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Defining Cardiac Dysfunction in ADPKD

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Cardiovascular manifestations in the era of RRT are the main cause of mortality for patients with autosomal dominant polycystic kidney disease (ADPKD). Although the main cause of cardiovascular dysfunction in patients with ADPKD has been ascribed to cyst compression of the renal vasculature, leading to increased renin-angiotensin-aldosterone system activity, hypertension, and ultimate cardiac failure,[1] it has been increasingly appreciated that the polycystin genes are expressed throughout many of the vascular tissues.[2] A nuanced understanding of the cardiac phenotype within ADPKD population is required to inform clinical practice. The recent study by Arjune and colleagues[3] of 141 patients with ADPKD from the German AD(H)PKD registry provides a comprehensive echocardiographic examination of cardiovascular function in the tolvaptan era of ADPKD treatment.

The primary goal of this study[3] was to determine the association between ADPKD and various cardiac manifestations as being an early risk factor for cardiovascular complications contributing to mortality, with the hope that identifying these cardiac manifestations would facilitate early intervention in the ADPKD patient population. The study design consisted of selecting from the 900 patients with ADPKD listed within the German AD(H)PKD registry. Of them, 166 patients had undergone standard transthoracic echocardiography at a single site. Exclusion criteria were patients with ejection fractions of <30% and/or poor image quality. Inclusion criterion was a typical ADPKD phenotype (Mayo class 1). Of the final 141 patients included, the average age was 44 years, the average eGFR was 70 ml/min, and 92% had arterial hypertension. Sixty kidney donor candidates were identified retrospectively and included as controls (average age of 55 years, eGFR >90 ml/min, and 33% with arterial hypertension). The echocardiographic images were read by two independent readers. The key findings included 65% of the patients with ADPKD demonstrating left ventricular hypertrophy (LVH) (as defined end-diastolic left ventricular septal wall thickness >10 mm), compared with 55% in the control group and that 88 patients with ADPKD had mild mitral valve regurgitation, with one classified as moderate (for a total of 63% in the ADPKD group compared with no cases noted in the control group). Of note, aortic root diameter and the pressure gradient across the aortic valve both correlated with height-adjusted kidney volume and the left ventricular septal wall thickness correlated with eGFR.

There are a few surprises that warrant discussion, namely, the higher-than-expected prevalence of LVH (65% of patients with ADPKD) and mitral valve regurgitation (63% of patients with ADPKD).[3] Both issues will be discussed in turn. LVH has been long associated with ADPKD. Chapman and colleagues reported in 1997 that 41% of patients with ADPKD with a similar eGFR profile and mean age of 41 years had cardiac hypertrophy as measured by left ventricular mass index by echocardiography.[4] In contrast to Arjune and colleagues,[3] baseline analysis of the HALT-polycystic kidney disease (PKD) study of 543 patients with ADPKD reported a much lower prevalence of LVH of 4%.[5,6] Where does this jarring discrepancy in reported incidences come from? Part of the lower prevalence of hypertrophy seen by Alam and Perrone[5] and Perrone and colleagues[6] could arise because of more efficacious blood pressure management in the time preceding the HALT-PKD study (with baseline studies completed in 2010). Alternatively, the imaging modality[5]–MRI, as used in the HALT-PKD study–could contribute to lower left ventricular mass measurements than that by echocardiography used by Arjune and colleagues or by Chapman *et al.* However, methodology alone does not explain the apparent mismatch in contemporaneous studies between the HALT-PKD study and the current German AD(H)PKD registry study. Closer examination reveals a discrepancy in the definition of hypertrophy. The German AD(H)PKD registry study defined hypertrophy as >10 mm in the free wall, whereas the HALT-PKD study defined it as the 95%, translating to approximately 122 g/m^2 for men and 104 g/m^2 for women. Gratifyingly, when the current study used the same definition, the number of patients with ADPKD with LVH dropped to 5.47%, very much in line with the HALT-PKD study.

However, can one simply harmonize the findings by definitions? The German patients with AD(H)PKD had a higher ejection fraction of 63% than the control group (60%), which accords with a functional hypertrophied heart. As the patients in the German AD(H)PKD registry were relatively young (44 years), it remains to be seen if the ejection fraction will in time drop, as

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would be expected in heart failure with reduced ejection fraction. Indeed, the study excluded three patients with ejection fractions <30%.

A second finding worth discussion is the prevalence of mild mitral valve regurgitation in 63% of the patients with ADPKD, compared with 0 instances in the control group.[3] The high prevalence of mitral valve regurgitation could be a result of hypertension because sustained elevated blood pressure increases in both primary and secondary risk of mitral valve regurgitation.[7] In this study,[3] 90% of the patients with ADPKD had arterial hypertension compared with 30% in the control group. The 63% prevalence of mitral valve regurgitation reported by Arjune and colleagues[3] is substantially higher than previous ADPKD studies from the United States, Japan, and Brazil which have ranged from 15% to 25%[8–10] and where >70% of patients analyzed had hypertension. One cannot rule out that the sensitivities of modern echocardiography are more likely to identify mild cases of regurgitation. However, with blood pressure control now a standard treatment for patients with ADPKD, one would expect if mitral value regurgitation was due to hypertension that this number would decrease over time. If, however, the underlying genetic mutations in the polycystin proteins do alter the mechanical properties of the valve, more direct intervention would be warranted. From the basic science perspective, the higher incidence of valvular disorders piques interest into how the forces generated in these areas are being directly altered. Mechanistically, the mitral valve regurgitation may be a contributing factor to the higher ejection fraction reported[3] because the left ventricle will have to pump harder if the ventricle is not filling as well.

Arjune and colleagues[3] demonstrate that cardiovascular abnormalities were confined to the left side, with minimal changes to the right heart (between control and patients with ADPKD). It should be noted that a very high percentage (>80%) of both control and patients with ADPKD had mild tricuspid regurgitation, but measurements of right ventricular systolic function were normal, and to date, pulmonary defects or hypertension are not a noted occurrence in ADPKD.

Another point of note is that the incidence of the cardiovascular dysfunction was not reflected in subgroup analysis of whether patients had either germline polycystin 1 or polycystin 2 mutations. Although it is well established that mutations to polycystin 1 make up most known ADPKD cases and contribute to a more aggressive cyst development, the lack of significance between the mutation type is most likely due to the small sample size. However, significant differences were noted in the aortic root diameter of patients, with less severe cysts (Mayo classes 1A/B) being associated with a smaller aortic root diameters and more severe cysts (Mayo classes 1C–E) associated with larger aortic root diameters. Whether this correlation continues to hold as the renal cysts get progressively larger will be of interest.

Where does this study leave our understanding of the cardiovascular manifestations in ADPKD? The work of Arjune and colleagues sets the platform for future longitudinal studies to examine whether the cardiac manifestations noted in these patients with ADPKD progress further or whether treatment with tolvaptan also confers cardiovascular benefits. At the basic science level, the clinical observations warrant mechanistic studies, especially for the valvular disorders. A conclusion from Arjune and colleagues[3] is that routine echocardiography be offered to all patients with ADPKD. Such a recommendation may be premature, until larger, multisite echocardiographic studies are undertaken with standardized criteria for defining the cardiac manifestations in ADPKD. The PKD Foundation has recently invested in multidisciplinary clinics, reflecting, from the patient perspective, the necessity of interdisciplinary and integrated care. The inclusion of cardiologists in these multidisciplinary care sites in the light of such studies as the current one is welcome and acknowledges that ADPKD is more than just a renal cystic disease.

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Author Contributions

I.Y. Kuo conceptualized the study, wrote the original draft, and reviewed and edited the manuscript.

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See related article, "Cardiac Manifestations in Patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD): A Single-Center Study," on pages 150–161.