Author’s Reply

Reply to Letter Regarding Article “Sildenafil Reduces the Risk of Thromboembolic Events in HeartMate II Patients with Low-Level Hemolysis and Significantly Improves the Pulmonary Circulation”

We appreciate the interest of Nitta, et al.11 in our study.7 The authors highlighted in their two interesting studies from Imamura, et al.12 and Nitta, et al.6 In the work from Imamura, et al.12 and Nitta, et al.6 the authors analyzed several hemodynamic and echocardiographic parameters and found that after LVAD implantation, the excessive left ventricle (LV) unloading by the pump may cause a septal shift towards LV and worsens the right ventricular (RV) function. We agree with Nitta, et al.11 that the geometric change of the LV cavity may also cause malposition of the inflow cannula angle, which results in pump thrombosis and hemolysis. In our analysis, we did not present a detailed echocardiographic analysis including RV end-diastolic volume, RV diameter, Tissue Doppler Imaging (TDI) of the lateral tricuspid annulus velocity (RV s’), and speckle tracking of the RV free wall. Nevertheless, we presented two echocardiographic values, RV fractional area change (RV-FAC), 5 which reflects in part the changes of RV geometry and tricuspid annular plane systolic excursion (TAPSE),6 a widely used parameter that allows us to assess RV systolic function.7 We absolutely agree with Nitta, et al.11 that 3D-RVEF, RV s’ and speckle-tracking provide better evaluation of the RV function.6,8 Our current study7 focused on the effect of sildenafil on the reduction of thromboembolic events. For the aim of our study we made an effort to include and evaluate several factors: hemolysis markers, and invasive hemodynamic and echocardiographic parameters. We agree with Nitta, et al.11 that it is necessary to explore other RV function markers like strain imaging or 3D RV geometrical analysis after sildenafil usage in future studies. On the other hand, imaging of the RV after LVAD implantation is still challenging due to many factors such as an inappropriate acoustic window after LVAD implantation.

However, we believe that the reduction of thromboembolic events in LVAD patients treated with sildenafil is not explained alone by the hemodynamic effects induced by sildenafil. Saced, et al.13 proposed a biochemical pathway and provided a hypothesis for their similar observations showing less thrombotic events during low-level hemolysis with the administration of sildenafil. They found that the increased bioavailability of nitric oxide (NO), which is induced by sildenafil, and the interaction between free plasma hemoglobin, NO, cyclic guanosine monophosphate (cGMP) and platelets is one possible effect of sildenafil leading to the reduction of thromboembolic events. Both effects of sildenafil, the hemodynamic effect by reduction of the RV afterload and the NO/cGMP interaction with platelet activation, explain in part the low incidence of thrombotic events in LVAD patients during low-level hemolysis with the administration of sildenafil.

The hemocompatibility related adverse events score (HCS), which has been proposed by Mehr, et al.11 and adapted by Uriel, et al.,15 is an important score to evaluate and compare HRAE between LVAD patients. We agree with Nitta, et al.11 that for reporting of HRAE in all future LVAD studies HCS should be provided.

For answering the question of Nitta, et al.,11 we had to reexamine our dataset, as this question had not been addressed in our study protocol. We calculated the HCS exemplary only for the two groups (LLH+Sildenafil and LLH no Sildenafil). The results are presented in the Table. The cumulative score in the LLH+Sildenafil group was 21 and in the LLH no Sildenafil group was 46 (P = 0.029*). According to these results, we may assume that sildenafil improves the overall HRAE.

We, like Nitta, et al.11 await further studies to examine the effect by using other pulmonary artery dilators, such as endothelin receptor antagonists or prostanlandin I2 (PGI2).

Disclosures

Conflicts of interest: None.

Table. Hemocompatibility Score

<table>
<thead>
<tr>
<th>HCS</th>
<th>LLH + Sildenafil Cumulative Score</th>
<th>LLH + Sildenafil Patients with Events</th>
<th>LLH + Sildenafil Score Median [Max]</th>
<th>LLH no Sildenafil Cumulative Score</th>
<th>LLH no Sildenafil Patients with Events</th>
<th>LLH no Sildenafil Score Median [Max]</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total score</td>
<td>21</td>
<td>9</td>
<td>0 5)</td>
<td>46</td>
<td>10</td>
<td>3 5)</td>
<td>0.029</td>
</tr>
</tbody>
</table>

5 P values are based on the 2 x 2 contingency table associated with patients experiencing an HRAE and patients who did not.

Address for correspondence: Rashad Zayat, MD, Department of Thoracic and Cardiovascular Surgery, RWTH University Hospital, Pauwelsstrasse 30, 52074 Aachen, Germany. E-mail: r.zayat@ukaachen.de

Received for publication March 13, 2019. Revised and accepted March 14, 2019. Released in advance online on J-STAGE June 28, 2019.

doi: 10.1536/hj.19-133

All rights reserved by the International Heart Journal Association.
References

1. Nitta D, Imamura T, Letter by Nitta, et al. Regarding Article, “Sildenafil Reduces the Risk of Thromboembolic Events in HeartMate II Patients with Low-Level Hemolysis and Significantly Improves the Pulmonary Circulation”. Int Heart J 2019; 60: XXX-.


5. Grant AD, Smedira NG, Starling RC, Marwick TH. Independent and incremental role of quantitative right ventricular evaluation for the prediction of right ventricular failure after left ventricular assist device implantation. J Am Coll Cardiol 2012; 60: 521-8.


Rashad Zayat, MD
Usama Ahmad, MD
Rüdiger Autschbach, PhD
Ajay Moza, PhD

Department of Thoracic and Cardiovascular Surgery, RWTH University Hospital, Aachen, Germany