Defining and Refining Heart Failure Risk Stratification to Optimize Patient Selection for Cardiac Transplantation

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VO₂, BNP, GFR, RAP, CI, LVEDP, EF, Na, BUN, MR, LVEDD, PCWP, PVCs, VT, QRS, LBBB, COPD, DM, Tpnl, alh, CAD, OSA, Hct, RDW, CRT, ICD, HRV—the complex alphabet soup of heart failure risk assessment used to inform clinical decision making, select patient cohorts for trials, and ensure that expensive and supply-limited treatments are utilized in the most effective and equitable manner. Despite the seeming complexity of this task, heart failure clinicians have become facile at integrating multiple distinct variables into a cohesive understanding of risk using baseline patient characteristics, measures of cardiac structure and function, biomarkers, and assessment of functional capacity. The prognostic significance of many risk-associated parameters, such as ejection fraction, ventricular size, and the pathogenesis of heart failure are firmly established. However, recognition of the importance of common comorbidities and the rapidly evolving field of novel biomarkers that represent perturbation of normal biological pathways or markers of early organ damage have reshaped and refined contemporary risk assessment. More recently, larger datasets have facilitated the derivation and validation of multivariable risk-prediction models, such as the Heart Failure Survival Score, the Seattle Heart Failure Model, and the ESCAPE Risk Score.1–3

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In this issue of Circulation: Heart Failure, Kato et al4 re-examine the pivotal role of cardiopulmonary exercise testing in heart failure risk assessment and extend the sentinel work by Mancini that validated VO₂ as a potent predictor of short- and intermediate-term mortality.5 Mancini’s original observation that a peak VO₂ <14 mL/kg per min was associated with excessive mortality led to its incorporation in patient selection criteria for cardiac transplantation and mechanical circulatory support. The prognostic value of peak oxygen consumption has withstood the rigors of new medical and device therapies. For example, the negative chronotropic effects of β-adrenergic receptor blockers might be anticipated to alter the predictive accuracy of peak VO₂. Rather than negating its importance in risk assessment, β-blockers improve survival to such an extent that the absolute value defining excessive mortality risk is simply lower.6 With this background, the authors examined a cohort of 424 consecutive patients referred for cardiopulmonary exercise testing at Columbia University to determine if peak VO₂ remains an important variable in heart failure risk assessment, and whether its accuracy is modified by plasma b-type natriuretic peptide (BNP) levels. The cohort was younger than typically enrolled heart failure trials reflecting referral bias to a center with expertise in cardiac transplantation. These patients were well-treated with >80% receiving β-blockers and angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists. The patients were stratified based on peak VO₂ (<10 mL/kg per min, 10–14 mL/kg per min, and >14 mL/kg per min) and BNP (dichotomized at 506 pg/mL). The authors compared the outcomes of these patients with a large cohort of patients transplanted at their institution during the same time period. Peak VO₂ remained highly predictive of survival, free from the need for a left ventricular assist device (LVAD) or transplant. All patients with a peak VO₂ >14 mL/kg per min survived 12 months, whereas those with a peak VO₂ of <10 mL/kg per min had a likelihood of death, urgent VAD, or transplant that exceeded the mortality rate of the transplant population, regardless of BNP concentration. In contrast, the prognosis of patients with a peak VO₂ of 10 to 14 mL/kg per min was refined with the addition of BNP levels. An intermediate peak VO₂ with a low BNP was associated with a 1-year event-free survival rate similar to transplant patients, whereas a similar peak VO₂ with a BNP >506 pg/mL predicted a survival rate that was inferior to the transplant population.

The benefits of cardiac transplantation are time-limited with a median survival of 10 years.7 Thus, transplanting patients whose a priori mortality risk is not sufficiently high may actually shorten overall survival. The present study confirms that patients with left ventricular systolic dysfunction whose peak VO₂ exceeds 14 mL/kg per min do not routinely derive a mortality benefit from transplantation and suggests that serial risk assessment is appropriate. Conversely, patients with a peak VO₂ <10 mL/kg per min have a predicted short-term mortality that exceeds transplantation regardless of modifiers and should be considered for transplantation if eligible. It is the patient population with an intermediate peak VO₂ that requires additional testing to accurately assess mortality risk. Elevated plasma BNP seems to fill this void and provides incremental prognostic information. If validated, this approach could be applied broadly to improve selection of patients more likely to benefit from transplantation.

There is beauty in the simplicity of this observation. The authors have demonstrated that risk assessment can be refined using data elements currently available in centers with
experience in the diagnosis and management of advanced heart failure, and it is appealing to combine a functional parameter and a biomarker that reflects heart failure physiology, two fundamental principles that might be anticipated to predict heart failure outcomes. This approach would also be expected to enhance risk stratification for other advanced heart failure therapies such as mechanical circulatory support, particularly as this field begins investigation in a less moribund, ambulatory heart failure population.

The importance of accurate risk assessment in heart failure cannot be overstated. During the past decade, there has been no appreciable change in number of cardiac transplant procedures performed in the United States, despite a growing number of patients who might potentially benefit from the therapy. This combination of factors has led to a call for the Thoracic Committee of the United Network for Organ Sharing to examine issues of access and equity in heart allocation. Recent changes in heart allocation policies focused on enhanced risk assessment, and regionalized organ sharing have reduced waiting-list mortality and improved post-transplant survival. However, it is thought that there are opportunities for further risk stratification of patients awaiting cardiac transplantation. For example, allocation of 30 days at the highest priority (status 1A) on the heart transplant waiting list for stable patients supported on an LVAD has been questioned.8,9 It has been accurately argued that the risk of death in LVAD patients using elective status 1A time is quite low and is not equivalent to the risk of similarly listed patients utilizing other 1A criteria. However, once an LVAD patient develops a device-related complication that qualifies for 1A transplant listing, the pre-transplant mortality risks are higher than nearly any other patient cohort. Waiting-list mortality for other conditions, such as congenital heart disease and restrictive cardiomyopathies, may also be underestimated and result in inequitable access to donor hearts. These conditions often do not require the therapeutic interventions that qualify a potential recipient for transplant listing at the highest priority.

The Thoracic Committee is currently considering several options to improve waiting-list risk stratification that would allow expedited transplantation of high-risk patients. Strategies being considered include expansion and more granular definition of the current listing statuses and development of a heart allocation score similar to that used to allocate lungs in the United States. There seems to be consensus that waiting-list prioritization should be based on the risk associated with objective pathophysiologic parameters, rather than potentially arbitrary therapeutic interventions. In addition, waiting-list mortality and post-transplant survival are intimately linked in the determination of organ allocation effectiveness, and both must be considered in any attempt to enhance allocation policy. Optimal utilization of the limited supply of donor hearts each year will require us to define new and innovative risk-stratification methodology and to refine our existing tools so that the sickest patients will be afforded the timely opportunity for transplantation.

Disclosures
Dr Rogers serves as the Vice Chairman of the Thoracic Committee for the United Network for Organ Sharing (UNOS). The views expressed in this editorial do not necessarily reflect those of UNOS. Dr Rogers reports no other disclosures.

References

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