Cardiac structure and function characterized across age groups and between sexes in healthy wild-born captive chimpanzees (Pan troglodytes) living in sanctuaries

Aimee L. Drane BS.
Rebecca Atencia PhD
Stephen-Mark Cooper PhD
Pablo Rodriguez DVM
Carlos Sanchez DVM, MSc
Sarah Simcox BSc
Yedra Feltre DVM
Bruce Peck DVM
Jaclyn Eng DVM
Sophie Moittie DVM
Steve Unwin DVM
Glyn Howatson PhD
David Oxborough PhD
Mike R. Stembridge PhD
Rob E. Shave PhD

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From the School of Sport and Health Sciences, International Primate Heart Project, Cardiff Metropolitan University, Cardiff, CF3 2YP, England (Drane, Cooper, Simcox, Feltre, Stembridge, Shave); Tchimpounga Chimpanzee Sanctuary, Jane Goodall Institute, Pointe Noire, Republic of Congo (Atencia); Buin Zoo, Panamericana Sur Km 32, Buin, Chile (Rodriguez); Fort Worth Zoo, 1989 Colonial Pkwy, Fort Worth, TX 76110 (Sanchez); Chimfunshi Wildlife Orphanage, Solwezi Rd, Chingola 50100, Zambia (Peck); International Animal Rescue, Ketapang, West Kalimantan, Indonesia (Eng); Tacugama Chimpanzee Sanctuary, Congo Dam Access Rd, Freetown, Sierra Leone (Moittie); Chester Zoo, Caughall Rd, Chester CH2 4BW, England (Unwin); the Faculty of Health and Life Sciences, Northumbria University, Newcastle-upon-Tyne NE1 8st, England (Howatson); and the Faculty of Science, Liverpool John Moores University, Liverpool, L3 5UA, England (Oxborough).

Address correspondence to Ms. Drane (adrane@cardiffmet.ac.uk).

OBJECTIVE
To comprehensively characterize cardiac structure and function, from infancy to adulthood, in male and female wild-born captive chimpanzees (Pan troglodytes) living in sanctuaries.

ANIMALS
290 wild-born captive chimpanzees.

PROCEDURES
Physical and echocardiographic examinations were performed on anesthetized chimpanzees in 3 sanctuaries in Africa between October 2013 and May 2017. Results were evaluated across age groups and between sexes, and potential differences were assessed with multiple 1-way independent Kruskal-Wallis tests.

RESULTS
Results indicated that left ventricular diastolic and systolic function declined at a younger age in males than in females. Although differences in right ventricular diastolic function were not identified among age groups, right ventricular systolic function was lower in adult chimpanzees (> 12 years old), compared with subadult (8 to 12 years old) and juvenile (5 to 7 years old) chimpanzees. In addition, male subadult and adult chimpanzees had larger cardiac wall dimensions and chamber volumes than did their female counterparts.

CONCLUSIONS AND CLINICAL RELEVANCE
Results of the present study provided useful reference intervals for cardiac structure and function in captive chimpanzees categorized on the basis of age and sex; however, further research is warranted to examine isolated and combined impacts of blood pressure, age, body weight, and anesthetic agents on cardiac structure and function in chimpanzees. (Am J Vet Res 2019;80:547–557)

Suddenly cardiac death and heart failure have been reported as the leading causes of death in captive chimpanzees (Pan troglodytes).1–3 Despite evolutionary similarities between humans and chimpanzees, there appear to be fundamental pathophysiologic differences between the species in regard to cardiac disease.4 Diffuse interstitial myocardial fibrosis has been proposed as the underlying cause of heart failure and sudden cardiac death in chimpanzees,2 whereas the

ABBREVIATIONS
A Peak inflow velocity during late diastole with atrial contraction and filling of ventricle (transmitral for the left side of the heart and transtricuspid for the right side of the heart)
A’ Tissue Doppler–derived peak late diastolic velocity (of septal and lateral wall myocardial tissue at the level of the mitral annulus for the left side of the heart and of right ventricular free wall for the right side of the heart)
E Peak inflow velocity during early diastole with passive filling of ventricle (transmitral for the left side of the heart and transtricuspid for the right side of the heart)
E’ Tissue Doppler–derived peak early diastolic velocity (of septal and lateral wall myocardial tissue at the level of the mitral annulus for the left side of the heart and of right ventricular free wall for the right side of the heart)
EF Ejection fraction
LA Left atrial
LV Left ventricular
PASA Pan African Sanctuary Alliance
RA Right atrial
RV Right ventricular
RWT Relative wall thickness
TDI Tissue Doppler imaging
TZ Tiletamine hydrochloride–zolazepam hydrochloride

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most common cause of cardiac death in adult humans is acute myocardial infarction and heart failure caused by coronary atherosclerosis. This notable difference, combined with the postural and metabolic differences between chimpanzees and humans, suggests that the 2 species also likely have fundamentally different cardiac phenotypes, highlighting the need for species-specific descriptions of cardiac parameters in chimpanzees. Although ECG reference intervals exist for wild-born chimpanzees, only 1 study attempted to provide normative data related to cardiac structure and function. However, the investigators presented data from a relatively small number of animals housed in a research facility, and the findings have limited application to wild-, sanctuary-, or zoo-based populations of chimpanzees and limited potential for evaluation of differences within the species on the basis of age and sex. Furthermore, published data concentrate on limited numbers of structural and functional cardiac parameters (eg, LV wall thickness and chamber size), providing limited understanding of normal cardiac structure and function in chimpanzees and not fully equipping veterinarians with reference data needed when caring for these animals. For example, although myocardial fibrosis has been suggested as a primary cause of death in captive chimpanzees, there may be various underlying causes with different pathological processes that affect cardiac structure and function differently. Therefore, to better understand cardiac health and disease progression in chimpanzees, it is essential that the healthy cardiac phenotype be thoroughly defined in both sexes and across the lifespan of chimpanzees. Thus, the primary aim of the study presented here was to comprehensively characterize cardiac structure and function, from infancy to adulthood, in male and female wild-born captive chimpanzees living in sanctuaries.

Materials and Methods

Animals
Eligible animals were wild-born captive chimpanzees housed at 3 sanctuaries for chimpanzees in Africa (the Tchimpounga Chimpanzee Rehabilitation Centre, Congo; Chimfunshi Wildlife Orphanage, Zambia; and Tacugama Chimpanzee Sanctuary, Sierra Leone). The sanctuaries were members of the PASA, and all chimpanzees were cared for in accordance with recommendations in the PASA operations manual. Chimpanzees in semifree-ranging enclosures had access to native vegetation during the day and had the option to access indoor cages at night. Chimpanzees were housed in mixed-sex groups, underwent annual health examinations, and were managed under contraceptive protocols recommended by PASA. Supplementary food was sourced locally and provided at routine times during the day, and water was available ad libitum.

All chimpanzees with no overt cardiac disease evident on physical and echocardiographic examinations were defined as cardiac healthy and included in the study. Chimpanzees were excluded if they had evidence of overt cardiac disease or had poor-quality echocardiographic images obtained during their examination. To evaluate differences in cardiac structure and function on the basis of age, chimpanzees were assigned to 4 age groups: infants (≤ 4 years old), juveniles (5 to 7 years old), subadults (8 to 12 years old), or adults (> 12 years old). Because definitive age categories in chimpanzees had not been established in the literature, age groups in the study were established on the basis of clinical experience of veterinarians on the research team. Protocols for the study were approved by the Pan African Sanctuary Advisory Council, were reviewed by the institutional ethics committee at Cardiff Metropolitan University, and adhered to all legal requirements of the involved countries.

Physical and echocardiographic examination protocols
As part of the International Primate Heart Project, wild-born captive chimpanzees at the involved sanctuaries were anesthetized and underwent physical examinations (including cardiac and pulmonary auscultation) and echocardiography conducted by experienced sanctuary clinicians between October 2013 and May 2017.

Anesthesia—Before physical examinations, food, but not water, was withheld from the chimpanzees overnight. Chimpanzees were anesthetized with 1 of 4 protocols: medetomidine (0.03 to 0.05 mg/kg) and ketamine hydrochloride (3 to 5 mg/kg) administered IM by handheld syringe injection, TZ (10 mg/kg) delivered IM by remote dart injection, TZ (2 mg/kg) and medetomidine (0.03 mg/kg) delivered IM by remote dart injection, or TZ (2 mg/kg) and ketamine (5 mg/kg) delivered IM by remote dart injection. The anesthetic protocol for each examination was determined by the lead veterinarian at the given sanctuary. During the physical examination and recovery, the anesthetic depth, respiratory rate, heart rate, and oxygen saturation of chimpanzees were monitored by a designated veterinarian or veterinary technician. After examination, chimpanzees were recovered from anesthesia, and those that earlier received medetomidine were administered atipamezole (0.25 mg/kg, IV) to reverse anesthesia.

Examinations—Once a chimpanzee was anesthetized, it was either examined in its night cage or transported to a field-based assessment center for examination. Body weight and crown-to-rump length were obtained. Crown-to-rump length was measured from the pole of the head to the base of the rump at the ischial symphysis with the chimpanzee in lateral recumbency. Throughout the anesthetic procedure, indirect blood pressure measurements were obtained manually every 3 to 5 minutes as previously described. To account for the typical initial elevation in blood pressure with anesthesia, the blood pressure for each individual chimpanzee was reported as the mean of 3 to 5 measurements obtained over a 10- to 20-minute period, starting 20
minutes after anesthetic induction, then mean blood pressure for each animal was used when calculating median blood pressure for each group. During this same 10- to 20-minute period, a 12-lead ECG was obtained with the chimpanzee in a supine position as previously described. Afterward, the chimpanzee was placed in left lateral recumbency for the approximately 10 minutes needed to perform transthoracic echocardiography.

All transthoracic echocardiographic examinations were performed by 1 of 2 experienced echocardiographers (ALD or SS) with a commercially available cardiac ultrasound machine and an appropriate transducer for the respective age group (infant and juvenile groups vs subadult and adult groups). Echocardiographic examinations followed a strict protocol developed on the basis of guidelines from the British Society of Echocardiography and American Society of Echocardiography, along with recent practical guidance for echocardiography in great apes. Echocardiographic images were acquired from the parasternal, apical, and subcostal windows in accordance with previously suggested guidelines, and all images recorded were analyzed with dedicated software by 1 experienced cardiac physiologist (ALD) who followed measurement guidelines outlined in human protocols. Each parameter was measured over 3 nonconsecutive cardiac cycles to minimize effects of heart rate and measurement variability.

Measurements of the structure and geometry of the left side of the heart (left heart) included wall thicknesses, internal chamber dimensions, and RWT at the basal level (at the level of the mitral valve tip) and midlevel (at the level of the midarea of the papillary muscle; Figure 1). The LV RWT was calculated as follows:

$$\text{LV RWT} = \frac{2 \times (\text{LV posterior wall thickness})}{\text{LV internal diastolic dimension}}$$

The LV eccentricity index and sphericity index were calculated, and the Simpson biplane and area-length techniques were used to calculate the LV and LA volumes, respectively. Left ventricular diastolic function was assessed with pulsed-wave Doppler ultrasonography measurement of transmitral A and E and with TDI of the mitral annular level A’ and E’ of the septal and LV lateral wall. Mean transmitral A’ and E’ for each individual animal were scaled to LV length as previously described. Left ventricular systolic function was determined by Simpson biplane EF, cardiac output, stroke volume, and TDI of systolic myocardial velocity.

Measurements of the structure and geometry of the right side of the heart (right heart) included RV wall thickness, RV and RA areas, and internal dimensions as previously outlined. Right ventricular diastolic function was assessed with pulsed-wave Doppler ultrasonography of transtricuspid A and E and by TDI of A’ and E’ of the RV free wall. Right ventricular systolic function was assessed with RV fractional area change and tricuspid annular plane systolic excursion.

Continuous wave Doppler ultrasonography was used to measure the peak velocities of blood crossing the aortic and pulmonary valves, whereas pulsed-wave Doppler ultrasonography was used to measure the velocity time integral of the LV outflow tract, A, and E. Each valve was evaluated for regurgitation with color flow Doppler ultrasonography. The aortic and mitral valves were assessed in the parasternal long-axis view and in the apical 4- and 5-chamber views, whereas the tricuspid and pulmonary valves were assessed in the parasternal short-axis, inflow, and outflow views. The tricuspid valve was also assessed in the modified apical 4-chamber view. Each valve was classified as having no, trivial, mild, or moderate regurgitation as previously described (Figure 2).

Statistical analysis

All measurements obtained for cardiac parameters were exported to commercially available software for statistical analysis. Data were tested for nor-
mality with the Kolmogorov-Smirnov test. Data that were normally distributed were reported as mean ± SD, whereas data that were not normally distributed were reported as median and the 2.5th and 97.5th percentiles. In addition, 1-way ANOVA was performed to evaluate potential relationships between cardiac parameters and body weight or crown-to-rump length. Multiple 1-way independent Kruskal-Wallis tests were used to evaluate differences between groups, and where differences were found, post hoc Mann-Whitney U tests were performed. Further, Spearman correlation analysis between systolic blood pressure and RWT was performed to evaluate potential relationships between blood pressure and LV structure. The RWT was chosen as an overall measure of LV structure because age would not confound this parameter. Values of $P < 0.05$ were considered significant.

**Results**

**Animals**

A total of 295 wild-born captive chimpanzees living in sanctuaries were evaluated and considered healthy on the basis of results from routine physical examination. On the basis of results from echocardiographic examinations, 290 of these chimpanzees were classified as cardiac healthy and included in the study. The remaining 5 chimpanzees were excluded because of poor-quality echocardiographic images (n = 3), gross LV hypertrophy (1), or markedly thinned and akinetic ventricular segments (1). All chimpanzees were wild born, orphaned, and captive and were living in semifree-ranging enclosures (n = 286) or large enclosed cages (4 adult males). Of the 290 chimpanzees, 149 (51.4%) were males (mean ± SD age, 14 ± 8 years; mean ± SD body weight, 42 ± 16 kg) and 141 (48.6%) were females (mean ± SD age, 14 ± 8 years; mean ± SD body weight, 38 ± 12 kg). The 290 chimpanzees were grouped according to age: infants (n = 17 [5.9%]), juveniles (39 [13.4%]), subadults (54 [18.6%]), and adults (180 [62.1%]).

Table 1—Morphometric data for 290 (male, 149; female, 141) wild-born chimpanzees (Pan troglodytes) examined in 3 PASA-member sanctuaries between October 2013 and May 2017 and stratified by sex and age group (infants [≤ 4 years old], juveniles [5 to 7 years old], subadults [8 to 12 years old], and adults [> 12 years old]).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Infants (n = 13)</th>
<th>Juveniles (n = 22)</th>
<th>Subadults (n = 25)</th>
<th>Adults (n = 89)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>3 ± 1</td>
<td>6 ± 1</td>
<td>10 ± 1</td>
<td>19 ± 6</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>12 ± 8</td>
<td>23 ± 5</td>
<td>35 ± 5</td>
<td>52 ± 8*</td>
</tr>
<tr>
<td>Crown-to-rump length (cm)</td>
<td>44 ± 10</td>
<td>52 ± 7</td>
<td>63 ± 8</td>
<td>70 ± 6†</td>
</tr>
</tbody>
</table>

Values reported are mean ± SD. $*P < 0.001$ for differences in results between adult male and adult female chimpanzees. †$n = 90$. ‡$P = 0.002$ for differences in results between adult male and adult female chimpanzees.
were significantly ($P < 0.001$ and $P = 0.002$, respectively) greater than those for adult females ($43 \pm 8$ kg and $67 \pm 8$ cm, respectively); however, body weight and crown-to-rump length were not meaningfully different between males and females in younger age groups.

**Anesthesia**

For the 290 chimpanzees, anesthetic protocols used included medetomidine (0.03 to 0.05 mg/kg) and ketamine (3 to 5 mg/kg) administered IM by handheld syringe injection ($n = 174$ [60.0%]; 89 males and 85 females), TZ (10 mg/kg) delivered IM by remote dart injection (30 [10.3%]; 15 males and 15 females), TZ (2 mg/kg) and medetomidine (0.03 mg/kg) delivered IM by remote dart injection (59 [20.3%]; 34 males and 25 females), or TZ (2 mg/kg) and ketamine (5 mg/kg) delivered IM by remote dart injection (27 [9.3%]; 11 males and 16 females). After physical and echocardiographic examinations, chimpanzees that had received medetomidine were administered atipamezole (0.25 mg/kg, IV) to reverse anesthesia. Multiple 1-way ANCOVAs were performed with anesthetic protocol as the covariate, and no significant relationships were identified between the anesthetic protocols and cardiac measurements.

**Blood pressure**

Median indirect systolic blood pressure for adult male chimpanzees (129 mm Hg) was significantly ($P = 0.06$ and $P = 0.014$, respectively) higher than that for juvenile males (111 mm Hg) and subadult males (120 mm Hg; Figure 3). However, there were no meaningful differences identified in systolic blood pressure on the basis of age for female chimpanzees. To facilitate comparison of systolic blood pressure results for adult chimpanzees in the present study with results from a previous study, the age benchmark of adult chimpanzees was modified only for this comparison to include all chimpanzees > 10 years old, and these animals, regardless of sex, were grouped by those weighing < 51.5 kg vs those weighing > 51.5 kg, for which the median systolic blood pressure was 120 mm Hg (range, 77 to 184 mm Hg; $n = 146$) vs 129 mm Hg (range, 91 to 178 mm Hg; 61), respectively. In addition, systolic blood pressure in male chimpanzees correlated positively and significantly ($p = 0.257$; $P = 0.002$) with RWT, whereas there was no meaningful relationship between systolic blood pressure and RWT in female chimpanzees. Further, diastolic blood pressure did not differ significantly between age groups or sexes.

![Figure 3](image-url)

**Echocardiography**

All echocardiography was performed by 1 of 2 experienced echocardiographers (ALD, $n = 270$; or SS, 20). Valvular regurgitation was noted in 229 of the 290 (78.9%) chimpanzees, but only 12 (5 males [mean ± SD age, 14 ± 6 years] and 7 females [mean ± SD age, 30 ± 5 years]) had moderate valvular regurgitation (Table 2). Of these 12 chimpanzees, 3 females and 1 male had > 1 valve affected.

**Left heart structures and volumes**—In line with age and body weight, left heart structure and volume increased with age in both sexes of chimpanzees in that the median basal and midlevel wall thicknesses, internal chamber dimensions, and end-diastolic and end-systolic volumes were each significantly ($P < 0.001$) greater for subadults, compared with juveniles, and for adults, compared with subadults (Table 3; Supplementary Tables S1–S3, available at avmajournals.avma.org/doi/suppl/10.2460/ajvr.80.6.547). Importantly, however, the RWT and the eccentricity and sphericity indices remained constant between
age groups, indicating a proportional increase in cardiac geometry with advancing age and a lack of age-related concentric remodeling. When results for age groups were further stratified by sex, the median basal and midlevel wall thicknesses, internal chamber dimensions, and end-diastolic and end-systolic volumes (but not the RVET or the eccentricity and sphericity indices) were significantly greater for subadult males versus subadult females ($P < 0.02$) and for adult males versus adult females ($P < 0.001$). No differences in those parameters were identified between sexes of chimpanzees in the juvenile age group.

**Left heart diastolic function**—Diastolic function of the left heart appeared to decline progressively across age groups in male chimpanzees as evidenced by a lower median transmitral E for adults (0.7 m/s) versus subadults (0.9 m/s; $P = 0.018$) and for subadults versus juveniles (1.0 m/s; $P = 0.04$); longer deceleration time for adults (124 milliseconds) versus subadults (112 milliseconds; $P = 0.008$) and for subadults versus juveniles (94 milliseconds; $P = 0.001$); longer septal isovolumic relaxation time for adults (108 milliseconds) versus subadults (93 milliseconds; $P = 0.004$); lower median scaled E’ for adults (0.017) versus subadults (0.020; $P < 0.001$), adults versus juveniles ($P = 0.047$); and lower median scaled A’ for adults (0.008) versus subadults and juveniles (each, $0.011$; $P < 0.001$; Table 3; Supplementary Table S3). In contrast to males, the only significant differences in results for diastolic function identified on the basis of age for female chimpanzees were lower median transmitral E for adults (0.9 m/s) versus subadults (1.0 m/s; $P = 0.003$) and lower median scaled E’ in adults (0.017) versus juveniles (0.021; $P = 0.046$) and in adults versus subadults (0.021; $P = 0.001$). Similarly, when median transmitral E:A ratio was considered, a decrease was noticed at an earlier age in males (ie, at the subadult age range), compared with that in females (ie, at the adult age range). Owing to this later decline in diastolic function in female chimpanzees, differences in transmitral E, deceleration time, and septal isovolumic relaxation time were apparent only between male and female chimpanzees in the subadult ($P < 0.04$ for all 3 parameters) and adult ($P < 0.002$ for all 3 parameters) age groups. On the basis of age and sex, differences as observed in transmitral A and E were not as substantial for A’ and E’ at the level of the mitral annulus.

**Left heart systolic function**—In male chimpanzees, median LV EF was significantly lower for subadults (56%) versus juveniles (58%; $P = 0.02$) and for adults (52%) versus subadults (56%; $P = 0.004$; Table 3; Supplementary Table S3). In female chimpanzees, however, median LV EF only differed significantly ($P = 0.019$) between subadults (60%) and adults (57%), potentially indicating a delayed decline in systolic function in female chimpanzees. In addition, median EFs were significantly ($P = 0.004$ and $P < 0.001$, respectively) higher for female subadults and adults (60% and 57%, respectively) than for their male counterparts (56% and 52%, respectively). Higher median EFs for subadult and adult female chimpanzees coincided with higher median A’ for adult females (0.07 cm/s) versus adult males (0.06 cm/s; $P = 0.004$), median scaled A’ for adult females (0.010 cm/s) versus adult males (0.008 cm/s; $P = 0.016$), and median E’ for subadult females (0.021 cm/s) versus subadult males (0.017 cm/s; $P = 0.016$).

**Right heart structure and function**—Similar to left heart structure measurements, right heart structure measurements progressively increased with age groups in male and female chimpanzees (Table 4; Supplementary Table S4, available at avmajournals.avma.org/doi/suppl/10.2460/ajvr.80.6.547). Yet in each age group, RV and RA volumes were notably smaller in females, compared with those in males. For instance, median RV diastolic area was significantly smaller for juvenile females (9.0 cm$^2$) versus juvenile males (11.0 cm$^2$; $P = 0.07$) and for adult females (12.8 cm$^2$) versus adult males (16.3 cm$^2$; $P < 0.001$). Similarly, median RV systolic area was significantly smaller for subadult females (5.9 cm$^2$) versus subadult males (7.8 cm$^2$; $P = 0.02$) and for adult females (7.4 cm$^2$) versus adult males (10.1 cm$^2$; $P < 0.001$). Median RV basal diameter was significantly ($P < 0.001$) smaller for adult females (3.0 cm$^2$) versus adult males (3.5 cm$^2$). In addition, median RA diastolic area was significantly smaller for subadult females (4.3 cm$^2$) versus subadult males (5.5 cm$^2$; $P < 0.05$) and for adult females (5.5 cm$^2$) versus adult males (7.3 cm$^2$; $P = 0.001$). In contrast to left heart measurements, RV diastolic function did not meaningfully decline across age groups. Median RV fractional area change, a measure of right heart systolic function, was significantly lower for adult males (38%) versus adult females (42%; $P = 0.02$) and for subadult males (41%) versus subadult females (50%)}


Table 3—Echocardiographic measurements of the left side of the heart (left heart) obtained on anesthetized juvenile, subadult, and adult chimpanzees in Table 1.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Males</th>
<th>Females</th>
<th>Males</th>
<th>Females</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV outflow tract diameter (cm)</td>
<td>1.4 (1.2–1.9)‡</td>
<td>1.4 (1.2–2.0)‡</td>
<td>1.6 (1.3–2.0)‡</td>
<td>1.5 (1.3–2.0)‡</td>
<td>1.6 (1.6–2.0)‡</td>
<td>1.6 (1.6–2.0)‡</td>
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<td>1.4 (1.2–2.0)‡</td>
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<td>1.5 (1.3–2.0)‡</td>
<td>1.6 (1.6–2.0)‡</td>
<td>1.6 (1.6–2.0)‡</td>
</tr>
<tr>
<td>LV systolic diameter (cm)</td>
<td>0.8 (0.6–1.1)‡</td>
<td>0.8 (0.6–1.1)‡</td>
<td>0.9 (0.7–1.2)‡</td>
<td>0.8 (0.6–1.1)‡</td>
<td>1.0 (0.6–1.1)‡</td>
<td>1.0 (0.7–1.2)‡</td>
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<tr>
<td>LV systolic diameter (cm)</td>
<td>0.8 (0.6–1.1)‡</td>
<td>0.8 (0.6–1.1)‡</td>
<td>0.9 (0.7–1.2)‡</td>
<td>0.8 (0.6–1.1)‡</td>
<td>1.0 (0.6–1.1)‡</td>
<td>1.0 (0.7–1.2)‡</td>
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<tr>
<td>Mid-LV systolic diameter (cm)</td>
<td>0.6 (0.4–0.9)§</td>
<td>0.6 (0.4–0.9)§</td>
<td>0.6 (0.5–0.9)§</td>
<td>0.6 (0.4–0.9)§</td>
<td>0.7 (0.5–1.0)§</td>
<td>0.7 (0.5–1.0)§</td>
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<tr>
<td>LV systolic diameter (cm)</td>
<td>1.4 (1.2–1.9)‡</td>
<td>1.4 (1.2–2.0)‡</td>
<td>1.6 (1.3–2.0)‡</td>
<td>1.5 (1.3–2.0)‡</td>
<td>1.6 (1.6–2.0)‡</td>
<td>1.6 (1.6–2.0)‡</td>
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<tr>
<td>LV systolic diameter (cm)</td>
<td>1.4 (1.2–1.9)‡</td>
<td>1.4 (1.2–2.0)‡</td>
<td>1.6 (1.3–2.0)‡</td>
<td>1.5 (1.3–2.0)‡</td>
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<tr>
<td>LA systolic (cm)</td>
<td>1.6 (1.2–1.9)§</td>
<td>1.6 (1.2–1.9)§</td>
<td>1.7 (1.5–2.0)§</td>
<td>1.6 (1.5–2.0)§</td>
<td>1.7 (1.6–2.0)§</td>
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<td>LA systolic (cm)</td>
<td>1.6 (1.2–1.9)§</td>
<td>1.6 (1.2–1.9)§</td>
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<td>1.7 (1.6–2.0)§</td>
<td>1.7 (1.6–2.0)§</td>
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<tr>
<td>LV systolic wall thickness (cm)</td>
<td>0.9 (0.7–1.1)</td>
<td>0.9 (0.7–1.1)</td>
<td>1.0 (0.8–1.1)</td>
<td>0.9 (0.7–1.1)</td>
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<td>LA systolic wall thickness (cm)</td>
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<td>1.1 (0.9–1.2)</td>
<td>1.0 (0.8–1.1)</td>
</tr>
</tbody>
</table>

Values reported as median (25th to 97.5th percentiles).

* P < 0.05 for juvenile versus subadult chimpanzees of the same sex. § P < 0.05 for juvenile versus subadult chimpanzees of the same sex. † P < 0.05 for male versus female chimpanzees in the same age group.

IVRT = Isovolumic relaxation time. IVS = Interventricular septum. MV = Mitral valve. S' = Systolic tissue velocity.

**P = 0.01.** There were no other substantial differences in RV function between age groups or sexes.

**Discussion**

The purpose of the present study was to comprehensively characterize cardiac structure and function, from infancy to adulthood, in male and female wild-born captive chimpanzees living in sanctuaries.

The main outcome was generation of reference intervals (2.5th to 97.5th percentiles) for cardiac structure and function in chimpanzees, and these reference intervals could be used in future clinical practice or research involving chimpanzees. Findings indicated that male chimpanzees in the present study had larger hearts than females and that between age groups and sexes there were differences in cardiac function,

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Table 4—Echocardiographic measurements of the right side of the heart (right heart) obtained on anesthetized juvenile, subadult, and adult chimpanzees in Tables 1 and 3.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Juveniles</th>
<th>Subadults</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
<td>Males</td>
</tr>
<tr>
<td>Right heart structure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal RV outflow diameter (cm)</td>
<td>2.1 (1.8–2.9)†</td>
<td>2.3 (1.8–2.9)†</td>
<td>2.7 (2.0–3.4)‡</td>
</tr>
<tr>
<td>Distal RV outflow diameter (cm)</td>
<td>1.7 (1.4–2.5)†</td>
<td>1.6 (1.3–2.0)‡</td>
<td>1.9 (1.4–2.2)‡</td>
</tr>
<tr>
<td>RA diastolic area (cm²)</td>
<td>4.0 (3.2–6.9)‡</td>
<td>3.7 (2.3–7.1)‡</td>
<td>5.5 (3.1–8.0)‡</td>
</tr>
<tr>
<td>RA systolic area (cm²)</td>
<td>6.2 (5.1–9.4)‡</td>
<td>6.1 (3.0–10.3)‡</td>
<td>8.4 (3.8–12.8)‡</td>
</tr>
<tr>
<td>RV basal diastolic diameter (cm)</td>
<td>2.7 (2.3–3.0)‡</td>
<td>2.5 (2.1–3.2)‡</td>
<td>3.0 (1.9–3.6)‡</td>
</tr>
<tr>
<td>RV mid-diameter (d) (cm)</td>
<td>2.3 (1.6–2.7)‡</td>
<td>1.9 (1.4–2.4)‡</td>
<td>2.3 (1.6–3.1)‡</td>
</tr>
<tr>
<td>RV length (d) (cm)</td>
<td>3.5 (4.7–6.7)†</td>
<td>5.6 (4.5–6.3)‡</td>
<td>6.4 (4.8–8.1)‡</td>
</tr>
<tr>
<td>RV diastolic area (cm²)</td>
<td>11.7 (7.8–15.2)†</td>
<td>9.1 (6.1–13.2)‡</td>
<td>14.3 (7.5–17.8)‡</td>
</tr>
<tr>
<td>RV systolic area (cm²)</td>
<td>6.4 (3.9–10.1)†</td>
<td>5.2 (3.1–7.7)‡</td>
<td>7.8 (3.7–12.4)‡</td>
</tr>
<tr>
<td>RV free wall thickness (cm)</td>
<td>0.4 (0.3–0.6)†</td>
<td>0.4 (0.2–0.6)</td>
<td>0.4 (0.3–0.9)†</td>
</tr>
<tr>
<td>RV diastolic function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transtricuspid E (m/s)</td>
<td>0.40 (0.28–0.57)</td>
<td>0.41 (0.35–0.64)</td>
<td>0.39 (0.21–0.58)</td>
</tr>
<tr>
<td>Transtricuspid A (m/s)</td>
<td>0.19 (0.13–0.26)</td>
<td>0.17 (0.10–0.31)</td>
<td>0.21 (0.14–0.44)</td>
</tr>
<tr>
<td>Transtricuspid E/A ratio</td>
<td>2.3 (1.3–2.8)‡</td>
<td>2.6 (1.8–4.2)‡</td>
<td>2.1 (1.0–3.0)</td>
</tr>
<tr>
<td>RV free wall E (cm/s)</td>
<td>0.11 (0.08–0.20)†</td>
<td>0.12 (0.09–0.26)‡</td>
<td>0.12 (0.09–0.19)</td>
</tr>
<tr>
<td>RV free wall A’ (cm/s)</td>
<td>0.06 (0.03–0.09)‡</td>
<td>0.06 (0.03–0.13)‡</td>
<td>0.08 (0.03–0.11)</td>
</tr>
<tr>
<td>Transtricuspid E’</td>
<td>3.3 (1.9–6.9)‡</td>
<td>3.3 (2.3–6.2)‡</td>
<td>3.1 (1.6–4.6)‡</td>
</tr>
<tr>
<td>RV systolic function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary peak velocity (m/s)</td>
<td>0.9 (0.5–1.2)</td>
<td>0.8 (0.6–1.5)</td>
<td>0.9 (0.7–1.3)</td>
</tr>
<tr>
<td>RV S’ (cm/s)</td>
<td>0.10 (0.08–0.12)</td>
<td>0.10 (0.08–0.18)</td>
<td>0.11 (0.08–0.15)</td>
</tr>
<tr>
<td>RV fractional area change (%)</td>
<td>42 (30–62)</td>
<td>45 (30–60)</td>
<td>41 (29–58)</td>
</tr>
<tr>
<td>TAPSE (cm)</td>
<td>1.8 (1.1–2.1)</td>
<td>1.6 (1.2–2.4)</td>
<td>1.8 (1.2–2.4)</td>
</tr>
</tbody>
</table>

TAPSE = Tricuspid annular plane systolic excursion.
See Table 3 for remainder of key.

specifically related to earlier decline in diastolic and systolic function in males, compared with females.

Previous studies in different species show that cardiac size increases with body size, and findings of the present study indicated that this was also true in chimpanzees. Similar to humans and other primates, chimpanzees display sexual dimorphism of body size and composition, with males having greater height, body weight, and lean muscle mass than do females. Therefore, it was not surprising that male chimpanzees had significantly larger cardiac volumes and ventricular wall thicknesses than did female chimpanzees in the present study. Findings also indicated that the typical pattern of concentric cardiac remodeling, characterized by increasing LV wall thickness combined with decreased LV chamber diameter, was not observed in chimpanzees of the present study but could have contributed to differences in results for chimpanzees evaluated by Sleeper et al who reported higher blood pressures than the chimpanzees in the present study, then that could explain why concentric remodeling was observed in those animals. Findings of higher systolic blood pressure in older male chimpanzees of the present study aligned with reports in chimpanzees and humans and could be related to the influence of testosterone. In addition, the complicated chimpanzee social hierarchy and associated stress should not be overlooked as a possible confounding variable that could contribute to higher systolic blood pressure for male chimpanzees, compared with that of females. Further research is needed to explore this potential relationship. In addition, advancing age and obesity influence development of hypertension and cardiac remodeling and could have contributed to differences in results for the present study, compared with results reported by Sleeper et al who evaluated chimpanzees that were older (male and female mean ± SD age, 27 ± 8 years and 27 ± 9 years, respectively) and heavier (male and female mean ± SD body weight, 62 ± 8 kg and 59 ± 14 kg, respectively), compared with those in the present study (male and female mean ± SD age, 19 ± 6 years for both sexes; male and female body weight, 52 ± 8 kg and 43 ± 8 kg, respectively). Thus, further research is required to examine isolated and combined impacts of blood pressure, age, body weight, and anesthetic agents on cardiac structure and function in chimpanzees.
Results of the present study also indicated that diastolic function differed between age groups and sexes. The lower transmitral E, transmitral E:A ratios, LV scaled A’ and scaled E’ along with the longer isovolumic relaxation times observed in males, compared with females, suggested marked decline in diastolic function with age in male chimpanzees. Conversely, female chimpanzees appeared to maintain diastolic function across age groups. In men with an earlier increase in cardiovascular risk, concentric remodeling and reduction in diastolic function occur at younger ages than in their premenopausal female counterparts, who are protected by circulating sex hormones. Postmenopausal women, however, experience accelerated concentric remodeling and subsequent decrements in diastolic function. Because female chimpanzees undergo menopause later in life, if at all, such continued hormonal influence could have explained the lack of change in diastolic function for progressively older age groups of female chimpanzees in the present study.

In humans, age-related concentric LV remodeling can result in diastolic dysfunction and is evidenced by a reversal of the E:A ratio (ie, making the ratio < 1.0) because transmitral E decreases owing to decreased compliance in the LV wall, increased LV end-diastolic pressure, and enhanced transmitral A. Interestingly, E:A ratio reversal was not evident in any of the chimpanzees in the present study. It was not clear whether this finding represented a species-specific difference or related to the relatively young age of the chimpanzees studied. Further research in large populations of geriatric chimpanzees (> 35 years old) is warranted.

Diastolic function decreased at a younger age range in males, compared with females, in the present study, and this difference may have been related to the blood pressure differences between the sexes. However, it was also possible that differences in diastolic function between male and female chimpanzees were the result of myocardial fibrosis, which is greater in aging chimpanzee males than their female counterparts. The replacement of functional myocardial fibers with rigid fibrotic tissue hinders diastolic stretch, increases LV wall stress and end-diastolic pressure, and ultimately reduces early diastolic filling velocities. Whether such fibrosis is caused by higher blood pressures or other causes in older male chimpanzees requires further longitudinal investigation.

In contrast to diastolic function, systolic function, as assessed by EF, increases with age, and this increase is more pronounced in women than men. The increase in EF is likely because of reduced cardiac volume and LV diastolic filling. In chimpanzees, however, results of the present study suggested that systolic function reduced with age. For instance, median IV EF was significantly lower in adult male chimpanzees, compared with that in subadult males. It was challenging to determine the underpinning reasons for the low EFs observed, and subclinical disease or the influence of anesthetic agents could have been possible even though the chimpanzees included in the present study did not have any clinical signs of cardiac disease evident on examination. It was also possible that larger animals with larger end-diastolic volumes could generate stroke volumes that met overall metabolic demand but with lower EFs. Recently, limitations associated with the use of EF as the sole marker of cardiac function have been examined in human medicine and such limitations may also be relevant in veterinary medicine. It is therefore likely that veterinarians working with anesthetized chimpanzees may encounter EFs < 40%, and results from the present study indicated that this could occur in the absence of overt cardiovascular disease. These findings also highlighted the need to adopt additional markers of overall systolic function, such as cardiac output, TDI velocities, and measures of strain and strain rate when assessing cardiac health.

Although to our knowledge the sample size of the present study was the largest chimpanzee cohort reported in the veterinary literature, it was still relatively small when compared with sample sizes used to generate normative echocardiographic reference intervals in humans. Further research examining larger samples, including greater numbers at the extreme ends of the age spectrum, is needed to extend and confirm our findings. Furthermore, differences in blood pressure likely contributed to differences in cardiac phenotypes observed between the present study and previous studies. Differences in blood pressure and heart rate with a number of different anesthetic protocols have been reported, and we acknowledge that the different protocols used in the present study could have influenced our findings. Although it was not possible to fully examine the influence of anesthesia in a field-based study such as this and we recognized that measurements in the present study were not normally distributed, we attempted to explore the influence of anesthetic protocols by conducting multiple 1-way ANCOVAs, with anesthetic protocol as the covariate. However, no significant differences were identified to have been associated with anesthetic protocols. We believe that further work specifically designed to assess the influence of anesthesia on echocardiographic measurements in chimpanzees is required. Additionally, it is important to acknowledge that body size is known to influence absolute cardiac structure; therefore, if data are to be compared between individuals, groups, or studies, then appropriate scaling techniques are required. Although fat-free mass is the most relevant scaling variable for cardiac structure because of its relationship to overall metabolic activity, we were unable to measure fat-free mass in the present study. In addition, because simplistic per-ratio scaling approaches are inappropriate, we chose to report only the absolute echocardiographic data. Further research is required to determine appropriate scaling approaches that may be used to compare populations that vary in...
size and body composition. Appropriate adjustments of cardiac data in relation to body size and fat-free mass could potentially highlight differences in cardiac remodeling on the basis of sex in chimpanzees, as has previously been shown in humans.22 Another limitation was that although attempts were made to include only healthy chimpanzees in the present study, we recognized that chimpanzees with subclinical disease could have been included.

Results of the present study provided important reference points for cardiac structure and function in captive chimpanzees categorized on the basis of age and sex. This comprehensive characterization of cardiac parameters in chimpanzees provided data across a broad spectrum of structural and functional parameters similar to those outlined in human medicine.11 The results of the present study could be used by clinicians to help identify chimpanzees with abnormal cardiac structure or function, cardiac disease, or risk of developing cardiac disease. Looking forward, when chimpanzees with cardiac structure and function measurements outside the ranges indicated by results of the present study are identified, further examination of other clinical parameters (eg, results of physical examinations, clinicopathologic analyses, histologic evaluations, and genetic sequencing) could help to better characterize abnormal patterns of cardiac remodeling and provide insight into pathological processes underpinning idiopathic myocardial fibrosis and sudden cardiac death in captive chimpanzees.

Acknowledgments

The authors declare that there were no conflicts of interest.

Footnotes

a. Sphygmomanometer and blood pressure cuff, Welch Allyn, Skaneateles Falls, NY.
b. Vivid q, GE Vingmed Ultrasound, Horten, Norway.
c. 6s pediatric cardiac ultrasound transducer, GE Vingmed Ultrasound, Horten, Norway.
d. M4S adult cardiac ultrasound transducer, GE Vingmed Ultrasound, Horten, Norway.
e. EchoPAC, PC version 112.1.0, GE Healthcare, Chicago, Ill.
f. SPSS, version 22 for Windows, IBM Corp, Armonk, NY.

References

13. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography’s Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440–1463.


