Commentary: Inflammation, hemocompatibility, and allosensitization—What is next?

Federico Pappalardo, MD,^{a,b} Andrea Montisci, MD,^{c,d} and Antonio Miceli, MD, PhD^e

From the ^aAdvanced Heart Failure and Mechanical Circulatory Support Program, San Raffaele Scientific Institute, Milan, Italy; ^bVita-Salute San Raffaele University, Milan, Italy; ^cDepartment of Anesthesia and Intensive Care, Cardiothoracic Center, Istituto Clinico Sant' Ambrogio, Gruppo Ospedaliero San Donato, University and Research Hospitals, Milan, Italy; ^dDepartment of Cardiac Surgery, University of Milan, Milan, Italy; and ^eDepartment of Minimally Invasive Cardiac Surgery, Cardiothoracic Center, Istituto Clinico Sant' Ambrogio, Gruppo Ospedaliero San Donato, Milan, Italy.

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Address for reprints: Antonio Miceli, MD, PhD, Department of Minimally Invasive Cardiac Surgery, Cardiothoracic Center, Istituto Clinico Sant' Ambrogio, Gruppo Ospedaliero San Donato, Via Giuseppe Faravelli 16, 20149 Milan, Italy (E-mail: antoniomiceli79@alice.it).

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Left to right: Federico Pappalardo, MD, Andrea Montisci, MD, and Antonio Miceli, MD, PhD

Central Message

Inflammation, hemocompatibility, and allosensitization are the new key factors to improving left ventricular assist device outcomes.

See Article page 155.

Outcomes of patients treated with left ventricular assist devices (LVADs) have continuously improved in recent years, reaching a similar survival to that of patients undergoing heart transplantation (HTx).¹ As result, LVADs have become an effective therapy for the growing number of patients suffering from end-stage heart failure in the era of reduced organ availability.

Previous studies reported that LVADs (mostly first- and second-generation devices) implanted as bridge to transplant or bridge to candidacy strategy are variably associated with allosensitization, which increases the time spent on the waiting list as well as the risk of antibody-mediated reactions after HTx.² In this issue of the *Journal*, Iyengar and colleagues³ report their investigation of immunologic responses of patients receiving mechanical supports, adding evidence of how inflammation may play an important role in the pathogenesis of allosensitization. Specifically, in a small cohort of patients receiving the HeartMate II (Abbott Laboratories, Abbott Park, Ill), Iyengar and colleagues³ found that (1) no patients had development of de novo HLA antibodies after device implantation, and (2) there was a remarkable increase in inflammatory cytokines after the implantation, which drove the maturation of B cell phenotypes and pointed out the role of inflammatory milieu in driving allosensitization guided by *already existing* sensitized B cells.

These findings arise a wider horizon of discussion, which goes beyond allosensitization. An important question is the timing of HTx after LVAD implantation. Recent studies have shown that HTx performed less than 3 months after LVAD implantation is associated with worse outcomes,⁴ whereas graft survival is significantly longer in those patients who have a decline of panel reactive antibodies activity.⁵ On this basis, we hypothesize that HTx should

be performed when cytokine storm induced by LVAD implantation has declined, providing the absence of life-threatening, device-related, complications.

Iyengar and colleagues³ showed a great increase in cytokines after LVAD implantation, with an early peak of monocyte chemoattractant protein and interleukins 6, 8, and 10, which are responsible of inflammatory response, and a late peak of vascular endothelial growth factor, fibroblast growth factors, epidermal growth factor, and interleukins 3, 4, and 5, associated with angiogenesis and fibroblast proliferation. This finding underlines the significance of cross talk between inflammation and coagulation, which can be defined as the presence of common biochemical pathways simultaneously determining inflammatory reaction and coagulative system activation.⁶

Among many mechanisms sustaining this multifactorial process, the hemocompatibility (ie, the nature and effects of interaction between biomaterials and blood⁷) of LVADs plays an essential role, in terms either of genesis of thromboembolic complications or of shear stress-induced inflammation. Improvement in hemocompatibility therefore not only would lead to less thromboembolic complications but also might possibly reduce initiation and maintenance of an inflammatory state. In this regard, the improved hemocompatibility of third-generation LVAD (HeartMate 3; Abbott Laboratories) should offer a possible solution to this vicious circle. The analysis of the hemocompatibility-related events in the MOMENTUM trial showed a greater freedom from HRAEs of HeartMate 3 in comparison with the HeartMate II LVAD at 6 months.⁸

In conclusion, Iyengar and colleagues³ have opened a discussion on the importance of the relationship among inflammation, hemocompatibility and allosensitization that will appear on the top of the research agenda in the next years.

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