Stress testing in patients with chronic kidney disease: The need for ancillary markers for effective risk stratification and prognosis

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More than 20 million adults have chronic kidney disease (CKD) and nearly one-half million people have end-stage renal disease (ESRD) in the United States¹ and with increasing prevalence of diabetes, obesity, and the elderly, this number is projected to increase exponentially by 2030.² Similarly, population studies in various countries indicate that CKD affects as many as 1 in 10 adults, or over 500 million people worldwide.³

Cardiovascular disease is the leading cause of morbidity and mortality among subjects with CKD,^{1,4,5} 15–30 times higher than the age-adjusted cardiovascular mortality rate in the general population.^{6,7} The prognosis of patients with CKD and especially those with ESRD is poor and is worse than that for the general population who have cancers, heart failure, stroke, or acute myocardial infarction (MI),¹ and as such patients with CKD are considered by some as coronary artery disease (CAD) risk equivalents.^{8,9} Although the prevalence of CAD is high, conventional cardiac risk factors such as hypertension, hyperlipidemia, smoking, or even the Framingham risk score are less predictive of CAD in CKD patients.¹⁰ Moreover, chest pain has poor sensitivity and specificity (65% and 66%, respectively) for predicting CAD in CKD

patients.¹¹ As such stress testing is used as a modality to risk stratify patients with CKD or ESRD.

STRESS TEST IN CKD/ESRD PATIENTS

Although stress testing is used widely in patients with CKD/ESRD, there is controversy over the utility of stress testing when compared with invasive angiography as the best screening modality.¹² Fundamental to this controversy is the low sensitivity of stress testing in the CKD/ESRD cohort compared with subjects without CKD (Table 1).¹³ Exercise electrocardiography (EKG) (treadmill or bicycle) is used in a minority of patients with CKD/ESRD as the prevalence of abnormal baseline EKG is high due to the presence of left ventricular hypertrophy, left bundle branch block, and ST-T changes that are either nonspecific or due to electrolyte abnormalities. Moreover, the exercise capacity of patients with CKD/ESRD is limited due to muscle fatigue, anemia, peripheral vascular disease, peripheral neuropathy, and other comorbidities. In addition, the sensitivity and specificity of exercise electrocardiography in CKD/ESRD patients is poor (Table 1).^{13,14}

Similarly, the sensitivity and specificity of myocardial perfusion single photon emission computed tomography (SPECT) to detect CAD in CKD/ESRD patients are highly variable. In a prospective study of 138 patients referred for pre-renal transplant cardiac evaluation (43% on dialysis) and underwent coronary artery calcium score, coronary computer tomography angiography, and SPECT, SPECT had a low sensitivity (53%) and modest specificity (82%) for detecting obstructive CAD ($\geq 50\%$ stenosis).¹⁵ Among patients with a normal SPECT, 14% of patients had obstructive CAD on invasive angiography.¹⁵ Marwick et al found that while the sensitivity of dipyridamole thallium scintigraphy for detecting obstructive CAD was 95%

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Table 1. Sensitivity and specificity of stress test modalities to predictive obstructive CAD in patients with CKD (potential kidney transplant recipients)

Stress test	Sensitivity	Specificity
Exercise stress test [†]	0.36–1.00	0.00–0.91
Myocardial perfusion scintigraphy	0.74 (95% CI 0.54–0.87)	0.70 (95% CI 0.51–0.84)
Dobutamine stress echocardiography	0.79 (95% CI 0.67–0.88)	0.89 (95% CI 0.81–0.94)

Data from Wang et al.¹³

[†]Data based on two studies only and no pooled estimates provided.

in non-CKD control group, it was only 37% in dialysis patients even after matching for severity and extent of CAD.¹⁶ In this study, the probability of obstructive CAD in patients with normal SPECT was 38%. Finally, in a meta-analysis of nine studies of myocardial perfusion SPECT in potential kidney transplant recipients, the pooled sensitivity was 74% with a pooled sensitivity of 70%, both with wide confidence intervals (Table 1).¹³ The reason for reduced sensitivity of myocardial perfusion SPECT in CKD/ESRD patients is not clearly known but has been attributed to a number of mechanisms¹⁶: (a) “balanced ischemia” due to multivessel disease resulting in global ischemia. Patients with CKD have increased prevalence of multivessel disease. Since myocardial perfusion SPECT is based upon comparison of perfusion between myocardial segments, balanced multivessel disease can potentially result in false-negative SPECT; (b) presence of collateral vessel that may prevent the establishment of zones of disparate flow thereby producing the appearance of homogeneous perfusion and a false-negative SPECT; and (c) higher resting levels of adenosine (resulting in higher resting coronary flow) seen in patients with ESRD may result in reduced vascular responsiveness to dipyridamole resulting in “inadequate stress.”

ANCILLARY STRESS TEST MARKERS OF HIGH RISK

Given the limitations of myocardial perfusion SPECT in CKD cohort, there is a need for ancillary markers to improve its accuracy. In this issue of the journal, AlJaroudi et al evaluate the use of one such ancillary marker—heart rate response during regadenoson stress MPI in patients with ESRD.¹⁷ Heart rate response was defined as $100 \times (\text{peak stress heart rate} - \text{resting heart rate}) / \text{resting heart rate}$ with values $< 28\%$ considered as a blunted heart rate response. From a cohort of 303 patients with ESRD, blunted heart rate response was associated with a twofold to threefold increased adjusted risk for all-cause mortality and also other cardiovascular endpoints and was associated with

increased event rate among patients with both normal and abnormal MPI and added incremental prognostic value.¹⁷ The strengths of the analyses are the large number of patients with ESRD and the use of robust statistical techniques including propensity score matching to account for measured confounders. The limitations are the post hoc nature of the analyses and the inability to account for unmeasured confounders such as frailty. In addition, although the authors evaluated long-term outcomes, no data were presented on the presence or absence of obstructive CAD on invasive angiography. It is also not known if the increased risk seen with blunted heart rate response is merely an epiphenomenon of underlying sickness/chronicity of comorbidities and frailty and if this marker be amenable to treatment and if it can be reversed. However, heart rate response is attractive as it is simple to calculate from data which is generally collected during stress test and does not add to the cost of the stress testing.

Various other ancillary markers have been shown to identify patients at high risk of cardiovascular outcomes (Table 2). In patients undergoing exercise stress test, a plethora of prognostic data is available from exercise stress test variables.¹⁸ Few of the markers of adverse prognosis include high resting heart rate, low time to peak heart rate, chronotropic incompetence (defined as inability to achieved $\geq 85\%$ age predicted maximal heart rate, low percent heart rate reserve, or a low chronotropic index), abnormal heart rate recovery (defined as difference in heart rate between peak exercise and 1 or 2 min later), abnormal functional capacity, and exercise-induced hypotension.¹⁸ Similarly, some of the above parameters have also been tested in patients undergoing pharmacological stress test including the heart rate response evaluated in this study and indices of chronotropic incompetence including heart rate reserve in those undergoing dobutamine stress test^{19,20} (Table 2). Moreover, the EKG parameters of ischemic ST-T changes during stress or recovery and ventricular arrhythmia during stress testing have been shown to have prognostic value.¹⁸ Ancillary markers of high risk for patients undergoing SPECT included increased lung

Table 2. Ancillary markers of high risk in patients undergoing stress test

	Ancillary marker	Description
Exercise parameters	<p>Chronotropic incompetence:</p> <ul style="list-style-type: none"> • <85% age predicted maximum heart rate • Low % heart rate reserve ($\leq 80\%$ or $\leq 62\%$ for patients on β-blockers) • Low chronotropic index (<0.8) <p>Impaired heart rate recovery</p>	<p>Age predicted maximum heart rate = $220 - \text{age}$</p> <p>Percent heart rate reserve = $[(\text{peak HR} - \text{HR at rest}) / (220 - \text{age} - \text{HR at rest})] \times 100$</p> <p>Chronotropic index = heart rate reserve/metabolic reserve</p> <p>Difference between HR at peak exercise and HR 1 or 2 minutes later. Abnormal values defined based on the stress test protocol:</p> <ul style="list-style-type: none"> • With upright cool-down period—≤ 12 bpm 1 min into recovery • With immediate supine position ≤ 12 bpm 1 min into recovery • With sitting ≤ 22 bpm 2 min into recovery <p>Predicted value in men: $14.7 - 0.11 \times \text{age}$</p> <p>Predicted value in women: $14.7 - 0.13 \times \text{age}$</p>
EKG parameters	<p>Abnormal estimated functional capacity (METs) ($<85\%$ of predicted)</p> <p>Exercise-induced hypotension</p> <p>Ischemic ST-T waves changes</p> <p>Ventricular arrhythmias</p>	<p>Frequent ventricular ectopics (>7 bpm), couplets, bigeminy, trigeminy, ventricular tachycardia, or fibrillation</p>
Duke treadmill score	Value of ≥ 5 low risk, between -10 and 5 intermediate risk, and <-10 high risk	Minutes (Bruce Protocol)— $5 \times \text{ST-Segment Deviation} - 4 \times \text{Angina Score}$
Pharmacological stress Vasodilator	Heart rate response $<28\%$ on vasodilator stress	100 * (peak stress heart rate – resting heart rate)/resting heart rate
Dobutamine	<p>Chronotropic incompetence</p> <ul style="list-style-type: none"> • <85% age predicted maximum heart rate • Low % heart rate reserve ($<70\%$) <p>Extent and severity of ischemia</p> <p>Increased lung uptake</p> <p>Transient ischemic dilatation</p> <p>Regional wall motion abnormalities</p> <p>Reduced LVEF</p> <p>Post stress LVEF drop $\geq 5\%$</p> <p>LV mechanical dyssynchrony with bandwidth ≥ 62 degree</p> <p>Global or regional myocardial blood flow reserve and/or absolute myocardial blood flow</p>	
SPECT findings: Perfusion		
SPECT: Gated		
Stress PET		

uptake and transient ischemic dilatation, both of which have been shown to be markers for extensive and severe CAD including multivessel disease, proximal left anterior descending artery disease or left main coronary artery disease.²¹ In addition, additional prognostic information can be gleaned from gated SPECT including information on regional wall motion abnormalities and left ventricular ejection fraction. Thus, there is a plethora of ancillary markers to identify patients at high risk of future cardiovascular events. Although many of the above ancillary markers have not been tested in the CKD/ESRD cohort and further studies are needed, given the low sensitivity and specificity of SPECT in this cohort, it is perhaps reasonable to use these ancillary markers for better risk stratification and prognostication of this high-risk group of patients. In addition to stress test variables, clinical variables such as age, duration of dialysis, diabetes, typical angina, and pre-test probability have been used as other ancillary markers of high risk in patients with CKD/ESRD. While it is not clear as to whether the various ancillary markers indicate presence of CAD in those with normal myocardial perfusion SPECT and if they should be referred for invasive angiography, it perhaps is helpful in patients with some ischemia on myocardial perfusion SPECT. The presence of ancillary markers may place such patients at a higher risk with considerations for more aggressive management including invasive angiography.

Although the above parameters identify patients with high risk, it is not known how best to treat such high-risk patients identified during stress testing. While several randomized trials in the past decade have evaluated revascularization or medical therapy alone for patients with stable ischemic heart disease, the majority of these trials have largely excluded patients with CKD/ESRD or included a very small proportion of these patients.^{22,23} The management of patients with CKD/ESRD has been extrapolated from data in the non-CKD cohort. It is not unknown if this extrapolation is justifiable. The International Study of Comparative Health Effectiveness with Medical and Invasive Approaches—Chronic Kidney Disease (ISCHEMIA-CKD) is an international comparative effectiveness study to determine the best approach to manage stable ischemic heart disease in patients with advanced chronic kidney disease (eGFR < 30 or on dialysis).²⁴ Patients will be randomized after an abnormal stress test to either an invasive strategy of cardiac catheterization with optimal revascularization and optimal medical therapy or to a conservative strategy of optimal medical therapy alone with cath reserved for OMT failures. The trial will provide important insights into the management of this high-risk group of patients.

In conclusion, the sensitivity and specificity of stress testing (including myocardial perfusion SPECT) are lower in subjects with CKD/ESRD when compared with non-CKD cohorts. A wealth of ancillary markers are available from a stress test which perhaps can be used to better risk stratify and prognosticate such patients.

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