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Biventricular diastolic dysfunction in patients with autosomal-dominant polycystic kidney disease

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Biventricular diastolic dysfunction in patients with autosomal-dominant polycystic kidney disease.

Background. Left ventricular diastolic dysfunction has been shown in patients with autosomal-dominant polycystic kidney disease (ADPKD). However, there is no study evaluating right ventricular functions in these patients.

Methods. In the present study, diastolic functions of both ventricles in normotensive and hypertensive ADPKD patients with well-preserved renal function were investigated. Fifteen hypertensive and 16 normotensive patients with ADPKD with well-preserved renal function, 16 patients with essential hypertension, and 24 healthy subjects were included in the study. Conventional left and right ventricular echocardiographic measurements were performed in all subjects. Left and right ventricular functions were investigated both by myocardial performance index (MPI) [calculated by dividing the sum of isovolumic contraction time and isovolumic relaxation time (IVRT) by ejection time] and by tissue Doppler imaging (TDI).

Results. Left ventricular deceleration time and IVRT were significantly prolonged in hypertensive patients with ADPKD compared with patients with essential hypertension and even in normotensive patients with ADPKD compared with healthy subjects. Left and right MPIs were significantly higher in patients with ADPKD compared with healthy subjects, showing systolic and diastolic dysfunction. Moreover, by using TDI, the peak early diastolic mitral annular velocity (Em) to peak late diastolic mitral annular velocity (Am) ratio and the peak early diastolic tricuspid annular velocity (Et) to peak late diastolic tricuspid annular velocity (At) ratio were decreased in patients with ADPKD, suggesting biventricular diastolic dysfunction.

Conclusion. Both hypertensive and normotensive patients with ADPKD show significant biventricular diastolic dysfunction, suggesting cardiac involvement very early in the course of ADPKD.

Autosomal-dominant polycystic kidney disease (ADPKD) is the most common hereditary renal disease, accounting for approximately 4% of end-stage renal disease (ESRD) in the United States and 8% to 10% in Europe [1]. Cardiovascular problems are a major cause of morbidity and mortality in patients with ADPKD [2, 3]. Hypertension and left ventricular hypertrophy (LVH), which are common findings in ADPKD, are associated with a faster progression to ESRD and an increased cardiovascular mortality [2–5]. Importantly, several studies have shown increased left ventricular mass (LVM) indexes, left ventricular (LV) diastolic dysfunction, endothelial dysfunction, increased carotid intima-media thickness, and exaggerated blood pressure response during exercise even in young normotensive patients with ADPKD with well-preserved renal function [4, 6–11]. These findings suggest that cardiovascular involvement starts very early in the course of ADPKD. However, there is no study evaluating right ventricular (RV) functions in these patients.

The aim of the present study was to investigate diastolic functions of both ventricles in normotensive and hypertensive ADPKD patients with well-preserved renal function.

METHODS

Patients

Thirty-one patients with ADPKD were included in the study. Fifteen of these patients had hypertension (blood pressure ≥140/90 mm Hg in the sitting position or taking antihypertensive drugs) and 16 were normotensive. Sixteen patients with essential hypertension and 24 healthy subjects were also included in the study.

The diagnosis of ADPKD was reached by the ultrasonographic criteria described by Ravine et al [12]. All of the patients had family history of ADPKD.

Creatinine clearances were calculated by the Cockcroft-Gault formula [13]. All patients had creatinine clearances greater than 60 mL/min/1.73m^2.

The study protocol was approved by the institutional medical ethics committee and written informed consent was obtained from all subjects included in the study.

Key words: diastolic dysfunction, autosomal-dominant polycystic kidney disease, hypertensive, normotensive, left ventricle, right ventricle.

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Table 1. Characteristics of patients

	Hypertensive patients with ADPKD ($N = 15$)	Normotensive patients with ADPKD ($N = 16$)	Patients with essential hypertension ($N = 16$)	Healthy subjects ($N = 24$)
Age *years*	39.6 ± 7.2	35.8 ± 8.8	40.8 ± 4.8	38.1 ± 8.8
Gender *M/F*	4/11	7/9	7/9	8/16
Body mass index kg/m^2	25.5 ± 3.5	23.7 ± 3.8	26.0 ± 3.2	24.7 ± 3.5
Systolic blood pressure *mm Hg*	138 ± 18[a]	120 ± 18	134 ± 14[a]	119 ± 14
Diastolic blood pressure *mm Hg*	85 ± 11[a]	74 ± 8	77 ± 13	75 ± 9
Age of diagnosis of hypertension *years*	37.3 ± 19.5	–	42.3 ± 17.5	–
Duration of hypertension *months*	56.3 ± 52.3	–	41.9 ± 48.4	–
Creatinine clearance $mL/min/1.73m^2$	91 ± 29	106 ± 17	112 ± 14	105 ± 12

[a] $P < 0.01$ vs. normotensive patients with ADPKD and healthy subjects.

Systolic and diastolic blood pressures were measured on the right arm of the subjects in an upright sitting position after at least 5 minutes of rest using an Erka sphygmomanometer (PMS Instruments, Ltd., Berkshire, UK) with appropriate cuff size. Two readings were recorded for each individual. The average of two readings was defined as the subject's blood pressure.

All of the patients had grade 1 functional capacity according to New York Heart Association classification. None of the patients had history, physical findings, and ECG findings suggesting congestive heart failure, myocardial infarction, and chronic obstructive pulmonary disease.

Venous blood samples for the biochemical analyses were taken after an overnight fast between 8 PM and 8 AM.

Echocardiographic examination

Echocardiographic examination was performed using a Vingmed System Five, Norway echocardiographic system equipped with 2.5-MHz transducers (Vingmed Sound, Norway). M-Mode and two-dimensional measurements were performed in accordance with methods recommended by the American Society of Echocardiography [14, 15]. Cardiac mass was calculated by means of the formula derived by Devereux and Reichek [16]. LVH was defined as left ventricular mass index (LVMI) >125 g/m^2 for males and >110 g/m^2 for females. The intraobserver and interobserver coefficients of variability for LV mass indexes were 4.1% and 7.1%, respectively.

Conventional left and right ventricular echocardiographic measurements were performed in all subjects. Measurements included LV deceleration time (LV DT), LV isovolumic relaxation time (LV IVRT), LV early to atrial peak velocity ratio (E/A ratio), RV E/A ratio. Left ventricular ejection fraction (LV EF) was measured by using the Teichholtz formula [17].

Left and right ventricular functions were also investigated by using myocardial performance index (MPI). MPI was calculated by the formula: MPI = (isovolumic contraction time + isovolumic relaxation time)/ejection time) [18].

Pulsed wave tissue Doppler imaging (TDI) was performed by activating the TDI function of the same machine. The spectral pulsed Doppler signal was arranged to obtain a Nyquist limit of 15 to 20 cm/s with the lowest wall filter settings. From the apical four-chamber view, a 5 mm sample volume was located at the ventricle free wall near to the lateral tricuspid and the posterior mitral leaflets. The resulting velocities were recorded for five cycles at a sweep speed of 50 mm/s and stored on videotape for later analysis. The following parameters were determined: peak systolic mitral annular velocity (Sm), peak early diastolic mitral annular velocity (Em), peak late diastolic mitral annular velocity (Am), mitral Em/Am ratio, peak systolic tricuspid annular velocity (St), peak early diastolic tricuspid annular velocity (Et), peak late diastolic tricuspid annular velocity (At), and tricuspid Et/At ratio.

The Doppler imaging calculations of both left and right ventricles were performed during the end of the expirium. Pulmonary artery pressures were calculated by the modified Bernoulli equation in patients with tricuspid regurgitation [19]. Since only 30% to 40% of the subjects in all groups had tricuspid regurgitation, pulmonary artery pressures were not determined in all of the subjects. The calculated pulmonary artery pressures were within normal limits (<30 mm Hg).

Statistical analyses

Comparison of groups was performed using Mann-Whitney *U* and chi-square tests. Mann-Whitney *U* test was applied to the groups in pairs, for all possible combinations. *P* less than 0.05 was considered statistically significant. All values are expressed as mean ± SD.

RESULTS

There was no significant difference between the groups regarding age, gender, body mass index, and renal function (Table 1). Hypertensive ADPKD patients and

Table 2. Conventional echocardiographic measurements

	Hypertensive patients with ADPKD ($N = 15$)	Normotensive patients with ADPKD ($N = 16$)	Patients with essential hypertension ($N = 16$)	Healthy subjects ($N = 24$)
LVMI g/m^2	132 ± 23[a]	108 ± 24	111 ± 16[b]	95 ± 17
LV EF%	68 ± 12	71 ± 14	70 ± 14	73 ± 14
LV DT *msec*	188 ± 37[c]	172 ± 44[d]	158 ± 21[d]	141 ± 15
LV IVRT *msec*	132 ± 17[e]	115 ± 19[d]	117 ± 14[d]	95 ± 9
LV E/A	0.91 ± 0.22[e]	1.31 ± 0.29[f]	1.09 ± 0.17[d]	1.49 ± 0.21
RV E/A	1.25 ± 032	1.33 ± 0.29	1.23 ± 0.23	1.31 ± 0.16
LA-D *mm*	31 ± 7	29 ± 7	30 ± 8	28 ± 6
RA-D *mm*	29 ± 4	27 ± 4	30 ± 3	27 ± 4
RV-D *mm*	23 ± 4	21 ± 3	22 ± 5	20 ± 3

Abbreviations are: LV MI, left ventricular mass index; LV EF, left ventricular ejection fraction; LV DT, left ventricular deceleration time; LV IVRT, left ventricular isovolumic relaxation time; LV E/A, left ventricular early to atrial peak velocity ratio; RV E/A, right ventricular early to atrial peak velocity ratio; LA-D, left atrium diameter; RA-D, right atrium diameter; RV-D, right ventricular diameter.

[a] $P = 0.02$ vs. normotensive patients with ADPKD, $P < 0.02$ vs. patients with essential hypertension, $P < 0.0001$ vs. healthy subjects.

[b] $P = 0.005$ vs. healthy subjects.

[c] $P = 0.01$ vs. patients with essential hypertension, $P < 0.001$ vs. healthy subjects.

[d] $P < 0.05$ vs. healthy subjects.

[e] $P < 0.05$ vs. normotensive patients with ADPKD and patients with essential hypertension, $P < 0.001$ vs. healthy subjects.

[f] $P < 0.05$ vs. healthy subjects.

essential hypertensive patients had significantly higher systolic blood pressures compared to normotensive ADPKD patients and healthy subjects. Hypertensive ADPKD patients also had significantly higher diastolic blood pressure compared to normotensive ADPKD patients and healthy subjects.

The patients continued to receive their antihypertensive medications during the study. Five patients were administered angiotensin-converting enzyme (ACE) inhibitors; 4 patients, calcium channel blockers (CCBs); 3 patients, angiotensin-receptor blockers (ARBs); 3 patients, a combination of ACE inhibitors and CCBs in the hypertensive ADPKD group. Six patients were administered ACE inhibitors; 3 patients, CCBs; 4 patients, ARBs; 3 patients, a combination of ACE inhibitors and CCBs; and 1 patient, a beta-blocker in the essential hypertensive group. No statistically significant difference in antihypertensive use was present between the hypertensive ADPKD group and essential hypertensive group.

Hypertensive ADPKD patients had significantly higher LVMI compared to all other groups. Patients with essential hypertension also had significantly elevated LVMI compared to healthy subjects. Normotensive ADPKD patients had higher LVMI compared to healthy subjects. Although this was not statistically significant, the P value was 0.06 (Table 2). LVH was present in 12 (80%) of the hypertensive patients with ADPKD, 6 (38%) of the normotensive patients with ADPKD, and 8 (50%) of the patients with essential hypertension. None of the healthy subjects had LVH.

Left ventricular EFs were similar and within normal limits in all groups. Left ventricular DT was significantly prolonged in hypertensive patients with ADPKD compared with patients with essential hypertension (188 ± 37 msec vs. 158 ± 21 msec, $P = 0.01$) and healthy subjects (188 ± 37 msec vs. 141 ± 15 msec, $P < 0.001$). Left ventricular DT was significantly longer even in normotensive patients with ADPKD than healthy subjects (172 ± 44 msec vs. 141 ± 15 msec, $P < 0.05$). Left ventricular IVRT was significantly prolonged in hypertensive patients with ADPKD compared with normotensive patients with ADPKD (132 ± 17 msec vs. 115 ± 19 msec, $P < 0.05$), patients with essential hypertension (132 ± 17 msec vs. 117 ± 14 msec, $P < 0.05$), and healthy subjects (132 ± 17 msec vs. 95 ± 9 msec, $P < 0.001$). Left ventricular IVRT was significantly longer even in normotensive patients with ADPKD than healthy subjects (115 ± 19 msec vs. 95 ± 9 msec, $P < 0.05$) (Table 2).

Left ventricular E/A ratio was significantly decreased in hypertensive patients with ADPKD compared with normotensive patients with ADPKD (0.91 ± 0.22 vs. 1.31 ± 0.29, $P < 0.05$), patients with essential hypertension (0.91 ± 0.22 vs. 1.09 ± 0.17, $P < 0.05$), and healthy subjects (0.91 ± 0.22 vs. 1.49 ± 0.21, $P < 0.001$). Left ventricular E/A ratio was significantly less in normotensive patients with ADPKD than healthy subjects (1.31 ± 0.29 vs. 1.49 ± 0.21, $P < 0.05$). There was no significant difference between the groups regarding RV E/A ratios (Table 2). Left atrium diameter, right atrium, and right ventricular diameters were within normal limits in all groups (Table 2).

Left ventricular MPI was significantly higher in hypertensive patients with ADPKD compared with normotensive patients with ADPKD (0.72 ± 0.18 vs. 0.57 ± 0.18, $P < 0.05$), patients with essential hypertension (0.72 ± 0.18 vs. 0.60 ± 0.12, $P < 0.05$), and healthy subjects (0.72 ± 0.18 vs. 0.46 ± 0.10, $P < 0.001$). Moreover, LV MPI was significantly higher even in normotensive patients with ADPKD than healthy subjects (0.57 ± 0.18 vs. 0.46 ± 0.10, $P < 0.05$) (Fig. 1).

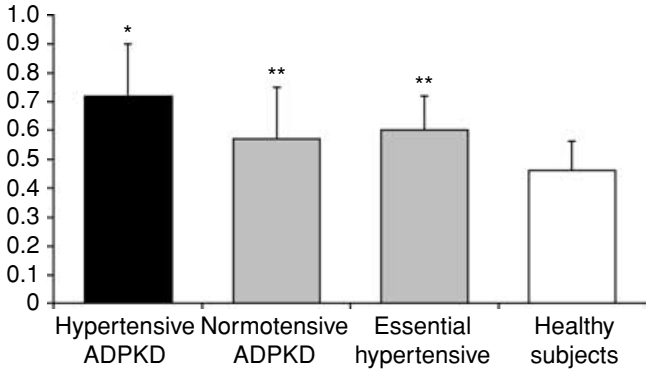

Fig. 1. Left ventricular myocardial performance index. $^{*}P < 0.05$ vs. normotensive patients with ADPKD and patients with essential hypertension, $P < 0.001$ vs. healthy subjects; $^{**}P < 0.05$ vs. healthy subjects.

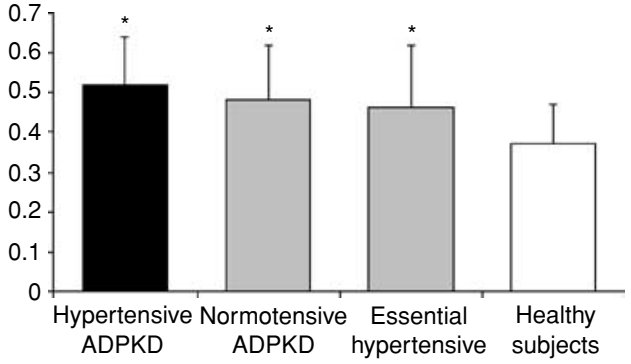

Fig. 2. Right ventricular myocardial performance index. $^{*}P < 0.05$ **vs. healthy subjects.**

Right ventricular MPI was significantly higher in hypertensive patients with ADPKD compared with healthy subjects (0.52 ± 0.12 vs. 0.37 ± 0.10, $P < 0.05$). Right ventricular MPI was significantly higher even in normotensive patients with ADPKD than healthy subjects (0.48 ± 0.14 vs. 0.37 ± 0.10, $P < 0.05$) (Fig. 2).

The subjects were also investigated by using TDI. The peak systolic mitral annular velocity (Sm) and the peak systolic tricuspid annular velocity (St), reflecting left and right ventricular systolic functions, were similar in all groups. However, Em/Am ratio, showing left ventricular diastolic function, was significantly decreased in hypertensive patients with ADPKD compared with normotensive patients with ADPKD (1.01 ± 0.43 vs. 1.34 ± 0.37, $P = 0.03$) and healthy subjects (1.01 ± 0.43 vs. 1.38 ± 0.19, $P = 0.001$). Similarly, Et/At ratio, showing right ventricular diastolic function, was significantly decreased in hypertensive patients with ADPKD compared with normotensive patients with ADPKD (0.93 ± 0.27 vs. 1.23 ± 0.29, $P = 0.008$) and healthy subjects (0.93 ± 0.27 vs. 1.42 ± 0.14, $P < 0.0001$). Moreover, Et/At ratio was significantly decreased even in normotensive patients with ADPKD compared with healthy subjects (1.23 ± 0.29 vs. 1.42 ± 0.14, $P = 0.02$) (Table 3).

DISCUSSION

Hypertension and LVH, which are powerful independent risk factors for cardiovascular morbidity and mortality, occur frequently in patients with ADPKD [2–4, 20]. Hypertension develops early in 50% to 70% of patients with ADPKD before any substantial decrease in kidney function [2, 21]. Activation of the renin-angiotensin-aldosterone system (RAAS) due to cyst expansion and local renal ischemia has been proposed to play an important role in the development of hypertension in ADPKD [2, 22]. The RAAS is activated at an early stage of ADPKD, even before the onset of hypertension and clinical findings [23, 24]. Since the RAAS plays a detrimental role in the pathogenesis of target organ damage, such as atherosclerosis, LVH, heart failure, and ESRD [25–28], the increased activity of the RAAS may contribute to the increased incidence of cardiovascular complications in patients with ADPKD.

In the present study, hypertensive patients with ADPKD had significantly higher LVMI compared to the subjects in all other groups. The high incidence of LVH has been reported in patients with ADPKD [4]. Importantly, a high prevalence of LVH has been reported even in normotensive patients with ADPKD compared to healthy control subjects [4, 6, 7]. In our study, normotensive ADPKD patients had higher LVMI compared to healthy subjects. Although this was not statistically significant, the P value was 0.06.

It has been reported that there is an association between insulin resistance and LVH [29, 30]. Lumiaho et al [31] reported that insulin resistance was significantly associated with LVMI in healthy relatives and patients with mutations in the PKD1 gene independently of other factors known to increase LVMI, such as age, weight, systolic blood pressure, and albuminuria. It can thus be hypothesized that the stimulation of angiotensin II and the sympathetic nervous system due to hyperinsulinemia may contribute to increased LVMI in these patients [32, 33].

In the present study, LV systolic functions were found to be within normal limits in all groups of patients, while LV diastolic functions were significantly impaired both in hypertensive and normotensive patients with ADPKD compared to healthy subjects. Left ventricular diastolic dysfunction was previously reported in young normotensive patients with ADPKD [7]. In our study, diastolic functions of both ventricles were investigated in patients with ADPKD with well-preserved renal function.

A limitation of the study was that the number of subjects in each group was relatively small. Thus, although there was no statistically significant difference between

Table 3. Tissue Doppler imaging measurements

	Hypertensive patients with ADPKD ($N = 15$)	Normotensive patients with ADPKD ($N = 16$)	Patients with essential hypertension ($N = 16$)	Healthy subjects ($N = 24$)
Sm *cm/sec*	9.0 ± 2.2	9.3 ± 1.8	8.6 ± 1.6	9.4 ± 1.6
Em/Am	1.01 ± 0.43[a]	1.34 ± 0.37[b]	1.03 ± 0.18[c]	1.38 ± 0.19
St *cm/sec*	15.3 ± 2.2	15.3 ± 2.3	13.9 ± 1.7	15.1 ± 2.3
Et/At	0.93 ± 0.27[d]	1.23 ± 0.29[e]	0.96 ± 0.29[c]	1.42 ± 0.14

Abbreviations are: Sm, peak systolic mitral annular velocity; Em, peak early diastolic mitral annular velocity; Am, peak late diastolic mitral annular velocity; St, peak systolic tricuspid annular velocity; Et, peak early diastolic tricuspid annular velocity; At, peak late diastolic tricuspid annular velocity.

[a] $P = 0.03$ vs. normotensive patients with ADPKD, $P = 0.001$ vs. healthy subjects.

[b] $P = 0.006$ vs. patients with essential hypertension.

[c] $P < 0.0001$ vs. healthy subjects.

[d] $P = 0.008$ vs. normotensive patients with ADPKD, $P < 0.0001$ vs. healthy subjects.

[e] $P = 0.02$ vs. patients with essential hypertension and healthy subjects.

the frequency of antihypertensive medication use, the effects of these drugs on our findings cannot be neglected.

In this study, in addition to the conventional echocardiographic measurements, left and right ventricular functions were also investigated by using MPI. Myocardial performance index, which was first described by Tei [18], is a simple and reproducible method used for the assessment of overall cardiac function [34–37]. It is defined as the ratio of total time spent in isovolumic activity (isovolumic contraction time and isovolumic relaxation time) to the ejection time. The increased rate of MPI in patients with ADPKD suggests diastolic dysfunction.

Interpretation of right ventricular functions is a challenging problem because of the complex and asymmetric architecture of the right ventricle. Three-dimensional echocardiography or magnetic resonance imaging can be used for the evaluation of right ventricle [38, 39]. Tissue Doppler imaging is a new technique that analyzes systolic and diastolic functions of both ventricles accurately. Annular velocities, determined by TDI, are reported to be independent from preload compensation [40]. In the present study, while the values of peak systolic tricuspid annular velocity (St) were similar in all groups, both hypertensive and normotensive patients with ADPKD had significantly lower Em/Am and Et/At ratios, showing left ventricular and right ventricular diastolic dysfunctions, respectively.

This is the first study investigating systolic and diastolic dysfunction of both ventricles in patients with ADPKD.

CONCLUSION

Both hypertensive and normotensive patients with ADPKD show significant biventricular diastolic dysfunction. The clinical significance of this finding needs to be determined in further studies.

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