Letter to Editor

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”

To the Editor,

It was with great interest that we read the article by Zayat, et al., which concluded that sildenafil reduces the risk of thromboembolic events in HeartMate II patients. Hemocompatibility-related adverse events: Bleeding and thromboembolic events are the most frequent complications after left ventricular assist device (LVAD) implantation. Although bleeding and thrombosis seem to be opposite phenomena, both of them derive from the same origin: hemocompatibility abnormality from the biological circulatory interface. The device-related hemolysis, pump thrombosis leading to malfunction, neurological events, and nonsurgical bleeding (particularly gastrointestinal bleeding) are significant concerns that influence the outcomes in mechanical circulatory support. We now need to discuss overall hemocompatibility-related adverse events (HRAEs) as the consequences of LVAD implantation.

Efficacy of sildenafil on pulmonary circulation and HRAEs: The pulmonary artery (PA) and right ventricle (RV) have an inseparable association with each other and the association is especially important following LVAD implantation. Pulmonary hypertension is definitely a risk factor of right ventricular failure (RVF). However, the impact of pulmonary circulation on HRAEs remains uncertain.

In the present manuscript, Zayat, et al. reported on the effect of sildenafil, a phosphodiesterase type 5 inhibitor which is administered to treat pulmonary hypertension in general, for the prevention of thromboembolic events following HeartMate II LVAD implantation. In their study, the sildenafil group showed significantly reduced mean pulmonary artery pressure (PAP), reduced mean pulmonary capillary wedge pressure (PCWP), reduced pulmonary vascular resistance (PVR), and a better cardiac index compared to the control group. Furthermore, sildenafil treatment significantly improved low-level hemolysis (LLH), while the von Willebrand factor (vWF) remained unchanged. One reason for the reduced hemolysis is that sildenafil increased the forward output by decreasing PVR, resulting in improved left ventricular (LV) circulation and pump flow.

A similar phenomenon was recently reported by Saeed, et al., who concluded that sildenafil therapy was associated with reductions in device thrombosis and ischemic strokes. Although there was no discussion of hemodynamics, the major reason for the reduced thromboembolic event may be the decreased PVR and improved hemodynamics. The impact of sildenafil on other pulmonary artery remodeling-associated variables, including trans-pulmonary artery gradient (TPG), diastolic pulmonary artery gradient (DPG), and pulmonary artery capacitance (PAC), etc., is another concern.

Efficacy of sildenafil on right ventricular function: After LVAD implantation, excessive LV unloading by the pump sometimes causes the septal shift to LV and worsens the right ventricular function. Geometric change of the LV cavity may also cause malposition of the inflow cannula angle, which results in pump thrombosis and hemolysis. Although the above 2 papers did not show left ventricular end-diastolic dimension, septal bouncing, or inflow cannula flow, the improved TAPSE and RV-FAC may indicate the normalization of RV function. In the future, it is necessary to explore other RV function markers like speckle strain or 3D RV geometrical analysis after sildenafil usage.

As described previously, the bleeding event rate was not significantly different and the levels of vWF were statistically comparable between the sildenafil (+) group and sildenafil (-) group. Considering the high shear forces from pump induces structural changes in the shape of the vWF multimer molecule and causes vWF degradation, the effect of sildenafil for the prevention of thromboembolic events may not be due to the local pump flow improvement but rather to systemic coagulation-fibrinolysis system intervention. From the viewpoint of the effects of sildenafil on NO/cGMP activation and inhibition of platelet activation, it may have a direct effect on the normalization of platelet aggregation activity. We may be able to expect a further effect of sildenafil beyond the simple hemodynamics improvement by reduction of RV afterload and enhancement of RV function (Figure).

Future perspectives: The next questions are as follows. Does sildenafil improve overall HRAEs? Although neither paper calculated the Hemocompatibility Score which was recently advocated, we should compare overall HRAEs according to the sildenafil presence/absence. Furthermore, can we expect a similar effect by using other pulmonary artery dilators, such as an endothelin receptor antagonist or prostaglandin I2 (PGI2)?

The association of endothelin blockade with platelet aggregation still remains unknown. It was reported that ET-1 has no major direct effect on platelet aggregation, however, some papers reported dual ET-1 antagonists have

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the novel effect of preventing prothrombotic and hemorrhagic tendencies.\(^7\) PGI2 definitely decreases platelet activity by inhibiting thromboxane A2 via cAMP increment, and sometimes causes severe bleeding complications. Thus, it may not be suitable for LVAD patients who are in a strong anticoagulative state. Whether the effect of sildenafil in the present manuscript is due to only an improvement of hemodynamics or a direct platelet-inhibitory effect via NO/cGMP by PDE5-inhibition should be determined next. In conclusion, the right ventricular system and pulmonary circulation appear to be deeply associated with HRAEs after LVAD implantation. By exploring the precise mechanism, we may be able to improve outcomes among LVAD implanted patients.

Disclosures

Conflicts of interest: The authors have no conflict of interest related to the manuscript.

References


