EDITORIAL

Interplay of pump design elements and bleeding predilection—Mechanisms for a forward momentum

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“I’m not interested in preserving the status quo; I want to overthrow it.” - Niccolo Machiavelli

Implantation of left ventricular assist devices (LVADs) is now associated with a 2-year survival that closely rivals the outcomes observed with heart transplantation (80%). Thus, attention has shifted beyond mere survival, to survival with freedom from adverse events, which still pose a major challenge to the widespread application of the therapy. Non-surgical bleeding represents the most prevalent component of hemocompatibility-related adverse events and is a common cause of readmission in contemporary patients with LVAD. To illustrate the magnitude of the issue, gastrointestinal bleeding occurs in approximately 33% of the patients with an LVAD implantation, and the etiology is complex, as well as multifactorial. While the use of anti-coagulation and anti-thrombotic therapy probably plays a major role, the use of these agents cannot explain all the bleeding events and other mechanisms, such as the development of mucosal angiodysplasias specifically associated with continuous flow (arteriovenous malformations), remain essential. The interference with a natural coagulation system disturbed by a blood-device interface and shear stress-dependent damage to coagulation proteins, in particular the degradation of high molecular forms of von Willebrand factor (vWF), has been previously corroborated as a contributor to bleeding risk in this patient population. HMvWF is a multimeric glycoprotein constituted from identical subunits with binding sites for platelet glycoprotein receptors and collagen. These hesticostatic components play a critical role in thrombus formation by enhancing platelet adhesion and aggregation at the sites of vascular injury. With the advent of rotary blood pumps, this figurative “blender” phenomenon appeared as a common denominator for all such devices and became accepted as a necessary shortcoming of this technology.

Curiously, while it was clear that high shear stress in the continuous flow LVADs reduces the levels of HMvWF, it was less obvious how or if different pump designs may influence the integrity of these multimers. From an engineering design perspective, the HeartMate 3 (HM3) fully magnetically levitated bearing-less pump with a wider blood flow path provided a promise of potentially lower shear damage during operation. As such, HM3 implantation could be associated with a more normal HMvWF profile than that seen with other rotary pumps. Notably, in a comparative effectiveness, single-center study, Netuka et al reported a significantly higher degree of HMWM preservation with the HM3 compared with an axial flow assist device. Consistent findings were reported in another single-center analysis comparing the HM3 and Heartware HVAD pumps, suggesting that the unique engineering features may in fact be responsible for a more forgiving effect on von Willebrand factor (vWF) multimers. Surprisingly, these structural mechanistic observations in both trials diverged with “functional” assays, which generally demonstrated preservation within normal physiological ranges between groups.

These early single-center exploratory findings were now investigated in the prospective, multicenter study by Bansal et al who compared and contrasted blood samples from 60 HM3 patients out of 5 centers within the Continued Access Protocol for the MOMENTUM 3 study to the results obtained from randomly selected bio-banked samples from the PREVENT study with the HeartMate II. Using data from the PREVENT rather than from the HeartMate II arm of the MOMENTUM 3 trial was an ambitious pursuit, since the previous trial was specifically designed to follow a strict
surgical implantation technique, maintain pump speed settings in controlled ranges, and attend to anti-coagulation in an effort to lower the incidence of pump thrombosis with the HeartMate II pump. The studies included either few or no women, an important limitation in understanding gender-related differences in outcomes.

Highly clinically relevant, the HMvWF was reduced compared with healthy controls before LVAD implantation, a unique demonstration of the sequelae of advanced heart failure on this protein multimeric structure. Once implanted with the pump, a further decrease in HMvWF at 90 days was noted but with a significantly lesser degradation in patients treated with HM3 compared with the axial flow device recipients. Importantly, a multivariable regression analysis confirmed that the preservation was independently driven by the selection of the HM3 LVAD for implantation. In contrast, functional measures of vWF represented by avWF:Act latex immuno assay remained in what are physiologically considered to represent the normal ranges for both pumps. It should be noted that such normal levels have not been established specifically within LVAD-treated patient cohorts, and therefore, this assertion of normalcy should be interpreted cautiously.

An interesting and fundamental finding for both groups was the independent association between the severity of heart failure and HMvWF. Lower profiles (INTERMACS 1-2) representing the highest severity of unstable hemodynamics were associated with a significantly greater degree of multimer degradation. Importantly, the authors went one step further by correlating the analyses with clinical outcomes within the HM3 cohort. These data elegantly substantiate that the HMvWF both at baseline and after 90 days were distinctly lower in patients who experienced non-surgical bleeding episodes in the follow up period.

How should we interpret these observations? First, the study appears to be conclusive in demonstrating that HMvWF is better preserved in the HM3 than in the HeartMate II pump and validates prior pilot observations. Second, an association between decreased levels of HMvWF and bleeding episodes was established. This finding is more challenging to interpret, since alterations and the propensity for bleeding pre-existing before the pump implantation. One may argue that the initial pre-implant HMvWF degradation is a substrate for downstream deterioration and supports the observations that point to a greater burden of adverse outcomes in the sickest individuals undergoing device implantation. On the other hand, since little is known about the dynamics in HMvWF within a clinical course, we lack information about the HMvWF immediately prior to the bleeding episode.

A disparity between the mechanistic and functional parameters of vWF supports a notion that a degree of HMvWF multimers represents a marker of risk rather than a risk factor for bleeding. In this regard, pathways that may be in the domain of an inflammatory response or in relationship to hormones upregulated at a tissue level in response to oxidative stress may be associated with non-surgical LVAD bleeding.11,12 There remains some intrigue in the interpretation of these findings, particularly since it is not known if the alterations in the functional assays of downstream effector proteins of vWF are indeed functionally normal or are only being picked up as within a range that is “considered” to be normal.

Accrued clinical correlations between mechanistic HMvWF performance and adjudicated bleeding events in LVAD recipients raises a logical question whether such degradation assessments may provide pertinent phenotypic information to assess bleeding risk and may eventually serve as a biomarker to use more individualized anti-thrombotic therapy. At this point, one should exercise several reservations. Such a strategy would require international standardization of the analyses used and in-depth evaluation of longitudinal HMvWF changes in the LVAD recipients, at discrete timepoints, and in relation to a wide variety of clinical conditions. Should an absolute threshold be established, or should we evaluate a relative cut-off for decrement? This would require specific LVAD population analyses, as well as matching with comorbid factors, to determine the bleeding risk. Notwithstanding these caveats, such initiatives may ultimately help to alleviate excess bleeding risk and consequently further improve the overall outcomes.

The demonstrated superiority of the HM3 in HMvWF preservation provides mechanistic support for the final results of the Momentum 3 Trial, which documented a significantly lower incidence of any bleeding episodes, as well as gastrointestinal bleeding, in favor of the HM3 pump arm. Obviously, we cannot deduce from the study by Bansal et al that the clinically important reduction in the bleeding risk seen in the Momentum 3 trial could be ascribed to greater preservation of HMvWF alone.10 Data also show that even if HMvWF played an important role in the context of bleeding events, the high risk of bleeding is by no means completely alleviated by the technological advances introduced by a specific pump design. For illustration, the European ELEVATE Registry encompassing 463 primary HM3 patients reported bleeding episodes within the first 6 months in 25% of the patients.13 As such, it is clear that factors other than the preservation of HMvWF must be controlled to mitigate the bleeding risk.

In this context, because of the encouraging low risk of thrombotic events reported with the HM3,1 one intriguing approach would be to reduce the burden of anti-thrombotic and anti-coagulation therapy. It remains unclear if patients treated with this new technology require both anti-platelet and a vitamin K antagonist to prevent thrombotic events. If this is not the case, which one may be reduced or eliminated? Could we get away with the complete avoidance of either anti-thrombotic or anti-coagulant agents if the HM3 pump is truly thrombo-resistant? Until recently, our experience with patients off acetylsalicylic acid and/or vitamin K antagonist has almost exclusively been restricted to the indication-dependent scenarios (i.e., recurrent bleeding), which are probably very different in patients from the prevailing non-bleeders. To date, only smaller non-randomized studies have evaluated the reduced intensity or even complete vitamin K antagonist withdrawal in a comprehensive safety algorithm-guided environment.14,15 Despite these highly encouraging preliminary findings given the complete
absence of thromboembolism, future randomized, multicenter studies further exploring these withdrawal strategies are warranted.

Intuitively, such an integrative approach combining HMvWF biomarker longitudinal analysis along with responsive tailored anti-thrombotic strategies may pragmatically contribute to new best practices development for optimized patient outcomes. Taken together, Bansal et al are to be congratulated for thoughtful study design, rigor in the study conduct, as well as compelling clinically matched revelations. Although they could not provide a “magic wand” solution to the yet undeciphered continuous flow pump bleeding conundrum, the study provides an important step forward in enhancing our understanding of this multi-dimensional equation.

Disclosure statement

FG was an advisor, speaker, investigator for Abbott and Carmat SA. IN received research grant site principal investigator (PI) or overall PI, consultant, travel, hotel or registration fee support from Abbott; research grant site PI or overall PI, travel, hotel or registration fee support from Carmat SA; served as a medical advisory board member, board member, and stockholder of LeviticusCardio Ltd.; and served as a scientific/medical advisory board member for Evaheart, Inc.

References