Echocardiographic parameters of clinically normal adult captive chimpanzees (Pan troglodytes)

Meg M. Sleeper, VMD; Ken Drobatz, DVM, MSCE; D. Richard Lee, DVM; Michael L. Lammey, DVM

Objective—To generate reference ranges for echocardiographic variables in clinically normal adult chimpanzees (Pan troglodytes).

Design—Retrospective cohort study.

Animals—88 clinically normal adult chimpanzees.

Procedures—Echocardiographic data obtained between 2002 and 2011 from chimpanzees at the Alamogordo Primate Facility were reviewed (263 echocardiograms obtained from 158 individuals). Data from clinically normal individuals (33 females and 55 males) were analyzed. Basic cardiac parameters measured in all individuals included aortic root diameter and left atrial diameter in the short and long axis during diastole. Left ventricular measurements included left ventricular internal diameter in systole and diastole and diastolic septal and posterior wall thickness. The E point to septal separation was also measured. Spectral Doppler measurements included the peak flow velocity of the pulmonary artery and aorta and diastolic transmural flow. The presence of arrhythmias was also noted.

Results—Standard echocardiographic findings for a large group of adult female and male chimpanzees were obtained. Female and male chimpanzees were grouped by age in 10-year blocks, and echocardiographic findings were analyzed statistically by 10-year block. In male chimpanzees, cardiac arrhythmias were noted to increase with age.

Conclusions and Clinical Relevance—Cardiovascular disease is an important cause of morbidity and death in captive chimpanzees; however, basic echocardiographic measurements from a large cohort of clinically normal animals have not previously been reported. The number of animals in the present study was insufficient to generate reference ranges; however, data from a large cohort of clinically normal animals are presented. This information will be useful for veterinarians working in clinical and research settings with this species. (J Am Vet Med Assoc 2014;244:956–960)

Cardiovascular disease is an important cause of morbidity and death in captive chimpanzees (Pan troglodytes). A survey of the chimpanzee colony at Alamogordo Primate Facility from 1990 to 2000 cited in a case report lists cardiovascular disease as the cause of death in most animals. Reported cardiovascular diagnoses in chimpanzees include congenital as well as acquired diseases, including myocardial fibrosis, dilated cardiomyopathy with congestive heart failure, pulmonary hypertension, sudden cardiac death, and various cardiac arrhythmias. Little is known regarding the specific etiologies and progression of cardiovascular disease in chimpanzees. As in other species, it is likely as varied as the forms of disease they develop. However, myocardial fibrosis appears to be a common cause of death in the male chimpanzee population. Various biomarkers have been evaluated to screen subclinically affected animals. Even though a blood-based screening test could be exceedingly helpful in identifying animals at risk, echocardiography remains the gold standard for identifying cardiac structural changes. Understanding normal and abnormal echocardiographic findings is essential for early detection and treatment of cardiac disease in this species.

Echocardiography is the most commonly used noninvasive diagnostic tool in veterinary and human cardiology, allowing assessment of chamber size, valvular anatomy, and myocardial function. However, echocardiography has not been performed routinely in chimpanzees, and there is only 1 report of echocardiographic data obtained from 20 clinically normal adult chimpanzees. Results of cardiac measurements were proportionally similar to those for human beings and those from assessment of 5 adult male gorillas. Trivial valvular regurgitation was apparent in some (n = 3) of the chimpanzees deemed clinically normal in the prior report; however, none of them had auscultable murmurs on physical examination. A study including a larger number of clinically normal individuals would be beneficial. Unfortunately, the most common form of cardiac disease in chimpanzees, myocardial fibro-
sis, can occur without obvious echocardiographic changes. The purpose of the study reported here was to generate normal echocardiographic reference ranges for adult chimpanzees.

Materials and Methods

Echocardiographic evaluations were performed in a colony of chimpanzees between 2002 and 2011. Each animal received a complete physical examination while under general anesthesia, as recommended by veterinary specialists for total chimpanzee health evaluation. Depending on age and health status, of tiletamine hydrochloride combined with zolazepam (2.0 to 3.0 mg/kg [0.9 to 1.4 mg/lb]) was administered IM. Most animals received a dose of 2.5 mg/kg (1.1 mg/lb). Animals had been trained to present a limb for injection. Blood pressure measurements, ECG, O₂ saturation, and core body temperature were recorded. Chimpanzees with clinical signs or physical examination findings consistent with underlying heart disease underwent evaluation (physical signs or physical examination findings consistent with this species). Echocardiography was performed with the goal of generating reference ranges for adult chimpanzees.

Animals were identified as clinically normal if the veterinary cardiologist performing the echocardiogram found no evidence of structural cardiac abnormalities on echocardiography. However, because myocardial fibrosis may be present in the face of a normal echocardiogram, only animals that survived at least 2.5 years past the time of the echocardiogram without clinical signs referable to cardiovascular disease were included. A 5-minute ECG was available from each animal during the examination period. Animals with sinus rhythms (normal sinus rhythm, sinus arrhythmia, sinus bradycardia, or sinus tachycardia), occasional supraventricular premature complexes, or occasional ventricular complexes were included in the data set if the requirements were met. Data from clinically normal chimpanzees were divided by age in 10-year blocks at the time of the echocardiogram. If > 1 echocardiogram was obtained from an animal (n = 5), only data from the earliest available echocardiogram were used for statistical analysis. Echocardiographic data from 12 animals have been previously reported and were included in this data set.

Currently and throughout the study, all chimpanzees at the Alamogordo Primate Facility ( Holloman Air Base, Alamogordo, NM) were fed a commercial primate diet. All caging and open-area spaces exceeded USDA guidelines for nonhuman primates. No more than 6 animals were maintained in each indoor den. Chimpanzees had 24-hour access to a large outdoor area as well as weekly access to an expanded play area equal to approximately 4 times their regular enclosures. Same-sex housing was maintained to ensure adherence to the National Institutes of Health policy that no government-owned chimpanzees are to breed for research purposes. Chimpanzees at the Alamogordo Primate Facility are maintained in accordance with National Institutes of Health guidelines.

Statistical analysis—Descriptive statistics including mean ± SD and median (range) were calculated for all echocardiographic data. Five animals were evaluated in two 10-year age blocks because each animal underwent serial evaluations. Data for each 10-year block of age were compared, and no difference was found between age ranges for males or females. Therefore, data
were combined into an adult male data set and an adult female data set. For the 5 animals with > 1 echocardiogram, only data from the earliest evaluation were included in this combined data set. Because of the small number of animals in the oldest 10-year block, there were not enough data to test the normal distribution assumption, and the Kruskal-Wallis test was used to compare these variables between age groups. For values of \( P < 0.05 \) for this test, the Wilcoxon rank sum test for pairwise comparisons and the Bonferroni correction for multiple testing \( P \) values were used to determine which 10-year blocks were significantly different. Frequency of arrhythmias was described by proportions and percentages, and the Fisher exact test was used to compare the frequencies between the various age groups. For all comparisons, a value of \( P < 0.05 \) was considered significant. Echocardiographic data from males with arrhythmias and males without arrhythmias were compared by use of a \( t \) test except for those values that were not normally distributed, in which case the Mann-Whitney test was used. Similarly, echocardiographic data from females with arrhythmias and females without arrhythmias were compared, but because there were few female chimpanzees with arrhythmias, the assumption for normality could not be met. A statistical software program was used for all calculations.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD</th>
<th>Median (range)</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diastolic interventricular septal diameter (cm)</td>
<td>1.1 ± 0.2</td>
<td>1.1 (0.7–1.5)</td>
<td>1.0–1.2</td>
</tr>
<tr>
<td>Left ventricular diameter (cm)</td>
<td>4.1 ± 0.5</td>
<td>4.2 (3.4–5.3)</td>
<td>4.0–4.3</td>
</tr>
<tr>
<td>Systole</td>
<td>2.5 ± 0.4</td>
<td>2.6 (1.7–3.3)</td>
<td>2.5–2.6</td>
</tr>
<tr>
<td>Left ventricular posterior wall thickness during diastole (cm)</td>
<td>1.1 ± 0.2</td>
<td>1.1 (0.8–1.8)</td>
<td>1.1–1.2</td>
</tr>
<tr>
<td>Fractional shortening (%)</td>
<td>41 ± 7.1</td>
<td>42 (30–55)</td>
<td>38–44</td>
</tr>
<tr>
<td>Aortic root diameter (cm)</td>
<td>2.4 ± 0.3</td>
<td>2.3 (2.0–3.0)</td>
<td>2.3–2.5</td>
</tr>
<tr>
<td>Left atrial diameter (cm)</td>
<td>3.2 ± 0.5</td>
<td>3.1 (2.4–4.5)</td>
<td>3.0–3.3</td>
</tr>
<tr>
<td>Short axis</td>
<td>3.4 ± 0.5</td>
<td>3.3 (2.4–4.2)</td>
<td>3.2–3.5</td>
</tr>
<tr>
<td>Long axis</td>
<td>0.2 ± 0.2</td>
<td>0.1 (0–0.6)</td>
<td>0.1–0.2</td>
</tr>
<tr>
<td>Peak flow velocity (m/s)</td>
<td>1.1 ± 0.2</td>
<td>1.1 (0.6–1.7)</td>
<td>1.0–1.2</td>
</tr>
<tr>
<td>Pulmonary artery</td>
<td>1.3 ± 0.4</td>
<td>1.4 (0.6–2.3)</td>
<td>1.2–1.5</td>
</tr>
<tr>
<td>Aortic valve</td>
<td>0.8 ± 0.1</td>
<td>0.78 (0.55–1.10)</td>
<td>0.69–0.88</td>
</tr>
<tr>
<td>Transmural flow (m/s)</td>
<td>0.43 ± 0.1</td>
<td>0.72 (0.42–0.48)</td>
<td>0.55–0.9</td>
</tr>
</tbody>
</table>

Chimpanzees were housed at the Alamogordo Primate Facility, Holloman Air Base, Alamogordo, NM, which is maintained according to National Institute of Health Guidelines, and underwent echocardiography under general anesthesia with a 2.5-MHz transducer and an ECG for cardiac cycle timing, with all examinations performed by the same board-certified veterinary cardiologist (MMS).

Table 1—Echocardiographic measurements obtained from 33 clinically normal adult female chimpanzees (\( Pan troglodytes \)) between 2002 and 2011, with a mean ± SD age of 27 ± 9 years (median, 26 years; range, 12 to 46 years) and mean ± SD body weight of 59 ± 14 kg (129.8 ± 30.8 lb; median, 68 kg [127.6 lb]; range, 32 to 97 kg [70.4 to 213.4 lb]).

Table 2—Echocardiographic measurements obtained from 55 clinically normal adult male chimpanzees between 2002 and 2011 with a mean ± SD age of 27 ± 7.7 years (median, 26 years; range, 15 to 47 years) and mean ± SD body weight of 62 ± 7.9 kg (136.4 ± 17.38 lb; median, 61 kg [134.2 lb]; range, 49 to 86 kg [107.3 to 189.2 lb]).
Results

Echocardiographic data obtained between 2002 and 2011 from chimpanzees at the Alamogordo Primate Facility were reviewed (263 echocardiograms obtained from 158 individuals). Eighty-eight animals were identified as clinically normal (33 females and 55 males for statistical evaluation) on the basis of the criteria described. Female and male chimpanzees were grouped by age in 10-year blocks, and echocardiographic findings were analyzed statistically by 10-year block. If an animal underwent multiple echocardiograms within a 10-year block, only data from the first evaluation were included. Only 1 echocardiogram was performed in a chimpanzee during the first 10 years of age. Data from this individual (a female) were not included in statistical analysis (data not shown). Eight 10- to 19-year-old females, fifteen 20- to 29-year-old females, ten 30- to 39-year-old females, and four 40- to 49-year-old females were evaluated. Six 10- to 19-year-old males, thirty-five 20- to 29-year-old males, eleven 30- to 39-year-old males, and four 40- to 49-year-old males were evaluated. Four females and 1 male were evaluated > 1 time (ie, their data were included in more than one 10-year block).

No significant difference was noted in echocardiographic findings among groups of female chimpanzees nor among groups of male chimpanzees 10 to 49 years of age. Therefore adult (ie, > 10 years of age) female data were combined and adult male data were combined (Tables 1 and 2). In those 5 animals with 2 available echocardiograms, the earliest imaging data were included (ie, the individual’s data were only included once) for the pooled data. The female group ranged from 12 to 45 years of age (median, 26 years), and the male group ranged from 15 to 47 years of age (median, 26 years).

Arrhythmias were noted in 12 of the female chimpanzees (4 with supraventricular premature complexes and 8 with ventricular premature complexes). Arrhythmias were present in 25 males (2 with supraventricular premature complexes, 22 with ventricular premature complexes, and 1 with both). There was no difference between female age groups regarding the presence of arrhythmias. In contrast, males were more likely to have arrhythmias as they aged until they became geriatric. For example, none of the 10- to 19-year-old males had arrhythmias, whereas 29% (10/34) of the 20- to 29-year-old males did (P = 0.02). In contrast, 73% (8/11) of 30- to 39-year-old males (P < 0.001) and 75% (3/4) of the 40- to 49-year-old males (P = 0.001) had ectopy.

There was no significant difference in any of the echocardiographic parameters between male chimpanzees with and without arrhythmias. When the echocardiographic parameters of the females with and without arrhythmias were compared, the females with arrhythmias had a larger left atrial diameter in the short axis (P = 0.016) than females without arrhythmias, but there was no difference in any other parameter.

Discussion

There has been an increase in the morbidity and mortality rates associated with cardiovascular disease in the past 20 years in the captive chimpanzee population, and it has been documented that cardiovascular disease is the major cause of death. Early recognition and accurate diagnosis are critical for successful treatment, and normal echocardiographic parameters must be elucidated for this species to facilitate this process. To generate robust reference ranges for chimpanzees, a larger data set will be required than was available in the present study. However, our findings represent the largest normal echocardiographic data set currently available. These data will benefit clinicians and researchers working with chimpanzees until further studies are available.

Although several types of heart disease have been reported in chimpanzees, the most common form appears to be associated with fibrosis of the myocardium, particularly in adult males. We suggest that the increase in recognized, acquired heart disease that has been reported is due to the aging chimpanzee populations in research and zoo facilities. Depending on the stage of disease when affected individuals are evaluated, there is a spectrum of echocardiographic findings associated with disease progression, ranging from normal ventricular wall thickness to left ventricular hypertrophy to dilated cardiomyopathy in those animals that do not die of arrhythmias. In our clinical experience, some of the individuals included in the present study may have been falsely considered clinically normal. To minimize this error, we included only animals that remained free of clinical signs for at least 2.5 years following the echocardiographic examination.

In the present study, the risk of developing ectopy increased with age in the male chimpanzees. This finding is consistent with a previous report, which found that ventricular ectopy was common in adult male chimpanzees and, similar to humans, the presence of ventricular ectopy increases the risk of sudden cardiac death in chimpanzees. Moreover, sudden cardiac death (presumably due to fatal arrhythmias) is often the cause of death in chimpanzees with myocardial fibrosis. The presence of ectopy in some of the animals included in this study suggests they may have had early myocardial disease at the time of echocardiography. Alternatively, there may be another underlying risk factor for arrhythmia development in this population of chimpanzees that has yet to be recognized. We believe this latter possibility is the more likely scenario, considering that all the included chimpanzees survived at least 2.5 years past their examination without developing other signs of cardiovascular disease. However, the presence of arrhythmias was concerning because their presence has been recognized in animals with myocardial fibrosis. It is possible they reflect early disease. We attempted to account for this possibility by comparing animals both with and without arrhythmias. There was no echocardiographic difference in the 2 groups of male chimpanzees (arrhythmia vs no arrhythmia). One parameter (left atrial diameter in the short axis) was different between the 2 groups of females, but the other left atrial diameter measurement was not different. Moreover, the number of female individuals was small, compared with the male data set. Future studies should be directed at definitively answering this question.

The effect of anesthesia could be a confounding factor; however, general anesthesia is necessary to per-
form a complete echocardiographic examination safely in this species. Moreover, given that all individuals received the same anesthetic protocol, any anesthetic effect on echocardiographic findings should have been consistent across the population. Furthermore, the protocol used to anesthetize these chimpanzees for examination is a standardized protocol used at many facilities. Unfortunately, too few juvenile chimpanzees were examined (n = 1) to present meaningful data for chimpanzees < 10 years of age.

References

17. Part 3—standards. Subpart D—specifications for the humane handling, care, treatment, and transportation of nonhuman primates. 9 CFR 1A.