FIGURE 2. Histologic findings of the explanted heart showing an extremely thin left ventricular wall with marked fibrosis (elastica van Gieson's stain).

function. Furthermore, an exercise stress test showed increased left VAD flow even at a fixed pump speed. Frazier et al² used a calf model in which both native ventricles were excised and replaced with 2 continuous-flow VADs. An exercise test demonstrated increased flow in both VADs.² Our results have confirmed their experimental findings, suggesting that even without native ventricular contraction, biventricular VADs can adjust their flow according to the flow

demand. We consider that these hemodynamic properties imply the possibility of clinical use of continuous-flow artificial hearts currently being tested in animal models.

When implanting 2 rotary pumps for biventricular support, concern exists about a flow imbalance between the pulmonary and systemic circulation. After the implant operation, the systemic and pulmonary vascular resistances become dynamic and are further influenced by use of inotropes, discontinuation of mechanical ventilation, and other factors. These altered hemodynamic states could exacerbate the flow imbalance during the perioperative period, especially in patients with a noncontractile heart. In the present case, the first extubation failed owing to severe pulmonary congestion caused by right VAD overflow.³ Interestingly, after resolution of these perioperative hemodynamic fluxes, the management became easier, with no additional pulmonary congestion noted. A natural flow balance appears to be achieved by the autoregulatory properties of continuous-flow VADs.⁴

The currently available pulsatile total artificial hearts have numerous restrictions. We believe that the present successful case will promote the clinical use of rotary blood pumps in patients with biventricular failure for bridging and, even, destination therapy.

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Acquired von Willebrand disease in a child with a ventricular assist device

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The ventricular assist device (VAD), as a bridge to heart transplantation, is being increasingly used in patients of all ages who are experiencing refractory heart failure. In these patients, massive bleeding remains a leading and challenging complication. Among the possible causes, the occurrence of acquired von Willebrand disease (avWD) has been reported in adult patients.¹ Indeed, the loss of high-molecular-weight (HMW) von Willebrand factor (vWF) multimers because of shear stress, similar to that seen in aortic stenoses,¹ is frequently observed in patients with axial flow in a left VAD.^{2,3}

FIGURE 1. Bleeding and allogenic transfusions. Quantification of bleeding, and red blood cell (RBC) counts and plasma requirements, after implantation of a biventricular assist device. Arrows, Surgical re-explorations; D, postoperative day.

To treat bleeding associated with avWD, various therapies, including reduced anticoagulation, the control of local bleeding, and plasma or platelet transfusions, are used. However, none of these therapies specifically address the abnormalities seen in avWD, and the effectiveness of these therapies remains uncertain. Herein, we describe the first case of avWD in a pediatric patient after implantation of a pulsatile biventricular assist device (BerlinHeart; Berlin Heart GmbH, The Woodlands, Tex), which caused severe perioperative bleeding but could be treated with von Willebrand factor concentrate. The child was successfully bridged until heart transplantation.

CASE REPORT

A 3-year-old, 13-kg boy, with a history of dilated cardiomyopathy, had a biventricular assist device implanted as a bridge until heart transplantation. The antithrombotic regimen consisted of only unfractionated heparin. Four days after the device was implanted, a bleed of $5 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ occurred, which required surgical re-exploration. A 700-mL red blood cell (RBC) transfusion was also necessary. By day 5, a bleed of $2 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ persisted and required transfusion of 500 mL of RBCs, 270 mL of plasma, 110 mL of platelets, and further surgical re-exploration. Despite these therapeutic measures, bleeding recurred and required several surgical re-explorations at 3-day intervals and allogenic transfusion of 9490 mL of RBCs and 3620 mL of plasma (Figure 1).

Prothrombin time and fibrinogen levels were closely monitored. ROTEM monitoring (Tem International GmbH, München, Germany) showed an EXTEM clotting time value of 66 seconds (normal range, 46-97 seconds), an EXTEM clotting formation time value of 196 seconds (normal range, 41-109 seconds), an α angle of 62° (normal range, 69° - 82°), and maximal clot firmness of 43 mm (normal range, 52-70 mm). By day 20, the patient developed increased

FIGURE 2. Normal plasma (lane 1) and plasma from our patient receiving a biventricular assist device (lane 2). The dye front is at the bottom of the discontinuous gel, and the large multimers are shown in the upper part of the gel. Lane 1 indicates normal plasma; lane 2, plasma from our patient who had lost high-molecular-weight multimers, as indicated by the missing bands in the upper part of the gel (red circle).

hemorrhagic syndrome ($9 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) with an increased requirement for transfusion of 1740 mL of RBCs, 895 mL of plasma, and 438 mL of platelets. Because bleeding was severe, an infusion of tranexamic acid ($3 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) was given. The patient also received 3 doses ($30 \text{ } \mu\text{g/kg}$) of recombinant activated factor VII, although these were unsuccessful (Novoseven; NovoNordisk, Princeton, NJ). We also stopped heparin for 3 hours while heparin activity was within normal limits (anti-Xa activity, 0.2-0.3 IU/mL).

Because avWD was suspected, human vWF concentrates of 80 IU/kg every 8 hours, associated with human factor

VIII (FVIII) concentrates of 40 IU/kg (Wilstart; LFB Biomédicaments, Les Ulis, France) every 8 hours, were started. Before giving these new therapies, blood was collected for an assay. The following day, the daily requirement for RBC transfusion had decreased to 400 mL (Figure 1). The results of the von Willebrand panel showed that the vWF antigen (vWF:Ag) was normal (77% by enzyme-linked immunosorbent assay; normal range, 50%-160%), as was factor VIII coagulant (62% vs normal range, 60%-150%). Collagen-binding activity (vWF:CB) was 58% by enzyme-linked immunosorbent assay (normal range, 50%-150%), as was vWF ristocetin cofactor (64% vs normal range, 60%-130%). The ratio of vWF:CB/vWF:Ag was 0.75, which was also within the normal range (≥ 0.70). Analysis of vWF multimers revealed an abnormal pattern, mainly characterized by a marked decrease in HMW forms, which was compatible with avWD (Figure 2). Because FVIII coagulant was normal, only therapy with human vWF concentrate was continued (Wilfactin; LFB Biomédicaments) and at the same dose. At 72 hours after beginning this therapy, the child did not require any further transfusion support until heart transplantation could be performed (on day 29). There were no thromboembolic complications. The postoperative course was uneventful, and the patient left the intensive care unit a week after heart transplantation.

DISCUSSION

To our knowledge, this is the first case of avWD to be described in a child, although avWD has been previously reported in adults after a VAD implantation. Heilmann and colleagues⁴ analyzed patients with a pneumatic VAD system or an axial flow pump for the presence of avWD and for bleeding complications. They observed bleeding episodes more frequently in VAD than in axial flow pump, in the early and the late course. However, they did not report any significant difference in the severity of the avWD. An avWD results from shear stress in the pump itself and in the tubes that connect the pump to the heart and great vessels. This shear stress causes unfolding of the HMW multimers of vWF with exposure of the D2 domains of the VWF monomers and subsequent cleavage by the protease ADAMTS-13.⁵ Bleeding phenomenon may be attributed to the loss of large vWF multimers, leading to abnormalities in platelet adhesion at the sites of vascular injury. The bleeding diatheses seen in these patients is out of proportion to that expected with postsurgical anticoagulation, and has been attributed to the additional hemostatic defect contributed by degradation of vWF.

In some patients, a loss or decrease of HMW multimers is the only laboratory abnormality. Various therapies, such as

desmopressin acetate, tranexamic acid, and control of local bleeding, have been traditionally used to treat major bleeding events during avWD. However, these therapies do not specifically address the abnormalities observed during avWD. Furthermore, the efficacy of these agents in patients with avWD secondary to VAD is unknown. In our case, many therapies, including recombinant FVIIa, were used in association with large-volume blood and plasma transfusions, but were ineffective. For this reason, we tried a more specific strategy that focused on the missing vWD factor.

Wilstart and Wilfactin (LFB Biomédicaments) are established treatment options for patients with vWD but are not usually prescribed for avWD. Before initiating this treatment, a von Willebrand panel was conducted to obtain values for vWF activity, vWF:Ag, and FVIII when bleeding was the most abundant. An absence of high-molecular-weight multimers was the only abnormal factor identified. Because hemorrhagic syndrome was not controlled, we wanted to provide the patient with the missing vWF. Once treatment with Wilfactin was started, we observed a significant decrease in the need for blood transfusions until heart transplantation was conducted. The average daily cost of this therapy was estimated at approximately €3210 (US\$4220).

In conclusion, because avWD can also occur in children with VAD, our approach should be considered every time there is persistent bleeding. To our knowledge, we have reported the first case of severe bleeding related to avWD in a child supported with a bi-VAD and in whom bleeding was stopped with the use of Wilfactin. Its use in VAD-associated avWD has not been reported previously, and this treatment should be explored further in children with avWD.

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