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Cardiac structural and functional findings in Persian cats with autosomal dominant polycystic kidney disease

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ABSTRACT: *Autosomal dominant polycystic kidney disease (ADPKD) has been related to left ventricular structural and functional abnormalities in human patients. The present study aimed to evaluate the cardiac structural and functional findings in Persian cats with ADPKD. Client-owned ADPKD (n=12) and non-ADPKD (n=12) Persian cats were enrolled in this study. The animals underwent echo- and electrocardiographic (ECG) examinations, and non-invasive measurements of systolic blood pressure (SBP) were obtained. Both groups were similar regarding hematological and biochemical parameters, including white blood cell count and levels of blood urea nitrogen, creatinine, total protein and thyroxine. There were no differences related to ECG parameters between ADPKD and non-ADPKD cats. Left ventricular hypertrophy (LVH) was demonstrated in 6/12 (50%) normotensive ADPKD cats with preserved renal function. There were no differences between animal groups regarding the echocardiographic parameters, including left ventricular ejection fraction and shortening fraction; however, basal interventricular septal thickness at end-diastole near the left ventricular outflow tract and aortic artery flow velocity showed slightly elevated values in ADPKD-cats. Our study revealed that Persian cats with ADPKD do not reproduce the functional and structural cardiac phenotype reported in human patients; however, large-scale cohort studies are necessary to distinguish the possibilities of a true linkage between ventricular myocardial hypertrophy and ADPKD in this breed.*
Key words: *feline, genetic disease, renal disease, heart, echocardiography.*

Achados estruturais e funcionais cardíacos em gatos persas com doença renal policística autossômica dominante

RESUMO: *A doença renal policística autossômica dominante (DRPAD) tem sido relacionada a anormalidades estruturais e funcionais de ventrículo esquerdo em pacientes humanos. O objetivo do presente estudo foi avaliar os achados estruturais e funcionais cardíacos em gatos persas com DRPAD. Gatos persas pertencentes à clientes com DRPAD (n=12) e sem DRPAD (n=12) foram envolvidos neste trabalho. Os animais foram submetidos aos exames de eco e eletrocardiografia (ECG) e foram obtidas medições não-invasivas da pressão arterial sistólica (PAS). Ambos os grupos apresentaram valores semelhantes em relação aos parâmetros hematológicos e bioquímicos, incluindo contagem de glóbulos brancos e níveis séricos de ureia, creatinina, proteína total e tiroxina. Não houve diferença em relação aos parâmetros do ECG entre os gatos com ou sem DRPAD. A hipertrofia ventricular esquerda foi demonstrada em 6/12 (50%) dos gatos normotensos com DRPAD e função renal preservada. Não houve diferenças entre os grupos em relação aos parâmetros ecocardiográficos, incluindo fração de ejeção e fração de encurtamento do ventrículo esquerdo, entretanto a espessura septal interventricular basal na diástole na via de saída do ventrículo esquerdo e a velocidade do fluxo da artéria aórtica mostraram valores ligeiramente elevados em gatos com DRPAD. Nosso estudo revelou que gatos persas com DRPAD não reproduzem o fenótipo cardíaco funcional e estrutural encontrado em pacientes humanos. No entanto, estudos de coorte em larga escala são necessários para distinguir as possibilidades de uma verdadeira ligação entre a hipertrofia ventricular do miocárdio e a DRPAD nesta raça.*
Palavras-chave: *felino, doença genética, doença renal, coração, ecocardiografia.*

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is phenotypically characterized by the presence of multiple cysts in the renal parenchyma and, occasionally, in liver and pancreas, being an important cause of end-stage renal disease (BASTOS & ONUCHIC, 2011). In humans, 78%

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of the cases are caused by mutations in the *PKD1* gene (type 1 ADPKD), while in 15% of the patients the disease occurs due to mutations in *PKD2* (type 2 ADPKD) (CORNEC-LE GALL et al., 2018). Approximately 7% of the affected families; however, are currently genetically unresolved. The *PKD1* and *PKD2* genes, in turn, encode the integral membrane glycoproteins polycystin-1 and polycystin-2, respectively. Disruption of polycystins affects proliferation, apoptosis and planar cell polarity, and promotes transepithelial chloride and fluid secretion (DELMAS, 2004).

Cardiovascular manifestations and complications, including systemic arterial hypertension, increased left ventricular mass and idiopathic dilated cardiomyopathy, are a major cause of morbidity and mortality in humans with ADPKD. Echocardiography in normotensive ADPKD individuals shows increased left and right ventricular mass and volume with normal ejection fractions and decreased end-diastolic relaxation compared to unaffected age and sex-matched controls, suggesting that deficiency of polycystin-1 or polycystin-2 is an independent factor for the development of the cardiac phenotype in affected individuals (CHAPMAN et al., 1997; ECDER et al., 1999). Other potential cardiovascular alterations in ADPKD human patients include biventricular diastolic and endothelial dysfunction, increased thickness of the intima-media, impaired coronary flow velocity reserve, aneurysms and valvular defects (ECDER, 2013).

In recent years, seminal studies addressed more deeply the mechanisms underlying the cardiac phenotype associated with ADPKD. BALBO et al. (2016) showed that different *Pkd1*-deficient mouse models, including noncystic normotensive $Pkd1^{+/-}$ and cystic hypertensive $Pkd1^{flox/flox}$:$Nestin^{cre}$ animals, developed systolic dysfunction and reduced myocardial deformation. $Pkd1^{flox/flox}$:$Nestin^{cre}$ mice also presented diastolic dysfunction. These findings strongly supported a primary role for *PKD1* deficiency in ADPKD-associated heart dysfunction, while suggested that hypertension may worsen this phenotype with age. In line with these findings, PEDROZO et al. (2015) have shown that polycystin-1 is required for the normal baseline function of cardiomyocytes. This study revealed, on the other hand, that this protein is also necessary for cardiomyocyte stretch-induced hypertrophy. Polycystin-2 has also been shown to play a significant role in cardiac function (PAAVOLA et al., 2013). This report not only revealed that ADPKD patients have an increased risk of developing idiopathic dilated cardiomyopathy, particularly type 2 ADPKD cases, but also showed that zebrafish lacking this protein develop manifestations consistent with heart failure.

The ADPKD is also a genetic disorder that affects 13-46% of Persian cats and Persian-related breeds populations worldwide (LEE et al., 2010). Ultrasound screening and molecular tests to detect the genetic point mutation (C-A transversion) at position 3284 in exon 29 of the *PKD1* gene have been employed routinely in the diagnosis of the feline disease (LYONS et al., 2004). Interestingly, cardiac abnormalities have been rarely described in cats with ADPKD; although cases involving LVH and biventricular cardiac dilation (BILLER et al., 1990; EATON et al., 1997), cardiomyopathy of unknown origin (BOSJE et al., 1998), minor increases in mean arterial pressure, endocardial echogenicity, restrictive diastolic filling pattern, mild dilatation of the left ventricle, and slight mitral valve regurgitation (PEDERSEN et al., 2013) have been reported. The purpose of this study was to assess the echo- and electrocardiographic profiles of ADPKD-affected Persian cats.

MATERIALS AND METHODS

An observational, transversal and descriptive study was carried out with a population comprised 82 Persian cats, males and females, originated from ten households. Initially, abdominal ultrasound scans were performed using an ultrasound machine with multifrequency (6–10 MHz) micro-convex or multifrequency (7.5–12 MHz) linear transducers (Logiq 7, GE Healthcare, Chalfont St Giles, UK). From those animals, twelve (14.6%) were diagnosed with ADPKD through abdominal ultrasonography, which revealed the presence of four to more than ten renal cysts per animal. Thereafter, genetic analysis confirmed the presence of the C-A mutation in exon 29 of the *PKD1* gene in all animals, which was detected on DNA samples extracted from blood by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) (GUERRA et al., 2019). For comparison, twelve age and sex-matched Persian cats, with no evidences of systemic disease, were randomly selected as control group (non-ADPKD cats). All of heathy animals did not exhibit renal cysts and were negative for the referred *PKD1* mutation.

After ultrasonography and genetic screening, each of 24 Persian cats underwent a complete physical examination that included measurement of systolic blood pressure (SBP) together

with electrocardiogram (ECG), echocardiographic, hematological and biochemical analyses, carried out according to standard methodologies (TILLEY, 1992; BROWN et al., 2007; BONAZZI et al., 2009; BOON, 2011; GUERRA et al., 2015; 2019). Clinical signs evaluated included emaciation, dyspnea, cough, fatigue, exercise intolerance, cyanosis, pre-syncope or syncope, edema or ascites, and convulsion.

Values of SBP were obtained by Doppler ultrasonography linked to an aneroid sphygmomanometer (Medmega DV610B instrument, Nova Med Tec, São Paulo, Brazil), according to the methodology previously described (LITTMAN, 2000). Briefly, cats were placed in a quiet and undisturbed room prior to measurement of SBP, in order to acclimatize them to the new environment and strange people (BELEW et al., 1999). Five consecutive measurements were performed and the results were expressed as arithmetic means. The ECG data were acquired using a standard six-lead device (Ecafix ECG6, Transform, São Paulo, Brazil), with non-sedated animals positioned in right lateral or sternal recumbency, evaluating the bipolar leads I, II and III and the unipolar leads aVR, aVL and VF, as well as the precordial leads CV5RL (rV2), CV6LL (V2), CV6LU (V4) and v10 at a recording speed of 25 mm/s and a calibration of 1 mV equal to 1 cm. Bipolar II lead was recorded at a speed of 50 mm/s. ECG traces were examined to rhythm and waveform according to standard procedures (TILLEY et al., 1992).

Blood was collected by jugular venipuncture and submitted to: (i) hematological examination - complete blood count (CBC), white blood cell count (WBC), hemoglobin (Hb) and blood urea nitrogen (BUN); (ii) biochemical assay - creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total protein, thyroxine (T4), sodium, calcium, potassium and phosphorus; and (iii) molecular analysis (PCR-RFLP).

Echocardiographic examinations were carried out with cats in right and left lateral recumbency using an ultrasound machine (Vivid-i, GE Healthcare, Chalfont St Giles, UK) with 8 and 12 MHz multifrequency phased array transducers as recommended by the Echocardiography Committee of the Specialty of Cardiology, American College of Veterinary Internal Medicine (THOMAS et al., 1993) and by the American Society of Echocardiography (BOON, 2011). At least three determinations were performed for each parameter evaluated in the different phases of the cardiac cycle, considering the average of the values obtained. Echocardiograms were analyzed using the commercial software package supplied with the system, and diagnosis was based on current literature (FERASIN, 2009). Images for the measurement of the left ventricle were acquired in the right parasternal window, cross-sectioned, at the time of insertion of the tendinous strings in the papillary muscles (M mode). The occurrence of myocardial hypertrophy was defined when the diastolic thickness of the interventricular septum (IVSd) and/or the left ventricular free wall (LVFWd) was equal to or greater than 0.6 cm. Cats with diastolic thicknesses less than 0.5 cm were considered normal. Concentric hypertrophy was considered symmetrical when the IVSd/LVFWd ratio was between 0.7 and 1.3. In the presence of asymmetric hypertrophy, segmental hypertrophy was measured by the two-dimensional mode. Measurements of the diameter of the aortic root (Ao) and the diameter of the left atrium (LA) were performed using the two-dimensional mode, right parasternal window, cross section, in the cardiac base region. An increase in AE was considered when the AE/Ao ratio was greater than 1.5 (WESS et al., 2010). The left atrial-to-aortic root diameter ratio (LA/Ao) was established by echocardiography from the right parasternal short-axis heart base view. Doppler echocardiography (color, pulsed wave and continuous wave) was employed to characterize flow disturbances (KITTLESON et al., 1999).

All statistical analyses were carried out using R-statistical environment software (http://r-project.org/). Continuous variables are presented as mean ± standard deviation (and median, minimum-maximum). The Shapiro-Wilk test was used to test data normality. Mann-Whitney or Student's *t* tests were used to compare the means or the medians, respectively, of continuous variables between two groups (ADPKD and non-ADPKD cats). Correlations between variables that were not normally distributed were investigated by means of the Spearman rank correlation test. To assess the difference in categorical variables between groups, Fisher's exact test was used. In all analyses, a two-tailed alternative hypothesis was employed, and the level of significance was set at 5%.

RESULTS

Of the 24 Persian cats enrolled in the study, 10 (41.67%) were male and 14 (58.33%) were female. Five males (20.84%) and four females (16.67%) were sexually intact, whereas 5 males (20.84%) and 10 females had been neutered (41.67%). The mean body weight of males was 4.18 ± 1.54 kg (range 2.0 to 6.15 kg) and that of females was 3.57 ± 1.10 kg (range 2.0

to 4.80 kg), but these values were not significantly different (P = 0.445). The mean age of the entire cat population was 92.46 ± 38.92 months (range 28 to 162 months), while the mean ages of males and females (94.9 ± 42.3 *vs.* 90.7 ± 37.9 months, respectively) did not significantly differ (P = 0.802). There were no significant differences between the ADPKD and non-ADPKD cats in regard to gender (Male:Female ratio: 6/6 *vs.* 4/8, P = 0.691), age (96.0 ± 46.9 *vs.* 88.92 ± 30.55 months, P = 0.666) and body weight (3.75 ± 1.65 *vs.* 4.17 ± 0.80 kg, P = 0.475). The most common clinical signs in the ADPKD population were emaciation (20.0%) and fatigue (13.3%). However, there were no statistical differences between the groups regarding the frequency of the clinical signs (data not shown). Also, there were no significative differences regarding hematological and biochemical parameters between ADPKD and non-ADPKD cats, including T4 levels (Table 1). None of the animals manifested symptoms of hypothyroidism or hyperthyroidism.

Cardiovascular evaluations showed that all animals were normotensive, and no statistical differences were observed between the groups with respect to systolic blood pressure. Also, there was no difference in heart rate (HR) between ADPKD and non-ADPKD cats (Table 2). Presence of left-sided heart abnormalities was observed in 3/12 (25%) and 6/12 (50%) cats in ADPKD and non-ADPKD groups, respectively. No statistical difference was observed regarding the frequency of these alterations (P = 0.126). The ECG traces of all animals exhibited normal sinus rhythms, with the exception of 1/12 (8.3%) cat in the ADPKD-affected group that presented sinus tachycardia, considering cases in which HR was greater than 240 bpm (TILLEY et al., 1992). No animals revealed supraventricular arrhythmias.

No differences were observed between the two groups with respect to heart rate, P-wave width, PR interval, QRS interval, R-wave amplitude, QT interval and R-wave or S-wave amplitudes in precordial chest leads CV5RL (rV2), CV6LL (V2) and CV6LU (V4). P-wave amplitudes on lead II were slightly elevated in ADPKD-cats, especially in those with concurrent LVH (0.200 ± 0.054 mV); however, there is no statistical difference (P = 0.069) (Table 2). With respect to defects in the impulse conduction system, an incomplete right bundle branch block was observed in 3/12 (25%) animals of the non-ADPKD group and in 2/12 (16.67%) animals of ADPKD group, with no statistical difference (P = 1.000). A left anterior fascicular block and a first-degree atrioventricular block were detected in one animal with ADPKD and LVH, but differences regarding the occurrence of these defects were not significant (P = 1.000) between the two groups. Abnormal ventricular repolarization and ventricular premature complexes

Table 1 - Hematological and biochemical profiles of Persian cats enrolled in the study.

Parameters	Non-ADPKD cats (n=12)	ADPKD cats (n=12)	P-value
Hb (g/dL)	13.93 ± 1.64 (14.10, 13.48-16.00)	13.95 ± 1.19 (14.39, 12.3-15.83)	0.600
WBC (mm^3x10^3)	11.96 ± 5.99 (10.15, 4.60-28.70)	12.26 ± 5.94 (14.22, 4.10-20.50)	0.926
BUN (mg/dL)	47.89 ± 8.26 (45.25, 38.30-58.00)	47.41 ± 12.89 (47.20, 28.70-74.90)	0.915
Creatinine (mg/dL)	1.12 ± 0.27 (1.19;0.86-1.60)	1.20 ± 0.24 (1.24, 0.78-1.61)	0.745
ALT (UI/dL)	58.00 ± 47.70 (42.80, 28.0-197.10)	42.70 ± 19.99 (31.00, 24.60-83.80)	0.374
AST (UI/dL)	21.48 ± 9.20 (18.45, 11.70-46.80)	17.16 ± 5.21 (16.00, 11.1-26.30)	0.126
ALP (UI/ dL)	19.92 ± 6.91 (21.35, 10.70-29.60)	17.10 ± 8.31 (15.40, 9.20-35.82)	0.407
Protein (g/dL)	6.79 ± 1.36 (7.23, 3.67-8.54)	7.23 ± 0.34 (7.13, 6.65-7.61)	0.365
Ca (mg/ dL)	10.51 ± 0.82 (11.8, 869-11.80)	10.49 ± 1.36 (10.23, 8.88-12.71)	0.964
P (mg/dL)	4.46 ± 0.84 (4.39, 2.90-6.17)	4.68 ± 0.83 (4.86, 2.65-5.62)	0.262
Na (mEq/dL)	154.93 ± 2.81 (155.30, 150.40-156.40)	153.03 ± 2.06 (152.60, 150.80-156.00)	0.156
K (mEq/dL)	4.64 ± 0.59 (4.54, 3.40-5.51)	4.62 ± 0.39 (4.70, 3.90-5.21)	0.947
T4 (µg/dL)	1.84 ± 0.33 (1.90, 1.37-2.39)	1.56 ± 0.18 (1.68, 1.24-1,74)	0.117

Hb, Hemoglobin; WBC, White blood cells; BUN, Blood urea nitrogen; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; ALP, Alkaline phosphatase; Ca; Calcium; P; Phosphorus; Na; Sodium; K; Potassium; T4, Thyroxine. *Student's *t* test or Mann-Whitney test (P<0.05). Continuous variables are expressed as mean ± standard deviation (median, minimum-maximum).

Table 2 - Cardiovascular and ECG profiles of Persian cats enrolled in the study.

Parameters	Non-ADPKD cats (n=12)	ADPKD cats (n=12)	P-value
HR (bpm)	197.00 ± 24.91 (200.00, 160.00-230.00)	194.17 ± 27.12 (195.00, 160.00-260.00)	0.757
SBP (mmHg)	146.25 ± 20.26 (147.00, 118.00-180.00)	143.67 ± 15.86 (143.00, 120.00-166.00)	0.731
P-wave width (sec)	0.032 ± 0.006 (0.030, 0.020-0.040)	0.031 ± 0.005 (0.030-0.020-0.040)	0.772
P-wave amplitude (mV)	0.125 ± 0.045 (0.150, 0.050-0.200)	0.170 ± 0.058 (0.175, 0.100-0.300)	0.069
PR interval (sec)	0.075 ± 0.007 (0.075, 0.060-0.090)	0.075 ± 0.011 (0.080, 0.060-0.100)	1.000
QRS interval (sec)	0.027 ± 0.006 (0.030, 0.020-0.040)	0.030 ± 0.011 (0.030, 0.020-0.060)	0.644
R-wave amplitude (mV)	0.170± 0.202 (0.100, 0.050-0.700)	0.279± 0.310 (0.175, 0.050-1.100)	0.418
QT interval (sec)	0.135 ± 0.019 (0.125, 0.120-0.180)	0.144 ± 0.019 (0.145, 0.120-0.180)	0.225

HR, Heart rate; SBP, Systolic blood pressure; bpm, beats per minute; mmHg, millimeter of mercury; mm, millimeter; sec, seconds; mV, millivolts. *Student's *t* test or Mann-Whitney test (P<0.05). Continuous variables are expressed as mean ± standard deviation (median, minimum-maximum).

were observed, respectively, in two (16.67%) and one (8.33%) ADPKD-cats with LVH.

Echocardiographic measurements revealed that 3/12 (25.0%) and 3/12 (25.0%) animals enrolled in the ADPKD and non-ADPKD groups, respectively, displayed left ventricular hypertrophy, which involve the basal septum adjacent to the left ventricular outflow tract and/or involving portions of the ventricular septum as well as the contiguous anterolateral and posterior free walls. No statistical difference was observed between the proportions of LVH in these two groups (P = 0.400). AoIVSd, IVSd, LVFWd and LVIDd thicknesses, and the IVSd/LVFW ratio did not significantly differ between the groups. Additionally, basal interventricular septal thickness at end-diastole showed no statistical difference in ADPKD-affected animals (P = 0.084). Left ventricular ejection fraction (LVEF) and shortening fraction (LVSF) also did not differ between ADPKD and non-ADPKD cats. No significant differences related to the remaining echocardiographic parameters were observed between the two groups either. Similar to AoIVSd, aortic artery flow velocity showed no difference in the ADPKD group (P = 0.064) (Table 3).

Additionally, neither a significant difference in SBP between ADPKD-affected cats with and without LVH (P = 0.902) nor a significant correlation between left ventricular wall thickness and SPB (IVSd, P = 0.843, r = 0.043; LVFWd, P = 0.171, r = -0.289) were observed.

Within the ADPKD group, 3/12 (25.0%) animals exhibited mild insufficiency of the mitral and tricuspid valves, and 1/12 (8.3%) exhibited only mitral valve insufficiency associated with increased ventricular septum echogenicity. Also, one (8.3%) animal presented mild obstruction of the left ventricular outflow tract. Among non-ADPKD cats, only 1/12 (8.33%) presented mild mitral valve insufficiency. No significant differences were observed between the two groups with regard to the frequency of appearance or movement of the valve leaflets (P = 0.316).

DISCUSSION

The aim of the current study was to evaluate the cardiac phenotype of Persian cats diagnosed with ADPKD. In humans, 89% of ADPKD-patients that died due cardiac causes exhibited LVH, a manifestation that constitutes an important risk factor for sudden cardiac death (FICK et al., 1995). Various studies involving ADPKD in humans and experimental animal models have shown that both hypertension and activation of the renin-angiotensin system (RAS) contribute to the development of LVH (ECDER et al., 1999; PHILLIPS et al., 2007). Cyst expansion and local hypoperfusion activates intrarenal RAS causing hypertension, while increased pressure load stimulates myocyte hypertrophy, collagen formation and fibroblast proliferation, thereby remodeling the myocardium with a disproportionate amount of fibrous tissue (CHAPMAN et al. 1997; KAHAN et al., 2005; FONSECA et al., 2014).

Our results revealed; however, no significant differences between the two groups of animals in regard to SBP; only one animal in non-ADPKD group presented SPB of 180 mmHg, not associated with LVH. It is unclear why ADPKD cats

Table 3 - Echocardiographic profile of Persian cats enrolled in the study.

Parameters	Non-ADPKD cats (n=12)	ADPKD cats (n=12)	P-value
AoIVSd (cm)	0.515 ± 0.062 (0.490; 0.450-0.620)	0.605 ± 0.158 (0.555; 0.400-0.850)	0.084
IVSd (cm)	0.478 ± 0.062 (0.480; 0.330-0.580)	0.540 ± 0.136 (0.500; 0.330-0.800)	0.165
LVFWd (cm)	0.442 ± 0.046 (0.445; 0.360-0.540)	0.482 ± 0.106 (0.470; 0.310-0.760)	0.193
IVSd/LVFWd	1.080 ± 0.090 (1.089; 0.916-1.260)	1.120 ± 0.157 (1.077; 0.952-1.510)	0.464
LVIDd (cm)	1.367 ± 0.151 (1.305; 1.170-1.620)	1.324 ± 0.211 (1.360; 1.030-1.680)	0.644
LVIDs (cm)	0.614 ± 0.144 (0.595; 0.430-0.930)	0.610 ± 0.172 (0.595; 0.370-0.930)	0.949
Shortening fraction (%)	55.25 ± 0.067 (55.00; 42.00-63.00)	54.58 ± 0.085 (54.50; 35.00-0.660)	0.834
Ejection fraction	0.882 ± 0.051 (0.885; 0.770-0.940)	0.874 ± 0.072 (0.885; 0.680-0.950)	0.862
Ao (cm)	0.889 ± 0.089 (0.905; 0.710-1.000)	0.915 ± 0.076 (0.995; 0.760-1.120)	0.540
LA (cm)	1.100 ± 0.150 (1.100; 0.800-1.400)	1.181 ± 0.254 (1.155; 0.840-1.610)	0.358
LA/Ao ratio	1.238 ± 0.124 (1.219; 1.031-1.489)	1.294 ± 0.256 (1.071; 0.970-1.892)	0.513
Aortic FV (m/s)	0.919 ± 0.106 (0.900; 0.760-1.070)	1.193 ± 0.451 (1.045; 0.720-2.190)	0.064
Aortic PG (mmHg)	3.423 ± 0.787 (3.285; 2.300-4.600)	6.430 ± 5.16 (4.400; 2.050-19.18)	0.141
Pulmonary artery FV (m/s)	0.998 ± 0.114 (0.970; 0.840-1.170)	0.918 ± 0.245 (1.015; 0.580-1.390)	0.317
Pulmonary artery PG (mmHg)	4.033 ± 1.929 (3.770; 2.800-5.500)	3.619 ± 1.938 (3.310; 1.370-7.740)	0.511
E-wave (m/s)	0.702 ± 0.113 (0.690; 0.540-0.890)	0.765 ± 0.275 (0.765; 0.410-1.290)	0.474
E-wave deceleration time (ms)	63.00 ± 16.43 (59.50; 45.00-91.00)	57.17 ± 24.09 (58.00; 18.00-90.00)	0.496
A-wave (m/s)	0.554 ± 0.163 (0.550; 0.340-0.870)	0.633 ± 0.178 (0.560; 0.440-0.940)	0.344
E/A ratio	1.286 ± 0.405 (1.230; 0.690-1.830)	1.186 ± 0.662 (0.915; 0.440-2.804)	0.377
IVRT (ms)	47.58 ± 3.90 (48.00; 41.00-52.00)	47.42 ± 9.61 (45.00; 28.00-65.00)	0.583

AoIVSd, Basal interventricular septal thickness at end-diastole near the left ventricular outflow tract; IVSd, Interventricular septal thickness at end-diastole; LVFWd, Left ventricular freewall thickness at end-diastole; LVIDd, Left ventricular internal diameter at end-diastole; LVIDs, Left ventricular internal diameter at end-systole; Ao, Aorta diameter at right transverse view in two-dimensional echocardiography; LA, Left atrium diameter at right transverse view in two-dimensional echocardiography; FV, Flow velocity; PG, Pressure gradient; IVRT, Isovolumetric relaxation time. Student's *t* test or Mann-Whitney test ($P<0.05$). Continuous variables are expressed as mean ± standard deviation (median, minimum-maximum).

did not reproduce the hypertensive pattern displayed by *Pkd1*-deficient cystic mice (FONSECA et al., 2014). A potentially lower renal cystic burden in cats than in the evaluated mice should be considered as a possible contributor to such a blood pressure behavior. Few reports are available addressing hypertension and alterations in hormonal determinants that regulate blood pressure in cats affected by ADPKD. However, PERDERSEN et al. (2003) showed that all cats with mild and severe forms of the disease (n = 14) exhibited higher mean arterial pressure and a trend towards higher SBP compared with healthy control animals. None of the cats; however, showed echocardiographic evidence of cardiac hypertrophy. Moreover, SNYDER et al. (2001) described that the frequency of LVH in hypertensive cats with systemic arterial pressure > 170 mm Hg was around 74%.

CHAPMAN et al. (1997) carried out echocardiographic tests in humans (77 healthy subjects and 116 adults diagnosed with ADPKD) and reported that LVH was present in 23% of normotensive ADPKD patients and 16% of the healthy controls; although, these parameters were not statistically significant. It is interesting to notice that, in both groups, presence of LVH did not correlate with blood pressure. Normotensive ADPKD adults; however, showed increased left ventricular mass index compared to controls. Similar findings have been reported by other studies (TIMIO et al., 1992; SAGGAR-MALIK et al., 1994). Moreover, increased left ventricular mass index has been reported in young normotensive humans with ADPKD and well-preserved renal function, and is apparently associated with biventricular diastolic and endothelial dysfunction, increased carotid intima-media thickness and impaired coronary flow velocity reserve, suggesting that cardiovascular involvement starts at early stages of ADPKD (MARTINEZ-VEA et al., 2000; 2004). Such cardiac alterations have been associated with hemodynamic factors, including lower nocturnal fall in blood pressure rhythm (VALERO et al., 1999). In the present study,

no significant differences were observed between the two groups of animals with respect to systolic and diastolic function as well as valve morphology and movement. The lack of difference in LVEF and LVSF observed between ADPKD and non-ADPKD animals did not reproduce previous findings of systolic dysfunction in *Pkd1*-deficient mice (BALBO et al., 2016). We presently have no robust explanation for this distinct heart functional pattern; however, it is possible that the allele harboring the *PKD1* mutation common to all affected cats exerts a hypomorphic effect on the feline heart. WANG et al. (2000) reported the occurrence of endothelial dysfunction and reduced nitric oxide synthase (NOS) activity in humans diagnosed with ADPKD even before the development of hypertension or renal insufficiency; although the abnormalities were shown to be more severe in the setting of hypertension.

Hypertrophic cardiomyopathy (HCM), the most common type of cardiomyopathic phenotype in cats, is characterized by diffuse or regional increased left ventricle (LV) wall thickness with a nondilated LV chamber. The HCM remains a major source of feline morbidity and mortality, with congestive heart failure and arterial thromboembolism as the most common cause of clinical signs and sudden death in this species (LUIS FUENTES et al., 2020). In some breeds, such as Maine Coon and Ragdoll cats, HCM is an autosomal dominant inherited disease caused by a mutation in the gene that encodes the cardiac myosin binding protein C (MYBPC3) (MEURS et al., 2005; 2007). Although, there is some evidence of inherited familial HCM in Persian cats, inherited mutations have not yet been reported in this breed (RUSH et al., 2002). In the present study, it was not possible to ascertain whether HCM was linked to ADPKD in Persian cats or if these two separate inherited diseases emerged concomitantly, since three animals in non-ADPKD group also displayed asymmetric LVH.

This study has some limitations; however, which included the observational nature of the investigation, the definition of hypertension in cats and the under-representation of animals within the groups. Nevertheless, the number of cats employed herein was equivalent to other ADPKD studies (PEDERSEN et al., 2013; LEE et al., 2010). In humans, some echocardiographic measurements, including LV free-wall thickness, can be influenced by age. When analyzing cats; therefore, comparisons should also be made using age-matched controls (GERSTENBLITH et al., 1977). In this context, we have carefully selected animals of comparable age and sex for non-ADPKD and ADPKD groups. The definition of systolic hypertension in cats, in turn, is still debated in veterinary medicine; although, the American College of Veterinary Internal Medicine consensus panel considers an SBP between 170 and 180 mmHg a risky condition to target organ damage (JEPSON, 2011). Of note, none of the animals had concurrent clinical signs that could support the diagnosis of hypertension. In this setting, abnormal high arterial pressure was not considered the cause of LVH in these animals.

CONCLUSION

Based on the feline population employed herein, our study revealed that Persian cats with ADPKD do not reproduce the functional and structural cardiac phenotype reported in human patients with this disease nor the heart dysfunction observed in *Pkd1*-deficient mouse models. Further studies with large-scale cohort of Persian cats; however, are necessary to distinguish the possibilities of a true linkage between ADPKD and LVH and an association between two distinct diseases in this breed. Differential diagnosis is important to pet owners because it allows early detection and treatment of disease complications.

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BIOETHICS AND BIOSSECURITY COMMITTEE APPROVAL

The owners were thoroughly informed about the research aims and protocols, and written informed consent was obtained from the owner of each pet prior the investigation. This study was approved by the Institution's Ethical Committee of the Faculdade de Medicina Veterinária e Zootecnia da Universidade de São Paulo (Protocol nº. 1812010514) and it was conducted in accordance with the guidelines of Colégio Brasileiro de Experimentação Animal (COBEA).

DECLARATION OF CONFLICT OF INTERESTS

The authors declare no conflict of interest. The founding sponsors had no role in the design of the study; in the

collection, analyses, or interpretation of data; in the writing of the manuscript, and in the decision to publish the results.

AUTOHR'S CONTRIBUTIONS

BC, JMG, LFO, FLQ and MHMAL conceived and designed experiments. JMG performed the laboratory analyzes, statistical analyzes of experimental data and the manuscript draft. NCC and GGL performed the laboratory analyzes. MFF performed the ultrasonography. AP and RBP performed the ECG and the echocardiography. AGTD performed the clinical evaluation and samples collection. All authors critically reviewed the manuscript and approved the final version.

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