
See related article, “Healthcare Intensity at Initiation of Chronic Dialysis among Older Adults,” on pages 143–149.

**Functional Cardiopulmonary Exercise Testing in Potential Renal Transplant Recipients**

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Patients receiving renal replacement therapy by dialysis and, to a lesser extent, renal transplantation are at greatly increased risk for premature cardiovascular disease.1,2 As a result, it has become routine practice to perform cardiovascular assessments in potential transplant recipients. The aim of these investigations is to identify, and remediate, significant coronary artery disease before transplantation.3 However, the role of cardiovascular assessment in asymptomatic patients awaiting transplantation remains controversial.4 Patients on maintenance dialysis often have limited exercise capacity, limiting the development of symptoms, and readily available noninvasive tests, such as stress echocardiography and isotopic scanning, lack sensitivity and specificity in this population. Routine angiography, even by computed tomography scanning, has risks and, even in the best centers, the intervention rate is low.5,6 One underlying reason is that coronary artery disease is only a part of the cardiovascular disease profile of patients with ESRD, in which uremic cardiomyopathy (the principal form of which is ventricular hypertrophy, with myocardial fibrosis) is an important determinant of sudden cardiac death and heart failure.1,2,3

On the other hand, it is clear from screening programs that exercise capacity in potential transplant recipients is a strong predictor of post-transplant outcomes.4 It is a reasonable statement that patients who are able to perform even modest, asymptomatic exercise (e.g., a few minutes of a treadmill test) can be included on the waiting list without the need for additional cardiovascular investigations.4

Against this background, the study by Ting et al. published in this issue of JASN adds to our understanding of the predictive value of cardiovascular fitness in patients awaiting transplantation. In a single-center study, the authors evaluated functional cardiopulmonary exercise testing in 240 patients awaiting renal transplantation. They followed up to 5 years, during which time 24 patients died and 124 received transplants. The investigators measured the anaerobic threshold (AT) (i.e., the VO2 [measured alveolar oxygen uptake] at which lactate is produced during exercise, which is approximately 50%–60% of peak VO2 in the general population. They categorized patients into those with an AT of <40% predicted peak VO2 and those at or above this level. The low AT was associated with increased left ventricular mass (131.8 ± 39.6 g/m2 versus 118.9 ± 36.3 g/m2; P = 0.02) and poorer systolic function (left ventricular ejection fraction 59.8% ± 11.1% versus 62.7% ± 9.5%; P = 0.04) on echocardiography. Moreover, low AT was associated with excess mortality. The mean AT was 29.9% ± 6.3% in 24 patients who died during follow-up compared with 39.7% ± 9.6% in the 216 survivors (P < 0.001). The corresponding peak VO2 was 50.1% of predicted in nonsurvivors and 65.2% in survivors. In a multivariate survival analysis, AT (40%) and whether the patient was transplanted were the only two independent risk factors for all-cause mortality, although age was not included and diabetes was close to significance (see below). Conventional risk factors such as hypertension and dyslipidemia were not statistically significant and even cigarette smoking only showed a trend toward adverse outcome.

In patients with a low AT (<40%), transplantation was associated with a substantial survival benefit compared with
those who did not receive a transplant (6 versus 17 deaths in 135 patients, 78 of whom received a transplant; \(P=0.002\)), whereas there was no difference in the group with AT \(\geq 40\%\), albeit with only a single death in the nontransplanted group.

The report should be viewed with some caution, particularly with regard to the generalizability of the observations. This is a relatively small study of 240 patients in a single center, with limited follow-up averaging 38 months. Moreover, there are some unusual observations that may reflect patient selection. The first is the failure to observe the usual risk associated with age. The second is the apparent protective value of diabetes. The hazard ratios for diabetes were 0.87 and 0.15 in the univariate and multivariate analyses, respectively, compared with a hazard ratio of 2–3 in most dialysis and transplant studies. Although only 15% of the overall study group had diabetes, one would have to postulate selection of only the fittest patients with diabetes and accelerated transplantation of this group to explain the observations. In short, these data will need to be reproduced in a larger study.

Putting aside these concerns, what do the study findings indicate and how do they advance our understanding of cardiovascular disease in ESRD? First, cardiopulmonary exercise testing offers a detailed assessment of cardiovascular reserve, which appears to be associated with structural abnormalities in the heart (left ventricular hypertrophy and systolic dysfunction) that we know are associated with adverse outcome. Second, these data confirm other series that used simpler measures of exercise tolerance (e.g., treadmill testing) that showed exercise capacity to be associated with good outcomes. The demonstrated survival benefits of the threshold chosen (AT \(\geq 40\%\) VO\(_2\) peak) identifies a very good prognostic group (whether or not they are transplanted) and might therefore identify a target for pretransplant (or maintenance dialysis) exercise training. Finally, patients with a low AT did have a significant survival benefit from transplantation compared with those with good cardiac reserve. This latter observation should be viewed with caution. The study sample is relatively small and we know that nearly all patient groups benefit from transplantation, regardless of comorbidity, limited only by the shortage of organs. Moreover, in survival analyses, survival to receive a transplant (with the associated survival advantage) perhaps exaggerates the effect of transplantation in Kaplan–Meier analyses.

In the future, more widespread use of such detailed cardiovascular testing may help to understand the effect of uremic cardiomyopathy, and associated abnormalities such as myocardial fibrosis and myocardial stunning, on cardiovascular outcomes in patients receiving maintenance dialysis or renal transplantation. More importantly, they identify a potential target for interventional trials of exercise training in patients with ESRD.

DISCLOSURES
None.

REFERENCES