Risk Assessment in Critically Ill Patients Awaiting Transplantation: a Step Forward

Evalúación del riesgo en pacientes en estado crítico a la espera de trasplante:
un paso adelante

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“Prediction is very difficult. Especially about the future.” Niels Bohr, 1885-1962.

Despite the advent of mechanical circulatory support, orthotopic heart transplantation (OHT) is still the long-term therapy of choice in selected patients with refractory heart failure. Most centers have experienced a change in “referral epidemiology” as increasingly sicker patients are being encountered with advanced heart failure symptoms refractory to inotropic therapy and with concomitant end-organ dysfunction. The reasons for this dramatic shift are elusive but are undoubtedly in part due to the lack of recognition among general clinicians that symptom control does not often translate into improved long-term prognosis in the contemporary cohort of late-stage heart failure patients. Importantly, the long endorsed classification of functional capacity using the New York Heart Association system is no longer optimal since pharmacological and device-based therapy have broadened the phenotypic presentation of late-stage heart failure. Clinicians now face a spectrum of phenotypes within the “advanced heart failure” group ranging from cardiogenic shock to impending shock, inotropic dependency with end-organ failure to introtropic dependency without end-organ dysfunction, intermittently stable symptomatic states with recurrent and frequent decompensation, or chronic persistent symptoms resulting in substantial morbidity.

The INTERMACS scale was a clinical attempt to further refine and stratify these myriad presentations of patients with late-stage heart failure undergoing left ventricular assist device (LVAD) implantation. The primary intent of this endeavor was to help stratify the appropriate population most likely to benefit from LVAD therapy but also to allow the community of clinicians to develop a communication strategy to convey disease severity. Using a linear scale from 1-7, the INTERMACS scale differentiates patients in a stepwise fashion from the sickest patients with shock (1) and organ hypoperfusion, requiring inotropic therapy, percutaneous mechanical circulatory support, and invasive hemodynamic monitoring, to those patients who suffer significant morbidity but maintain the ability to function adequately at home (7). This clinically useful scale was never subjected to validation of its prognostic accuracy, until recently. Not surprisingly, sicker patients with a lower INTERMACS score have increased mortality following LVAD implantation. Similarly objective, quantitative criteria have not been applied to patients undergoing primary heart transplantation. This is not to say that heart failure survival scores do not abound. In fact, there are several validated inpatient prognostic heart failure scoring systems, but these are not fully reflective of the entire spectrum of phenotypic presentation since they typically exclude the more critically ill INTERMACS 1-2 patients.

In the article published in Revista Española de Cardiología, Barge-Caballero et al. sought to determine the usefulness of the INTERMACS scale in predicting outcomes for patients undergoing “urgent” transplantation. While “urgent” transplantation is not fully defined, the transplant times averaging 3 days imply consistency with the United States United Network for Organ Sharing status 1A listing, a category assigned to the sickest of patients. The rather short waiting times are once again a testimony to the success of the well admired “Spanish donation model”. The investigators retrospectively analyzed nearly 2 decades of patient encounters with OHT from a single Spanish center between 1991-2009, and included all patients, including those on percutaneous or extracorporeal mechanical circulatory support. Notwithstanding the alterations in medical and percutaneous device therapy over these years, the authors independently adjudicated these patients into distinct categories of INTERMACS 1, INTERMACS 2, and INTERMACS 3/4 (combined into a third cohort of patients).

The classification of patients appears accurate: INTERMACS 1 patients had an increased incidence of preoperative infections and hepato-renal dysfunction. As expected, the patients with the worse INTERMACS scores had poorer survival, with increased perioperative complications, including primary graft failure and renal failure. Survival curves dropped rapidly early and then plateaued, suggesting that the biggest obstacle in the patients classified as INTERMACS 1 was getting through the early perioperative phase of transplantation.

What can we learn from the current study? In addition to pointing to the validity of the INTERMACS scale in yet another clinical therapeutic scenario, the study quantifies what clinicians have known and practiced for several years: that patients must be...
stabilized with restoration of end-organ function and tissue perfusion prior to heart transplantation.\textsuperscript{8} The donor heart is typically subjected to a series of graded insults from brain death to cold ischemic time and subsequent ischemic-reperfusion injury. It is therefore necessary to assure that the milieu into which this very vulnerable organ is reset is as physiologically stable to accept it as possible. Heart transplantation should not be performed as salvage therapy in patients with active infections, coagulopathy, advanced end-organ dysfunction and shock states.

In the current era, patients with inadequate tissue perfusion despite maximal inotropic support are routinely considered for LVAD implantation as a bridge to transplantation. Most commonly, to minimize risks of postcardiomyotomy syndrome, right ventricular failure and bleeding, intra-aortic balloon pump counterpulsation and inotropic therapy are optimally utilized to improve hepatorenal function in preparation for LVAD implantation. If inadequate hemodynamic support is evident, extracorporeal membrane oxygenation may be employed for stabilization prior to LVAD implantation. Although the current generation of continuous flow LVADs offer improved survival with enhanced device durability and lower complication rates,\textsuperscript{9} the surgical risk for LVAD must be carefully assessed prior to implantation. Several LVAD risk scores have been developed, and have identified, amongst other factors, poor nutrition, respiratory failure, hepatorenal dysfunction, and coagulopathy as predictors of increased perioperative complications.\textsuperscript{10,11} If performed successfully in properly selected candidates, the post LVAD phase allows for enhanced nutritional and rehabilitative support that can facilitate improved outcomes from heart transplantation in these profoundly sick patients, yielding outcomes that parallel those patients receiving transplantation in less moribund situations.

How sick is too sick for transplantation? While specific criteria vary between institutions, transplantation should not be offered unless the 1-year survival can be reasonably predicted to exceed 85%.\textsuperscript{1} In the current era, effective therapies exist for patients who are failing despite maximal support. The current investigation spans 20 years—a lifetime in the arena of advanced heart failure therapeutics. Immunosuppression, surgical techniques, donor preservation, and LVAD devices have evolved dramatically in this time period. Despite these changes and differences, we believe that even if the authors had stratified their patients in varying eras, the results would likely have changed only minimally. It would appear that one of the potential perils of the wildly successful availability of donors in the “Spanish model” is the comfort that regulators and clinicians may have had with the rapid availability of a biological replacement, seemingly rendering the mechanical assistance option somewhat redundant. However, this important analysis by Barge-Caballero et al.\textsuperscript{7} should provide pause and inculcate a shift in thinking and practice within the region. It is time for adoption of selected but greater mechanical supportive care by the use of pre-emptive LVAD therapy to enhance overall post-transplant outcomes.

**CONFLICTS OF INTEREST**

Dr. Mehra reports a conflict as Editor in Chief of the *Journal of Heart and Lung Transplantation*; He receives research funding from the National Institutes of Health and consulting fees from Geron, Medtronic and St. Jude Medical.

**REFERENCES**