannus formation; the reason for that might be attributed to a more regular transvalvular flow in the presence of a larger mitral prosthesis.**[1]**
Was any further annular debridement performed?

Response: Firstly, we debrided all the ingrowth tissue. We have tried to dissect a little of peri-annulus fibrotic tissue, but we didn’t debride so aggressively in case of any major complications. Moreover, in order to minimize the “foreign body” reactions caused by stitches, we used 3-0 prolene with bovine pericardium felt to implant the 27# mitral prosthesis.

Was the valve rotated from the initial position?

Response: No, we didn’t rotate the valve from the initial position

Reviewer Dr. Edwin

Comments:

1. The authors describe prosthetic mitral valve obstruction secondary to pannus ingrowth occurring within three months of mitral valve replacement for mitral stenosis. The rarity value of the case lies in the etiology and time frame of occurrence of prosthetic valve obstruction and I expected the authors to build their discussion around that observation. The report however falls short of making a satisfactory argument as to why the patient developed this rare complication, let alone postulate a means of avoiding possible recurrence. I would prefer the authors to look further into that.

Response: Firstly, the purpose of the present case report is to show the extraordinary short time interval from the time of valve replacement to
presented in this case that may cause the acute pannus overgrowth. Accordingly, we made a literature table to show the incidence and the time interval for the occurrence of this rare complication. As shown in the table, the duration of occurrence of the pannus-induced PVO is the shortest in our case. However, we are not certain about the real reason of the acute formation of the pannus. Therefore, in the second paragraph of the Discussion part, we summarized several risk factors that were reported to contribute to the pannus formation, and then we briefly discussed the possible risk factors presented in this case that may cause the acute pannus overgrowth.

<table>
<thead>
<tr>
<th>Authors, years, [Ref.]</th>
<th>Type of studies</th>
<th>Position of Valves</th>
<th>Incidence &amp; Time Interval</th>
<th>Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitale et al., 1997, [4]</td>
<td>Case series (n=1878)</td>
<td>Mitral valves</td>
<td>3.5%, Mean ≥ 4 years</td>
<td>Female, Tilting-disc valves, Bileaflet valves</td>
</tr>
<tr>
<td>Rizzoli et al., 1999, [7]</td>
<td>Case series (n=2680)</td>
<td>Mitral &amp; Aortic &amp; Tricuspid valves</td>
<td>0.24%/patient/year, Median=13 years</td>
<td>Tilting-disc valves, Caged-disk/ball valves</td>
</tr>
<tr>
<td>Teshima et al., 2003, [5]</td>
<td>Case series (n=615)</td>
<td>Aortic valves</td>
<td>1.95%, Mean=83±52 months</td>
<td>Inadequate anticoagulation, SJM valves</td>
</tr>
<tr>
<td>Sakamoto et al., 2006, [9]</td>
<td>Case series (n=390)</td>
<td>Aortic valves</td>
<td>1.8%, Mean=10±7.9 years</td>
<td>Small prosthesis size, Turbulent Flow</td>
</tr>
<tr>
<td>Kondruwelt et al., 2008, [8]</td>
<td>A case report</td>
<td>Aortic valve</td>
<td>6 months</td>
<td>Small prosthesis size, Rheumatic fever</td>
</tr>
<tr>
<td>Mullenix et al., 2008, [3]</td>
<td>A case report</td>
<td>Aortic valve</td>
<td>15 years</td>
<td>Female, A tilting-disc valve</td>
</tr>
<tr>
<td>Hurwitz et al., 2009, [2]</td>
<td>A case report</td>
<td>Aortic valve</td>
<td>8 years</td>
<td>Female, Endocarditis</td>
</tr>
</tbody>
</table>
2. I would question the authors' suggestion that "the history of severe rheumatic disease, small mitral annulus and implanted SJM prosthesis in this female patient may have prompted acute pannus formation". There are many patients who would qualify for acute pannus formation under these circumstances; the rarity of their reported case itself casts doubt on that supposition. Can the authors offer more evidence in support of it?

Response: Due to the rarity of this complication, there was no proven evidence that suggests any specific factors tightly correlating with the occurrence of the pannus. As reported in a series of literatures (reference [5]-[15] in the submitted manuscript), several common risk factors may have linked to the accelerated formation of pannus, including female, the history of rheumatic diseases, small annulus and the type of prosthetic valves. Therefore, in line with the previous reports, we suggested several similar risk factors presented in this case that may accelerate the pannus formation. As we stated in our report, although the specific role of these

<table>
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<tr>
<th>Authors</th>
<th>Type of Report</th>
<th>Valve</th>
<th>Duration</th>
<th>Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khan et al., 2009, [15]</td>
<td>A case report</td>
<td>Mitral</td>
<td>7 years</td>
<td>Female, Subvalvular chordae preservation</td>
</tr>
<tr>
<td>Park et al., 2011, [14]</td>
<td>A case report</td>
<td>Mitral</td>
<td>9 years</td>
<td>Female, Subvalvular chordae preservation</td>
</tr>
</tbody>
</table>
Risk factors are not known yet, they may help us to further explore the underlying mechanisms.

3. Can the authors describe their postoperative anti-coagulation protocol following mechanical valve replacement? It is generally understood that prosthetic valve obstruction occurs according to the interplay between prosthesis thrombogenicity and adequacy of anticoagulation. In the early postoperative phase, thrombogenic suture rings can contribute to thrombus formation around the prosthetic valve ring, promoting inflammatory processes that facilitate pannus ingrowth. Pannus ingrowth when it occurs, is usually in the late postoperative period. However, early cases have been reported. Cleveland et al [Ann Thorac Surg 1982;33:496-498] reported a case in whom pannus ingrowth occurred 20 days after mechanical aortic valve implantation. In the present case, pannus ingrowth occurred 3 months after mitral valve replacement. The predisposing factors for such excessive fibrous tissue ingrowth are not clearly defined. One must wonder about the possible role of inadequate anticoagulation in the early postoperative period in such cases. It is important to be clear in such a case that inadequate anticoagulation has not played a significant role in the genesis of pannus ingrowth. This has obvious implications for the postoperative management following reoperation.

Response: We totally agree with you that the inadequate anticoagulation
plays an important role in the pathogenesis of pannus formation. However, the target INR may be different between the Asian and the western countries. It has been verified that the pharmacodynamics of warfarin in the Caucasians and Asians are not the same. As reported in studies focusing on the Chinese population [1], the incidence of warfarin-related bleeding was significantly higher in patients with oral anticoagulation therapy targeting at INR intensity 2.5-3.0. Mori and colleagues also found that the bleeding-related morbidity was significantly increased in Japanese patients with an INR above 2.5 [2]. In a series of 1,157 Japanese patients with mechanical heart valves, Uetsuke et al. [3] reported that the incidence of thromboembolism did not increase even when the INR 1.5. In another study (target INR range 1.4–1.9 for AVR, 1.5–2.0 for MVR and DVR) by the Uetsuka group, the linearized rate of bleeding was 5.83% per patient/year, but only 0.26% per patient/year for thromboembolism. For Chinese patients with mechanical heart valves, bleeding was the major complication rather than thromboembolism. Low-dose anticoagulation (international normalized ratio 1.4-2.0) could markedly decrease bleeding and effectively prevent thromboembolism [4]. Therefore, we think the patient in this case is adequately warfarinized (INR>2.0) after the first-time surgery. Whereas, we could not exclude the possibility that the anticoagulation therapy (INR>2.0 for MVR), which was adequate for general Chinese population, failed to prevent thrombus
formation in this particular patient. However, the microscopic examination of the specimen from this case revealed that the explanted tissue is not thrombotic origin.

4. For mechanical mitral valve prostheses, I would imagine that an INR of 2 constitutes a low-intensity anticoagulation: we prefer to anticoagulate patients with mitral prostheses to an INR of 2.5-3.5, up-scaling the target INR by 0.5 if there is atrial fibrillation or LV dilatation. At that degree of anticoagulation, prosthetic valve obstruction (4 from thrombus, 1 from pannus) occurred at 0.56% per patient-year in 114 patients followed over 15 years [reference: Journal of Cardiothoracic Surgery 2011, 6:57; doi:10.1186/1749-8090-6-57]. It would be interesting to know the authors’ opinion on increasing the target INR for this particular patient.

Response: Thanks for your very thoughtful comment. As discussed in the above question, it is generally effective to prevent thrombosis with the INR above 2.0 for an isolated MVR in the Chinese population. Moreover, this patient had no history of atrial fibrillation and other concomitant diseases may cause a hyper-coagulant status. As for this particular patient, in order to reduce the possibility of the pannus recurrence, we maintained the INR about 2.5 after the reoperation.
Reviewer Dr. Devbhandari

Comments: I have found few grammatical errors which need addressing before going on to publication.

Response: we have consulted native English speakers for paper revision before the resubmission.

REFERENCES

