




Review

Cardiac Involvement in Autosomal Dominant Polycystic Kidney Disease

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Abstract: Cardiovascular disorders are the main complication in autosomal dominant polycystic kidney disease (ADPKD), contributing to both morbidity and mortality. This review considers clinical studies unveiling cardiovascular features in patients with ADPKD. Additionally, it focuses on basic science studies addressing the dysfunction of the polycystin proteins located in the cardiovascular system as a contributing factor to cardiovascular abnormalities. In particular, the effects of polycystin proteins' deficiency on the cardiomyocyte function have been considered.

Keywords: autosomal dominant polycystic kidney disease; polycystin; cardiomyocyte function; left ventricular diastolic function



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1. Epidemiology, Genetics and Pathogenesis

Autosomal dominant polycystic kidney disease (ADPKD) is the most common monogenic renal disorder, implies a progressive loss of renal function and accounts for 4% to 10% of patients with end-stage renal disease (ESRD) [1,2]. The disease, which occurs worldwide with an estimated prevalence of 1:400 to 1:100, is characterized by the age-dependent growth of renal cysts such that ESRD typically ensues during mid adulthood [3–5].

Mutations in Polycystic Kidney Disease 1 and 2 (PKD-1 and PKD-2, respectively) genes have a well-defined role in uncontrolled cystogenesis in both kidneys, the hallmark of the disease, as well as in the liver, and less frequently in the pancreas, seminal vesicles and arachnoid membrane [1,2,6–14]. Approximately 85% of ADPKD cases are caused by mutations in the PKD1 gene [MIM 601313], which is located on chromosome 16p13.3, while the remaining cases are due to mutations in PKD2 [MIM 173910], located on chromosome 4q21 [9,10].

The protein products of PKD1 and PKD2, polycystin-1 (PC1) and polycystin-2 (PC2), are membrane proteins that probably form a functional complex [15–19]. They have been shown to localize predominantly, although not exclusively, in primary cilia and mediate the sensitivity of kidney epithelial cells to fluid shear stress [6–8]. PC1 has been proposed to be a mechanosensitive molecule, given its large extracellular domain and remarkable mechanical strength [1]. The distribution of the polycystin proteins at different subcellular locations is required for them to orchestrate a network of signaling pathways that have been implicated in the pathogenesis of PKD [8,20].

PC1 or PC2 dysfunction may result in decreased intracellular calcium inflow with increased 3', 5'-cyclic adenosinemonophosphate (cAMP) production and the activation of mechanisms which contribute to cyst cell growth by stimulating both epithelial cell proliferation and transepithelial fluid secretion [21]. Indeed, relevant downstream responses of the changed calcium signaling ultimately lead to increased proliferation and increased apoptosis [22]. Factors impacting upon disease progression include the level of PKD protein expression and the penetrance of pathogenic alleles [23,24]. However, both ADPKD type 1 and type 2 share the full spectrum of renal and extrarenal manifestations, although type 2 has a delayed onset compared to type 1 [1,2,25–27]. In type 2 patients, the common

complications of ADPKD, such as hypertension, hematuria and urinary-tract infection, seem to be milder than in type 1 patients at the same age. The median age at death or onset of end-stage renal disease has been reported as 53 years in type 1 patients and 69 years in type 2 [25].

1.1. Kidney Polycystic Disease

The renal phenotype in patients with ADPKD ranges from elderly patients without renal failure to rare cases of enlarged kidneys that are detected in utero [28]. The disease course is highly variable, as a significant minority of patients do not reach ESRD even in old age, while a small number exhibit early-onset disease, with a diagnosis made in infancy by the identification of enlarged echogenic kidneys.

Renal cyst expansion results from aberrant proliferation of the cyst wall epithelial cells and the accumulation of fluid within the cavity of the cyst. There is increased extracellular matrix remodeling as the cyst invades the adjacent parenchyma, leading to abnormal matrix deposition and fibrosis. The gradually growing renal cysts start to develop in utero and can originate from all areas of the kidneys, although cysts usually form in the distal regions of the nephron and the collecting duct [29–33].

Impaired urinary concentrating capacity has been well documented as common even in early stages [1,26–28].

Another important feature of ADPKD is the increase in plasma vasopressin concentrations. This defect is often attributed to the disruption of the medullary architecture, because its presence and severity correlate with the extent of the cystic disease. There is substantial evidence that the urinary concentrating defect and raised vasopressin concentrations could contribute to cystogenesis [34–36]. They might also contribute to the glomerular hyperfiltration seen in children and young adults, the development of hypertension and chronic kidney-disease progression [37].

Another early functional defect is a reduction in renal blood flow, likely due to the development of cysts with changes in intrarenal pressures, and to neuro humoral or local mediators [38–40]. As mentioned above, the identity of the mutated gene in patients with ADPKD explains part of the phenotypic variability observed in clinical practice, so that patients with a mutation in PKD1 have earlier-onset ESRD, lower glomerular filtration rate (GFR) and larger kidney volumes than patients with a mutation in PKD2 [1,25,41].

1.2. Arterial Hypertension

Even though enlarged cystic kidneys are the most obvious phenotype in ADPKD, cardiovascular disorders are the main complication contributing to both morbidity and mortality [42]. Systemic arterial hypertension is an early finding, occurring in about 60% of patients prior to a significant decline in GFR [3]. In particular, hypertension is observed in patients with ADPKD about a decade earlier than in the general population and even before the loss of renal function [43–45]. Although the mechanism underlying hypertension is not completely understood, the up-regulation of the renin angiotensin aldosterone system (RAAS), due to cystic compression of the renal vasculature, is considered a key mechanism in the pathogenesis of hypertension in ADPKD, as it leads to an increase in vascular resistance, and contributes to cardiac hypertrophy [46,47]. The RAAS pathway is the subject of clinical trials in patients with ADPKD in the HALT study, a US multicenter trial conducted on about 1000 ADPKD patients for 5.5 years. The benefits of blood-pressure control by antihypertensive drugs on patients with ADPKD have been largely demonstrated [48]. In patients with eGFR above 60 mL/min/1.73 m², a target blood pressure of 110/70 mm Hg was suggested, especially in young patients with a high progression risk [49], while a target blood pressure below 120/80 mm Hg was recommended in chronic kidney disease stage 3 [50]. Thus, the aggressive control of hypertension in ADPKD patients appears to be clinically necessary and practically relevant. Nevertheless, as hypertension is likely dependent on the interaction of hemodynamic, endocrine and neurogenic factors, it has been postulated that mechanisms including increased sympa-

thetic nerve activity [51], increased plasma endothelin-1 concentrations [52] and insulin resistance [53,54] contribute to the pathogenesis of hypertension in ADPKD. These theories can account for the high prevalence of hypertension but fail to explain why hypertension is frequently observed in patients with ADPKD, including children, even before the onset of renal insufficiency [55,56].

The PKD genes are expressed in a wide range of tissues beyond the kidney, and their expression is developmentally regulated in most of these tissues [57,58]. The fact that PC1 and PC2 are expressed in vascular smooth muscle and endothelial cells suggests that a reduced polycystin protein function in the vasculature could play a primary role in the early development of hypertension [59,60].

The primary dysfunction of the PC1 and PC2 complex results in decreased intracellular calcium inflow, with enhanced vascular smooth muscle contractility in response to adrenergic stimulation [61], increased muscular cell proliferation and apoptosis [62], and impaired endothelial-dependent vasorelaxation [63], functional abnormalities that might play a role in vascular remodeling and the early development of hypertension [64].

1.3. Vascular Abnormalities

The reduced expression of the polycystin proteins (haploinsufficiency) in the endothelial cells and vascular smooth muscle cells of most blood vessels, including the aorta and cerebral arteries, are likely to cause the vascular abnormalities in patients with ADPKD [59,65].

The functions of PC1 and PC2 in the vasculature indicate that they have a crucial role in mechano-sensation [66–69]. In endothelial cells, the proteins are involved in fluid-shear stress sensing, thereby regulating calcium signaling, and there is NO release or vasodilatation in response to the increased blood flow [70–77]. In vascular smooth muscle cells, the polycystins regulate pressure sensing by modulating the activity of the stretch-activated cation channels and myogenic contraction [78–80]. A loss of myogenic tone may contribute to aneurysm formation owing to an increase in arterial wall stress [81,82].

Indeed, the risk of cerebral aneurysms is higher in families with a positive family history of ADPKD than in those without, probably because of modifying genes [83,84]. Moreover, patients with ADPKD are more prone to coronary arteries aneurysms and acute dissection, which are a source of coronary syndromes and death [85–87]. Likewise, primary defects in vascular structure may lead to acute aortic dissection, that occurs in ADPKD patients more frequently than in the general population [88–90].

1.4. The Heart in ADPKD

ADPKD is a systemic disease associated with several extrarenal manifestations, including aortic root dilatation and cardiac valvular abnormalities, mostly mitral valve prolapse [91,92]. The early development of hypertension leads to LV hypertrophy, a major cardiovascular risk factor, and to LV diastolic dysfunction [67]. The occurrence of advanced kidney failure contributes to the increased frequency of cardiovascular events seen in ADPKD, as it is a well-known key factor in the development of cardiac function impairment.

The relevance of LV hypertrophy in ADPKD has been established by clinical studies [93–98]. Among 116 consecutive ADPKD patients, LVH was found in 46% of males and 37% of females, and the LV mass, as measured by two-dimensional echocardiography and indexed by body surface area, correlated significantly with the blood pressure level. An early onset of hypertension and a frequently inadequate treatment may account for the role of blood pressure as a contributing factor to LV hypertrophy in ADPKD patients. In the HALTPKD study (NCT0028368), the rigorous blood pressure control obtained with the use of RAAS inhibitors was able to achieve a significant reduction of LV mass as measured by MR imaging [48]. It is worth noting that LV hypertrophy can also be observed in normotensive ADPKD patients [56,91–94]. In a single-site study [99] including 126 ADPKD patients (78% with hypertension), the prevalence of LV hypertrophy was not influenced by

the co-diagnosis of hypertension (21% vs. 17%). Factors other than hypertension, including anemia, obesity and sodium intake, as well as the increased activity of the RAAS, vitamin D deficiency [100] and secondary hyperparathyroidism, might be involved in the increase of the LV mass in ADPKD. Note that the vitamin D receptor is expressed in renal juxtaglomerular cells, vascular smooth muscle cells and, most interestingly, cardiac myocytes. Insulin resistance could be a further factor responsible for the onset of cardiac hypertrophy in ADPKD patients [53,54]. Endothelial dysfunction, oxidative stress and nitric oxide deficiency are also related to cardiac hypertrophy owing to arterial hypertension. Alterations in fluid shear stress mechanosensitivity are evident early on in ADPKD [71–74,77]. Normotensive ADPKD patients display a loss of nitric oxide release and an associated reduction in the endothelium-dependent dilation of conduit arteries during sustained flow increase (hand skin heating), notwithstanding a preserved flow mediated dilation during transient flow stimulation (postischemic hyperemia) [77]. However, the occurrence of LV hypertrophy in young adult patients before the onset of hypertension [56,94,95] and even in children [101] suggests a role of ADPKD's specific mechanisms in the pathogenesis of cardiac involvement. It has been reported that cardiac diastolic dysfunction is an early feature of ADPKD, as it is often present prior to the loss of kidney function and even in normotensive individuals. Bi-ventricular diastolic dysfunction has been documented even in young ADPKD patients with still normal blood pressure [102].

A single-site study utilized speckle-tracking echocardiography to assess the LV function in a cohort of ADPKD patients with normal ejection fraction as compared to matched healthy subjects as well as to matched chronic kidney disease (other than ADPKD) patients [103,104]. ADPKD patients were found to have subclinical systolic dysfunction with reduced LV global longitudinal strain and twist in association with LV diastolic dysfunction. Interestingly, the impairment of the torsional function was associated to the increase in diastolic filling pressures as evaluated by Doppler measures of E/e' , that is, the velocity of the mitral valve inflow compared to the mitral annulus velocity. The subclinical changes in the LV function were considered as due to myocardial cell dysfunction, which was directly related to the disease rather than to confounding factors such as hypertension or renal insufficiency.

Understanding the mechanisms involved in ADPKD-associated cardiac manifestations may open up specific therapeutic perspectives; nevertheless, the precise pathways and interactions remain largely unknown. Several *in vivo* studies have attempted to clarify the role of polycystin proteins in heart cells. To gain insight into the disease mechanisms and pathogenesis of ADPKD, various mouse models have been genetically engineered, including inducible, conditional knockout mice and mouse models with hypomorphic or hypermutable alleles of PKD1 or PKD2. Otherwise, the ablation of both alleles of PKD1 or PKD2 results in embryonic lethality, and heterozygous mice develop only a very mild form of the disease [105–107].

PC1 and PC2, the PKD1 and PKD2 products, are essential for the development of the heart. One of the major sites of PKD1 expression is in the developing and mature cardiovascular system [105]. Moreover, PC1 has been found to regulate L-type calcium channel protein levels through the AKT pathway and cardiomyocyte contractility in a mouse model, suggesting a crucial role for this protein in cardiac function [108–110]. PC1 has been shown to act as a mechanosensor in cardiomyocytes, required for stretch-induced cardiomyocyte hypertrophy as well as for pressure overload-induced hypertrophy [108]. PC1 is a critical modulator of apoptosis and fibrosis. Cardiomyocyte PC1 plays a pivotal role in regulating fibroblast-to-myofibroblast differentiation, with implications for cardiac fibrosis and remodeling [111]. Also noteworthy is the fact that mice harboring a cardiomyocyte-selective conditional silencing of PC1 do not develop fibrosis after being subjected to transverse aortic constriction [108], supporting the role of this protein in cardiac remodeling. Moreover, PC1 mitigates cardiac damage during ischemia/reperfusion, likely through AKT activation, and regulates the connective tissue growth factor expression

in cardiomyocytes [111]. The cardiomyocyte-specific deletion of PKD1 impairs the systolic and diastolic functions in mice [112].

PC2 is involved in the cardiomyocyte regulation of ion transport and calcium signaling [113–116]. Heart function has been shown to depend on PKD2 activity, as evidenced by the fact that a lack of PC2 in zebrafish led to signs of heart failure. Moreover, patients with ADPKD due to reduced PC2 activity are particularly prone to develop idiopathic dilated cardiomyopathy [113]. While PC2 regulates intracellular calcium cycling, a follow-up report showed that PKD2-haploinsufficient mice present a desensitized calcium contraction coupling in cardiomyocytes and an altered response to adrenergic stimulus [114]. PC2 is also important for the regulation of ryanodine receptors' RyR2 function, and, thus, the loss of RyR2 regulation that occurs when PC2 is mutated results in altered calcium signaling in the heart [107]. Moreover, cardiomyocyte specific PC2 knockout mice manifest an impaired autophagic flux in the setting of nutrient deprivation, due to the altered control of intracellular calcium homeostasis [115]. The role of polycystin proteins for autophagy, through which the cell can remove the buildup of deleterious protein components, might affect cardiomyocytes' sarcomeric function and impair the ability of the cardiomyocytes to contract, and ultimately results in a stiffer and less compliant heart [117]. This mechanism may in part explain the decreased torsional compliance of ADPKD patients' hearts [104].

A study that used ADPKD patient-specific induced pluripotent stem cells differentiated toward ventricular-like cardiomyocytes, confirmed the PC1 and PC2 cardiomyocyte expression and showed that the PKD mutation per se is a cause of cardiomyocyte calcium cycling abnormality and is proarrhythmogenic [118]. These findings are consistent with previous observations in mouse models. The most relevant result was the close correspondence between the iPSC-derived cardiomyocytes behavior and the donor patient's clinical phenotype.

Nevertheless, unraveling the organ-specific pathophysiology of a human disease with multiple organ involvement such as ADPKD is very challenging. Figure 1 provides an overview of the mechanisms of cardiac involvement.

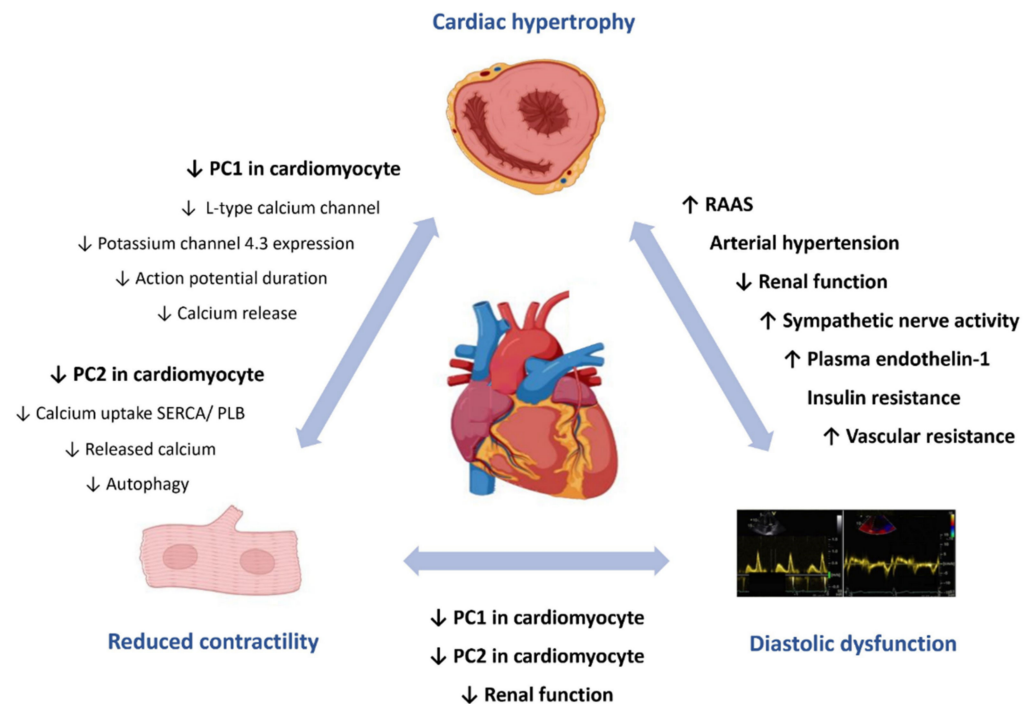


Figure 1. Autosomal dominant polycystic kidney disease and the heart. Current understanding of pathophysiological mechanisms underlying cardiac involvement in autosomal dominant polycystic

kidney disease. Activation of RAAS and other mechanisms, including the increased activity of the sympathetic nervous system, the decline of renal function, insulin resistance, disturbances in the fine-tuning of vascular tone and arterial hypertension, are responsible for cardiac hypertrophy and left ventricular diastolic dysfunction. A reduced activity of cardiomyocyte PC1 or PC2 is thought to reduce myocardial contractility and contribute to diastolic dysfunction. PC, polycystin; RAAS, renin–angiotensin–aldosterone system; SERCA, sarco/endoplasmic reticulum calcium-ATPase; PLB, phospholamban.

A relatively frequent coexistence of ADPKD and inherited cardiomyopathies such as idiopathic dilated cardiomyopathy and hypertrophic obstructive cardiomyopathy has been found out by reviewing the ADPKD database of a large tertiary center [119]. A genetic interaction between the PKD genes and the genes mutated in inherited cardiomyopathies can be hypothesized, rather than ADPKD being the direct cause of the cardiomyopathies.

2. Conclusions

Taken together, data from clinical and experimental studies provide compelling evidence that the cardiovascular complications of ADPKD are due at least in part to primary manifestations of the mutant proteins. Considering the importance of the polycystin proteins in cardiac development and myocardial function, the heart should be regarded as a target organ in ADPKD patients. Understanding the pathophysiologic mechanisms of heart involvement may be the foundation of novel therapy development.

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