Echocardiography: Providing Additional Insights into Cardiovascular Structural and Functional Abnormalities in Advanced CKD

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It is now a well recognized fact that cardiovascular disease is an important determinant of poor outcomes in patients with ESRD. Perhaps less well recognized is that cardiovascular outcomes in patients with advanced CKD are similar to and, on the basis of certain observational studies, worse than outcomes in patients with ESRD (1). Several hypotheses could account for this observation; one possible explanation relates to underlying structural and functional cardiovascular abnormalities such as left ventricular (LV) hypertrophy and LV dysfunction. At the outset, it is important to emphasize that advanced CKD and ESRD are on a clinical continuum. The transition from advanced CKD to ESRD requiring renal replacement therapy is based on the judgment of the clinician, which factors in several clinical and nonclinical variables, including symptoms and laboratory data indicative of uremia, clinical context, and patient preference. Hence, although this transition can be considered discrete or binary in clinical studies, it is dynamic in clinical practice. However, this transition to dialysis is extremely important from a physiologic standpoint, because the period after dialysis initiation is associated with increased risk of adverse clinical, particularly cardiovascular, outcomes (2), putatively related to increased electrolyte fluxes, hemodynamic stressors, and infectious complications. The rate of sudden cardiac death is markedly increased in incident hemodialysis patients, peaking at 2 months after dialysis initiation (3).

The Chronic Renal Insufficiency Cohort (CRIC) study offers a unique opportunity to examine a longitudinal profile of cardiovascular changes occurring during the transition from advanced CKD to ESRD. Bansal et al. (4) studied a select cohort of 190 patients from the CRIC study (n = 638) in whom echocardiograms were performed when patients were diagnosed with advanced CKD and after dialysis initiation; a subset of 89 of these patients underwent three serial echocardiograms, including an additional echocardiography study when they were diagnosed with moderate CKD. Patients who underwent echocardiograms in this study probably represented a somewhat lower-risk population than patients who did not (with significantly lower proteinuria levels and higher hemoglobin levels, and a higher proportion of black patients). Nonetheless, in the overall cohort, 7.2% of patients (46 of 638) died during the transition from advanced CKD to ESRD, signifying the cohort’s high-risk nature. Several important clinical observations that arise from this study deserve careful attention and add to our knowledge of structural and functional physiologic cardiovascular changes that occur during the transition.

First we must consider the technique that the authors used to measure LV mass and ejection fraction in this study. Cardiac magnetic resonance imaging (cMRI) is now widely accepted as the gold standard imaging modality for assessing LV mass and LV ejection fraction. However, cMRI is not portable, it is expensive, and it carries the risk of gadolinium toxicity in patients with advanced CKD and ESRD (the latter risk is relevant in the context of scar tissue detection and not routine assessment of LV mass and function). Echocardiography-derived formulae for LV mass estimation have been determined to correlate closely with necropsy estimates and have been well validated in epidemiologic studies over several years. Among echocardiographic techniques for estimating LV mass, indexing for either body surface area or height to the 2.7 power are both routinely performed and accepted methods. The CRIC core laboratory chose to standardize the latter formula for the study. However, reporting results using both formulae for LV mass estimation, as some studies have done (5), may perhaps have been more ideal. High profile studies (familiar to nephrologists in CKD stage 5HD, such as the Frequent Hemodialysis Network Daily Trial (6), have reported LV mass indexed to body surface area. As echocardiographers (and dues-paying members of the American Society of Echocardiography [ASE]), we sympathize with the CRIC echocardiography core laboratory’s decision to utilize the ASE/European Society of Cardiology–approved method of reporting LV mass. However, from the perspective of “nephro-cardiologists” (supporting the American Society of Nephrology, ASE, and the American College of Cardiology), we wish that the CRIC investigators had provided “LV hypertrophy calibration data” to allow nephrologists and cardiologists to frame the Bansal et al. (4) findings in the context of prior studies utilizing cMRI or other...
studies indexing LV mass to body surface area. Standardization of formulae for LV mass by echocardiography guidelines in the future would be helpful to prevent variation among clinical studies by addressing the fundamental question of whether indexing for weight and height (7,8) or height alone most accurately depicts LV mass.

With these caveats in mind, is the lack of change in LV mass during the transition from advanced CKD to ESRD in the study by Bansal et al. (4) surprising? These findings corroborate findings from the Initiating Dialysis Early and Late (IDEAL) study (7), and signify that cardiovascular structural abnormalities are a function of the underlying process of CKD itself, can occur early in the disease process, and are not significantly affected by dialysis initiation. Using the CRIC study population, Park et al. (9) elegantly demonstrated that an inverse correlation exists between LV mass and renal function and that patients with moderate degrees of CKD (estimated GFR 30–44 ml/min per 1.73 m²) also have significantly higher levels of echocardiographically measured LV mass, which increase with more advanced CKD. Previous work using cMRI provides a pathophysiologic basis for these findings, by showing that increased LV mass and hypertrophy independently correlate with hypertension, LV end-diastolic volume, and calcium/phosphorus metabolism, which are all markers of advancing CKD (10). These studies add substantially to our understanding of physiologic cardiovascular changes accompanying CKD, and suggest that the oft-used term "uremic cardiomyopathy" should more accurately be referred to as "cardiomyopathy of advanced CKD." More interestingly, in contrast to the above physiologic changes that occur with renal replacement therapy through dialysis initiation, regression of LV mass may occur after renal transplant (8), possibly due to a favorable modification in the hemodynamic and metabolic milieu of advanced CKD.

Finally, is the statistically significant reduction in LV ejection fraction (mean drop from 53% to 50%) during the transition from advanced CKD to ESRD clinically significant? In this regard, results of the CRIC study deviate from those of the IDEAL study (7), which found no significant difference in the LV ejection fraction before and after dialysis initiation, including in patients randomized to early initiation. Although this modest drop in LV ejection fraction is probably not numerically relevant in clinical practice, it should be conceptually interpreted in the context of potentially favorable therapeutic changes that can be implemented to prevent or reverse reduction in LV systolic function. Moreover, in one prospective cohort study of 230 peritoneal dialysis patients in Hong Kong, a reduction of only one ejection fraction point was associated with a statistically significant (6%; P = 0.004) increased hazard of sudden cardiac death in a multivariate model, underscoring the potential mechanistic importance of even modest degrees of LV systolic dysfunction in the survival of ESRD patients (11). These data serve as a reminder of the potential value of medications like carvedilol, which has been shown to improve long-term survival in the context of reduced systolic function among dialysis patients (12).

Overall, the CRIC and IDEAL studies underline the broader role and utility of transthoracic echocardiography in patients with advanced CKD and ESRD. Echocardiography remains an extremely versatile and portable technology that can provide valuable information in these patients. Beyond the assessments of LV mass, geometry, and ejection fraction addressed by these studies, echocardiography provides important information pertaining to right- and left-sided filling pressures, estimated right ventricular/pulmonary artery systolic pressure, and important valvular disease; thus, in composite, a hemodynamic snapshot or "noninvasive right and left heart catheterization" is helpful not only in assessing prognosis but also in directly influencing management. Guideline 1.1a of the National Kidney Foundation clinical practice guidelines for cardiovascular disease in dialysis patients from the Kidney Disease Outcomes Quality Initiative (13) recommends that echocardiograms be performed in all patients (pediatric and adult) at initiation of dialysis once patients have achieved dry weight (ideally within 1–3 months of initiation) and at 3-yearly intervals. On the basis of information from the Annual Data Report of the US Renal Data System, only about half the patients aged >65 years in 2010 received a transthoracic echocardiogram within the first year after dialysis initiation (14). The Bansal et al. study should serve to reinforce to clinicians the important role of echocardiography for detection of structural and functional cardiac abnormalities (which are not necessarily clinically apparent) in this high-risk population.

Disclosures
None.

References


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