Risk stratification for renal transplantation: A role for heart rate response?

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Cardiovascular disease is the leading cause of death among individuals with end-stage renal disease (ESRD) and in those who undergo renal transplantation, accounting for up to 40%-50% of all deaths.[1–3] Clinical risk factors for coronary artery disease (CAD) are more prevalent in patients with ESRD, and 35%-45% of patients on dialysis and kidney transplant recipients have CAD.[3,4] Accordingly, the American Heart Association and American College of Cardiology Foundation (AHA/ACCF) released a scientific statement in 2012 to define high-risk clinical features in pre-transplantation patients and have recommended noninvasive cardiac stress testing in asymptomatic renal transplant candidates with three or more risk factors, irrespective of functional status.[5]

In the general population, noninvasive stress myocardial perfusion imaging (MPI) is a powerful tool for risk stratification in patients with an intermediate pre-test probability of CAD and ischemic heart disease.[6] However, its utility in advanced renal disease patients under consideration for transplantation is less clear. Small studies have shown that in ESRD patients referred for kidney transplant, stress MPI has relatively low sensitivity (67%) and specificity (77%) for detecting coronary artery disease ($\geq$ 70% stenosis).[7] Diagnostic challenges with MPI are multifactorial, but likely stem from several conditions associated with ESRD, including left ventricular hypertrophy and endothelial dysfunction, which affect interpretability of perfusion defects.[8,9]

More recently, several non-perfusion variables measured during stress MPI have been identified in the search for added prognostic information, and heart rate response (HRR) to vasodilator stress has appeared promising.[10] Large retrospective cohorts have shown that blunted HRR is not only an independent predictor of cardiovascular events and all-cause mortality, but may also reclassify up to 20% of individuals when added to traditional risk factors and MPI results.[11,12] The added prognostic impact of HRR has been reproduced in patients with ESRD,[9] but studies examining the role of HRR in predicting perioperative or long-term events in renal transplant patients are lacking.

In this issue of the *Journal of Nuclear Cardiology*®, Al Jaroudi and colleagues build upon their previous findings[13] and describe the prognostic utility of blunted HRR in patients with ESRD undergoing renal transplantation.[14] The authors include 352 consecutive patients from a single center who received vasodilator stress MPI during pre-renal transplantation evaluation, of whom 140 (40%) had blunted HRR, defined as a $<$ 28% change from baseline to peak heart rate after regadenoson administration or a $<$ 20% change after adenosine, based on previously established cutoffs. Patients were followed for an average of 3.2 years for the primary endpoint of overall cardiac death or myocardial infarction (MACE); with secondary events of MACE within 30 days of surgery (post-op MACE) and all-cause death. The authors found that patients with blunted HRR during MPI had an increased risk of MACE (HR 1.7; CI 1.1-2.6) and post-op MACE (HR 2.2; CI 1.2-4.0) as compared to those with normal HRR. This association persisted after adjustment for AHA/ACCF risk factors,[5] gender, baseline heart rate, summed stress score (SSS), and β-blocker use.

The present study by Al Jaroudi *et al.* is an important addition to existing literature and

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demonstrates the potential value of this easily acquired measure, HRR, in improving risk stratification in CKD and pre-transplant patients, a population for whom many diagnostic and prognostic challenges exist. Frequently, patients with advanced renal disease are asymptomatic despite a high burden of underlying cardiovascular disease. Conversely, many cardiac symptoms such as angina or dyspnea lack sensitivity and specificity for severe CAD in patients with ESRD,[15] and general guidelines for perioperative cardiac risk assessment[16] do not specifically address or account for the complex, heterogeneous clinical milieu of transplantation candidates.

Despite these issues, the prognostic value of MPI in this patient population appears robust—abnormal findings on stress MPI are associated with adverse outcomes.[9,17] A recent post-hoc analysis of clinical trial data showed that an abnormal MPI (SSS $\geq$ 4) was associated with a nearly twofold increase in risk for cardiac death or MI among patients with ESRD, consistent with several other studies.[18–21] Unfortunately, this report also highlights a significant shortcoming of MPI in high-risk ESRD patients, as lower risk patients with a normal MPI still had an approximate 5% annual rate of cardiovascular death or MI.[18] To this end, Al Jaroudi *et al.* reported that the association between blunted HRR and MACE remained significant even in patients with a normal stress MPI (HR 1.8; CI 1.1-3.0), as well as in subgroups of patients with few clinical CAD risk factors. As such, HRR may be a useful adjunct to the traditional evaluation of CAD risk and MPI findings by improving discrimination of ESRD patients at risk for future events following transplantation irrespective of baseline risk.

Several important questions remain regarding the use of HRR, and stress MPI in general, when evaluating pre-renal transplant candidates. Although a blunted HRR appears to identify higher risk patients with ESRD who undergo renal transplantation, studies on the benefit of revascularization prior to renal transplant have not been promising. For instance, Kim *et al.*, performed gated SPECT on 215 asymptomatic patients with ESRD at the time of dialysis initiation. Of the 165 patients deemed high-risk by clinical risk factors, perfusion defects were present in nearly half of all patients. Although ischemia was predictive of adverse cardiovascular events (HR 2.1; CI 1.1-4.2), high-risk individuals who were revascularized fared no better than those who were medically managed (HR 0.6; CI 0.3-1.5).[22]

Similarly, results from multiple large clinical trials such as COURAGE or BARI-2D have shown no added benefit of revascularization over medical therapy for patients in the general population with stable CAD.[23,24] Importantly, patients with advanced renal disease, including renal transplant recipients, were excluded from these studies. An ancillary study of the ongoing, multicenter randomized controlled ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) trial, ISCHEMIA-CKD (ClinicalTrials.gov Identifier: NCT01985360), seeks to provide new insight on this matter for patients with renal disease. With a target enrollment of approximately 1,000 patients, the objective of ISCHEMIA-CKD is to compare an initial strategy of optimal medial therapy (OMT) vs revascularization plus OMT among stable patients with at least moderate ischemia on stress testing and advanced CKD (eGFR $<$ 30 or on dialysis) for a primary composite endpoint of death or nonfatal MI through 4 years of follow-up. Results from ISCHEMIA-CKD may help elucidate the role of stress MPI in guiding revascularization in patients with renal dysfunction. Future studies will be needed to determine whether the use of HRR can further discriminate patient subsets that would benefit from revascularization.

Alternatively, perhaps HRR, in combination with MPI, can also be used to guide post-transplant management of CAD risk factors. Renal transplant patients have a high prevalence of cardiovascular risk factors as up to 90% have hypertension, 70% have dyslipidemia, and 50% have diabetes.[25] In particular, the presence of diabetes has been strongly associated with risk of all-cause mortality (HR 1.6) and MACE (HR 1.8) in renal transplant candidates.[26,27] Given that cardiac autonomic dysfunction from poorly-controlled or long-standing diabetes has been implicated in the pathophysiology of blunted HRR,[28] integrating HRR into the pre-transplantation evaluation may help identify patients who may benefit from more aggressive diabetic therapies and strict glucose control.

Al Jaroudi *et al.* demonstrated the promise of HRR for risk stratification in patients with ESRD prior to renal transplantation; however, several steps remain before it is established as a critical component of risk stratification among these high-risk patients. Prospective validation across several institutions would improve the generalizability of HRR in this population. Additionally, definitions of normal and abnormal HRR in the literature are variable,[29] and although these definitions may be population- and/or vasodilator-specific, future studies should address this question prior to clinical utilization. Finally, how can we best integrate the prognostic information gained from HRR? Can we use HRR to determine which transplant candidates should undergo revascularization prior to surgery? Or should we use HRR to tailor medical therapy and more aggressively manage comorbid cardiovascular risk factors? These

questions represent the paucity of evidence available on risk detection and clinical management of ESRD patients. Given the clinical benefit afforded by kidney transplantation and the relative scarcity of kidney donors,[3] we look forward to additional studies to expand the available high quality evidence targeting risk detection and potential improvement in patient outcomes based on imaging-guided care.

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