Standard Echocardiography, Strain and Strain Rate by Two-Dimensional Speckle Tracking in Capuchin Monkey (*Cebus Apella*, Linnaeus, 1758)

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Abstract

Introduction: The capuchin monkey is a type of nonhuman primate that has shown great potential for preclinical studies because of its anatomical and physiological similarities to humans.

Objective: To study the indices of myocardial deformation in anesthetized capuchin monkeys using speckle tracking.

Methods: Sixteen animals from the Zoobotanical Park, Teresina, Piauí, Brazil, were used and chemically restrained using a combination of ketamine and midazolam. Echocardiography recordings were obtained in B, M and Doppler modes, and strain and strain rate were measured using speckle tracking.

Results: The variables that showed statistically significant correlation coefficients in relation to weight were LVFWd, LVIDd, LVIDs, E wave, A'RV, MAM and TAPSE. HR showed a positive correlation with the E wave and A wave and a negative correlation with IVRT. FS presented a positive correlation with the E/A wave relationship (r = 0.61). TAPSE showed positive correlations with E'RV and A'RV. The values obtained for circumferential (-18.17 ± 4.68%), radial (47.13 ± 5.24%) and longitudinal (- 26.46 ± 5.15%) strain for the capuchin monkeys were within the normal ranges for males and females.

Conclusion: The present study provides the first reference values for echocardiographic measurements in B, M and Doppler modes for capuchin monkeys anesthetized with ketamine and midazolam. The strain and strain rate values obtained using speckle tracking showed similarities with those obtained in humans, suggesting that this tool has the potential to be exploited in preclinical studies using the capuchin monkey model. (Arq Bras Cardiol: Imagem cardiovasc. 2018;31(1):4-13)

Keywords: Echocardiography/standards; Myocardial/abnormalities; Myocardial Contraction; Models, Animal.

Introduction

Capuchin monkeys (*Cebus apella*, Linnaeus, 1758) are an arboreal species of non-human primates with diurnal habits and a wide geographic distribution in almost all South American countries.[1] From a cognitive point of view, they are considered the most competent primates in the Americas due to their abilities in obtaining food.[2] Because of the wide availability of individuals of this species and their great anatomical and physiological similarities to humans, the capuchin monkey has become an alternative model for studies of the evolution of diseases, particularly cardiovascular diseases.

Advances in echocardiography allow for more accurate cardiovascular evaluation, reliable diagnoses and accurate monitoring of cardiac alterations. In this context, two-dimensional echocardiography by speckle tracking (2D-ST) is one of the most recent and promising tools for the evaluation of myocardial segment function.[3] This technique is based on the tracking of points created by the interference between the sonographic beam and the myocardium, superimposed on two-dimensional grayscale images.[4]

As with most wild animals, due to their non-human behavior, non-human primates need chemical restraint or even general anesthesia so that medical or management procedures can be performed.[5] Preliminary trials showed that, despite sedation, strain rate measurements by speckle tracking were similar to those in humans.[6]

The combination of ketamine and midazolam promotes adequate muscle relaxation, thus reducing muscle hypertonicity, and promoting tranquilization, hypnosis and amnesia, in addition to having anticonvulsive activity. This is an anesthetic protocol commonly used in procedures with small animals, and is a good alternative for work with wild animals, including primates.[7]

Although strain analysis by speckle tracking (2D-ST) is well established in veterinary medicine for companion animals, it remains scarce in the literature.[8]

The Rhesus monkey is the most commonly used non-human primate in scientific research, despite the wide variety

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of species potentially available for preclinical studies.[9] Given the large population and availability of capuchin monkeys throughout Brazil, the present study acquired conventional echocardiographic measurements and evaluated myocardial function using the speckle tracking technique to verify the applicability of these animals as models for the study of cardiovascular alterations in humans.

Methods

For this study, sixteen capuchin monkeys (eight males and eight females), aged between 2 and 3 years old, from the Zoobotanical Park, Teresina, Piauí, Brazil, were used. This study was approved by the Committee of Ethics in Animal Experimentation at the Federal University of Piauí (Nº. 0117/2015) and by the System of Authorization and Information of Biodiversity - SISBIO of the Brazilian Institute of the Environment and Natural Renewable Resources - IBAMA (Nº. 26101-1).

The animals were submitted to hematological, biochemical and general clinical examinations.[10] Auscultation of pulmonary fields and cardiac sounds were performed to identify valve insufficiencies and cardiac rhythm disturbances. Follow-up consisted of electrocardiographic examination and echocardiogram screening. Animals that presented valvular insufficiencies identified on cardiac auscultation and confirmed on the echocardiogram, as well as those with rhythm disorders diagnosed by ECG, were excluded from the experiment.[11]

Anesthetic protocol

The animals were pre-prepared with 12 hours of solids fasting and 4 hours of water fasting. These animals were initially caught in individual traps and restrained physically using leather gloves. For chemical restraint, a combination of 5% ketamine hydrochloride at a dose of 15 mg/kg and midazolam at a dose of 1 mg/kg, given intramuscularly, was used. The protocol achieved an average anesthetic time of 30 to 40 minutes in all animals, and there was no need to re-administer the drugs during the exams.

Standard echocardiographic assessment

Transthoracic echocardiography with continuous ECG monitoring was performed using an M-turbo system 5 (FUJIFILM® SonoSite, Washington 21919, USA) equipped with a 4.0-8.0 MHz phased-array transducer (Px10, FUJIFILM® SonoSite, Washington 21919, USA). Hair was clipped between the right fourth and sixth intercostal spaces and Coupling gel (Mercur®, São Paulo, Brazil) was applied to this thoracic area.

The echocardiographic examination and standard measurements were performed according to previously established protocols for non-human primates and humans.[11,12] In the parasternal right projection, the left ventricular free-wall and interventricular septal thickness in diastole and systole (LVFWd, LVFWs, SIVd, SIVs), left ventricular end-diastolic and end-systolic diameter (LVIDd and LVIDs), diameter of the aortic root 2D (Ao) and left atrium (LA) were measured. The fractional shortening (FS) and the ejection fraction (EF-Simpson's Method) were calculated. In addition, measurements of the mitral E-point septal separation (EPSS), the final diastolic ratio between the aorta and the left atrium (LA/AO) and the velocity of flow in the pulmonary artery (Pmax) were performed (Figure 1).

By the left parasternal window, through the apical four-chambers view, the aortic velocity peak (AV), isovolumetric relaxation time (IVRT), mitral early diastolic flow (E wave), mitral late diastolic flow (A wave), E/IVRT ratio, mitral annular motion (MAM), and tricuspid annular plane systolic excursion (TAPSE) were calculated. The pulsed-wave tissue Doppler imaging (PWTDI) for the left (E' and A' waves) and right ventricle (E'RV and A'RV) was then measured (Figures 2 and 3).

The heart rate (HR) was obtained from the Doppler tracing of the pulmonary artery. Flow assessment of the mitral, tricuspid and semilunar valves, as well as of the large vessels was performed using color and spectral Doppler on each individual valve. The 2D sector size was adjusted to improve image quality and calibrate the color gain to demonstrate excellent filling of the investigated chambers and vessels. The highest pulse repetition frequency (PRF) was used to prevent signs of aliasing in normal flows.

Strain measurement by speckle tracking measurements

To obtain the values of cardiac deformation, an Affiniti 50 ultrasound device (Philips Healthcare®) coupled to a multifrequency sectorial transducer (5-8 MHz) was used, and ACMQ[A.I] (Automated Cardiac Motion Quantification) software was used for analysis of the radial and longitudinal myocardium deformation of the left ventricle. After the conventional echocardiographic examination, the right and left parasternal windows for video acquisition were assessed at a frame reproduction rate of between 70 and 110 frames/s, as previously described for humans (Figure 4).[13]

The right parasternal window was used to assess the left transverse cardiac diameter, and the left parasternal window was used to assess the longitudinal axis (apical 4 chambers, 2 chambers and 5 chambers). The endocardial edges of the left ventricle were traced manually at the end of diastole. In each cut plane, a region of interest was automatically delineated from the endocardial border. The software algorithm then automatically divided the cut plane of the short and long axes of the left ventricle into 6 segments, involving the interventricular septum and the free wall, for the tracing of points in the myocardium (speckles).

The speckle search was performed frame-by-frame, generating a score that represents the reliability of the tracking, ranging from poor to excellent, based on blocks matching the algorithm. Six radial profiles of ST (strain rate) and SR (strain velocity) values were obtained, corresponding to the mean of the values for each segment. These values for the radial ST and SR maxima in the radial systolic peak were referenced by the means of six curves, and the average of the values was calculated to characterize the overall ST and SR during the left ventricular systolic peak. The myocardial synchronism was assessed according to the difference between the initial and final systolic peak moment.

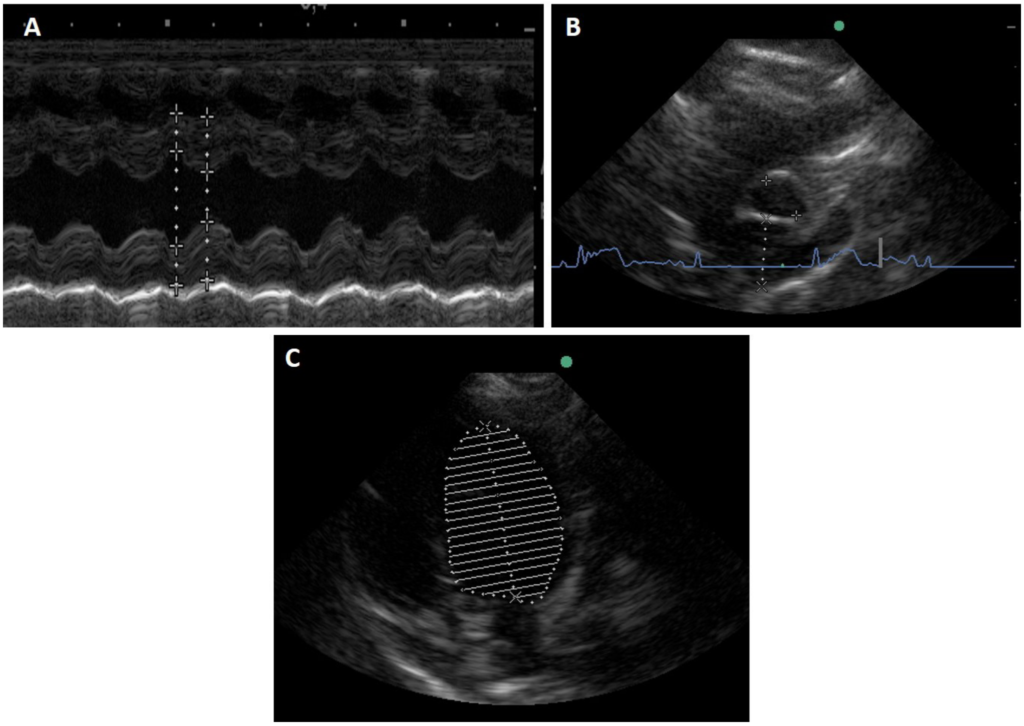

Figure 1 – *M-mode and two-dimensional (2D) echocardiographic images obtained from anesthetized capuchin monkey. (A) M-mode was used for the measurements of the interventricular septal wall, left ventricular wall, and left ventricular internal dimensions. (B) The two-dimensional right short axis view at the cardiac base used to measure the LA/AO ratio. (C) Left apical 4-chamber view for measurement of the echocardiographic end-diastolic and end-systolic left ventricular volumes using Simpson's method of discs.*

A total of 18 myocardial segments were analyzed for each specimen, and the average of values was used for the statistical analysis. During all echocardiographic examinations, the animals were maintained under continuous electrocardiographic monitoring coupled to the ultrasound equipment (Figure 5).

Statistical analysis

The software *GraphPad Prism 7* was used to analyze the data and to run the non-parametric Wilcoxon-Mann-Whitney test (U of Mann-Whitney) to verify the existence of differences between the variables addressed according to the sex of the animals. The Spearman rank correlation coefficient was used to assess dependence. In the test, $p < 0.05$ was considered the threshold for significance.

Results

Table 1 shows the echocardiographic parameters of the group of animals studied. The comparison of means between genders did not show a significant difference ($p > 0.05$, $p = 0.448$). Thus, the other statistical treatments were based on the total sample of 16 animals. The variation reference intervals were determined by the calculated 95% tolerance interval, designed to cover 99% of all future events. The variables that showed a statistically significant correlation coefficient in relation to the weight are presented in Table 1. The other variables that showed correlation are as follows: HR showed positive correlation with the E wave ($r = 0.56$), A wave ($r = 0.40$) and E/IVRT ($r = 0.44$) and a negative correlation with IVRT ($r = -0.41$). The LA variable showed a positive correlation with AO ($r = 0.54$). FS presented a positive correlation with the E/A wave relationship ($r = 0.61$).

MAM presented a correlation with the LVIDd ($r = 0.37$) and LVIDs ($r = 0.34$). TAPSE showed positive correlations with E'RV ($r = 0.41$) and A'RV ($r = 0.47$). Table 2 shows the values found for the advanced echocardiographic measurements derived from the strain analysis by speckle tracking.

Discussion

A number of studies have described normal echocardiographic parameters for species such as the Rhesus monkey.[9] However, this is the first study to measure echocardiographic variables for the capuchin monkey, in addition to the use of strain measurement by speckle tracking in the evaluation of cardiac function.

The HR was higher than that found for animals of the same species restrained with ketamine and xylazine[14] and lower than that in monkeys pre-anesthetized with midazolam and propofol.[15] In this study, the anesthetic protocol using ketamine and midazolam did not provoke negative effects on HR, which was within the range of normality for the species. The elimination of stress promoted by chemical restraint requires a relatively low dose of ketamine. The antagonism of the cardio-depressant effects of ketamine promoted by midazolam contribute to the maintenance of a normal heart rate.[16]

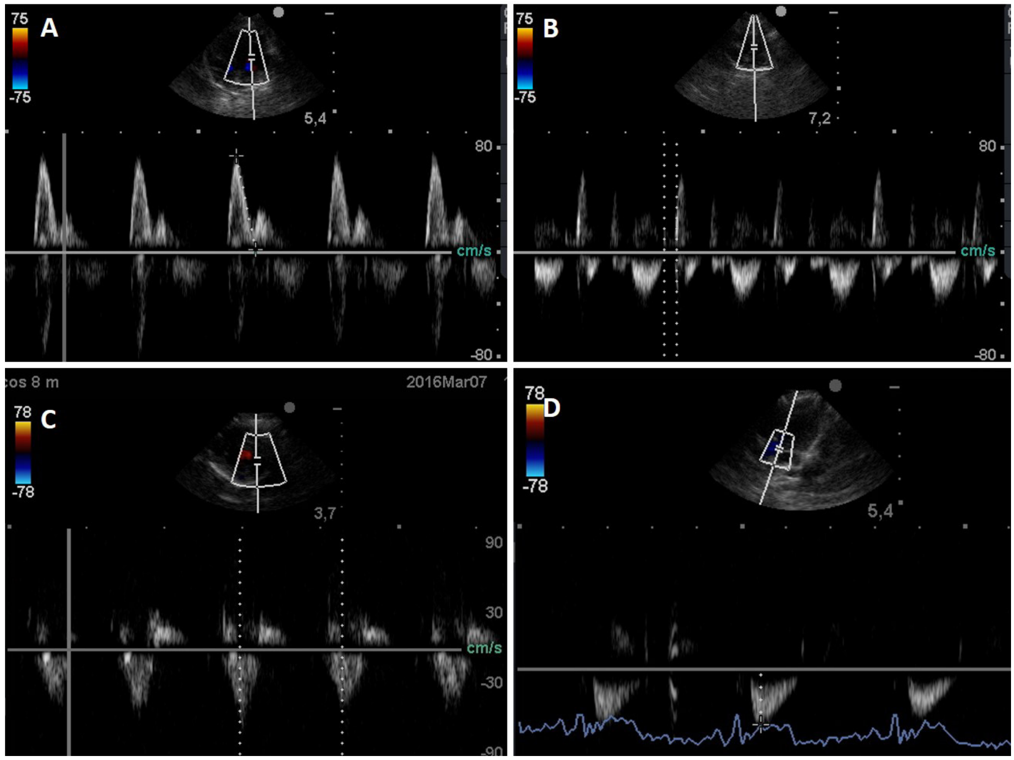

Figure 2 – *Doppler echocardiographic images obtained from anesthetized capuchin monkey. (A) Pulsed-wave Doppler inflow assessment of the mitral valve showing the early diastolic mitral inflow (E) and late diastolic mitral inflow. (B) Doppler measurements, including the peak aortic blood flow velocity and the mitral inflow, were used to measure the isovolumic relaxation time (IVRT) obtained from the left apical 5-chamber view. Pulsed Doppler assessment of the pulmonary (C) and aortic flow velocity curves (D).*

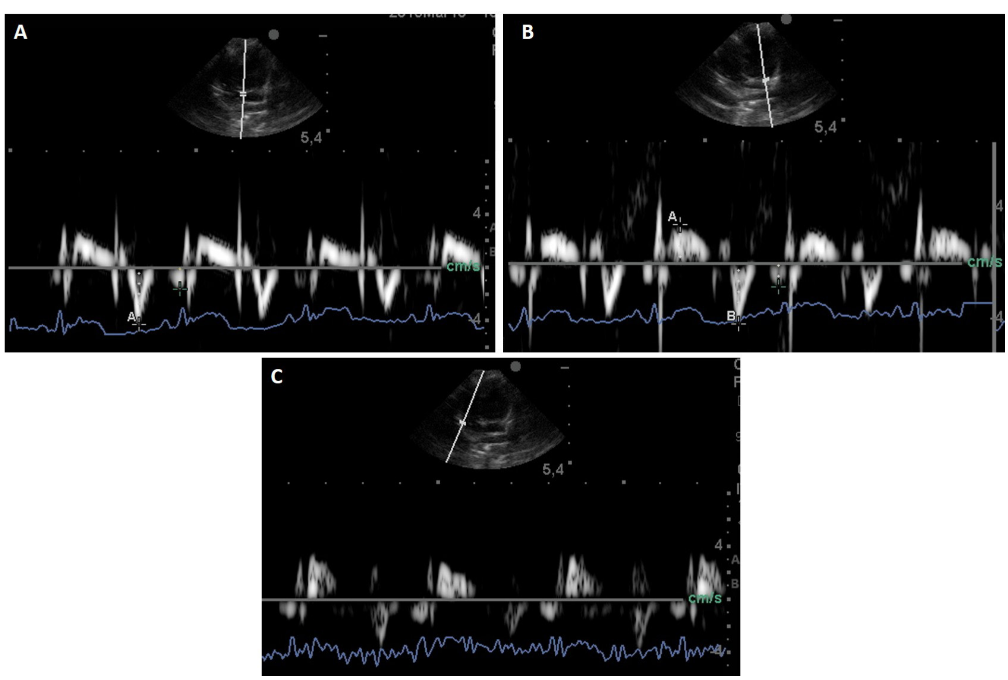

Figure 3 – *Pulsed-wave tissue Doppler imaging (PWTDI) mode images obtained from anesthetized capuchin monkey. (A) PWTDI from the apical 4-chamber view sampling the septal mitral annulus and left ventricular free-wall (B). (C) Myocardial velocity curve from the tricuspid annulus.*

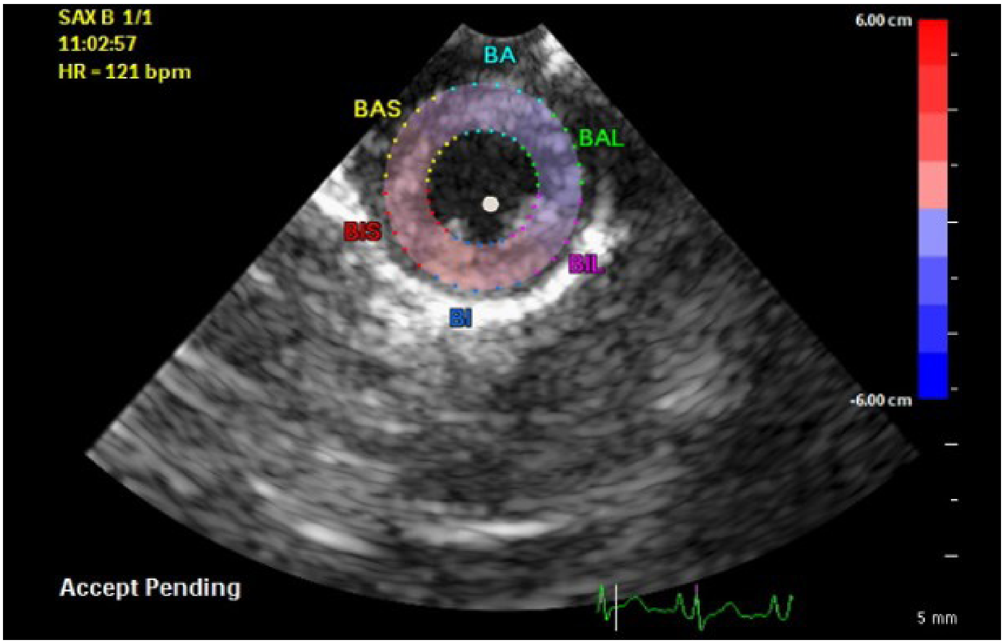

Figure 4 – *Speckle tracking echocardiography at the level of the cardiac base in a capuchin monkey. The software algorithm automatically separates the LV short-axis into 6 myocardial segments to include the interventricular septum and the LV free wall. The tracking approval of each individual myocardial segment is displayed on the screen.*

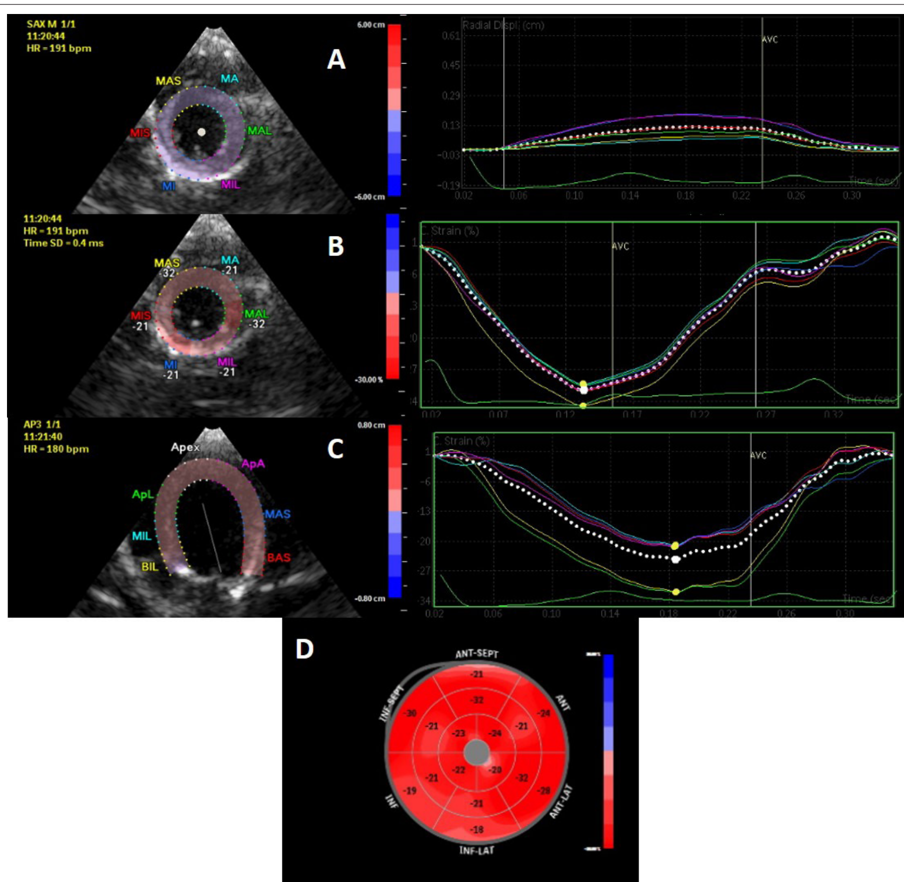

Figure 5 – *Echocardiographic examination evidencing radial (A), circumferential (B) and longitudinal strain (C) of a capuchin monkey. Note that all segments of the myocardium contract adequately and the strain values are within the reference values, including for humans.*

Table 1 – Cardiac parameters of capuchin monkey

Variable	Mean	SD	Reference range	R	p value
BW (Kg)	1.95	0.40	1.3 - 2.90	-	-
AO (cm)	0.62	0.12	0.42 - 0.78	0.081	0.803
LA (cm)	0.74	0.15	0.61 - 1.04	-0.212	0.507
LA/AO	1.13	0.25	0.69 - 1.48	0.075	0.816
IVSd (cm)	0.33	0.08	0.22 - 0.48	0.288	0.363
IVSs (cm)	0.42	0.12	0.3 - 0.69	0.031	0.923
LVFWd (cm)	0.34	0.09	0.18 - 0.5	0.585[a]	0.045
LVFWs (cm)	0.46	0.12	0.3 - 0.74	0.324	0.303
LVIDd (cm)	1.37	0.33	0.74 - 2.04	-0.540[a]	0.069
LVIDs (cm)	0.99	0.28	0.54 - 1.54	-0.501[a]	0.095
EF (%)	56.7	12.56	40 - 82	0.138	0.668
FS (%)	28.62	8.63	17 - 47	0.040	0.901
HR (bmp)	181.1	36.54	95 - 229	-0.367	0.240
EPSS (cm)	0.17	0.05	0.1 - 0.28	0.248	0.436
E wave (cm/s)	76.21	14.82	44 - 101	-0.509[a]	0.090
A wave (cm/s)	43.82	10.13	26.7 - 58	-0.321	0.308
AV max (cm/s)	76.32	22.52	40 - 113.8	0.179	0.575
Pmax (cm/s)	64.17	14.83	37.6 - 90	-0.248	0.436
IVTR (ms)	78.2	23.9	52 - 120	0.189	0.554
E' wave (cm/s)	7.85	2.14	4.28 - 11.2	-0.304	0.336
A' wave (cm/s)	4.67	1.38	1.61 - 6.62	0.035	0.915
E'-RV	9.53	2.32	4.98 - 14	-0.299	0.344
A'-RV	5.42	1.73	3.44 - 8.1	-0.513[a]	0.088
MAM (cm)	0.27	0.04	0.21 - 0.35	-0.544[a]	0.067
TAPSE (cm)	0.48	0.14	0.3 - 0.74	-0.578[a]	0.049
E/A	1.77	0.33	1.42 - 2.63	-0.101	0.755
E/IVRT	1.08	0.46	0.36 - 1.94	-0.442	0.151

[a] *Variables that correlated significantly with weight*

Table 2 – Left ventricle peak systolic strain and twist measurements obtained by speckle tracking echocardiography (STE), measurement, standard deviation and reference intervals from capuchin monkey

Variables	Measurements	SD	Reference interval
Peak apical systolic radial strain (%)	46.22	6.24	37.5 to 55.7
Peak apical circumferential strain (%)	-24.13	5.61	-31.5 to -15.3
Peak basal systolic radial strain (%)	47.13	5.24	38.8 to 53.2
Peak basal circumferential strain (%)	-18.17	4.68	-25.1 to -10.9
Peak longitudinal strain (%)	-26.46	5.15	-36.8 to -18.2
Left ventricle torsion (degrees)	2.46	0.38	2.1 to 3.2
Global Strain (%)	-21.87	1.17	-24.1 to -21.87
Basal Torsion (%)	-4.6	2.0	-6.9 to -1.37
Apical Torsion (%)	-10.23	2.58	-15.3 to -7.7

The variables LVFWd, LVIDd, LVIDs, MAM and TAPSE exhibited a statistically significant correlation with body weight. Similar correlations were also demonstrated between body weight and the variables AO, LVEF, LA/AO, LVIDd, and LVIDs for Cynomolgus monkeys and Rhesus monkeys.[9] In sheep, a positive correlation was found between body weight and LVIDd, SIV, LVFW, LA and AO.[17]

The left atrium/aorta ratio of capuchin monkeys presented values similar to those found for Cynomolgus and Rhesus monkeys[9] and in man.[18] In addition, it was within the normal range for several mammals used in scientific research, such as domestic pigs, minipigs and rabbits.[19] The size and volume of the left atrium and the aorta of the capuchin monkey were lower than those observed in humans, particularly once adjusted for the influence of body weight. However, transvalvular blood flow relationships are similar, suggesting the similarity of pressure indices inside the cardiac chambers and, consequently, an equalization of the LA/AO relationship found in humans and the capuchin monkey. [18]

The EPSS presented a value similar to that found for the Cynomolgus monkeyand lower than that for Rhesus monkeys[9] and domestic pigs.[20] Most species, including humans, present a normal value for EPSS of less than 1.0 cm.[18] In humans, magnetic resonance imaging studies confirmed the applicability of this value as a quantitative predictor of left ventricular function.[21]

The values found for the left ventricular ejection fraction (EF) were, on average, lower than the standard values for domestic pigs and humans.[18,20] In medicine, EF values can be influenced by several variables, such as contractility, heart rate, preload and afterload. The fractional shortening (FS) showed no correlation with body weight.[22] Nevertheless, there was a positive correlation with the E/A ratio ($r = 0.61$), suggesting that in these animals, SF may moderately reflect pressure changes in the left atrium. Although within the limits of normality compared to animal models such as domestic pigs,[20] EF and FS showed values lower than those in humans,[18] likely due to the cardiodepressant effect of ketamine and because all animal models presented were studied under sedation or anesthesia.[7]

The Doppler echocardiographic evaluation revealed aortic flow velocities greater than the pulmonary artery flow velocity (PV), which was also observed in animal models such as domestic pigs and in humans.[18] The A and E waves showed positive and laminar flow, with the E wave exhibiting a higher peak than the A wave. The E/A ratio tends to decrease with advancing age in humans, concomitant with the increase in IVRT time.[23] In this study, all animals evaluated were young specimens, suggesting preservation of the diastolic function for the studied age group.

In humans, HR can alter the transmitral flow, exacerbating isovolumetric relaxation, reducing diastolic filling time and accelerating early left ventricular diastolic elastic recoil.[24] In this study, although there was little variation in the HR, it presented a negative correlation with the IVRT, with a lower IVRT in animals in which the HR was higher, despite the sedation state. The MAM showed a slight correlation with LVIDd ($r = 0.37$) and LVIDs ($r = 0.34$), and the TAPSE showed a moderate positive correlation with E'RV ($r = 0.41$) and A'RV ($r = 0.47$). Variations in ventricular diameters indirectly reflect the ventricular function, as well as the hemodynamic repercussion of volume overloads.[25] Studies in humans showed that the mitral annular motion obtained by 3D echocardiography correlated moderately well with the left ventricular ejection fraction (LVEF) measured by magnetic resonance imaging. In the same study, it was observed that values below 12 mm for this variable were good thresholds for the detection of LVEF < 50%, with high sensitivity and precision.[26] The S wave velocity of the tissue Doppler is one of the variables established in veterinary medicine to determine the systolic function of the right ventricle. The moderate correlation of the E'RV and A'RV variables, derived from the tissue Doppler, suggests that these measurements may also help with better characterization of right ventricular function in capuchin monkeys.[27]

The pattern of E' and A' waves measured at the septal border of the mitral annulus was similar to those reported in domestic pigs and humans.[19,28] Human studies demonstrated an inverse correlation between left ventricular diastolic velocity and age, resulting from a gradual reduction in myocardial relaxation.[19] The animals studied presented similar PWTDI values to those of healthy humans, with no evidence of contractility deficits.[29] Other parameters, such as the LA/AO ratio, were within normality patterns described for other non-human primates and experimental animal models, and the diastolic filling velocities (E wave velocity, A wave velocity and E/A relationship) were also within the limits of normality.[19,29] It is presumed, for this study, that all animals had preserved diastolic function. Although studies in humans show a change in this pattern with age, we cannot discuss these findings, because all animals in the study were young specimens.[30]

The right ventricular (RV) tissue Doppler examination, evaluated at the tricuspid lateral annulus (E' RV and A' RV), showed negative diastolic velocity curves similar to those of humans.[31] In humans, the assessment of RV tissue Doppler provides important information regarding the prediction of coronary lesions and myocardial infarction, even in the absence of electrocardiographic alterations. TAPSE showed a positive correlation with the E'RV ($r = 0.41$) and A'RV ($r = 0.47$) waves, likely as a response to tricuspid annular movement, suggesting that similar to TAPSE, these RV PWTDI values can also be used as predictors of right ventricular function.[32]

As in humans, the velocity for the apical systolic radial strain ($46.22 \pm 6.24\%$) in capuchin monkeys was slightly lower than that obtained for the basal systolic radial strain ($47.13 \pm 5.24\%$), whereas the apical circumferential strain ($-24.13 \pm 5.61\%$) was greater than the basal circumferential strain ($-18.17 \pm 4.68\%$). The values obtained for the basal systolic radial strain ($47.13 \pm 5.24\%$) and longitudinal strain ($-26.46 \pm 5.15\%$) for the capuchin monkey were within normal ranges for males and females.[33]

Similar to humans, capuchin monkeys present positive radial strain on systole, whereas the longitudinal and circumferential strains have negative values.[34] Thus, in capuchin monkeys, positive radial strain during systole also reflects a myocardial thickening, the final length of which is larger than the initial one, whereas the negative longitudinal and circumferential strains show an inverse situation.[33]

The twist in capuchin monkeys was qualitatively similar those of humans.[35] Although the torsion angle allows comparative studies between different species, these values appear to differ in relation to the size and mass of the myocardium. A similar situation was observed for the cardiac twist between humans and mice, in which despite the discrepant size between hearts, the torsion was quantitatively comparable between the two species.[36]

The bull's eyes generated from the analyses performed presented a homogeneous pattern, with no evidence of contractility deficits in the 18 segments generated. Despite the sedation performed, the rate of cardiac deformation did not differ from data obtained for other animal models and in the human species.[11,33,34]

There are few studies on the indices of myocardial deformation in animals, and none specifically for a group of non-human primates. Despite the relatively small number of capuchin monkeys, this study suggests that the measurement of myocardial strain and strain rate indices constitutes a technique that can be used to improve the clinical management conditions of these animals and is a potential tool for pre-clinical trials.

Conclusion

The present study demonstrated the first reference values for echocardiographic measurements in B, M and Doppler mode for capuchin monkeys anesthetized with ketamine and midazolam. The strain and strain rate values obtained using speckle tracking showed similarities with the human species, suggesting that this tool can be potentially exploited in preclinical studies using the capuchin monkey animal model.

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Authors' contributions

Conception and study design: Alves FR, Pessoa GT, Moura LS, Rodrigues RPS; Data acquisition: Rodrigues RPS, da Silva ABS, Sousa FCA; Data analysis and interpretation: Alves FR, Bezerra-Neto L; Statistical analysis: Alves JJRP, Macedo KM; Manuscript writing: Alves FR, Rodrigues RPS, da Silva ABS. Critical review: Alves FR, Bezerra-Neto L, Vieira MC.

Potential Conflict of Interest

We declare there is no relevant conflict of interest.

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Academic linkage

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