

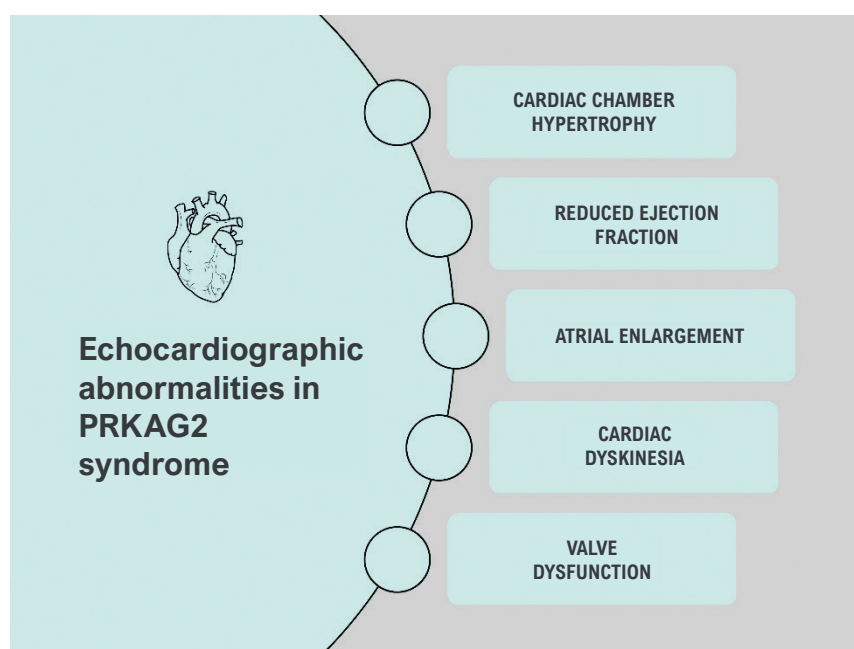
Echocardiographic Characteristics of PRKAG2 Syndrome: An Integrative Review

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Central Illustration: Echocardiographic Characteristics of PRKAG2 Syndrome: An Integrative Review



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Abstract

PRKAG2 syndrome is a rare, early-onset, autosomal dominant, inherited lysosomal glycogen storage disease that develops with ventricular preexcitation syndrome, supraventricular arrhythmias, and cardiac hypertrophy. The disease is caused by mutations in the gene encoding the adenosine monophosphate-activated protein kinase (AMPK)

protein, leading to glycogen accumulation in cardiomyocytes. Echocardiography is a noninvasive, widely available, and highly effective technique for identifying and quantifying left ventricular hypertrophy (LVH). Therefore, this review focuses mainly on echocardiographic patterns, describing the main alterations in patients with PRKAG2 syndrome.

The objective of this paper is to conduct an integrative review of the echocardiographic features presented by patients with PRKAG2 syndrome.

We conducted an integrative review of echocardiographic features in PRKAG2 syndrome by searching PubMed, SciELO, IBECS, and LILACS electronic databases using the following keywords: “PRKAG2 syndrome” and “PRKAG2.”

The predominant echocardiographic finding in patients with PRKAG2 syndrome was cardiac chamber hypertrophy, particularly affecting the left ventricle. In addition, other findings included abnormal ejection fraction, changes in strain patterns, and heart valve abnormalities.

Keywords

Glycogen Storage Disease; Echocardiography; Cardiomyopathy, Hypertrophic

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Cardiac chamber hypertrophy was demonstrated in most studies, with a predominance of LVH. Reduced ejection fraction was also described, both in the left and right ventricles. Other features reported included atrial enlargement, cardiac dyskinesia, and valve dysfunction. However, the findings varied widely, highlighting the phenotypic variability of this syndrome.

Introduction

PRKAG2 syndrome is a rare, early-onset, autosomal dominant, inherited lysosomal glycogen storage disease that develops with ventricular preexcitation syndrome, supraventricular arrhythmias, and cardiac hypertrophy. The disease is caused by mutations in the gene encoding adenosine monophosphate-activated protein kinase (AMPK) in the gamma 2 subunit. The mutation causes anomalous AMPK activity, leading to glycogen accumulation in cardiomyocytes that causes their progressive increase. PRKAG2 syndrome can be expressed in different ways, both by left ventricular hypertrophy (LVH) and by arrhythmic features, ranging from an asymptomatic condition, Wolff-Parkinson-White syndrome, and progression of atrioventricular block requiring pacemaker (PM) implantation to sudden cardiac death (SCD).¹

Regarding clinical parameters, the onset of symptoms usually occurs in the first 3 decades of life and is often characterized by tachycardia and bradyarrhythmias; less often, heart failure or SCD may be the first manifestations of the disease. Prolonged dynamic electrocardiogram monitoring and exercise stress testing are useful tools in patients with syncope, palpitations, or with a family history of SCD.²

Regarding echocardiographic patterns, echocardiography is a noninvasive, widely available, and highly effective technique for identifying and quantifying ventricular hypertrophy, assisting in the evaluation and monitoring of the disease and allowing early follow-up.³ Increasing access to genetic testing to diagnose this syndrome, associated with the description of echocardiographic parameters, has made it possible to distinguish and assess disease progression. Since the pathogenesis and natural history of this syndrome differ from other arrhythmogenic cardiomyopathies, a differentiated diagnostic approach and follow-up are required.⁴ Therefore, this review focuses mainly on echocardiographic parameters, describing the main alterations in patients with PRKAG2 syndrome.

This review is justified by the fact that there are few published studies that have provided evidence of echocardiographic findings in PRKAG2 syndrome. Therefore, describing these parameters will have practical implications for the diagnosis and follow-up of patients with this condition. The echocardiographic findings are illustrated in the Central Figure.

Objectives

To conduct an integrative review of the echocardiographic features presented by patients with PRKAG2 syndrome, with the following guiding question: "What are the echocardiographic features presented by patients with PRKAG2 syndrome?". Thus, we aim to show which short-term and long-term cardiac abnormalities are found in this condition.

Methods

We conducted an integrative review of echocardiographic features in PRKAG2 syndrome. Studies were identified by searching the following electronic databases from inception to April 24, 2023: PubMed, SciELO, IBECs, and LILACS. A simple search was performed in all database fields (title, abstract, text word, etc.) using the following keywords: "PRKAG2 syndrome" and "PRKAG2," using the Boolean operator "OR." Studies eligible for inclusion in this review were published in English up to the date the last search was run and answered the guiding question, that is, addressed echocardiographic findings in PRKAG2 syndrome. Studies providing a systematization of data, such as integrative or systematic reviews, were excluded. Two reviewers independently screened titles and abstracts, and then screened candidate full-text articles for selection on the basis of our eligibility criteria. For studies meeting eligibility, data were extracted using a standardized table, with a specific column for each information to be collected, as follows: author/year, article title, study design, sample, and results.

Results

The database searches resulted in a total of 98 articles. Of these, 80 were excluded for the following reasons: 13 integrative or systematic reviews, 3 duplicates, 1 editorial about another article, and 63 studies that did not answer the guiding question. Therefore, 18 studies were included in this review. The flow diagram of study selection is shown in Figure 1. Table 1 summarizes the included studies, which are presented in ascending order of year of publication, according to the database from which the article was retrieved.

Discussion

Cardiac chamber hypertrophy

According to Lipshultz et al.,⁴ hypertrophic cardiomyopathy (HCM) has a reported incidence of 0.24-0.47 per 100,000 children and is a leading cause of SCD in young people. It is characterized by abnormal thickening of the heart muscle, especially of the left ventricle (LV) and the interventricular septum. In this context, cardiac hypertrophy is one of the main manifestations of the PRKAG2 syndrome, being a finding in all of the 18 studies analyzed in this review.

There is still no consensus on when this abnormality begins, but some studies indicate that it may be present during intrauterine development. In the case reported by Gorla et al.,¹⁶ cardiac hypertrophy was observed as early as 28 weeks of gestation, demonstrating a severe form of HCM with involvement of both ventricles, the interventricular septum, and the right atrial wall. Torok et al.¹³ reported 2 cases of PRKAG2 mutation carriers, with presentation of this condition in infancy. One of the patients presented with hypertrophy of the interventricular septum at birth, which, however, was no longer observed at age 3 months, whereas the other patient presented with severe biventricular hypertrophy at birth. Also, regarding manifestations in the pediatric population, Aggarwal et al.¹¹ reported the case of an adolescent female

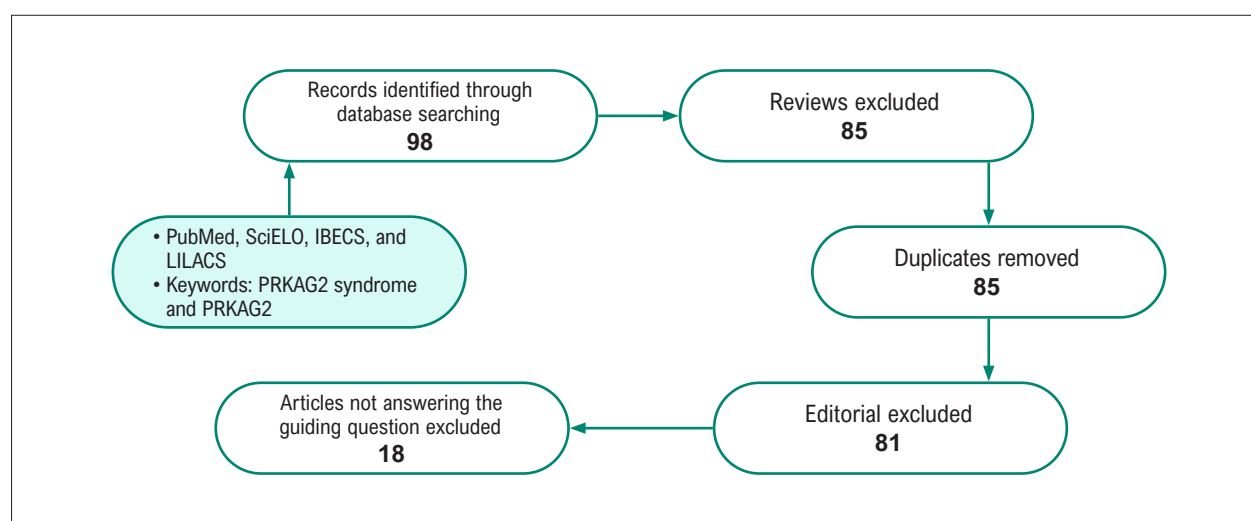


Figure 1 – Flow diagram of study selection. Source: Designed by the authors.

affected by *PRKAG2* gene mutation and found that she had concentric LVH.

Tan et al.,⁷ in the first published study on *PRKAG2* mutations, although without a focus on echocardiographic abnormalities in *PRKAG2* mutation carriers, reported that, of the 17 retrospectively studied patients, 8 had undergone echocardiography and 7 of them had cardiac hypertrophy. An interesting finding of the study was the histopathological confirmation of this diagnosis. Later, in the comparative study by Sternick et al.,⁸ 30% of patients with *PRKAG2* mutation ($n = 10$) had LVH, whereas control patients ($n = 9$), without the mutation, had no structural heart disease.

Fabris et al.⁹ reported the case of a 17-year-old individual with echocardiography showing mild asymmetric LVH with posterolateral distribution and maximum wall thickness (MWT) of 13 mm. Sternick et al.¹⁰ reported the case of an 18-year-old patient with severe LVH associated with acute myocardial infarction, with an LV septal thickness of 44 mm. In the case of a 40-year-old patient reported by Müllertz and Jensen,¹² LVH was initially misinterpreted as hypertensive heart disease, highlighting the importance of considering rare causes of HCM in patients presenting with tachycardia, preexcitation, and atrioventricular block. Van Der Steld et al.¹⁴ observed that, in 60 patients who were members of a Brazilian family with *PRKAG2* syndrome, the predominant pattern was generalized and diffuse LVH, which predominated in the apical and medial portions later in life. Epicoco et al.¹⁵ reported the case of a 30-year-old patient identified with *PRKAG2* gene mutation whose echocardiogram showed marked and symmetric HCM without outflow obstruction, with an MWT of 28 mm.

Regarding the remaining studies analyzed in this review, the most recent ones, published in the last 3 years, also reported the patterns found in the previously mentioned studies. Ahamed et al.,¹⁷ for example, observed that 19 individuals (86%), from a cohort of 22 individuals with a mean age of 39.5 ± 18.1 years, had evidence of diffuse and concentric LVH, with right ventricular (RV) hypertrophy being observed in 19 patients with LVH (19/22; 86%). Hu et al.¹⁸ reported

that 4 patients (80%) had LVH; in 3 of them, the analysis showed diffuse asymmetric hypertrophy, with a pattern of LV middle-anterior-lateral-inferior hypertrophy and especially interventricular septal hypertrophy. In contrast, 1 patient showed symmetric hypertrophy. The study also brought to light a new finding at that time, atrial enlargement, which was present in half of the patients, with or without hypertrophy, suggesting that this phenomenon might precede hypertrophy in the early stages. Furthermore, the youngest patient, aged 9 years, presented with mild symmetric hypertrophy, speculating that this is also a finding that might occur in the early stages. Lopez-Sainz et al.¹⁹ reported that patients with *PRKAG2* syndrome, with a mean age of 37 years, had LVH with an MWT of 19 ± 7 mm. Pena et al.²⁰ analyzed 30 individuals with *PRKAG2* syndrome, with a mean age of 39.1 ± 15.4 years, and found LVH in different degrees in 25 patients (86%), with a mean LV septal thickness of 14.1 ± 4.2 mm. The relative wall thickness (RWT) was increased (0.56 ± 0.18), characterizing concentric hypertrophy, and RV hypertrophy occurred in 90% of patients. Furthermore, regarding sex differences, men had higher myocardial mass than women. Regarding age, no correlation was found between age and hypertrophy-related variables. In the study conducted by Magalhães et al.,⁵ of 16 individuals with a mean age of 40 ± 11 years, 7 (54%) had LVH on echocardiography.

In the past year, 2 studies have made significant contributions to the understanding of the disease – the first, conducted by Tang et al.,²² by comparing *PRKAG2* mutation carriers with a group of healthy individuals, and the second, conducted by Pena et al.,²¹ by describing a feature little explored in this syndrome, the involvement of the RV. The cross-sectional study by Tang et al.,²² including 9 patients with *PRKAG2* mutation and mean age of 40.22 ± 14.01 years, showed that these individuals had increased LV wall asymmetry compared with the group of 202 healthy individuals (1.42 ± 0.52 vs 0.14 ± 0.14 mm, $p = 0.001$), with asymmetric septal hypertrophy. Furthermore, RWT was higher in the *PRKAG2* group than in the healthy group (0.48 ± 0.15 vs 0.39 ± 0.07 , $p = 0.002$),

Table 1 – Summary of evidence of echocardiographic findings in PRKAG2 syndrome

Author/year	Article title	Study design	Sample – what was the study population?	Results
LILACS				
Magalhães LP et al. (2022) ⁵	Long-Term Cardiac Complications of PRKAG2 Syndrome	Ambispective observational cohort study	n = 16 Members of a single family carrying the Arg302Gln mutation in the PRKAG2 gene.	Seven patients (54%) had LVH (defined as interventricular septum or posterior wall thickness ≥ 13 mm, with no apparent cause) on echocardiography.
PUBMED				
Charron P et al. (2007) ⁶	A familial form of conduction defect related to a mutation in the PRKAG2 gene	Case report	n = 4 Members of the same family with a mutation in the PRKAG2 gene.	The study describes a family with a mutation in the PRKAG2 gene and a particular phenotype characterized by the absence of echocardiographic hypertrophy.
Tan HL et al. (2008) ⁷	Nodoventricular Accessory Pathways in PRKAG2-Dependent Familial Preexcitation Syndrome Reveal a Disorder in Cardiac Development	Retrospective observational cohort study	n = 17 Medical records, collected between 1955 and 2007, of 17 members of a 5-generation Dutch family.	Among the patients studied, 8 underwent echocardiography and 7 had cardiac hypertrophy.
Sternick EB et al. (2011) ⁸	Clinical, electrocardiographic, and electrophysiologic characteristics of patients with a fasciculoventricular pathway: the role of PRKAG2 mutation	Retrospective observational cohort study	n = 19 Two groups of patients: group A consisted of 10 patients with PRKAG2 mutation (Arg302Gln); and group B consisted of 9 patients without the mutation.	In group A, 30% of patients had LVH and none had an additional accessory pathway. Patients in group B had no structural heart disease.
Fabris E et al. (2013) ⁹	Cardiac hypertrophy, accessory pathway, and conduction system disease in an adolescent: the PRKAG2 cardiac syndrome.	Case report	n = 1 A 17-year-old asymptomatic patient was referred for family screening because of his father's unexplained LVH.	Echocardiography showed mild asymmetric LVH with posterolateral distribution. Cardiac magnetic resonance imaging confirmed asymmetric LVH (MWT of 13 mm).
Sternick EB et al. (2014) ¹⁰	Myocardial infarction in a teenager	Case report	n = 1 An 18-year-old man was diagnosed with an AMI of the interventricular septum, and genetic analysis identified a mutation in the PRKAG2 gene.	An echocardiogram showed massive LVH. The LV septal thickness was 44 mm. The authors speculated that the septal AMI resulted from a demand-supply mismatch of a severely hypertrophied septum.
Aggarwal V et al. (2015) ¹¹	PRKAG2 mutation: An easily missed cardiac specific non-lysosomal glycogenosis	Case report	n = 1 An adolescent female affected by a mutation in the PRKAG2 gene.	The patient had concentric LVH.

Review Article

Müllertz KM et al. (2016) ¹²	Variable primary phenotypic manifestations in a rare familial form of Wolff-Parkinson-White syndrome and HCM	Case report	n = 3 Different primary phenotypic manifestations of <i>PRKAG2</i> -gene heart disease in a 3-generation family were described. The proband presented with atrial fibrillation, her daughter with Wolff-Parkinson-White syndrome, and her mother with atrioventricular block.	Echocardiographic examination of the index patient's mother revealed marked LVH, initially misinterpreted as hypertensive heart disease. Several years later, LVH also developed in the index patient and her daughter, and <i>PRKAG2</i> -gene heart disease became evident.
Torok RD et al. (2017) ¹³	<i>PRKAG2</i> mutations presenting in infancy	Case report	n = 3 Report of 3 cases of <i>PRKAG2</i> mutation carriers.	Patient in case 1 presented with hypertrophy of the interventricular septum at birth, but at age 3 months this abnormality was no longer observed. The mitral valve was thickened and tethered by shortened chordae. There was moderate mitral regurgitation and subsequent LV dilation. Patient in case 2 presented with severe biventricular hypertrophy, severe mitral regurgitation, and moderate tricuspid regurgitation. Patient in case 3 did not undergo echocardiography.
Van Der Steld LP et al. (2017) ¹⁴	Wolff-Parkinson-White Syndrome with Ventricular Hypertrophy in a Brazilian Family	Case series	n = 60 Sixty patients from 84 members of a Brazilian family with <i>PRKAG2</i> syndrome.	The predominant pattern was generalized and diffuse LVH and mitral valve insufficiency. Hypertrophy predominated in the apical and medial portions later in life. The prevalence of mitral regurgitation occurred in the second and third decades of life.
Epicoco G et al. (2018) ¹⁵	An Unusual Pattern of Ventricular Pre-Excitation: Electrophysiological and Genetic Substrate	Case report	n = 1 A 30-year-old man known for ventricular preexcitation and recurrent episodes of typical atrial flutter.	Twelve-lead electrocardiogram showed ventricular preexcitation during sinus rhythm and common atrial flutter. Echocardiography and cardiac magnetic resonance imaging revealed marked and HCM without outflow obstruction (MWT = 28 mm).
Gorla SR et al. (2018) ¹⁶	Infantile Onset HCM Secondary to <i>PRKAG2</i> Gene Mutation is Associated with Poor Prognosis	Case report	n = 1 A premature infant delivered at 36 weeks due to fetal hydrops secondary to severe HCM.	A fetal echocardiogram performed at 28 weeks of gestation was significant for a severe form of HCM with involvement of both ventricles, the interventricular septum, and the right atrial wall. Serial postnatal echocardiograms demonstrated hyperdynamic ventricular function (shortening fraction of 49%), diastolic dysfunction, decreased end-diastolic LV volumes (z score of -6), and dynamic LV outflow tract obstruction (peak instantaneous systolic gradient of 58-88 mm Hg) with near complete obliteration of the LV cavity in end systole.
Ahamed H et al. (2020) ¹⁷	Phenotypic expression and clinical outcomes in a South Asian <i>PRKAG2</i> cardiomyopathy cohort	Ambispective observational cohort study	n = 50 Twenty-two patients with <i>PRKAG2</i> cardiomyopathy belonging to 3 unrelated families from Ernakulam and Trichur district in central Kerala, India. The remaining 28 individuals did not exhibit the clinical phenotype of the disease.	The mean LV MWT (n = 19) was 25.3 ± 6.5 mm (range 13-33 mm). The mean LV MWT for the entire 22 patient cohort was 22.9 ± 8.7 mm. Right ventricular hypertrophy was observed in 19 patients with LVH (19/22; 86%), with a mean RV free wall thickness of 7.5 ± 1.3 mm (range 6-11 mm). The mean LV ejection fraction (EF) of all 22 patients was 53.4% ± 6.6% (40%-65%). None of the 22 patients had LV outflow tract obstruction > 30 mm Hg or evidence of systolic anterior movement of the mitral valve.
Hu J et al. PE (2020) ¹⁸	Familial Atrial Enlargement, Conduction Disorder and Symmetric Cardiac Hypertrophy Are Early Signs of <i>PRKAG2</i> R302Q	Estudo observacional coorte retrospectivo	n = 10 Ten members of a Chinese family with HCM, 5 of whom were diagnosed with the <i>PRKAG2</i> R302Q mutation.	Four (80%) of the patients diagnosed with <i>PRKAG2</i> R302Q mutation had LVH. The analysis showed diffuse asymmetric hypertrophy in 3 patients, with a pattern of LV middle-anterior-lateral-inferior wall hypertrophy and especially interventricular septal hypertrophy. One patient showed symmetric hypertrophy, with a thickness of the LV wall and the interventricular septal wall of 1.2 cm (normal value: 0.8-1.0 cm). All patients had atrial enlargement.
Lopez-Sainz A et al. (2020) ¹⁹	Clinical Features and Natural History of <i>PRKAG2</i> Variant Cardiac Glycogenosis	Retrospective observational cohort study	n = 90 Patients with <i>PRKAG2</i> genetic variants recruited from 27 European cardiomyopathy centers.	At the last evaluation in the entire cohort, individuals with <i>PRKAG2</i> syndrome (68%-75.6%) had LVH (maximum LV thickness ≥ 13 mm) with an MWT of 19 ± 7 mm. In this group, mean LVEF was 57% ± 13%, and 10 patients had LVEF < 50%.

Pena JLB et al. (2021) ²⁰	Glycogen storage cardiomyopathy (PRKAG2): diagnostic findings of standard and advanced echocardiography techniques	Estudo observacional transversal	n = 30 Thirty patients with genetically proven PRKAG2 syndrome belonging to 5 families with PRKAG2 gene mutation.	Mean patient age was 39.1 ± 15.4 years. LVH was found in varying degrees in 25 patients (86%), with a mean LV septal thickness of 14.1 ± 4.2 mm. Myocardial mass on M-mode, in g/m ² and 4D, was above normal limits in these 25 patients. There was no statistically significant difference between patients with and without a PM. The mean RWT was increased for all hypertrophic patients (0.56 ± 0.18), characterizing concentric hypertrophy. The LAVI was increased in 70% of patients, with a mean value of 38.41 ± 14.9, and patients with PM had a significantly increased LAVI. The mean EF measured by the 3D technique was 55.7% ± 11.2%, but in 7 patients (24%) the EF was below normal limits. Patients with PM had lower fractional shortening and 4D EF, fractional shortening, and global circumferential strain values than patients without PM. No statistically significant difference was detected when comparing other echocardiographic parameters. Men had higher myocardial mass (p = 0.01) and indexed mass values (p = 0.05) than women. No correlation was found between age and hypertrophy-related variables. RV hypertrophy occurred in 90% of patients, and the mean RV lateral wall thickness was 7.9 ± 2.9 mm. Regarding LV diastolic dysfunction, 26% of patients had normal diastolic function, whereas the remaining patients had varying degrees of dysfunction, with a predominance of Grade I and III (according to ASE/EACVI guidelines).
Pena JLB et al. (2022) ²¹	Right Ventricle Involvement by Glycogen Storage Cardiomyopathy (PRKAG2): Standard and Advanced Echocardiography Analyses	Observational cross-sectional study	n = 30 Thirty patients from 5 families with PRKAG2 gene mutation (28 with Arg302Gln and 2 with His401Gln).	The median RV lateral wall thickness was 7.0 mm (range 6.0-9.0 mm). In 3 patients, the RV 4-chamber longitudinal strain (RV4LS) was significantly reduced, demonstrating RV wall dyskinesia. The RV was affected in most patients, and RV hypertrophy occurred in 90% of patients, with a regular pattern that involved all portions of the chamber. RVEF was below normal limits (≥45%) in 56.7% of patients, and in 7 patients, RVEF was <35%. RV4LS and RV free wall longitudinal strain (RVFWLS) were below normal reference limits even in asymptomatic patients. A positive correlation was confirmed between RVFWLS and RVEF, indicating that such strain indices are a fast and widely available method to detect dysfunction. Tricuspid regurgitation was detected in half of the patients, but only 4 had pulmonary artery systolic pressure above normal limits.
Tang L et al. (2022) ²²	Echocardiographic characteristics of PRKAG2 syndrome: a research using three-dimensional speckle tracking echocardiography compared with sarcomeric HCM	Retrospective cross-sectional study	n = 252 Nine patients with PRKAG2 syndrome, 41 with sarcomere gene mutations and 202 healthy volunteers.	Patients with PRKAG2 syndrome had significantly higher LV wall asymmetry than healthy volunteers (1.42 ± 0.52 vs 0.14 ± 0.14 mm, p = 0.001), with asymmetric septal hypertrophy. RWT was higher in the PRKAG2 group than in the healthy group (0.48 ± 0.15 vs 0.39 ± 0.07, p = 0.002), reaching a pattern of concentric hypertrophy (RWT > 0.42). The LV end-systolic diameter was significantly larger in the PRKAG2 group than in the healthy group (p < 0.05). Patients with PRKAG2 syndrome demonstrated impaired LV diastolic function parameters, including A, e', and E/e', but their LVEF remained normal (PRKAG2 group 62.67% ± 8.56% vs healthy group 65.79% ± 6.88%, p = 0.189). As a limitation of the study, the sample consisted of patients with PRKAG2 syndrome with LVH, but some patients did not have LVH, in addition to the small sample size (n = 9).

Source: Designed by the authors.

n: number of individuals; LVH: left ventricular hypertrophy; PM: pacemaker; MWT: maximum wall thickness; RWT: relative wall thickness; AMI: acute myocardial infarction; HCM: hypertrophic cardiomyopathy; LV: left ventricle; RV: right ventricle; LVEF: left ventricular ejection fraction; EF: ejection fraction. RVFWLS: RV free wall longitudinal strain; LAVI: left atrial volume index

reaching a pattern of concentric hypertrophy. Pena et al.,²¹ unlike the previous studies analyzed, brought the perspective of RV involvement in PRKAG2 syndrome by analyzing 30 patients with genetically proven PRKAG2 syndrome. The results showed that the RV was affected in most patients, and RV hypertrophy occurred in 90% of patients, with a regular pattern that involved all portions of the chamber, with a median RV lateral wall thickness of 7.0 mm (range 6.0-9.0 mm). This feature is consistent with the findings of Ahamed et al.¹⁷

In one of the included studies, Charron et al.,⁶ in contrast to the pattern shown by the other studies, described 4 members of the same family with an atypical phenotype of PRKAG2 gene mutation, characterized by the absence of echocardiographic hypertrophy.

Ejection fraction

In the case reported by Gorla et al.,¹⁶ serial postnatal echocardiograms demonstrated hyperdynamic ventricular function (shortening fraction of 49%), diastolic dysfunction, decreased end-diastolic LV volumes, and dynamic LV outflow tract obstruction (peak instantaneous systolic gradient of 58-88 mm Hg) with near complete obliteration of the LV cavity in end systole.

According to Ahamed et al.,¹⁷ the mean LV ejection fraction (EF) of all 22 patients was $53.4\% \pm 6.6\%$ (40%–65%), and none of the 22 patients had LV outflow tract obstruction > 30 mm Hg. In the retrospective cohort study by Lopez-Sainz et al.,¹⁹ LVEF was $57\% \pm 13\%$, and 10 patients (11.1%) had LVEF < 50%. Pena et al.²⁰ also found abnormal EF in individuals with PRKAG2 syndrome, with a prevalence of 7 patients (24%) with EF below normal limits, although the mean EF was $55.7\% \pm 11.2\%$ among the 30 participants. Data from the study conducted by Pena et al.²¹ showed that in 56.7% of the 30 study participants with mutations in the PRKAG2 gene, RVEF was below normal limits ($\geq 45\%$), and in 7 patients, this value was < 35%. In the analysis performed by Tang et al.,²² LVEF remained normal (PRKAG2 group $62.67\% \pm 8.56\%$ vs healthy group $65.79\% \pm 6.88\%$, $p = 0.189$).

Strain patterns

Pena et al.²⁰ showed that the left atrial volume index (LAVI) was increased in 70% of patients, with a mean value of 38.41 ± 14.9 mL/m², and patients with PM had a significantly increased LAVI. Therefore, there is a change in atrial volume in PRKAG2 syndrome, and patients with PM seem to be more affected. Also, regarding LV diastolic dysfunction, 26% of patients had normal diastolic function, and the remaining patients had varying degrees of dysfunction, with a predominance of Grade I and III (according to ASE/EACVI guidelines).

Tang et al.²² reported that the LV end-systolic diameter was significantly larger in the PRKAG2 group than in the healthy group ($p < 0.05$), and that the PRKAG2 group also had impaired LV diastolic function parameters.

Using the strain method, a measure of cardiac deformation, Pena et al.²¹ found that the RV 4-chamber longitudinal strain (RV4LS) and the RV free wall longitudinal strain (RVFWLS)

were below normal reference limits, even in asymptomatic patients. In 3 patients (10%), the RV4LS was significantly reduced, demonstrating RV wall dyskinesia. Furthermore, the authors confirmed a positive correlation between RVFWLS and RVEF, indicating that such strain indices are a fast and widely available method to detect dysfunction.

Heart valve abnormalities

Among the included studies, the first one to report heart valve abnormalities was that of Van der Steld et al.,¹⁴ who observed that the predominant pattern was mitral valve insufficiency, with its prevalence occurring in the second and third decades of life. Later, Torok et al.¹³ reported that, of 2 children followed up, one had thickened mitral valve leaflets with shortened chordae, in addition to moderate mitral regurgitation and subsequent LV dilation, whereas the other child was identified with severe mitral regurgitation and moderate tricuspid regurgitation. In the study conducted by Pena et al.,²¹ tricuspid regurgitation was detected in half of the patients ($n = 15$), but only 4 had pulmonary artery systolic pressure above normal limits.

In the article published by Ahamed et al.,¹⁷ none of the 22 patients with PRKAG2 cardiomyopathy had evidence of systolic anterior movement of the mitral valve, an abnormality commonly observed in HCMs secondary to significant septal enlargement.

Limitations

The main limitation is that the evidence included in this review is mostly derived from observational studies, more specifically: 8 case reports; 3 ambispective studies; 2 cross-sectional studies; 4 retrospective cohorts; and 1 case series. Therefore, the evidence is considered to be of low quality, where the main limitations include inadequate patient selection and inclusion, lack of blinding, failure to adequately control for confounding factors, and incomplete patient follow-up.²³ An important factor to be mentioned is the non-standardization of the echocardiographic data, such as the parameters observed during examination (wall thicknesses, strain pattern, EF, etc.), with discrepancies between the studies in the analyzed variables. In addition, some studies have not reported the reference values used to characterize their findings, thus interfering with the conclusions. Furthermore, because PRKAG2 syndrome is rare and probably underdiagnosed, the sample size of the included studies should also be considered a major limitation.

Conclusion

Familial ventricular hypertrophy, associated with other abnormalities, such as ventricular preexcitation and atrial tachyarrhythmias, is one of the signs that should raise the suspicion of PRKAG2 syndrome, and echocardiographic parameters are essential for this diagnosis. Cardiac chamber hypertrophy was demonstrated in most of the included studies, with variations in the location of this hypertrophy and thickness. LVH was the predominant finding, but some studies also reported RV involvement. It is worth noting

that one of the studies detected no cardiac hypertrophy in the patients. Additionally, in the included studies, patients presented with quite different echocardiographic abnormalities and clinical courses, supporting the notion of wide phenotypic variability in patients with *PRKAG2* mutations. Another finding was EF changes in the heart chambers, with reduced LVEF and RVEF. As in the case of hypertrophy, one study also showed conflicting results, where patients with *PRKAG2* syndrome had normal LVEF compared with controls, highlighting the instability of the phenotypic expression. Other findings included atrial enlargement and changes in the heart strain pattern, with the presence of wall dyskinesia. Finally, heart valve abnormalities were also described, with reports of the presence of mitral valve insufficiency and thickened mitral valve leaflets, as well as mitral and tricuspid regurgitation.

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Author Contributions

Conception and design of the research, acquisition of data, analysis and interpretation of the data, statistical analysis, writing of the manuscript and critical revision of the manuscript for intellectual content: Pena JLB, Souza Neto I, Barbosa AP, Santos Neto DA.

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Review Article

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