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Prospective echocardiographic and tissue Doppler screening of a large Sphynx cat population: Reference ranges, heart disease prevalence and genetic aspects

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Abstract *Objectives:* (1) To investigate heart morphology and function using echocardiography and tissue Doppler imaging (TDI), (2) to determine heart disease prevalence and characteristics, and (3) to assess potential genetic features in a population of Sphynx cats presented for cardiovascular screening.
Animals: A total of 147 echocardiographic examinations, including 33 follow-ups, were performed by trained observers on 114 Sphynx cats of different ages (2.62 ± 1.93 years [0.5—10.0]) from 2004 to 2011.
Methods: Sphynx cats underwent a physical examination, conventional echocardiography, and, if possible, two-dimensional color TDI.

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Results: Conventional echocardiographic findings included 75/114 normal (65.8%) and 39/114 (34.2%) abnormal examinations with a diagnosis of either congenital heart diseases ($n = 16$) or hypertrophic cardiomyopathy (HCM, $n = 23$). In adult healthy cats, a significant body weight effect was observed for several echocardiographic variables, including end-diastolic left ventricular (LV) free wall ($P < 0.01$), interventricular septum ($P < 0.001$), and LV diameter ($P < 0.001$). Mitral valve dysplasia (MVD) was observed as a single or associated defect in 15/16 cats with congenital heart diseases. A significant increase in HCM prevalence ($P < 0.001$) was observed according to age. The pedigree analysis of a large family ($n = 81$) suggested an autosomal dominant mode of inheritance with incomplete penetrance for HCM.

Conclusions: Body weight should be taken into account when interpreting values of diastolic myocardial wall thicknesses in Sphynx cats. Additionally, HCM and MVD are two relatively common heart diseases in this feline breed. More pedigree data are required to confirm the inheritance pattern of HCM at the breed level.

Abbreviations

2D	two-dimensional
Ao	aorta
HCM	hypertrophic cardiomyopathy
IVCT	isovolumic contraction time
IVRT	isovolumic relaxation time
IVS	interventricular septum
LA	left atrium
LV	left ventricle
LVFW	left ventricular free wall
MVG	myocardial velocity gradient
TDI	tissue Doppler imaging

The Sphynx (or Canadian hairless cat) is an uncommon almost hairless feline breed, which was first recorded in Canada in 1966.[1–3] This breed is related to the Devon Rex breed, and both of them are characterized by mutations in the Keratin *KRT71* gene.[1] The Cat Fanciers Association accepted this unusual looking breed for registration and competition in 1998.[3] The Sphynx breed has been expanding in Europe for several years, and in November 2003 a Sphynx cat club was created in France in order to promote this breed.

The Sphynx cat has been mostly studied for skin diseases and muscular dystrophy.[4,5] However, little data is available for this feline breed regarding normal two-dimensional (2D) echocardiographic and tissue Doppler imaging (TDI) variables, or the prevalence of heart diseases including hypertrophic cardiomyopathy (HCM).[6] This acquired heart disease is a primary myocardial disorder which is characterized by increased cardiac mass with a concentrically hypertrophied, non-dilated left ventricle (LV).[7–10] It is considered the most common feline heart disease and remains a major cause of morbidity and mortality (the latter associated with a risk of sudden death).[7–13] One previous report has specifically characterized echocardiography in the Sphynx breed. Out of the 132 Sphynx cats that were examined during the study period, 35 presented with echocardiographic abnormalities consistent with a diagnosis of HCM.[6] Regarding HCM in the Maine Coon and Ragdoll breeds, the epidemiological and clinical characteristics, echocardiographic hypertrophic patterns, survival, and genetic aspects have been described.[14–18] The aims of this prospective observational study were therefore (1) to investigate heart morphology and function using 2D echocardiography and TDI, (2) to determine heart disease prevalence and characteristics, and lastly, (3) to assess potential cardiac genetic features in a population of Sphynx cats presented for cardiovascular screening at the Cardiology Unit of Alfort from 2004 to 2011.

Animals, materials and methods

Animals

Client- and breeder-owned Sphynx cats, brought to the Cardiology Unit of Alfort (National Veterinary School of Alfort, France) for cardiovascular screening between April 2004 and January 2011, were prospectively recruited. Cats receiving cardiac medications (i.e., benazepril, diltiazem, furosemide) were not included in the study. All animals underwent a complete physical and conventional echocardiographic examination. If the animal was calm, a 2D color TDI examination was also performed.

Reference intervals were established from healthy adult ($\geq$12 months) Sphynx cats without

any history of heart and respiratory diseases, and with LV myocardial wall thicknesses <6 mm.[7] All healthy cats with end-diastolic myocardial wall thicknesses between 5 and 6 mm had to have a TDI examination showing no radial and longitudinal TDI diastolic abnormalities (i.e., early/late myocardial ratio (E/A) should be >1) to be considered truly normal.[19]

Conventional echocardiography and Doppler

Standard transthoracic M-mode, 2D and Doppler blood flow measurements were performed with continuous ECG monitoring by trained observers (CCS, VC, VG) in awake standing cats by use of 2 ultrasound units[f] equipped with 7.5−10 MHz phased-array transducers, as previously described and validated.[20] A mean of 3 measurements was obtained for each M-mode parameter on 3 consecutive cardiac cycles on the same frame. Left ventricular end-diastolic and end-systolic diameters, and LV free wall (LVFW) and interventricular septal (IVS) thicknesses at end-diastole and end-systole were measured by use of the 2D-guided M-mode from the right parasternal short-axis view,[21,22] and the LV shortening fraction was then calculated. The right ventricular end-diastolic diameter was also measured using the same M-mode view. As already performed in large feline populations,[19] the right ventricular myocardial wall thickness was measured when it was the best defined, i.e., when maximal at end-systole.

The sub-aortic IVS thickness was measured at end-diastole using 2D mode from the right parasternal 5-chamber view at the level of the attachments of the chordae tendineae to the mitral valve leaflets.[23]

The left atrium-to-aorta ratio (LA/Ao) was obtained from the right parasternal short-axis view at the level of the aortic valve using a 2D method, as previously described and validated by our group,[20] and LA enlargement was defined as an LA/Ao >1.2 (upper cut-off obtained from a population of 100 prospectively recruited healthy cats).[19]

Pulsed-wave Doppler parameters included peak systolic aortic and pulmonary flow velocities, early and late diastolic mitral inflow velocities, and the isovolumic relaxation time (IVRT, time interval between end of aortic flow velocity and onset of transmitral inflow). Continuous-wave Doppler was also used to measure the maximal systolic aortic flow velocity and to confirm an LV outflow tract obstruction characterized by turbulent aortic flow of high velocity (>2 m/s).[19] The presence of a systolic anterior motion of the mitral valve, defined as a motion of the anterior mitral valve leaflet toward the LV outflow tract, was also assessed using both 2D and M-modes.[24] Additionally, both color-flow and continuous-wave Doppler modes were used to rule in or out a dynamic right ventricular outflow tract obstruction from the right parasternal short-axis view at the level of the aortic valve.

Hypertrophic cardiomyopathy was diagnosed as previously described, based on the following 2D and M-mode criteria: end-diastolic LVFW and/or IVS thickness ≥6 mm on the M-mode exam or sub-aortic end-diastolic IVS thickness ≥6 mm.[8] Hypertrophy was considered as symmetric if the IVS/LVFW ratio at end-diastole was 0.7−1.3, or as asymmetric with predominant IVS or LVFW thickening (if the end-diastolic IVS/LVFW was >1.3 or <0.7, respectively) or if only 1 of these 2 myocardial walls were thickened.[25] The whole morphological aspect of the heart (including papillary muscles) was also assessed using the 2D mode.

In cats >6 years old with an LV hypertrophic pattern, HCM was diagnosed after excluding both systemic arterial hypertension (normal: systolic arterial blood pressure <160 mmHg in unstressed cats using the Doppler method)[26,g] and hyperthyroidism (total plasma thyroxin levels [T4], reference range: 10−50 nmol/L).

Tissue Doppler study

All 2D color TDI examinations were performed in awake standing cats with continuous ECG monitoring by the same observers as for conventional echocardiography and using the same ultrasound units,[f] as previously described and validated.[27] All TDI examinations were interpreted by a single trained observer (VC). Real-time color Doppler was superimposed on the gray scale with a high frame rate (between 180 and 280 frames/s). The Doppler receive gain was adjusted to maintain optimal coloring of the myocardium (i.e., without any black spots), and the Doppler velocity range was set as low as possible to avoid aliasing. All digital images were stored and analyzed using specific software.[h] A 1 × 1 mm sample was used and a tissue velocity profile displayed in each sample location. Myocardial velocities resulting from radial LVFW motion were measured using the right

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parasternal ventricular short-axis view and measurements were made between the 2 papillary muscles in sub-endocardial and sub-epicardial segments of the LVFW. Longitudinal velocities were measured using the standard left apical 4-chamber view in 3 myocardial segments, i.e., 2 from the LVFW (at the base and the apex) and 1 from the IVS (at the base). Radial myocardial velocity gradients (MVG, cm/s, defined as the difference between sub-endocardial and sub-epicardial velocities) and longitudinal MVGs (defined as the difference between basal and apical LVFW velocities) were also calculated for each phase of the cardiac cycle. Time indices (TDI IVRT and isovolumic contraction time (IVCT)) were assessed on the same 3 consecutive cardiac cycles, with IVRT defined as the time interval between end of the TDI systolic wave (S) and onset of the TDI early diastolic wave (E), and IVCT as the time interval between end of the TDI late diastolic wave (A) and onset of the TDI S wave. The heart rate was calculated by ECG monitoring during each radial and longitudinal TDI examination and by averaging the same 3 cardiac cycles used for the velocity measurements.

Genetic analysis

Pedigrees of the examined Sphynx cats and their relatives, provided by breeders and owners, were mapped and drawn using the GenoPro software.[i]

Statistical analysis

Statistical analyses were performed by computer software.[j] All data were expressed as mean $\pm$ standard deviation. Reference ranges were assessed for echocardiographic and TDI parameters from the mean $\pm$ 2 standard deviations. Normality of the different variables was tested using a Kolmogorov−Smirnov analysis in healthy cats. The normally distributed conventional echocardiographic and TDI variables were compared between healthy males and females with a Student t-test. Non-normally distributed parameters, including body weight and other conventional echocardiographic and TDI variables, were compared between healthy males and females using a non-parametric Mann−Whitney analysis. Similarly, an unpaired Student t-test was used to compare endocardial vs epicardial velocities and basilar vs apical velocities at each phase of the cardiac cycle in healthy cats for normally distributed variables, while non-normally distributed variables were compared using a Mann−Whitney test. Since body weight was not normally distributed, its correlation with conventional echocardiographic and TDI variables was assessed with a Spearman analysis (r_s) in healthy cats. Since heart rate was normally distributed, correlation with conventional echocardiographic and TDI variables was assessed using the Pearson product moment correlation (r) in healthy cats. The overall prevalence of heart diseases in the study population was calculated according to the number of cats. Prevalence of heart diseases according to age was assessed using the number of examinations per age category. The percentage of animals with or without HCM was compared among age classes (<2, $2−4$, $4−6$, and >6 years) using a Chi-square test. The level of significance was set at $P < 0.05$.

Results

Study feline population

A total of 147 echocardiographic examinations, including 33 follow-ups, were performed between April 2004 and January 2011 on 114 owners' or breeders' untreated Sphynx cats. The feline population ($n = 114$; age: 2.62 ± 1.93 years [0.5−10.0]; body weight: 3.95 ± 1.1 kg [2.0−7.3]) consisted of 54 males (3 neutered and 51 intact) and 60 females (5 neutered and 55 intact).

Conventional echocardiographic and Doppler findings: reference ranges and prevalence of heart diseases

Reference ranges
Conventional echocardiographic findings included 91/147 normal (61.9%) and 56/147 (38.1%) abnormal examinations with a diagnosis of either congenital or acquired heart diseases. The 91 normal examinations were obtained in 75 different healthy Sphynx cats (with 16 follow-ups). Fifty-three of these 75 healthy Sphynx cats were used to establish 2D and M-mode echocardiographic and Doppler reference ranges (21 males (all intact) and 32 females (31 intact and 1 neutered); age: 2.04 ± 1.27 years [1.0−6.0]; body weight: 3.76 ± 1.09 kg [2.0−7.1]). Ten healthy Sphynx cats were excluded from the assessment of reference ranges because of their young age (<12 months). Twelve additional healthy Sphynx cats (7 males and 5 females) were excluded because they

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[i] GenoPro: www.genopro.com.
[j] Systat, version 10.0, SPSS Inc., Chicago, IL, USA.

showed TDI diastolic abnormalities and were therefore considered as equivocal. According to the above-mentioned inclusion criteria, the 53 normal Sphynx cats used for the assessment of echocardiographic reference ranges had myocardial wall thicknesses either <5 mm ($n = 43$) or ≥ 5 mm and <6 mm with a normal TDI examination ($n = 10$). All normal Sphynx cats with myocardial wall thicknesses ≥ 5 and <6 mm had a body weight ≥ 4.0 kg. Reference ranges are provided in Table 1. A significant gender effect was observed on body weight ($P < 0.001$) and on the right ventricular end-systolic myocardial wall thickness ($P < 0.05$). A significant positive correlation ($r_s = 0.54$, $P < 0.001$) was observed between the end-diastolic IVS thickness and body weight (Fig. 1(A)). A similar significant positive correlation was observed for the LVFW ($r_s = 0.43$, $P < 0.01$, Fig. 1(B)) and the LV diameter ($r_s = 0.51$, $P < 0.001$, Fig. 1(C)) at end-diastole. Lastly, a significant positive correlation was also observed with the LVFW ($r_s = 0.62$, $P < 0.001$), the IVS ($r_s = 0.47$, $P < 0.001$) and the right ventricular wall thickness ($r_s = 0.42$, $P < 0.01$) at end-systole.

Fusion of the 2 diastolic transmitral inflow waves (E and A) was observed in 8 of the 53 healthy Sphynx cats due to high heart rate. However, no correlation was found between heart rate and 2D, M-mode or Doppler variables.

Heart disease prevalence and characteristics

Two-dimensional and M-mode echocardiographic findings included 75/114 normal (65.8%) and 39/114 (34.2%) abnormal examinations with a diagnosis of either congenital heart diseases ($n = 16$) or HCM ($n = 23$). The overall prevalence of congenital heart diseases and HCM were therefore 14.0% (16/114) and 20.2% (23/114), respectively. Fig. 2 shows the distribution of heart disease prevalence according to age. The analysis of cardiac morphology using 2D echocardiography showed thick fibrous bands (3–4 mm) linking the two LV papillary muscles in 6 cats, concomitant with an atrial septal defect ($n = 1$), mitral valve dysplasia ($n = 2$) and HCM ($n = 3$). None of the recruited cats were presented with right ventricular outflow tract obstruction.

Congenital heart diseases included mitral valve dysplasia ($n = 10$), mitral valve dysplasia with a secundum-type atrial septal defect ($n = 3$), mitral valve dysplasia with sub-valvular and valvular aortic stenosis ($n = 1$), mitral valve dysplasia with a membranous ventricular septal defect ($n = 1$), and a secundum-type atrial septal defect ($n = 1$). Mitral valve dysplasia was characterized by thickening of the two mitral leaflets and of the chordae tendineae, leading to systolic mitral regurgitation confirmed by color-flow Doppler mode. A systolic heart murmur was detected in all these cats on cardiac auscultation. All of them were

Table 1 Means $\pm$ SD, minimum (Min) and maximum (Max) values, and reference ranges of conventional echocardiographic and Doppler variables assessed in 53 healthy Sphynx cats older than 12 months. Reference ranges were considered as mean $\pm$ 2SD.

	Mean $\pm$ SD	Min–max	Reference ranges
Heart rate (beats/min)	196 $\pm$ 21	163–243	153–240
Morphologic parameters			
Left atrium/aorta	0.90 $\pm$ 0.14	0.56–1.17	0.63–1.18
Left ventricular end-diastolic diameter (mm)	15.2 $\pm$ 1.6	12.8–19.2	12.0–18.4
Left ventricular end-systolic diameter (mm)	7.2 $\pm$ 1.5	3.6–11.4	4.1–10.3
Left ventricular end-diastolic free wall (mm)	4.2 $\pm$ 0.6	2.9–5.3	3.0–5.3
Left ventricular end-systolic free wall (mm)	7.8 $\pm$ 1.0	5.7–10.7	5.8–9.9
Interventricular end-diastolic septum (mm)	4.4 $\pm$ 0.4	3.2–5.2	3.6–5.3
Interventricular end-systolic septum (mm)	7.5 $\pm$ 1.1	5.5–11.4	5.4–9.7
Sub-aortic septum thickness at end-diastole (mm)	3.7 $\pm$ 0.8	2.3–5.4	2.0–5.3
Right ventricular end-diastolic diameter (mm)	3.0 $\pm$ 1.4	0.5–6.6	0.3–5.8
Right ventricular end-systolic wall thickness (mm)	3.4 $\pm$ 1.3	1.5–6.6	0.9–5.9
Systolic function parameters			
Fractional shortening (%)	53 $\pm$ 7	36–67	39–67
Systolic maximal aortic flow velocity (m/s)	1.3 $\pm$ 0.2	0.8–1.7	0.8–1.7
Systolic maximal pulmonary flow velocity (m/s)	1.2 $\pm$ 0.2	0.8–1.8	0.8–1.6
Diastolic Doppler parameters[a]			
Mitral E wave (m/s)	0.9 $\pm$ 0.2	0.5–1.4	0.6–1.3
Mitral A wave (m/s)	0.6 $\pm$ 0.2	0.3–1.1	0.3–1.0
Mitral E wave/A wave ratio	1.5 $\pm$ 0.4	1.1–2.6	0.8–2.2
Isovolumic relaxation time (ms)	43 $\pm$ 7	22–55	28–58

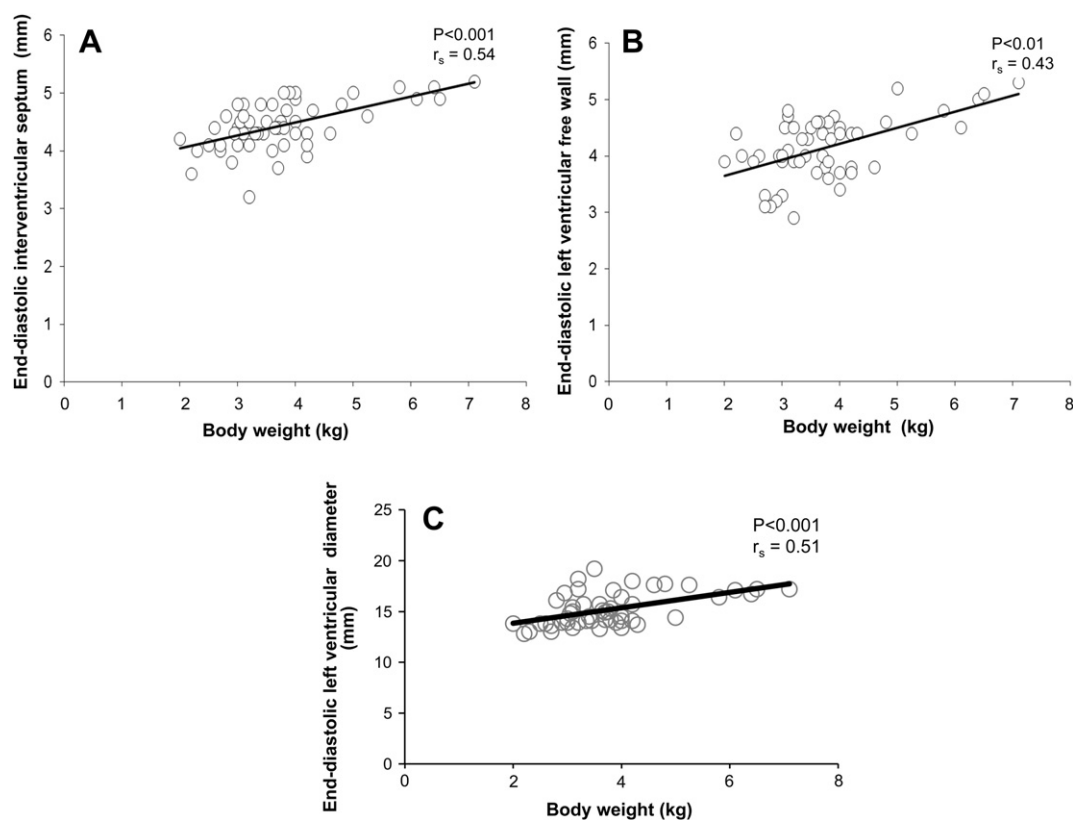[a] Data obtained in the 45 Sphynx cats with distinct E and A waves.

Figure 1 Correlations between body weight and interventricular septum thickness (A), left ventricular free wall thickness (B) and left ventricular diameter (C) at end-diastole assessed in 53 healthy Sphynx cats older than 12 months.

asymptomatic except for the one with a 5 mm-ventricular septal defect that was presented with pulmonary edema when 10 years old. Only 2 cats showed dilated heart chambers using

Figure 2 Distribution of heart disease prevalence according to age. Out of the 114 recruited Sphynx cats, 39 (34.2%) were found abnormal with a diagnosis of either congenital heart diseases (16/114, 14.0%) or hypertrophic cardiomyopathy (HCM; 23/114, 20.2%) using conventional echocardiography.

echocardiography, i.e., one with the ventricular septal defect (markedly increased LA/Ao ratio = 2.94) and one with sub-valvular and valvular aortic stenosis characterized by a maximal aortic flow velocity of 5.3 m/s and a slightly increased LA/Ao ratio (1.34; reference range [0.5−1.2]).[19]

The HCM population consisted of 14 males and 9 females (age: 4.2 ± 2.5 years [1−10 years]). A significant increase in HCM prevalence was observed according to age ($P < 0.001$, Fig. 2), with most HCM cats being ≥4 years old (13/23, 57%) and 6/23 cats (26%) ≥6 years (Fig. 2). All HCM cats except the one with congestive heart failure (pulmonary edema) were asymptomatic at the time of diagnosis. The majority (21/23, 91%) had a left apical systolic heart murmur on cardiac auscultation. All HCM cats had normal regular sinus rhythm on ECG tracings (concomitant with echocardiographic examinations), except for 2 cats that had single LV premature complexes (<10/min). Two-dimensional and M-mode echocardiography revealed four LV hypertrophic patterns: a concentric symmetric LV hypertrophic pattern (5/23, 22%), a concentric asymmetric LV hypertrophic patterns with predominant LVFW (7/23, 30%) or IVS (8/23, 35%) thickening, and a sub-aortic focal IVS hypertrophic pattern (3/23, 13%) characterized by normal 2D-
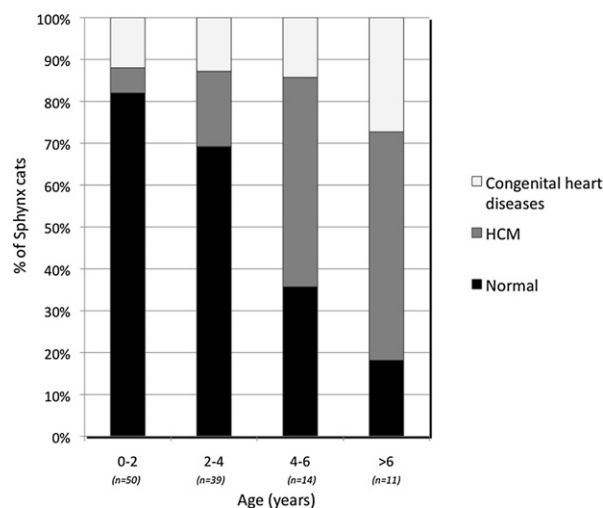
guided M-mode ventricular measurements and an increased sub-aortic IVS at end-diastole using 2D mode. An LV outflow tract obstruction characterized by turbulent aortic flow of high velocity (>2 m/s)[19] was observed in 10/23 HCM cats, including 2/5 cats with concentric symmetric LV hypertrophy, 2/7 cats with predominant LVFW hypertrophy, 3/8 cats with predominant IVS hypertrophy, and all 3 cats with sub-aortic focal IVS hypertrophy.

At the time of writing, follow-up data were available for 18 of the 23 HCM cats (5 were lost to follow-up). All cats with follow-up had been asymptomatic at the time of diagnosis and all received one or more treatments after the initial HCM diagnosis, including furosemide ($n = 1$) and benazepril ($n = 18$). One of the 18 HCM cats with follow-up (6%) decompensated at the age of 7 years (congestive heart failure associated with syncope). Thirteen of the 18 cats with follow-up were still alive (age: 6.0 ± 2.9 years [2.0–11.0]), while 5 (4 males and 1 female) had died for a strongly suspected cardiac reason (sudden death) at the age of 7.3 ± 1.9 years [4.5–11.0]. Four of the 5 cats that died suddenly had an asymmetric HCM with predominant LVFW hypertrophy, either isolated ($n = 1$) or associated with sub-aortic focal IVS hypertrophy ($n = 3$). The other cat was presented with sub-aortic localized IVS hypertrophy.

Two-dimensional color TDI examination: reference ranges

A TDI examination could be performed in 47 out of the 65 adult healthy cats (72.3%) involved in the study. Twelve cats were excluded from the establishment of reference ranges because they showed TDI diastolic abnormalities. Reference ranges for 2D color TDI examination were therefore established from 35 of the 53 healthy Sphynx cats used to assess the 2D and M-mode echocardiographic reference ranges (13 males [all intact] and 22 females [21 intact and 1 neutered]).

As already described in the cat (Fig. 3),[19,27] all velocity profiles included 1 positive wave (S wave) and 2 negative waves (E and A waves in early and late diastole, respectively). Velocity patterns also included 2 isovolumic phases (IVCT [end of the A wave to the beginning of the S wave] and IVRT [end of the S wave to the beginning of the E wave]). Also as already described in cats from various breeds, myocardial velocities were significantly higher in the endocardial segments compared with the velocities in the epicardial segments, during systole, early and late diastole ($P < 0.0001$), thus defining significant MVG between the inner and outer layers of the LVFW. Similarly, myocardial velocities were significantly higher in the basal segment, compared with velocities in the apical segment, during both systole and diastole ($P < 0.001$), thus defining a significant longitudinal MVG in the LVFW from the base to the apex.

Reference ranges of TDI variables are provided in Table 2 for the radial motion of the LVFW and in Table 3 for the longitudinal motion of the LVFW and the basal IVS. No significant correlation was observed between TDI variables and body weight or heart rate, except between body weight ($P < 0.05$) and S wave at apex ($r_s = 0.43$), the systolic gradient between base and apex ($r_s = -0.56$), and E ($r_s = 0.39$) and A ($r_s = 0.37$) waves at the apex.

Tissue Doppler imaging variables were not significantly different between males and females, except for E wave at the apex ($P < 0.01$) and A wave at the base and the apex ($P < 0.05$). Fusion of radial E and A waves was observed in 2/35 cats because of high heart rates (220 bpm and 253 bpm, respectively). Fusion of E and A waves was observed in the same 2/35 cats for the longitudinal motion of the LVFW (heart rate of 232 bpm and 253 bpm, respectively).

Genetic aspects

Pedigrees were obtained from the breeders or owners of 43 Sphynx cats; 16 HCM-affected cats, 21 HCM-non-affected cats, and 6 cats with TDI diastolic abnormalities only. All these cats were related (Fig. 4). Cats of both sexes were equally affected with HCM (males: $n = 8$; females: $n = 8$). Three HCM-affected cats were born to an HCM-affected parent, 2 HCM-affected cats were born to a parent that was not affected with HCM but that had a congenital heart disease (atrial septal defect associated with mitral valve dysplasia), 1 HCM-affected cat was born to a parent that showed TDI abnormalities, and 2 HCM-affected cats were from 2 healthy parents. Eight HCM-affected cats were from 2 parents of unknown status. Additionally, 1 HCM-non-affected cat was from 2 HCM-affected parents. Finally, in a six-generation lineage, HCM-affected cats were present at 4 generations. These results suggest that HCM displays an autosomal dominant mode of inheritance with incomplete penetrance in this population. There were not enough pedigree data to explore the inheritance patterns of the congenital heart diseases observed in this Sphynx family.

Discussion

The first aim of the present study was to prospectively assess heart morphology and function using conventional echocardiography
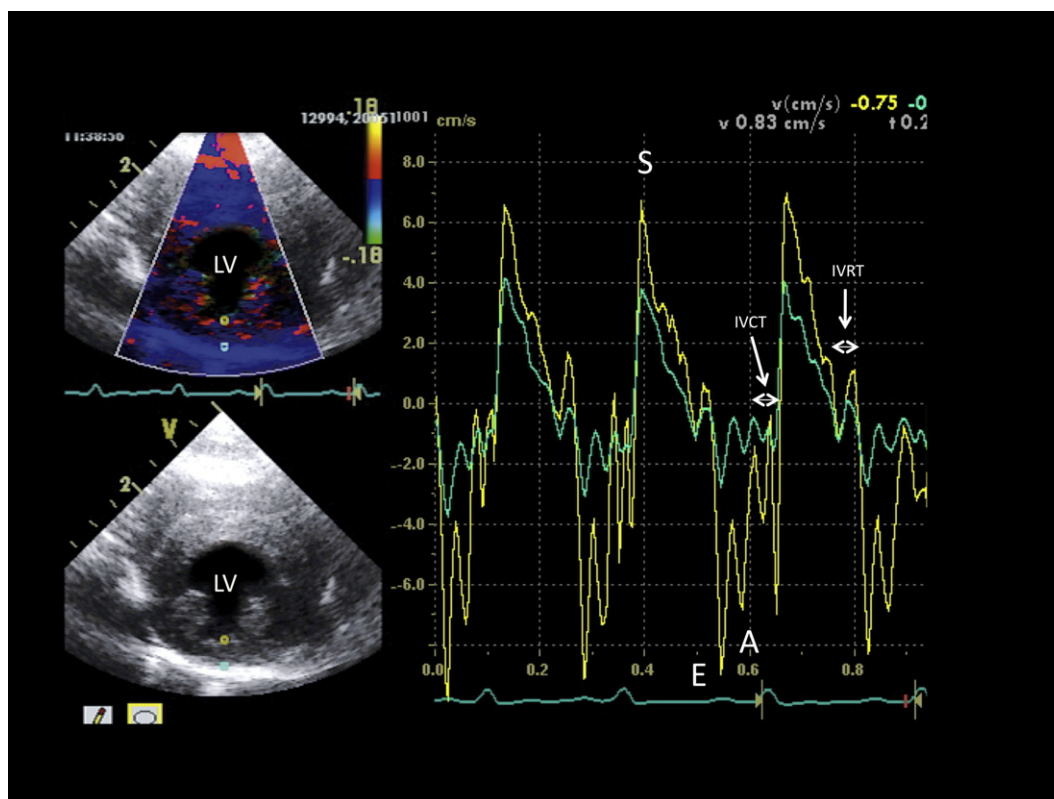
Figure 3 Representative normal radial velocity profiles obtained in a healthy Sphynx cat by two-dimensional color tissue Doppler imaging from the right parasternal transventricular short-axis view, simultaneously in a sub-endocardial (yellow) and sub-epicardial (green) segment of the left ventricular free wall. The endocardial segment is moving more rapidly than the epicardial segment in systole and diastole. S, E and A: peak myocardial velocity during systole, early diastole and late diastole, respectively. IVCT: isovolumic contraction time. IVRT: isovolumic relaxation time. LV: left ventricle.

Table 2 Means ± SD, minimum (Min) and maximum (Max) values, and reference ranges of tissue Doppler imaging variables for the radial motion of the left ventricular free wall assessed in 35 healthy Sphynx cats aged more than 12 months with normal conventional echocardiographic and Doppler examination. Reference ranges were considered as mean ± 2SD. Statistical comparisons were only performed between sub-epicardial and corresponding sub-endocardial values.

	Mean ± SD	Min—max	Reference ranges
Heart rate (beats/min)	196 ± 22	163—243	153—240
Systolic variables			
S wave in the sub-endocardium (cm/s)	6.0 ± 1.3	3.9—9.2	3.3—8.7
S wave in the sub-epicardium (cm/s)	3.3 ± 0.9[b]	1.8—5.9	1.5—5.3
Systolic gradient between sub-endocardium and sub-epicardium	2.8 ± 0.9	1.4—5.5	1.0—4.6
Diastolic variables[a]			
E wave in the sub-endocardium (cm/s)	5.9 ± 1.4	3.8—9.7	3.1—8.6
E wave in the sub-epicardium (cm/s)	2.3 ± 0.9[b]	0.9—5.0	0.5—4.1
A wave in the sub-endocardium (cm/s)	3.2 ± 1.0	1.4—5.1	1.2—5.1
A wave in the sub-epicardium (cm/s)	1.3 ± 0.7[b]	0.4—3.8	0—2.7
E/A ratio in the sub-endocardium	1.9 ± 0.7	1.2—3.8	0.6—3.2
E/A ratio in the sub-epicardium	2.0 ± 0.9	1.0—5.4	0.2—3.9
Isovolumic relaxation time (ms)	35 ± 9	19—50	17—52

[a] Data obtained in 33 Sphynx cats with distinct E and A waves.
[b] $P < 0.0001$ *vs* corresponding sub-endocardial value.

Table 3 Means ± SD, minimum (Min) and maximum (Max) values, and reference ranges of tissue Doppler imaging (TDI) variables for the longitudinal motion of the left ventricular free wall (LVFW) and the interventricular septum (IVS) established in 35 healthy Sphynx cats aged more than 12 months with normal conventional echocardiographic and Doppler examination. Reference ranges were considered as mean ± 2SD. Statistical comparisons were only performed between basal and corresponding apical values.

	Mean ± SD	Min—max	Reference ranges
Heart rate (beats/min) during LVFW TDI examination	203 ± 22	157—253	159—247
Systolic LVFW variables			
S wave at the base (cm/s)	5.4 ± 1.6	2.7—10.1	2.1—8.6
S wave at the apex (cm/s)	2.7 ± 1.7[c]	0.6—7.0	0—6.0
Systolic gradient between base and apex (cm/s)	2.9 ± 1.4	1.2—6.9	0.1—5.8
Diastolic LVFW variables[a]			
E wave at the base (cm/s)	6.6 ± 1.8	3.8—10.4	3.0—10.1
E wave at the apex (cm/s)	3.1 ± 1.8[c]	0.6—7.6	0—6.7
A wave at the base (cm/s)	3.5 ± 1.4	1.1—6.8	0.7—6.2
A wave at the apex (cm/s)	1.3 ± 1.0[c]	0.3—3.7	0—3.4
E/A ratio at the base	2.1 ± 0.8	1.1—4.0	0.5—3.7
E/A ratio at the apex	2.9 ± 1.9[d]	1.1—10.7	0—6.7
Isovolumic relaxation time at the base (ms)	47 ± 11	26—63	26—68
Heart rate (beats/min) during IVS TDI examination	205 ± 19	185—253	167—242
Systolic IVS variable[b]			
S wave (cm/s)	6.4 ± 1.5	4.0—9.0	3.5—9.3
Diastolic IVS variables[b]			
E wave at the base (cm/s)	5.8 ± 2.0	3.5—9.9	1.7—9.8
A wave at the base (cm/s)	3.7 ± 1.0	2.3—5.6	1.7—5.7
E/A ratio at the base	1.6 ± 0.4	1.2—2.6	0.9—2.3

[a] Data obtained in 33 Sphynx cats with distinct E and A waves.
[b] Data obtained in 19 Sphynx cats.
[c] $P < 0.001$ vs corresponding basal value.
[d] $P < 0.05$ vs corresponding basal value.

combined with 2D color TDI in healthy Sphynx cats. A 2D and M-mode echocardiographic examination provides global information on myocardial function, whereas TDI enables regional longitudinal and radial myocardial function to be quantified from measurements of myocardial velocities in different segments over time. These two ultrasound techniques are thus complementary, and so both were used in these investigations of the Sphynx breed. Two-dimensional color TDI, which has been shown to be repeatable and reproducible in the awake cat,[27] is also more sensitive than 2D and M-mode echocardiography in detecting myocardial dysfunction in this species, despite the absence of overt myocardial changes. For example, in a feline model of HCM (dystrophin-deficient hypertrophic muscular dystrophy), our group demonstrated that TDI could consistently detect LVFW dysfunction despite the absence of myocardial hypertrophy in all mutated animals.[28] Similarly, in cats affected by spontaneous HCM and in Maine Coon cats heterozygous for the A31P mutation in the myosin-binding protein C gene, TDI was shown to be capable of detecting segmental functional changes in non-hypertrophied myocardial wall segments.[29–31] This led us in the present study to define specific TDI reference intervals for the Sphynx breed, which, like other feline breeds, seems predisposed to HCM.[6] Moreover, owing to the above-mentioned high sensitivity of the TDI technique, only 53 of the 65 healthy Sphynx cats older than 12 months were used to establish conventional echocardiographic reference ranges in the present study: 12 healthy Sphynx cats were excluded because of TDI diastolic abnormalities consistent with those observed at an early stage of occult HCM (i.e., longitudinal E/A ratio <1 in the IVS and/or the LVFW).[29–31]

We have already reported an overall effect of breed on both standard echocardiographic and 2D color TDI variables in the dog, using a general linear model.[32] A similar breed-dependent response has also been reported by our group in the cat based on a population of 100 healthy cats from 6 different breeds.[19] In the latter prospective study, the effect of breed, body weight, sex and age was tested on the same conventional echocardiographic and radial TDI variables as those assessed here. These effects were also tested on the same longitudinal TDI variables,
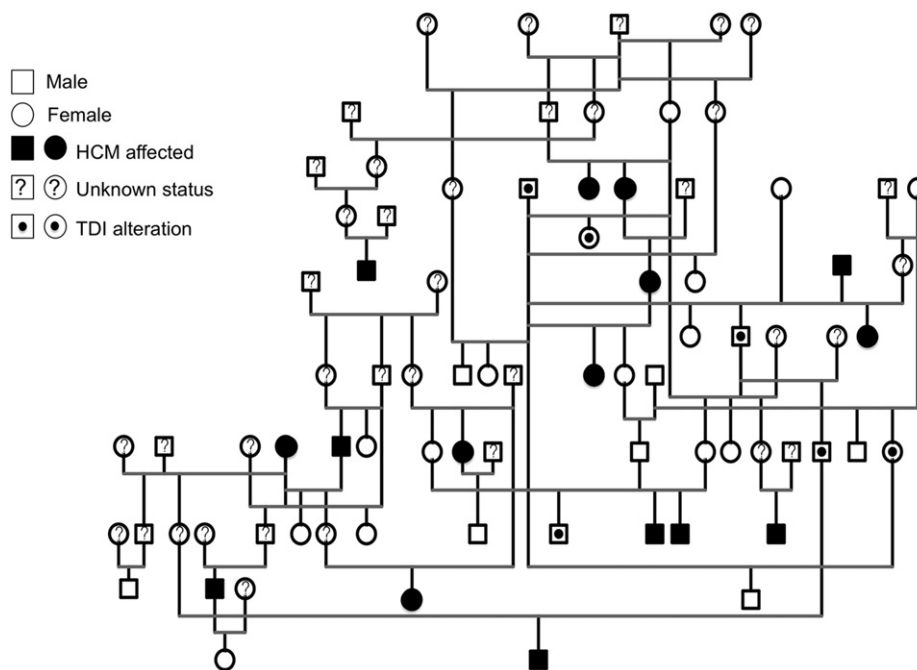
Figure 4 Pedigree of a large Sphynx cat family ($n = 81$) segregating hypertrophic cardiomyopathy (HCM) and tissue Doppler imaging (TDI) diastolic myocardial abnormalities. Circles represent females, squares represent males. HCM-affected cats are shown in black ($n = 16$), HCM-non-affected cats are shown in white ($n = 21$). Cats with a dot in their symbol showed TDI abnormalities ($n = 6$) and cats with an interrogation mark were not examined (unknown status, $n = 38$). This pedigree suggests that HCM displays an autosomal dominant inheritance pattern with incomplete penetrance.

except for IVS (the mitral annulus was studied instead).[19] A breed effect was detected for all M-mode and 2D end-diastolic variables (LVFW, LV and right ventricular diameters, IVS, sub-aortic IVS thickness) and for several standard Doppler variables (mitral E wave, IVRT, peak systolic pulmonary flow velocity), with a body weight effect for end-diastolic ventricular diameters and LVFW.[19] Similarly, the effect of breed was predominant for the radial and longitudinal TDI variables for which a significant effect was detected (i.e., 44% of the radial TDI variables and 27% of the longitudinal diastolic variables). These results implied that reference ranges for both standard and TDI techniques should be determined for each feline breed. However, as there were too few Sphynx breed cats ($n = 6$) in the latter study, standard echocardiographic and TDI reference ranges were determined only for the 2 feline breeds with the highest number of animals, i.e., Maine Coon and Domestic shorthair cats.[19]

In the present study, specifically devoted to the Sphynx breed, a significant correlation was observed between body weight and several end-diastolic variables (i.e., LVFW, IVS, and LV diameter). This again illustrates the effect of body weight on standard echocardiographic measurements, suggesting that even in a given breed, body weight should be

taken into account when interpreting values of diastolic myocardial wall thicknesses (particularly in the upper ranges between 5 and 6 mm). In the present study, all normal Sphynx cats had end-diastolic myocardial wall thicknesses <5.4 mm and those with myocardial wall thicknesses between 5.0 mm and 5.3 mm weighed more than 4.0 kg. According to these results, upper cut-offs of 5.0 mm and 5.5 mm, for end-diastolic myocardial wall thicknesses in Sphynx cats weighing <4 kg and ≥4 kg, respectively, would probably be more suitable than a 6.0 mm cut-off. Similar results were obtained in a recent retrospective report by Mottet et al.,[6] in which the aim was to determine normal reference values for 2D and M-mode echocardiographic variables in 89 non-sedated healthy young adult Sphynx cats.[6] The mean values obtained for end-diastolic LVFW and IVS were 4.13 mm and 3.98 mm with 95% confidence intervals (based on mean $\pm$ 1.96 standard error of the mean) of 4.00–4.25 mm and 3.82–4.15 mm, respectively. As in our study, a significant correlation was observed between body weight and several variables, including LA and Ao in 2D and M-mode and the end-diastolic LVFW in M-mode. Additionally, the body weight of males was significantly higher than that of females and, as a probable consequence, several echocardiographic

variables, such as LA and Ao in 2D and M-mode, end-diastolic LV diameter and LVFW in M-mode, differed significantly between males and females.

As in the report by Mottet et al.,[6] relatively high heart rates were recorded in the present study (196 ± 21 bpm [163–243] during standard echocardiographic examinations). This might be related to the young age of the recruited animals but might also be a breed specificity, in part related to stress sensitivity and low body weight. By comparison, the heart rate in a similar study performed in healthy young adult Maine Coon cats (body weight of 5.0 ± 1.0 kg [3.5–7.1]) was 176 ± 17 bpm [140–200].[33]

The second aim of the present study was to determine the prevalence of heart diseases and their characteristics, including potential genetic features, in the study feline population. As reported by Mottet et al.,[6] mitral valve dysplasia and HCM were the two main heart diseases diagnosed in Sphynx cats in the present study. Mitral valve dysplasia was observed in 15 out of the 114 recruited cats (13.2%) and was found as a single or associated defect in all Sphynx cats (except one) that were affected by congenital heart diseases. Tricuspid valve dysplasia is known to have a genetic basis in the dog, and a heritable basis for mitral valve dysplasia in cats and some breeds of dogs is highly suspected.[34–36] Unfortunately the pedigree data obtained in the present study were insufficient to confirm the inheritance pattern of this congenital heart disease in the Sphynx breed.

In the present study, HCM (including various echocardiographic LV hypertrophic patterns) was detected in 23 of the 114 cats investigated (20.2%), and was the only acquired heart disease diagnosed in the study population. This confirms that the Sphynx cat, like other feline breeds,[7–16,23] is highly predisposed to HCM, which is characterized by a heterogeneous phenotypic expression. As previously reported,[8,12,13] most HCM cats were young adults (mean age of 4.2 years) with a significant increase in prevalence according to age but a wide age range at diagnosis (1–10 years) and at death (4.5–11 years). These results confirm that HCM may develop in Sphynx cats at any adult age, with one quarter of HCM cats being diagnosed at 6 years old or more (i.e., after the main breeding period). This emphasizes the difficulty of eradicating or at least decreasing the disease prevalence in affected strains. These results confirm that HCM may allow for normal longevity (as suggested by Mottet et al.),[6] but on the other hand may be associated with a risk of cardiac death (all deaths reported here were sudden deaths).

Although males are commonly overrepresented in feline HCM populations,[7–9,12,13] in our study Sphynx cats from both sexes were affected by HCM (14 males and 9 females) with an equal proportion of males and females in the large family subjected to pedigree analysis (8 males and 8 females). Unlike the HCM cats in previous studies, most of those in our study were asymptomatic at the time of diagnosis (i.e., 96% vs 47% and 33% in the reports by Payne et al. and Rush et al., respectively).[12,13] However, this difference may be explained by the specific recruitment of HCM cats in the present study, with most being cardiac screenings performed on young cats involved in a breeding program as is mandated by the French Sphynx club.

In the Maine Coon breed, a causative mutation for inherited HCM was identified within the gene encoding the sarcomeric cardiac myosin-binding protein C (MYBPC3).[15] This mutation was shown to be a guanine-to-cytosine transition in MYBPC3 exon 3 (G93C), inducing the production of an aberrant protein by changing the conserved alanine of the 31st codon into a proline (A31P).[15] A second separate causative mutation has been identified in the same gene in the Ragdoll cat.[16] Two reports (one American and one European), demonstrated a high prevalence of the G93C mutation in the Maine Coon breed (34%–41.5%, respectively).[17,18] However, none of the Sphynx cats tested in the latter studies were positive for the G93C mutation ($n = 8$ and $n = 60$, respectively).[17,18] Additionally, in a recent study by Meurs et al., the analysis of MYBPC3 and 7 other sarcomeric candidate genes in cats with HCM, including Sphynx cats, did not allow for the identification of a causative mutation for HCM.[37] Nevertheless, in the present study, the pedigree analysis of a large family ($n = 81$, including 43 echo and TDI tested cats) suggests that HCM displays an autosomal dominant mode of inheritance with incomplete penetrance in this breed. A similar inheritance pattern has been described in Maine Coons and British shorthairs.[15,38]

This report presents several limitations. The study population was relatively young, as most recruited cats were breeder-owned animals that underwent cardiac screening before mating. As only 23 cats were diagnosed with HCM, the results regarding HCM are only preliminary data that need to be verified by larger multicenter studies including higher numbers of affected cats. No histopathologic examination could be performed in cats that died suddenly. Therefore, peracute congestive heart failure could not be distinguished with certainty from sudden death, and causes of sudden death other than HCM could not be

excluded. Lastly, as screening tests represented the main part of the echocardiographic examinations, the present study population may not fully represent the "natural" Sphynx cat population.

Conclusions

In conclusion, the present report provides reference ranges for conventional echocardiographic and 2D color TDI examinations, and demonstrates a significant body weight effect on M-mode and 2D myocardial wall thickness values. It also confirms the genetic predisposition of Sphynx cats to HCM, with an autosomal dominant mode of inheritance and incomplete penetrance as is seen in Maine Coon and British shorthair cats. However, more clinical and pedigree data are required both to confirm these results at the breed level and to analyze the segregation of mitral valve dysplasia in the Sphynx breed.

Conflict of interest

There are no conflicts of interest for any author.

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