

EVALUATION OF CARDIAC ABNORMALITIES IN AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE UTILISING ECHOCARDIOGRAPHY IN THANJAVUR MEDICAL COLLEGE

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ABSTRACT

BACKGROUND

Autosomal Dominant Polycystic Kidney Disease (ADPKD) is a multisystem disorder characterised by multiple, bilateral renal cysts associated with cysts in other organs. Non-cystic manifestations of ADPKD involve cardiac valvular abnormalities also, which supports the hypothesis that a defect in extracellular matrix is the basic pathology.

The aim of the study is to find out the prevalence of cardiac valvular abnormalities in patients with ADPKD.

MATERIALS AND METHODS

This was a cross-sectional study conducted in 50 patients admitted with ADPKD over a period of one year in Thanjavur Medical College Hospital. M-mode, 2D echo and Doppler were used to study the valvular abnormalities.

RESULTS

Out of 50 patients with ADPKD (males- 70% and females- 30%), 24% had MVPS, 36% had MR, 20% had AR and 16% had TR.

CONCLUSION

Echocardiography is easily performed, noninvasive, safe, reproducible and accurate in assessment of cardiac function in ADPKD. Echocardiographically detectable concentric left ventricular hypertrophy and valvular abnormalities were present in asymptomatic patients. Hence, this necessitates screening of patients without cardiac symptoms for cardiac abnormalities after the diagnosis of ADPKD has been made.

KEYWORDS

ADPKD, Cardiac Abnormalities, Echo.

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BACKGROUND

Autosomal dominant polycystic kidney disease¹ is a multisystem disorder characterised by multiple, bilateral renal cysts associated with cysts in other organ such as liver,²⁻⁵ pancreas and arachnoid membranes.

Non-cystic, extrarenal manifestations of ADPKD include mitral valve prolapse, hernias, diverticulosis,⁶ intracranial aneurysms,⁷ abdominal aortic aneurysms⁸ and annuloaortic ectasia.⁹

The diagnosis of ADPKD in an individual with a positive family history relies on imaginary testing. Renal ultrasound is commonly used.

Sonographic¹⁰ diagnostic criteria for individuals at 50% risk for diagnosis include at least two unilateral or bilateral cysts in individuals younger than 30 years of age; two cysts

in each kidney in individuals 30 to 59 years of age; four cysts in each kidney in individuals 60 years of age or older.

ADPKD is inherited an autosomal dominant trait with complete penetrance. Therefore, each child of an affected parent has a 50% chance of inheriting abnormal gene. ADPKD is by far the most frequent inherited kidney disease. ADPKD is genetically heterogeneous. The gene responsible in about 85% of families (PKD1) is located on chromosome 16p13.3. There is another gene (PKD2) located on chromosome 4q22 accounting for remainder.

PKD1 and PKD2 are widely expressed in human 5-6 weeks old embryo mainly in neural tissue, cardiomyocytes, endodermal derivatives and mesonephros. This expression pattern is in agreement with the cardiovascular and liver manifestation of the disease.

A coordinate expression of polycystins-1 and 2 has been documented in the developing and mature epithelia lining biliary and pancreatic ducts as well as in the heart and the vasculature.

Echocardiography¹¹ including Doppler analysis was performed to assess the prevalence of cardiac abnormalities in patients with autosomal dominant polycystic kidney disease. The prevalence of mitral valve prolapse was 25%, prevalence of mitral incompetence was 31%, aortic

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incompetence 8% and tricuspid incompetence 15% and tricuspid valve prolapse 6% was found in patients with ADPKD.

These findings reflect the systemic nature of polycystic kidney disease and support the hypothesis that the disorder involves a defect in the extracellular matrix¹²⁻¹⁴ and the cardiac abnormalities are an expression of that defect.

Aim of the Study

1. To study the prevalence of cardiac valvular abnormalities in patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD).
2. To study the left ventricular systolic function, left ventricular hypertrophy and valvular abnormalities with echocardiography including Doppler analysis.

MATERIALS AND METHODS

The study was conducted in patients with autosomal dominant polycystic kidney disease admitted in Thanjavur Medical College Hospital during the period January 2016 to January 2017.

Inclusion Criteria

The following criteria were used in selection of cases-

1. Patients who were known autosomal dominant polycystic kidney diseases.
2. Patients were classified as having autosomal dominant polycystic kidney disease if renal cysts were present bilaterally and totalled five or more in number in abdominal ultrasonography.
3. Patients of all age groups and both sexes with ADPKD were included.

Exclusion Criteria

1. Patients who had no renal cysts on renal ultrasound.
2. Patients who were known valvular heart disease and coronary heart disease.

In all patients, a detailed history was taken with special interest regarding any history of chest pain and palpitations. Cardiovascular symptoms like dyspnoea, chest pain, pedal oedema and pallor were noted. Blood pressure was measured. Cardiovascular examination was done. Complete haemogram, blood urea and serum creatinine were measured. Patient was subjected to abdominal ultrasonogram and chest x-ray, presence of cardiomegaly, pulmonary interstitial oedema and pleural effusion was looked in chest x-ray posteroanterior view. Evidence of left ventricular hypertrophy, low voltage complexes and ischaemic changes were looked for in ECG. A 12-lead electrocardiogram was performed.

CT scan brain and MRA were taken for those patients whose parents were suffered from intracranial aneurysm^{15,16} as suggested by history of ICH.

All the patients underwent standard echocardiographic studies. The following parameters were looked for-

Systolic Function- (M-Mode, 2-D Echo, Doppler).

In our study, systolic function is assessed mainly based upon M-Mode measurements of LV function. The ejection fraction is measured.

Normal Range	: 55 to 80%.
Mild systolic dysfunction	: 45 to 50%.
Moderate systolic dysfunction	: 35 to 45%.
Severe systolic dysfunction	: Less than 35%.

Diastolic Function- (Pulse Wave Doppler Study)

Diastolic function is assessed by measuring mitral inflow E/A measurements.

1. EV - m/s it indicates mitral flow, which causes ventricular filling following the opening of mitral valve.
2. AV - m/s ventricular filling due to atrial systole.
3. E/A usually more than 1. E/A less than 1 indicates diastolic dysfunction.

Grades- Type I- Relaxation abnormality, Type II- Pseudonormalisation. Type III- Restrictive type.

Regurgitation-(Colour Flow Doppler Study)

The location, direction and size of the regurgitation flow are readily depicted by the colour flow system. There are several methods to quantitate severity of regurgitation.

Mitral Regurgitation/Tricuspid Regurgitation- When regurgitation jet extends-

Up to 1/3 of the atrium	: Mild.
Up to 1/3 of the atrium	: Moderate.
Up to posterior wall of atrium	: Severe.

Mitral Regurgitation-

(1) Area of jet-

Mild	: Less than 4 cm ² .
Moderate	: 4 to 8 cm ² .
Severe	: 8 cm ² .

(2) Area of jet/left atrial area-

Mild	: Ratio less than 20.
Moderate	: Ratio 20 to 40.

Aortic Regurgitation- Jet width/LVOT

Mild	: Ratio less than 25.
Moderate	: 25 to 65.
Severe	: Ratio more than 65.

Note- In colour Doppler echo, 90% of normal individuals show trivial TR and 75% show PR.

LV Contraction- (2D Echo)

LV performance is assessed by several ways. LV is divided into number of segments. Determining the motion of each segment provides a wall motion score for the entire chapter.

Note- Regional wall motion abnormalities may occur in other conditions also. (LBBB, right ventricular pacing and following the open heart surgery).

M-Mode studies were performed with use of 2 Dimensional images to direct the M-Mode sweep according to conventions of American Society of Echocardiography.¹⁷

Two-dimensional studies were performed from parasternal long axis and short axis views, apical four chamber and apical long axis two chamber views and subcostal view.

Pulsed Doppler studies of aortic, mitral, tricuspid and pulmonary valves were performed in multiple views.

The criteria for mitral valve prolapse on M-Mode studies consisted of posterior systolic displacement of the mitral valve echo by 2 mm or more beyond an imaginary line joining the C and D portions of the mitral valve echogram.¹⁸

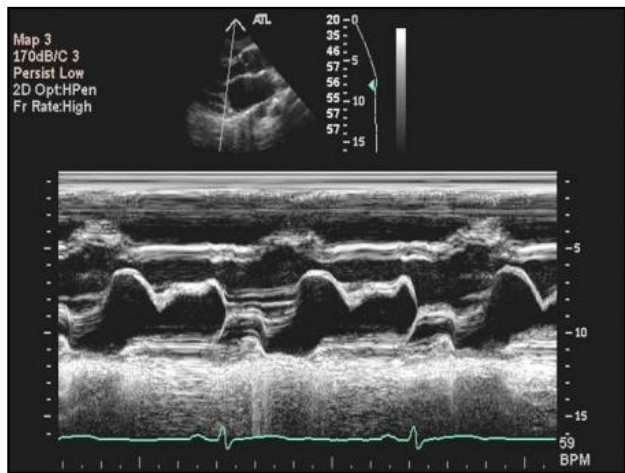


Figure 1. M-Mode Criterion for Left Ventricular Hypertrophy in Adults was a Wall 11 mm Thick or More was Used



Figure 2. Previously Defined Two-Dimensional Echocardiographic Criteria for Mitral Valve,¹⁹ Aortic Valve²⁰ and Tricuspid Valve²¹ Prolapse was used

Major Criteria	
1.	Late systolic posterior displacement of mitral leaflet on M-mode.
2.	Bulging of mitral leaflet into left atrium in parasternal long axis view.
3.	Thickened and redundant leaflet.
Minor Criteria	
1.	Holosystolic posterior prolapse on M-mode.
2.	Bowing of mitral leaflets into left atrium in apical 2-chamber view.
3.	Late systolic mitral regurgitation on Doppler study.
Echocardiographic Criteria for the Diagnosis of MVP	

For the purpose of this study, MVP was considered to be present if in addition to two-dimensional evidence of prolapse, any one or more of the following was present.²²

- A mitral click or regurgitant murmur.
- M-Mode evidence of prolapse.
- Doppler evidence of MR.

We think this definition addresses the objections to basing the diagnosis of MVP on isolated two-dimensional findings.^{23,24}

I graded the severity of Doppler detected regurgitation as mild, moderate and severe using modification of previously described qualitative method.^{25,26}

*RJA/LAA (%)	Severity
<20	Mild
20-40	Moderate
>40	Severe
*Regurgitation Jet Area (RJA) (maximum or average from three planes) is expressed as a percentage of the Left Atrial Area (LAA) obtained in the same plane as the maximum regurgitation area.	
Assessment of Severity of Mitral Regurgitation by Colour Doppler with Orthogonal Planes	

Study Method- Cross-sectional and analytical study.

OBSERVATION AND RESULTS

The study included a total of 50 patients, which included 35 (70%) males and 15 (30%) females (Table 1).

Male	Female	Total
35 (70%)	15 (30%)	50
Table 1. Sex Distribution		

Age Distribution- Age of patients included in study varied from 18 to 80 years (Table 2).

Age	Male	Female	Total
10-20	1		1
21-30		1	1
31-40	4		4
41-50	7	7	14
51-60	12	5	17
61-70	9	1	10
71-80	3		3
Total	36	14	50
Table 2. Age Distribution			

Symptoms- Chest pain and dyspnoea (34%) were the predominant symptoms, palpitation in 26% of patients (Table 3).

Chest pain	17 (34%)
Palpitation	13 (26%)
Dyspnoea	17 (34%)
Table 3. Symptom Analysis	

Blood Pressure- Almost, all patients had high blood pressure. The systolic BP varied from 120 to 210 mm of Hg and the diastolic BP from 80 to 110 mm of Hg (Table 4).

Systolic BP	No. of Pts.
<140	13 (26%)
140-160	31 (62%)
>160	6 (12%)
Diastolic BP	No. of Pts.
<90	17 (34%)
90-110	33 (66%)
>110	-

Table 4. Analysis of Blood Pressure

Creatinine- The range of creatinine was 1.2 to 15.8 mg/dL and the mean was 5.2 mg/dL (Table 5).

Creatinine (mg/dL)	Number of Patients
Less than 5	34 (68%)
5 to 10	11 (22%)
More than 10	5 (10%)

Table 5. Range of Serum Creatinine Level

Chest X-Ray

Normal study -47 (94%)
 Cardiomegaly -3 (6%)
 Cardiomegaly with pulmonary interstitial oedema -0.

Electrocardiography

The electrocardiograms were classified according to changes in ST segments and T waves previously reported to be associated with MVP.^{27,28}
 LVH with pressure overload pattern -12 (24%).
 ST and T changes like MVP -3 (6%).

Echocardiography Abnormalities

Concentric left ventricular hypertrophy was the most common abnormality detected in echocardiography.

Valvular Abnormalities.

Mitral valve abnormalities like MVPS and MR and LVH were the predominant valvular abnormalities noted in this study.

Morphology- MVPS	12 (24%)
AML	5 (10%)
PML	6 (12%)
AML and PML	1 (2%)
Mitral Regurgitation	
Trivial	12 (24%)
Mild	6 (12%)
Moderate	
Aortic Regurgitation	
Trivial	8 (16%)
Mild	2 (4%)
Moderate	
Tricuspid Regurgitation	
Mild	8 (16%)
Moderate	
Concentric LVH	26 (52%)

Table 6. Distribution of Valvular Abnormalities

DISCUSSION

The study included a total of 50 patients. Of these 50 patients, 35 (70%) were males and 15 (30%) were females.

The age of the patients varied from 18 to 80 years with majority of patients falling within 41 to 60 years group.

The mean age was 53 years with mean age in males being 54 years and in females being 49 years. Dyspnoea on exertion was present in 17 patients. Dyspnoea maybe due to anaemia, volume overload or pulmonary congestion due to failing left ventricle.

Chest pain was found in 17 patients. Of these 17 patients, 17 were found to have concentric hypertrophy. The cause of chest pain in concentric LVH group could be due to increased demand by the hypertrophied muscle mass or constriction of the smaller coronary vessels by the muscular contraction during systole. Chest pain can also be due to pericarditis, in which the pain is more on lying down posture and alleviated by sitting up and leaning forward. History of palpitation was obtained from 13 patients.

Clinical Findings

Almost, all patients had high blood pressure. The mean systolic BP was 149 mm of Hg and the mean diastolic BP was around 97 mm of Hg. About 17 (34%) of patients had moderate hypertension and 10 (20%) patients had severe hypertension. All the patients were receiving antihypertensives after admission during the study. Echocardiographically demonstrable left ventricular hypertrophy in 52% and the risk of death increases by 14%. Urea and creatinine were elevated in all patients.

Lowest creatinine was 1.2 mg/dL and highest was 15.8 mg/dL. About 11 (22%) patients had creatinine values ranging from 5 to 9 mg/dL and 5 (10%) patients had creatinine value greater than 10 mg/dL. In all cases, ultrasound proved to have autosomal dominant polycystic kidney disease. Chest x-ray was normal in 47 (94%) patients. Cardiomegaly was seen in 3 (6%) patients. Cardiomegaly with pulmonary interstitial oedema was not seen. ECG showed evidence of left ventricular hypertrophy with pressure overload pattern in 12 patients. The diagnosis of left ventricular hypertrophy in ECG was made by using Sokolov-Lyon criteria.

Echocardiographic Profile

Concentric LVH- Concentric left ventricular hypertrophy is the most common abnormality detected. It was found in 26 (52%) patients.

Echocardiographically-proved left ventricular hypertrophy is an independent risk factor for cardiovascular morbidity and mortality. Lowering of cardiac size and increase in fractional shortening were both associated with reduced subsequent likelihood of cardiac failure.

These associations were independent of baseline age, diabetes mellitus, ischaemic heart disease and baseline echocardiographic parameters.

The mean BP in patients who had concentric hypertrophy was 149 mm of Hg (systolic) and 97 mm of Hg (diastolic). ECG showed concentric left ventricular hypertrophy with pressure overload type in 12 (24%) patients. Echocardiography showed concentric left ventricular hypertrophy in 26 (52%) patients. 3 of the 24 patients who

had concentric left ventricular hypertrophy did not have cardiac symptoms. About 10 patients had normal ECG, but proved to have left ventricular hypertrophy by echocardiography. This signifies the role of echocardiography in diagnosing left ventricular hypertrophy.

Increasing age, hypertension and anaemia were the causes of concentric left ventricular hypertrophy in uraemia. Hyperparathyroidism can also cause left ventricular hypertrophy.

Valvular Abnormalities

Mitral valve prolapse was found in 12 (24%) patients, among which AML prolapse was seen in 5 (10%) patients, PML prolapse was seen in 6 (12%) patients and both AML and PML prolapse was seen in 1 (2%) patient.

Mitral regurgitation was found in 18 patients, among which mild mitral regurgitation was found in 6 patients and trivial mitral regurgitation was found in 12 patients. Aortic regurgitation was found in 10 patients among, which mild aortic regurgitation was found in 2 patients and trivial aortic regurgitation was found in 8 patients. Tricuspid regurgitation was found in 8 patients.

One of the pathogenetic mechanisms postulated for polycystic kidney is a generalised defect of collagen. A demonstration of an increased prevalence of valvular abnormalities in particular mitral valve prolapse would support this concept. Collagen analysis of the valve and of chordae tendineae revealed the presence of type I collagen in normal quantities and a striking absence of type III and AB collagen.²⁹

Several studies have suggested that there is increased frequency of cardiac abnormalities in polycystic kidney disease.^{30,31} The result of our study shown a marked increase in prevalence of MVP among patients with polycystic kidney disease.

Further evidence of generalised cardiac involvement was the increased frequency of valvular regurgitation of the mitral, tricuspid and aortic valve detected by Doppler echo in this study.

Doppler evidence of regurgitation increases with age.³²

Valvular regurgitation began to appear in subjects 50 or more years, increasing in prevalence with advancing age. Multivalvular regurgitation appeared in subjects 60 or more years old and was very common in those 80 or more.

The high prevalence of valvular regurgitation in the aged might be related to myxomatous degeneration of valves and their supporting structures. Longstanding mechanical stress may also play a role. Left-sided valves (aortic and mitral) are exposed to high pressures and may therefore undergo degenerative changes earlier than right-sided valves.

The pathologic processes of mitral valve and tricuspid valve prolapse clearly involves abnormalities of collagen tissue. Marfan's syndrome and Ehlers-Danlos syndrome are frequently associated with aortic and mitral abnormalities. We suggest that the demonstration of an increased frequency of these valvular abnormalities caused by collagen defects lends support to the hypothesis that such defect maybe involved in polycystic kidney disease.

Moreover, epithelial cell cultures from cysts in human polycystic kidneys reveal an extracellular matrix with an electron microscopic appearance different from that of normal renal tubular epithelium culture.¹⁴

In addition, the cystic epithelium appears to elaborate different extracellular proteins than normal renal epithelium.¹³ Thus, the clinical abnormality of mitral valve prolapse is compatible with observed data.

Atypical chest pain³¹ and palpitations^{33,34} are symptoms often associated with mitral valve prolapse. An increased frequency of these symptoms was present in the subjects with polycystic kidney disease. However, the frequency of the same symptoms in the control group suggests that they are rather nonspecific and are not unique features of mitral valve prolapse. This conclusion is consistent with findings of the Framingham survey.¹⁸ Thus, cardiac symptoms are not helpful in identifying the patient with polycystic kidney disease who also has mitral valve prolapse. Similarly, electrocardiographic changes in the ST segments and T waves are not very specific. The importance of isolated evidence of mitral valve prolapse on two-dimensional echocardiography has been questioned; in this study, however, the diagnosis of prolapse was based on two-dimensional echocardiography combined with other findings. The prevalence of prolapse in the control group was low (2 percent) and similar to that found in the Framingham study³⁵ and in other studies³⁶ that have used rigid diagnostic criterion. Clinical features of a mitral valve click or systolic murmur were present in 2 percent of the subjects given a diagnosis of mitral valve prolapse.

Doppler echocardiographic studies are not recommended in all subjects with polycystic kidney disease. Rather, they should be reserved for patients with clinical signs of mitral valve prolapse or other valvular abnormalities.

The frequency of mitral valve prolapse in the unaffected family members was significantly lower. It is possible that some subjects classified as unaffected on the basis of normal renal ultrasonograms may in fact have the gene for polycystic kidney disease. The mitral valve prolapse may represent the first or sole phenotypic manifestation of the gene.

Variability in the phenotypic presentation of autosomal dominant disorders is common. Therefore, it is highly likely that at least some persons with the gene for polycystic kidney disease manifest only extrarenal abnormalities.

It is also possible that mitral valve prolapse is a manifestation of another gene. Previous studies suggest that certain forms of prolapse are transmitted in an autosomal dominant fashion. If there is another gene for mitral valve prolapse, a higher incidence of that defect may still be observed in subjects with autosomal dominant polycystic kidney disease.

Primary mitral valve prolapse probably results from abnormal extracellular matrix. The putative gene for this abnormality and the gene for polycystic kidney disease may have a magnification effect. Given the systemic nature of polycystic kidney disease, the concept of a single disease is

more appealing. Final conclusions, however, will depend on gene identification.

The finding of an increased prevalence of cardiac abnormalities among patients with polycystic kidney disease has potentially important clinical implications. For example, such patients have an increased likelihood of having urinary tract infection and associated septicaemia. Such infections may tend to result in endocarditis in patients with valvular abnormalities. However, the incidence of endocarditis in polycystic kidney disease remains to be examined.

The advent of antihypertensive therapy, dialysis and renal transplantation has permitted patients with advanced polycystic kidney disease to enter the sixth and seventh decades of life- a time when the incidence of severe mitral valve incompetence due to prolapse increases dramatically. The natural history of this abnormality in polycystic kidney disease remains to be defined.

In a patient with polycystic kidney disease, sudden death or a cerebrovascular event is often attributed to a ruptured berry aneurysm. However, given the frequent association of polycystic kidney disease with mitral valve prolapse, embolism and arrhythmias should also be considered as causes.

Results of the study done by Hossek et al showed concentric LVH was 18%, MVPS was 26%, MR was 31%, AR was 8% and TR was 15%. But, in our study, concentric LVH was found to be 52%, MVPS was 24%, MR was 30%, AR was 20% and TR was 16%. Our study results closely related with the study done by Hossek et al, but there was a slight increase in incidence of LVH and AR.

CONCLUSION

1. Echocardiography is easily performed, noninvasive, safe, reproducible and accurate in assessment of cardiac function in autosomal dominant polycystic kidney disease.
2. Concentric left ventricular hypertrophy was the commonest abnormality in autosomal dominant polycystic kidney disease.
3. In echocardiography, MVPS was seen in 12 (24%) patients, MR was seen in 18 (36%) patients, AR was seen in 10 (20%) patients and TR was seen in 8 (16%) patients.
4. Echocardiography is more sensitive in diagnosing left ventricular hypertrophy than by x-ray and ECG.

Echocardiographically detectable concentric left ventricular hypertrophy and valvular abnormalities were present in asymptomatic patients. Hence, this necessitates screening of patients without cardiac symptoms for cardiac abnormalities after the diagnosis of autosomal dominant polycystic kidney disease has been made.

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