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The Great Ape Heart Project

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Cardiovascular disease (CVD) is a significant cause of morbidity and mortality in great apes that are managed in zoological institutions. The impact of CVD on captive great ape populations is concerning and detection can be difficult because of the lack of definitive clinical signs prior to death. The purpose of this paper is to provide an overview of the efforts of the Great Ape Heart Project (GAHP) and current understanding of CVD in captive great apes, and outline the key considerations for assessing and treating CVD in these populations.

Key-words: cardiomyopathy; cardiovascular disease; echocardiography; Great Ape Heart Project; great apes; health monitoring.

INTRODUCTION

Great apes in the wild face many threats to continued survival. The threats of infectious disease, habitat loss and poaching continue to make the future grim, and all taxa of great apes are now Endangered or Critically Endangered (IUCN, 2017). Cardiovascular disease (CVD) is a concern for all great ape taxa that are managed in zoological institutions – Western lowland gorillas *Gorilla gorilla gorilla*, Bornean orangutans *Pongo pygmaeus*, Sumatran orangutans *Pongo abelii* and *Pongo* hybrids, Chimpanzees *Pan troglodytes* and Bonobos *Pan paniscus* – and has also been documented in Chimpanzees housed in research facilities (Lammey, Lee *et al.*, 2008; Seiler *et al.*, 2009; McManamon & Lowenstine, 2012).

Mortality reviews have reported that CVD is the cause of death in 41% (n = 16 of 39 individuals) of adult and older adult gorillas, 29% (n = 24 of 83 individuals) of subadult to adult orangutans, and 77% (n = 27 of 35 individuals) of Chimpanzees housed at Association of Zoos and Aquariums (AZA)-accredited zoological institutions, and has been significant in Chimpanzees housed in US research facilities as well (Meehan & Lowenstine, 1994; Gamble *et al.*, 2004; Lowenstine *et al.*, 2008; Varki *et al.*, 2009). Global studbook data on Bonobo mortalities [AZA Species Survival Plan Program (SSP) and European Association of Zoos and Aquaria (EAZA) European Endangered Species Programme (EEP)] have been analysed twice. A review of the main cause of death between 1990 and 2000 as reported to the programmes (Clyde, 2000), and analysis of complete necropsy reports of Bonobos dying between 2004 and 2014 (V. Strong, V. Clyde, J. Stevens, K. Baiker, Z. Pereboom, S. Redrobe, M. Cobb & K. White, unpubl. data), respectively showed that CVD accounts for 47% (n = 7 of 15 individuals) of deaths in Bonobos over 1 year of age and 65% (n = 13 of 20 individuals) of deaths in Bonobos over 15 years of age. When these mortality statistics are broken down even further, there is a clear male sex predilection for CVD, with 75% (n = 12 of 16) of deaths in adult and older adult male gorillas (Meehan & Lowenstine, 1994) and 69% (n = 9 of 13 individuals) of deaths in adult and older adult male Bonobos (V. Strong, V. Clyde, J. Stevens, K. Baiker, Z. Pereboom, S. Redrobe, M. Cobb & K. White, unpubl. data. Case reports and

mortality reviews of Chimpanzees in the United Kingdom and Ireland revealed that CVD was the second major cause of death in mature adult Chimpanzees with a mortality rate of *c.* 16%, with no sex predilection (Le Rochais, 2011). A retrospective mortality review in Western lowland gorillas in European zoological institutions between 2004 to 2014 showed that CVD accounted for *c.* 15% of all deaths and *c.* 27% of deaths in gorillas over 15 years of age, with data suggesting male sex predilection (Strong *et al.*, 2017).

There is limited information available about the prevalence of CVD in wild ape populations. Cardiovascular disease has been identified during post-mortem examinations in 3% of both male and female wild Mountain gorillas *Gorilla beringei beringei*, and in six out of eight (75%) Grauer's eastern lowland gorillas *Gorilla beringei graueri* in the Democratic Republic of Congo (Kambale *et al.*, 2014; Lowenstine *et al.*, 2015). A study of wild Chimpanzees identified mild to moderate myocardial interstitial fibrosis in two out of 11 (18%) wild Common chimpanzees *Pan troglodytes schweinfurthii* at necropsy (Terio *et al.*, 2011).

THE GREAT APE HEART PROJECT

The Great Ape Heart Project (GAHP), based at Zoo Atlanta (Atlanta, GA, USA), is a group of dedicated and coordinated subject-matter experts that provides a network of clinical, pathologic and research strategies aimed at understanding and treating CVD in great apes, with the ultimate goal of reducing CVD-related mortalities, and improving the health and welfare of great apes in human care. This innovative and coordinated programme is a result of the zoo community recognizing the need for a multi-institutional and cross-disciplinary approach to understand better the classification, aetiology, clinical manifestations and effects of CVD on managed populations of great apes. As a result of over 15 years of echocardiogram data collection, GAHP project partners have established echocardiographic parameters for gorillas (Murphy *et al.*, 2011), Chimpanzees (Sleeper *et al.*, 2014) and more recently Bonobos (K. K. Schultz, V. L. Clyde, L. P. N. Beehler, S. Wann & B. K. Bell, unpubl. data). Because of the opportunistic nature and technically challenging aspects of collecting echocardiographic information in great apes, no published echocardiographic parameters yet exist for orangutans. Through grant funding from the Institute of Museum and Library Services (IMLS) (Washington, DC, USA) the GAHP created a custom medical database for tracking great ape cardiac-related health information and addressing the critical need to systematically collect and evaluate cardiac-related findings in captive great apes. The GAHP encourages institutions that care for great apes worldwide to submit cardiac-related information so that we can gain a broader understanding of cardiovascular disease in great apes across multiple populations. The vast majority of data submitted to the GAHP comes from AZA-accredited institutions in North America, although in the last decade there have been some limited submissions from Mexico, New Zealand, Australia and Japan as well as a few from European zoos. The GAHP encourages and welcomes all cardiac submissions from any institution caring for great apes and will review, archive and provide reports for any submissions that have diagnostic-quality data. The GAHP is available as a resource to other great ape cardiac working groups, human and veterinary cardiac experts, veterinarians and anyone caring for great apes, and serves in this capacity when asked. All information submitted to the GAHP is confidential and data are not shared unless permission is given by the submitting institution. Submitted data may be used for research and publications, and all data used are blinded so that individual apes and/or submitting institutions cannot be identified. Submission forms and instructions can be found on the GAHP website (www.greatapeheartproject.org/forms). The database contains data fields that are populated from echocardiograms, cardiovascular-related blood-analyses values, electrocardiograms, anaesthesia records, medical conditions and treatments, as well as post-mortem

evaluations. Ape life-history information from the SSP studbooks is also included, allowing for categorization and evaluation of data by age, sex, institution and even family lines.

The GAHP acts as a hub for activities relating to the assessment and treatment of heart disease in great apes. This has been accomplished through the development of the GAHP website, relevant publications, training workshops for zoo professionals, and reviews of great ape echocardiograms accompanied by subject-matter expert evaluation reports. Guidelines and recommendations have been developed that provide support to zoological professionals in the diagnosis and treatment of CVD in great apes, and clinical support to attending veterinarians is provided by subject-matter experts, such as cardiologists, pathologists and species experts. These guidelines are available on the GAHP's website (www.greatapeheartproject.org). By focusing on collaboration and information sharing, the hope is that zoos and those who care for apes do not need to 'reinvent the wheel' of establishing a network of subject-matter experts, diagnostic approaches and treatment methods in the care of their great apes (Fig. 1).

CARDIOVASCULAR DISEASE IN CAPTIVE GREAT APES

As great apes age, a certain amount of cardiovascular systemic ageing should be expected, as happens in other animals. These age-related changes typically result in left ventricular wall thickening, increased myocyte size with decreased numbers, increased interstitial connective tissue and loss of elasticity. Histological examinations of the heart in great apes that have died as a result of cardiac disease have shown signs of typical cardiovascular ageing, but the cardiac changes seen have also occurred in non-geriatric great apes and have typically been more advanced than would be attributed to normal ageing processes (McManamon & Lowenstine, 2012; Lowenstine *et al.*, 2015).

The most common finding at necropsy on apes affected by CVD is replacement of the normal contractile muscle fibres of the

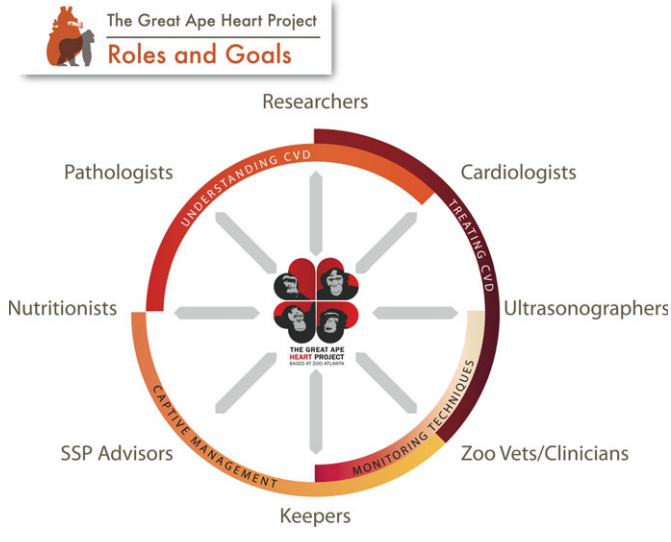

Fig. 1. By focusing on collaboration and information sharing, zoos and those who care for apes do not need to 'reinvent the wheel' of establishing a network of subject-matter experts, diagnostic approaches and treatment methods in the care of their great apes: CVD, cardiovascular disease; SSP, Species Survival Plan Program. *Becky Scheel/The Great Ape Heart Project.*

heart with fibrous 'scar' tissue, often termed myocardial fibrosis or fibrosing cardiomyopathy (Lammey, Baskin *et al.*, 2008; Lowenstine *et al.*, 2015). Typically, post-mortem changes such as these are thought to be the result of injury to the myocardial cells, such as that caused by inflammation, ischaemia, vasospasm or high blood pressure, or other unknown causes. Regardless of the inciting process, myocardial fibrosis, thickening of the heart muscles (hypertrophy), loss of its contractile ability, increased risk of abnormal or fatal heart rhythms and progressive loss of effective heart function have all been documented in apes with cardiac disease (Lowenstine *et al.*, 2015).

The most common finding in affected apes is left ventricular hypertrophy, with some apes then progressing to dilated and enlarged hearts in end-stage heart failure (Miller *et al.*, 1999; Lowenstine *et al.*, 2008; Grim *et al.*, 2010; Murphy, 2010; McManamon & Lowenstine, 2012). In female gorillas, left ventricular hypertrophy may be absent even in the presence of myocardial fibrosis (Lowenstine *et al.*, 2015). Aortic dissections are the second leading cause of cardiovascular-related deaths in gorillas and Bonobos, and typically result in acute collapse and death (Kenny *et al.*, 1994; Lowenstine *et al.*, 2015). Other types of CVD that have been seen in great apes include hardening of the small arteries of the body, which can be related to kidney disease or stroke, valvular degeneration, infectious myocarditis and congestive heart failure (Miller *et al.*, 1999; Lowenstine *et al.*, 2008; Grim *et al.*, 2010; Murphy, 2010; McManamon & Lowenstine, 2012). It is notable that obstruction of the coronary arteries, which is prevalent in human CVD, is rarely found to any significant degree in the great apes (Varki *et al.*, 2009).

Clinical signs

Many veterinarians are trained to look for exercise intolerance or open-mouth breathing as signs of heart disease in domestic animals, but these signs are rarely observed in apes with CVD. Instead, clinical signs in affected apes are much more subtle and care staff should be aware of this in order to monitor for social changes which can include social withdrawal from troop activities, voluntary avoidance of antagonistic or aggressive interactions with conspecifics or loss of social rank. Accompanying behavioural changes may include mild to moderate lethargy, partial anorexia or ingestion of only preferred food items, or unexplained weight loss or gain. Other non-specific signs that have been reported include coughing (possibly related to congestion), teeth-grinding (possibly related to pain or aortic dissection) or unilateral weakness (possibly related to stroke). Nasal bleeding has been noted in Bonobos, possibly related to underlying hypertension (V. Clyde, pers. obs). As CVD progresses more obvious signs, such as weight gain, peripheral oedema, marked anorexia or progressive respiratory compromise, may occur.

Prior to routine echocardiographic screening of apes, some animals have been found dead without premonitory signs being observed by care staff. The term 'sudden death' was sometimes used to refer to these cases; however, in human cardiology, this term is reserved for deaths resulting from cardiac arrhythmias. While it is true that arrhythmias can occur secondary to extensive myocardial fibrosis, without electrocardiographic documentation, the presence of an arrhythmia cannot be verified. Other causes of death in apes resulting from CVD without premonitory signs can include aortic dissections, haemorrhagic strokes, thromboembolic events or decompensated congestive heart failure with multi-systemic failure (Kenny *et al.*, 1994; Varki *et al.*, 2009). Risk of mortality from CVD in apes appears to be heightened during or immediately following either respiratory disease or stressful events.

CLINICAL ASSESSMENTS

After an ape echocardiographic study is completed by an institution, it can be submitted to the GAHP along with related information that includes signalment of the patient, weight,

crown–rump length, any current medications or concurrent diagnoses, anaesthesia details, blood-pressure measurements, and laboratory values. Submission forms and specific information regarding submissions can be found at https://greatapeheartproject.org/projects/forms/. The echocardiogram and related information is evaluated by both a GAHP cardiologist and a veterinary advisor, and a report will be generated within 6 weeks of submission. Upon request, a report can be expedited if illness has been reported in the ape concerned. In general, after complete review, apes are found to fall within one of four categories of clinical assessment used by the GAHP.

1. No recognized cardiac dysfunction.
2. Left ventricular hypertrophy but no systolic dysfunction.
3. Left ventricular hypertrophy and systolic dysfunction.
4. Dilated cardiomyopathy.

When possible and desired by the submitting institution, subject-matter experts can advise institutional veterinarians on treatment considerations.

AETIOLOGY

There have been many theories and publications describing potential aetiological factors that contribute to myocardial fibrosis and great ape cardiovascular-related mortalities. Factors such as hypertension, obesity, genetics, diet, vitamin and mineral imbalances, stress, endocrine disorders and concurrent diseases, such as renal disease, dental disease, respiratory disease and musculoskeletal issues, have all been considered (McManamon & Lowenstine, 2012).

Blood pressure and hypertension

In humans, elevated blood pressure is a major risk factor for the development of heart failure, and long-term treatment of both systolic and diastolic hypertension has been shown to reduce the risk of heart failure (Yancy *et al.*, 2013). Hypertension in humans has been associated with cardiac fibrosis and remodelling, heart failure and cardiomyopathy, and myocardial fibrosis resulting from hypertension has been linked to left ventricular hypertrophy and diastolic cardiac dysfunction (Janardhanan & Kramer, 2011). Echocardiographic evidence of concentric left ventricular hypertrophy, combined with similarities in cardiac and systemic changes seen post-mortem such as dissecting interstitial fibrosis between affected apes and humans with confirmed systemic hypertension, has strongly implicated hypertension as playing a role in great ape CVD (Lowenstine *et al.*, 2015).

Defining blood-pressure reference ranges for healthy adult great apes has been logistically challenging. Historically, blood-pressure measurements were only attained from anaesthetized great apes, but these measurements are influenced by various anaesthetic agents, and do not shed light on the resting blood pressure in the awake, non-anaesthetized ape. By human standards, consistent systolic readings of >140 mmHg or diastolic readings ≥90 mmHg fit the definition of hypertension (Ely, Zavaskis, Lammey & Rick Lee, 2011). In Chimpanzees, obesity has been shown to be a risk factor for the development of systolic hypertension in females and increasing age is a risk factor for development of diastolic hypertension in both sexes (Ely *et al.*, 2013).

Attempts to define blood-pressure ranges in non-anaesthetized great apes are under way. Repeated evaluation of blood-pressure readings, carried out in a consistent manner over time, may help to provide an ancillary monitoring method for both affected individuals and also for apes that are at high risk of developing CVD. This information could generate a baseline for individual animals to be used to monitor changes in blood pressure over time and during CVD treatment regimes for that individual. Until long-term prospective studies are done, it would appear reasonable to consider antihypertensive medications for apes with systolic BP consistently >160 mmHg, as measured in an awake ape or at the time of first hands-on in an immobilized ape, early

during an anaesthetic procedure in which no alpha-2 adrenergic agonist was used (i.e. no medetomidine or xylazine), and prior to supplementation with a vasodilating inhalant gas such as isoflurane.

Diet

Diet, lifestyle, body weight, metabolic syndrome and sodium intake have all been linked to hypertension and heart disease in humans (Yancy *et al.*, 2013). Great apes have a predominantly vegetarian, low-fat, high-fibre and very-low cholesterol diet in the wild (Popovich *et al.*, 1997). While some blood lipids, measured as high-density lipoprotein (HDL) and low-density lipoprotein (LDL), and total cholesterol, change or increase with age in captive apes, and may be well above the mean for the human population and for wild-living great apes, these levels were not found to be predictive for CVD in Chimpanzees and do not appear to correlate to increased risk of ape CVD (Kenny *et al.*, 1994; Popovich *et al.*, 1997; Baitchman *et al.*, 2006; Schmidt *et al.*, 2006; Seng *et al.*, 2007; Varki *et al.*, 2009; Ely *et al.*, 2010). Analysis of low-starch, biscuit-free diets for gorillas has shown that these diets can reduce circulating insulin levels and the addition of resistant starch also lowered cholesterol levels; however, the potential link between these metabolic parameters and the development of CVD in great apes needs further research (Less *et al.*, 2014).

Increased sodium intake in humans is associated with increased systolic blood pressure, cardiovascular events and death in people with hypertension. Conversely, low sodium intake has been associated with an increased risk of cardiovascular events and death in both normotensive and hypertensive humans (Mente *et al.*, 2016). In one study carried out in Chimpanzees, salt was progressively added to the diet over 20 months and caused a significant rise in body weight, and systolic, mean and diastolic blood pressure, which was reversed after cessation of additional salt. Dietary sodium requirements for great apes are poorly understood and the above study concluded that in Chimpanzees it would be advisable to feed a balanced diet, as close to the wild diet as possible, with no more than 30–40 mmol of sodium per day (Denton *et al.*, 1995). The current recommended levels for non-human primates of 0·25–0·65% dietary sodium is potentially too high and until more research can be done, it is prudent to monitor great ape dietary sodium intake closely (National Research Council, 2003).

CARDIAC HEALTH MONITORING

High-quality echocardiography provides for the most practical, clinically relevant and accurate assessment of cardiac functionality, valve anatomy, chamber sizes and ventricular mass (Lang *et al.*, 2015), and is a valuable tool to have available when caring for great apes. Therefore, it is recommended that echocardiographic assessments be performed during every anaesthetized examination once the ape reaches adulthood. Each great ape SSP encourages examinations every 2–3 years in healthy adult apes (Table 1). Critical knowledge and considerable expertise are needed in order to attain a diagnostic echocardiogram in great apes. Chest dimensions differ between the ape species, and there is a learning curve for both veterinary and medical sonographers to obtain the necessary probe angles and echocardiographic views needed for a complete cardiac examination (Shave *et al.*, 2014). For this reason, the GAHP strongly recommends that institutions housing great apes establish relationships both with experts such as local cardiologists and echo-sonographers, as well as great ape subject-matter experts. For apes affected by CVD, individual risk analysis should be used to determine anaesthesia and examination frequency. While challenging in some species, diagnostic echocardiograms can be obtained in non-anaesthetized apes, which can allow ongoing monitoring of cardiac status without frequent anaesthetic immobilizations.

AGE/HEALTH STATUS	FREQUENCY OF EXAMINATIONS
Neonate	opportunistically: if a neonate has to be removed from the dam for any reason, a neonatal examination should be carried out
9 years	baseline examination
10–20 years	every 3–5 years
>20 years	every 2–3 years
Animals with cardiac disease	examination frequency should be determined on a case-by-case basis in order to monitor and manage treatment

Table 1. The Great Ape Heart Project recommendations for frequency of echocardiography examinations based on age and health status of great apes.

Additional screening may also include a standard electrocardiogram (ECG). A useful guide for performing a standard electrocardiographic examination in great apes has been produced and made available online by the EAZA Great Ape Taxon Advisory Group (TAG)-Endorsed Ape Heart Project (https://twycrosszoo.org/wp-content/uploads/2014/11/C4-Protocol-for-Performing-a-Standard-Electrocardiogram.pdf). Blood tests for cardiac biomarkers such as brain natriuretic peptide (BNP) and troponin have shown some promise as additional diagnostic tools when performing a full cardiac assessment; however, validation of these biomarkers for the great apes has not occurred and the majority of zoos in North America have trouble finding a facility that is willing to process non-human blood samples (Ely *et al*., 2010; Ely, Zavaskis, Lammey, Sleeper & Rick Lee, 2011).

TREATING CVD IN GREAT APES

In humans, elevations in both systolic and diastolic blood pressure are major risk factors for developing left ventricular hypertrophy, and targeted blood-pressure reduction also lowers the occurrence of heart-failure events. Consequently, long-term treatment of both systolic and diastolic hypertension in humans reduces the risk of progressive heart failure (Yancy *et al.*, 2013).

Treatment of CVD in the apes has been targeted at reducing the pressure in the left ventricular wall during blood ejection (afterload reduction), lowering systemic blood pressure and ameliorating other potential negative effects of cardiovascular compromise, such as fluid retention and arrhythmias. It must be clarified that no clinical studies on the efficacy, safety or pharmacokinetics have been carried out on any of these treatment regimes in apes, so recommendations are based purely on experience with using them in apes over the course of the GAHP studies, as well as hypothetical assumptions that apes would react to these drugs in much the same way as humans.

POST-MORTEM CARDIAC EVALUATIONS

The pathology group of the GAHP has collected, compiled and reviewed available necropsy and histopathology reports from apes managed in captive situations. All information collected is reviewed and entered into the GAHP database for each individual ape and the post-mortem information is analysed for correlation to any clinical information that has been collected for that animal. Trends within species and between the species can be highlighted in this way and the critical step of comparisons between ante-mortem diagnostics and disease classifications can be verified via this comparison to post-mortem information.

Standardized post-mortem tissue collection and evaluation techniques for great ape cardiac necropsies, revolutionary for the veterinary profession, have been developed by expert ape SSP pathologists in collaboration with cardiovascular pathology experts (Terio *et al.*, 2014). These protocols have established a new ‘best practices’ approach to ape heart evaluation, which is more closely aligned with techniques used in human cardiac autopsies. These protocols have vastly improved the quality of data in the

GAHP database, allowing for more accurate population-wide and cross-species comparisons. These guidelines can be found at www.greatapeheartproject.org.

CONCLUSIONS

The GAHP has become an important resource to the zoological community facilitating the detection and treatment of CVD in great apes. Through the implementation of advanced cardiac imaging and post-mortem protocols, as well as introduction of innovative technologies, the GAHP has not only been able to empower zoo professionals with the best possible veterinary care and animal-management capabilities but also develop a robust cardiac-health database to aid in the understanding and treatment of cardiac disease in all the ape species. The ultimate goals of the GAHP are to reduce cardiovascular-related mortalities, and improve the health and welfare of captive great apes.

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