

## Unforeseen Consequences of Therapy With Continuous-Flow Pumps

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*For use almost can change the stamp of nature.*

—Hamlet, *Act III, Scene IV*

Hamlet's statement may well be applied to the marked alteration in normal mammalian physiology introduced by the use of left ventricular assist devices (LVADs), particularly the nonpulsatile devices. This alteration of the "stamp of nature" has led to changes in the normal circulatory physiology not previously encountered in the field of medicine. Two unanticipated consequences of the clinical application of LVAD technology—acquired aortic valve insufficiency (AI) and acquired von Willebrand syndrome (VWS)—are reported in this issue of *Circulation: Heart Failure*.

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### Articles see pp 668 and 675

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The report by Cowger et al<sup>1</sup> quantifies a single-center experience with acquired AI after implantation of both the pulsatile HeartMate XVE (HM-XVE) and the nonpulsatile HeartMate II (HM-II) LVAD (Thoratec Corporation, Pleasanton, Calif). These investigators used echocardiography to study 78 patients who received the HeartMate XVE (n=25) or HeartMate II (n=53) LVAD between 2004 and 2008. They performed 315 studies at set time intervals and graded AI and aortic valve opening according to classic echocardiographic methodology. Trends in the development of AI were assessed in the group as a whole and were then compared by device type. Because this was a single-center study, the numbers available for follow-up evaluation were limited (49 patients at 6 months, 29 patients at 12 months, 13 patients at 18 months, and 5 patients at 24 months). However, an increase in both the development and the severity of AI was noted during this period. The grade of moderate-to-severe AI was approximately 11% at 6 months, 26% at 12 months, and 51% at 18 months. Compared with patients with the HM-XVE device, those with the HM-II pump had an increased incidence and severity of AI; however, in no patient was the AI severe enough to require intervention. The authors proposed several possibilities as to the cause of the AI but made no substantive conclusions about the etiology other than the presence of the device.

Development of AI in HM-XVE recipients was first noted clinically both in the bridge-to-transplant population and the

REMATCH trial.<sup>2</sup> Although not of critical clinical importance, the regurgitation could cause accelerated pump flow and further contribute to the already limited durability of these pumps. In the wake of these clinical observations, we attempted to quantify our experience with aortic valve deformity in HM-XVE recipients by analyzing 33 cases in which autopsy specimens or post-transplant explants were available. In 17 of these cases, we found some degree of aortic cusp fusion.<sup>3</sup> Sixteen of the HM-XVE patients and only 1 of the HeartMate pneumatic (HM-IP) pump patients had cusp fusion. The implantable pneumatic HeartMate required venting every 24 hours; this ensured native aortic valve opening during the short (8-second) venting period. This minimal opening of the native aortic valve interrupted commissural fusion and protected against the development of AI.<sup>4</sup> Aortic valve opening temporarily interrupts the stress of systolic pressure on the closed commissures, protecting them against resultant fusion, distortion, and AI. The protective effect of the periodic aortic valve opening was confirmed by the lack of clinically important AI on echocardiography in any of the patients supported by the pneumatic pump.

A follow-up study of this same patient group<sup>4</sup> assessed the relationship of the echocardiographic findings and LVAD pump flow to the degree of cusp fusion. Of the 17 patients with abnormal aortic valve pathology, 8 had echocardiographic evidence of AI, and in only 2 of them did pump outflow need to be increased. There were no clinical consequences related to these findings. The HM-XVE pump, operating in the automatic mode (as in Cowger's study), captures the entire cardiac output, and the aortic valve never opens. Indeed, for the aortic valve to open, the cardiac output would have to exceed 12 L/min, which is unlikely in this patient population. The HM-II may work either in series or in parallel with the native heart; if the pump is operating in series with the heart, the aortic valve does not open. If the pump is operating in parallel, the aortic valve opening should protect against commissural fusion and development of AI. This unforeseen consequence of the pump, and not the pump per se, is the most important factor in determining the development of AI.

The added stress of systolic pressure on the closed aortic valve is important to the development of AI. Therefore, it is essential that blood pressure be accurately recorded. If there is no pulsatility (ie, the aortic valve does not open), blood pressure, which cannot be accurately recorded with a conventional blood pressure cuff, must be measured by using the Doppler technique.<sup>5</sup> In the early clinical experience with the HM-II, blood pressure was not assessed by Doppler, and this may be a limitation of the Cowger et al study, particularly the early portion. It would be interesting to know the recorded

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pressures and the correlation of the pressures with the development of AI.

Despite limitations, the study of Cowger et al is an important contribution to the literature on mechanical circulatory support. The authors have precisely observed and quantified the incidence of AI, an unanticipated and undesirable complication of LVAD support. Their observations should prove useful in assessing the success of therapeutic interventions to lessen the occurrence of AI.

The second article, by Meyer et al,<sup>6</sup> describes acquired VWS in 26 patients supported by the HM-II LVAD (median support time, 4.5 months; range, 1 to 24 months). In all patients, the large von Willebrand factor multimers disappeared and normal platelet aggregation was impaired. The changes were presumed to result from high shear stress imposed on the blood by the HM-II continuous-flow pump. One to 19 months after pump implantation, 8 patients had spontaneous bleeding. Four of these patients had minor gingival bleeding or epistaxis, 1 had hematuria, and 3 had gastrointestinal (GI) bleeding. In only 1 case was the bleeding of clinical consequence. All patients were taking anticoagulants. An interesting aspect of this study is that acquired VWS was present in all patients, but bleeding complications occurred in less than a third of the patients and were relatively minor.

Gastrointestinal bleeding has been associated both with VWS and aortic stenosis. Heyde<sup>7</sup> first noted the relationship between GI bleeding and aortic stenosis in the 1950s.<sup>8</sup> In the early 1990s, Warkentin et al<sup>9</sup> speculated that the GI bleeding seen in AI could be related to acquired VWS. In 2003, Vincintelli et al<sup>10</sup> found a direct correlation between the severity of aortic stenosis, the level of multimer deficiency, and the occurrence of GI bleeding. In 2003, we were the first to note the relationship of bleeding to intestinal angiodysplasia in patients supported by a continuous flow pump.<sup>11</sup> Three patients had bleeding from arteriovenous malformations that was treated by discontinuation of anticoagulants, direct endoscopic cauterization, intestinal resection (in 1 patient), and the restoration of maximal pulsatility by minimizing pump flow. More recently, a number of single-center, retrospective studies have documented increased bleeding with the HM-II.<sup>12–14</sup> All the investigators reported a higher incidence of bleeding complications than we have seen at our center, which has the largest experience with implantable continuous-flow LVADs (more than 250 pumps of varying types). We documented late bleeding in 19% of our 171 HM-II recipients, including GI bleeding in 6%. This experience is similar to that encountered with the Novacor pulsatile LVAD (Novacor, WorldHeart Inc, Oakland, Calif), which, like the HM-II (but unlike the HM-XVE), necessitated anticoagulant therapy.<sup>15,16</sup>

An earlier iteration of the HM-II, which was implanted in 10 European patients, was associated with pump thrombosis and high mortality. To correct these problems, we recommended that the manufacturer eliminate the sintered titanium in the flow path of the pump and replace the rigid inlet cannula with a flexible one. These changes would minimize stasis and protect against inlet obstruction, thereby decreasing the risk of pump thrombosis. Despite these changes, aggres-

sive anticoagulation was still advised, based on the results of the initial European experience. We recommended anticoagulation for patients with the Jarvik pump (Jarvik Heart Inc, New York, New York)—not because of the pump itself but because of its secondary physiological effects on circulation, specifically aortic root stasis if the aortic valve did not open. Such stasis is not an issue with the HM-II pump because the outflow graft is in the ascending aorta. Meyer's findings may support the belief that induced hypocoagulability and VWS may, in fact, be an important characteristic of continuous-flow pumps, thus reducing the overall need for anticoagulation. Although we continue to give HM-II patients anticoagulants, we do so on an individualized basis and try to minimize such therapy, particularly when the aortic valve is opening regularly and other indications for anticoagulation are not present.

The 2 articles featured in this issue<sup>1,6</sup> may reflect a common thread in the etiologies of 2 unanticipated complications of continuous flow. In our experience, increasing the pulsatility of the HM-II by decreasing the pump rate has been effective therapy for GI bleeding. Similarly, opening the aortic valve will decrease the incidence of AI. Dr Jarvik addressed this problem in his pump by introducing an automatic, intermittent speed change. For 8 seconds of every minute, the pump flow decreases to 7000 rpm, which allows for aortic valve opening, parallel flow between the heart and the pump, and washout of the aortic root. With parallel flow—the optimal operational mode of these devices—the blood is subjected to lower shear stress. This change should lessen not only aortic commissural fusion and aortic insufficiency but also GI bleeding related to angiodysplasia and acquired VWS. The potential efficacy of this approach was further suggested by Vincentelli et al<sup>10</sup> in the study cited above of decreasing shear stress by decreasing pump flow is validated by the finding of Vincentelli et al<sup>10</sup> relating severity of AI to multimer deficiency.

No successful therapy for mortal illness can be employed without risk. The use of LVADs is currently indicated as a life-saving therapy for patients with terminal heart failure. The unforeseen complications described herein<sup>1,6</sup> are examples of the risk associated with this new technology. Although both of the studies are small, single-center studies and limited because of their size, they make an important contribution to the literature. The multicenter data generated from the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) should give us larger, longitudinal studies that will further clarify the clinical significance of Cowger's and Meyer's work.

The “stamp of nature” of pulsatile blood flow has been permanently altered by the introduction of nonpulsatile flow. Thus far, nature has tolerated nonpulsatile blood flow in the mammalian circulation. However, this is a totally new physiology, and we must address it in ways totally different from those of the past. “As our case is new, so we must think anew, and act anew.”<sup>17</sup> We must “disenthral” ourselves from the old maxims of classic physiology to properly manage the physiological complexities introduced by nonpulsatile blood flow.

## Disclosures

None.

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