

## A retrospective review of great ape cardiovascular disease epidemiology and pathology

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*Right-hand running title:* GREAT APE CARDIOVASCULAR DISEASE REVIEW

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## ABSTRACT

Cardiovascular disease is associated with significant mortality in zoo-housed great apes and yet little is known about its epidemiology and aetiopathogenesis, and therefore its diagnosis, treatment and prevention. In this retrospective study, the frequency and patterns of cardiovascular disease associated mortality in zoo-housed great apes is explored. Data relating to 71 great apes [Bonobos *Pan paniscus* ( $n = 13$ ), Chimpanzees *Pan troglodytes* ( $n = 37$ ), Western lowland gorillas *Gorilla gorilla gorilla* ( $n = 15$ ), and Bornean orangutans *Pongo pygmaeus* and Sumatran orangutans *Pongo abelii* ( $n = 6$ )], which died between 2004 and 2014, were studied and key information relating to their signalment (taxa, age, sex), and manner and cause of death analysed. Male sex and increasing age were found to be associated with an increased risk of cardiovascular disease associated death. Relative to the other taxa, orangutans appeared to be less at risk of heart-disease associated mortality. Deaths were often found to be sudden and unexpected.

Cardiomyopathies were the most frequently diagnosed cardiovascular disorder. Of these, a group of cardiomyopathies characterized by the presence of myocardial fibrosis were most common, although there were inconsistencies with regards the reporting of other histopathological features. The study identified potential risk factors involved in great ape cardiovascular disease aetiopathogenesis which warrant further exploration. The findings also suggest a need for proactive screening to identify those affected earlier in the disease course. Finally, the study highlights a critical need for improvements to be made to the current approach to post-mortem investigation of great ape heart disease and the subsequent reporting of cardiovascular lesions.

*Key-words:* aetiopathogenesis; bonobos; Bornean orangutans; captive; chimpanzees; heart disease; mortality; Sumatran orangutans; western lowland gorillas; zoological.

## INTRODUCTION

Wild great apes are under growing threat and, as such, the maintenance of self-sustaining *ex situ* populations is imperative to preventing their total planetary extinction. Great apes are susceptible to a wide range of infectious and non-infectious disorders, a review of which is outside the remit of this paper. Cardiovascular diseases in particular have received significant literature coverage over recent years (Strong *et al.*, 2016) and have long been cited as a significant cause of morbidity and mortality of great apes housed in North American collections (Meehan & Lowenstine, 1994; Gamble *et al.*, 2004; Lowenstine *et al.*, 2008). Cardiovascular disorders have also more recently been identified as a frequent cause of death among European zoo-housed great apes (Strong, 2017; Strong *et al.*, 2017).

The term cardiovascular disease, however, does not refer to just one condition but instead represents a group of non-communicable disorders affecting the heart and/or vasculature (World

Health Organization, 2011). The term encompasses a wide spectrum of diseases and lesions including coronary heart disease, cerebrovascular disease, hypertension, peripheral vascular disease, rheumatic heart disease, congenital heart disease, cardiomyopathies and heart failure.

In human medicine, the key pathologic features and epidemiology of these individual disease processes have been well studied and the aetiopathogeneses elucidated. Many lifestyle risk factors have been identified as playing an important role in human cardiovascular disease predisposition, development and progression, including tobacco use, diet and alcohol consumption (Anderson *et al.*, 1991; Jousilahti *et al.*, 1999; Institute of Medicine, 2010; D'Agostino *et al.*, 2013; World Health Federation, 2017). Unlike humans, however, zoo-housed great apes do not have a diet heavy in saturated fats, nor are they exposed to the harmful effects of alcohol or tobacco smoke. Their susceptibility to heart disease despite this is, therefore, of great interest. It might be that other risk factors are of greater importance among great apes. Such factors might include, for example, other dietary factors, physical inactivity, age, gender, social status, stress, family history and/or genetics. To ascertain the role that these and perhaps other risk factors might play in the aetiopathogenesis of great ape cardiovascular disease requires more in depth epidemiological studies of affected individuals to be carried out in the future.

This retrospective study attempts to explore the frequency and patterns of cardiovascular disease associated mortality in a sample of zoo-housed great apes between 2004 and 2014. The preliminary results of this review have identified some potential risk factors that may be involved in the aetiopathogenesis of great ape cardiovascular disease and which therefore warrant further exploration. This study adds to the growing body of literature aimed at improving our understanding of the causes and effects of cardiac disease in great apes.

## MATERIALS AND METHODS

### **Study population**

A prior review of European and North American zoo-housed great ape mortality between 2004 and 2014 (Strong, 2017; Strong *et al.*, 2017) identified 71 animals (from a total 411 studied) that had died as a result of disease of the cardiovascular system. These Bonobos *Pan paniscus* ( $n = 13$  of a total 38 studied), Chimpanzees *Pan troglodytes* ( $n = 37$  of a total 211 studied), Western lowland gorillas *Gorilla gorilla gorilla* ( $n = 15$  of a total 102 studied), and Bornean orangutans *Pongo pygmaeus* and Sumatran orangutans *Pongo abelii* ( $n = 6$  of a total 60 studied) were the subjects for this retrospective study.

### **Data collection and processing**

For each animal, the following information was entered to an electronic spreadsheet: animal identification information (regional studbook number; name), species and zoological collection at

the time of death. Some animals were wild born and so their exact dates of birth were unknown; therefore, best estimates of age were used. Age at death was calculated from the dates of birth and death.

Each animal was categorized by their age at the time of death. To ensure consistency across the taxa, all animals less than 1 year of age were classified according to the definitions used for human infant mortality: foetal (stillborn/premature/abortion; had never breathed), perinatal/early-neonate (breathed, but died aged 0–7 days) and infant (8–364 days) (World Health Organization, 2006). Animals 1 year of age or older were grouped into species specific, discrete age categories (Galdikas, 1981; Meehan & Lowenstine, 1994; Rowe, 1996; Furuichi *et al.*, 1998; Gamble *et al.*, 2004; Alberts *et al.*, 2013) (Table 1).

The post-mortem reports for each animal were reviewed in detail and key information relating to the manner of death and cardiovascular disorder/lesion responsible was extracted. The manner (nature and circumstance) of death was classified as: euthanasia; peri-anaesthetic; natural (sudden); natural (following period of illness). Peri-anaesthetic deaths were defined as those that occurred following anaesthetic induction, intra-operatively or during anaesthetic recovery, or those that occurred when the animal did not regain full consciousness post anaesthesia. Deaths were classified as sudden if they were non-violent, unexpected and occurred within 24 hours of the animal last being seen in a stable, apparently healthy condition (Virmani *et al.*, 2001). The main cardiovascular lesion associated with death (as stated within the original report) was categorized according to the criteria described in Table 2. The categories used were based on those in the International Classification of Diseases (ICD) system (World Health Organization, 2010).

Cardiomyopathies were further subcategorized by diagnosis (as stated in the post-mortem report). Subcategories used were as follows: dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), restrictive cardiomyopathy (RCM) and arrhythmogenic right ventricular cardiomyopathy (ARVC) (Richardson *et al.*, 1996; Davies, 2000; National Heart Lung and Blood Institute, 2016). Those cardiomyopathies that did not conform to any of these diagnoses were categorized as 'unclassified'.

## **Data analysis**

Statistical analyses were carried out using Microsoft Excel (Microsoft 2010) and GraphPad Prism 7 for MacOS X (2016). Data were assessed for normality using the Shapiro–Wilk test. Normally distributed data are expressed as mean and standard deviation, and non-normally distributed data as median (min; max) unless stated otherwise. One-way ANOVA and log-rank (Mantel–Cox) analysis were used to assess for differences in age at death between taxa. A Fisher's exact test of

independence was carried out to assess for sex variation in risk of death. Confidence intervals (CI) were set at 95% and  $P$  values of  $< 0.05$  were considered significant.

## RESULTS

### **Post-mortem examination and data quality**

It was evident from the reports that the approach to post-mortem investigation of heart disease was inconsistent between zoological collections. There was great variation with regards the expertise of the individual performing the examination, the extent of the examination performed, the samples examined, terminology applied, and quality and quantity of information provided in the final report.

### **Age at death**

Age at death as a result of cardiovascular disease was found to be normally distributed across the taxa. It ranged from 7.80 to 52.57 years, with the youngest animal being a Chimpanzee and the eldest a Bonobo (Table 3). When viewed graphically, chimpanzees appeared to succumb to cardiovascular disease much younger when compared with the other taxa (Fig. 1). However, neither one-way ANOVA nor log-rank (Mantel–Cox) analysis demonstrated a statistically significant difference in age at death as a result of cardiovascular disease between the taxa. More than 90% ( $n = 64$  of the total 71) of the animals that succumbed were adult or aged/elderly at the time of death, with three-quarters [ $n = 53$  of the total 71 (75%)] being over 25 years of age.

### **Manner of death**

The deaths of 55 (78%) animals were categorized according to the nature and circumstances (the data provided was insufficient to allow such categorization for the remaining 16 animals). Twenty per cent ( $n = 11$  of the 55) of the deaths were following euthanasia and 29% ( $n = 16$ ) were peri-anaesthetic in nature. Five (9%) of the deaths followed a period of illness, ranging in duration from 24 hours to 6.5 years. The biggest proportion of deaths [ $n = 23$  of the 55 (42%)], however, were sudden or unexpected; these animals were found dead with no signs of cardiac ill health observed in the preceding 24 hours.

### **Cardiovascular disorders**

The category of cardiovascular disorders most frequently associated with death [ $n = 38$  of the total 71 (54%)] were the cardiomyopathies (Table 4). Also associated with a significant proportion of all cardiovascular mortalities were cerebrovascular disorders (cerebral haemorrhages and infarctions) [ $n = 11$  of the total 71 (15%)] and diseases of the arterial and capillary system [ $n = 8$  of the total 71 (11%)]. Arterial disorders were particularly common amongst gorillas [ $n = 3$  of 15 affected individuals (20%)] and were the second most common disease for this species. Arterial disorders were also the cause of 15% ( $n = 2$  of 13 affected individuals) of Bonobo and 8% ( $n = 3$  of 37

affected individuals) of Chimpanzee deaths, but none of the orangutan cardiovascular mortalities. Three quarters [ $n = 6$  of 8 affected individuals (75%)] of the deaths which were the result of disease of the arterial and capillary system were aortic dissections or aneurysms, while the remaining deaths ( $n = 2$ ) were caused by arterial thrombosis.

*Cardiomyopathies* Cardiomyopathies were responsible for over half [ $n = 38$  of a total 71 (54%)] of all cardiovascular deaths in this study. They were responsible for 62%, 54% and 47% of all deaths occurring as a result of cardiovascular disease in Chimpanzees ( $n = 23$  of 37 CVD deaths), Bonobos ( $n = 7$  of 13 CVD deaths) and gorillas ( $n = 7$  of 15 CVD deaths), respectively. Cardiomyopathies were, however, identified as the cause of death for only one (17%) of the six cardiovascular disease associated deaths in orangutans.

*Manner of death* Information relating to the manner of death was available for > 80% ( $n = 31$  of a total 38) of those deaths that occurred as a result of cardiomyopathy. Euthanasia accounted for < 10% ( $n = 3$  of a total 31) of these deaths. Peri-anaesthetic mortality accounted for a further 29% ( $n = 9$  of a total 31), six (67%) of which occurred in the intra-operative period, two (22%) during anaesthetic recovery and one (11%) 48 hours post-procedure, during which time the animal never fully regained consciousness. Only two [ $n = 2$  of a total 31 (6%)] of the animals had shown overt clinical signs of disease in the period leading up to their deaths.

*Diagnosis* Hypertrophic cardiomyopathy (HCM;  $n = 2$ ), dilated cardiomyopathy (DCM;  $n = 2$ ), arrhythmogenic right ventricular cardiomyopathy (ARVC;  $n = 1$ ) and restrictive cardiomyopathy (RCN;  $n = 1$ ) were responsible for six of the 38 (16%) cardiomyopathy induced deaths identified by this study. The remaining deaths [ $n = 32$  (84%)], however, were the result of cardiomyopathy that did not conform to any of these diagnoses (an unclassified cardiomyopathy). Often referred to as 'fibrosing cardiomyopathy' (FCM), but also 'myocardial scarring' or 'cardiac fibrosis' within the post-mortem reports, these disorders had one consistent feature; all were typified by the histological finding of an increase in fibrous connective tissue. There were, however, great inconsistencies with regards the more specific pathological features, such as the type (interstitial vs replacement) and distribution of fibrosis, as well as accompanying macroscopic (e.g. hypertrophy, cardiomegaly) and other histopathologic (cellular infiltration, myofibre disarray, myocyte necrosis) changes.

## **Sex variation**

*Sex variation in proportional mortality: adult and aged/elderly animals* Cardiovascular disease was associated with a greater proportional mortality among adult and aged males than females across all taxa (Table 5). For all taxa combined, the relative risk of death as a result of cardiovascular disease associated with the male sex was 2.4. This discrepancy was most obvious for gorillas, among which males were more than eight times more likely to die as the result of cardiovascular

disease than females. For Chimpanzees, the risk for males was almost twice that of females. Although still evident in Bonobos and orangutans, the sex variation in risk of cardiovascular death was not statistically significant, perhaps because of the comparatively smaller sample size.

*Sex variation in cardiovascular disease* Cardiomyopathies were responsible for 64% of all male compared with only 35% of female cardiovascular disease deaths (Table 4); the male gender being associated with a more than twofold increase in risk of death as a result of cardiomyopathy ( $P = 0.0089$ ; CI: 1.19 to 3.71). This sex difference was most notable for Chimpanzees, among which 90% ( $n = 18$  of 20 individuals) of male cardiovascular disease deaths were the result of a cardiomyopathy, compared with only 29% ( $n = 5$  of 17 individuals) of females (relative risk, ♂ > ♀: 3.06;  $P = 0.0002$ ; CI: 1.63 to 6.85).

Arterial diseases were only reported among male, not female, Bonobos and gorillas. However, in Chimpanzees they were associated with 12% ( $n = 2$ ) of female cardiovascular disease deaths compared with only 5% ( $n = 1$ ) of those in males (Table 4).

## DISCUSSION

### **Age at death**

In this study, cardiovascular disease was found to predominantly be a disease of adult and aged/elderly animals, with the mean age at death for all taxa combined being 32.5 years (range: 7.8 to 52.6 years). Given that advancing age is a well-known risk factor for heart disease in humans (Ho, K. K., *et al.*, 1993), this finding was not unexpected. Nonetheless, cardiovascular disease was also associated with the death of seven Chimpanzees under 20 years of age (i.e. c. 19% of the Chimpanzees considered in this study). The future reproductive potential of an animal of this age means that the impact of its death on the growth and sustainability of the population could be great. The possibility that Chimpanzees might be affected by heart disease at a younger age should therefore be monitored closely and potential reasons for this factor explored. Given that the period of adolescence and subadulthood, especially for males, is associated with an increase in reproductive behaviour, intense sexual competition and often also changes in social hierarchy, the potential interplay between sex, stress and disease risk in this subpopulation, in particular, would be an interesting avenue for future research.

### **Male sex and cardiovascular disease risk**

As is the case in other species, male sex was identified by this study as a risk factor for cardiovascular disease associated death in great apes. As reviewed by Pérez-López *et al.* (2010), various hormonal, biochemical and genetic factors might be responsible for this sex variation in risk. Both oestrogen and testosterone have been shown, in humans, to be cardioprotective (Rosano & Panina 1999; Bain, 2007; Tsang *et al.*, 2007; Pérez-López *et al.*, 2010; Knowlton *et al.*, 2014). The

reduction of these steroid hormones, whether naturally occurring as the result of ageing, because of social factors or contraception, might be associated with an increased risk of cardiovascular disease, therefore making this another important topic for further investigation.

Males have been reported to experience higher mortality, more rapid ageing and reduced longevity across the primate species (Hill *et al.*, 2001; Reinartz *et al.*, 2003; Bronikowski *et al.*, 2011; Schubert *et al.*, 2013), with numerous physical, social and behavioural explanations for this being proposed. The most popular theory is that, in polygamous species, intense sexual competition requires males to invest in mating success and reproductive fitness at the cost of health maintenance and longevity (Rolf, 2002; Clutton-Brock & Isvaran, 2007). This might in part explain the increased risk of death as a result of cardiovascular disease in males when compared with females, as suggested by this study. The interplay between social status, sex and disease would therefore be an interesting focus for further investigation into great ape heart-disease aetiopathogenesis.

### **Species variation in risk of cardiovascular disease associated death**

In a prior review of European and North American zoo-housed great ape mortality from 2004 to 2014 (Strong, 2017; Strong *et al.*, 2017), only six orangutans [of 38 adult and aged/elderly (i.e. > 15 years of age) orangutans scrutinized] were identified as having died as a result of cardiovascular disease. The comparatively lower proportional mortality in adult and aged/elderly orangutans [ $n = 6$  out of 38 reviewed (16%)], when compared with Bonobos [ $n = 13$  of 20 reviewed (65%)], Chimpanzees [ $n = 30$  of 96 reviewed (31%)] and Western lowland gorillas [ $n = 15$  of 56 reviewed (27%)] of similar ages, is suggestive that orangutans might be less susceptible to cardiovascular disease when compared with the other great ape taxa (Fig. 1). Orangutans differ from the other great ape taxa in several ways (Caldecott & Miles, 2005). These species are the only great apes to inhabit South East Asia, the other taxa all being endemic to Africa. The orangutan is also predominantly frugivorous, their diet consisting of a much higher proportion of fruits and seeds than the more folivorous and omnivorous gorilla, Bonobo and Chimpanzee (see Cabana *et al.*, 2017). Unlike the other taxa, which exist usually in family groups, the orangutan is a largely solitary species. They are also an arboreal species, spending a much greater proportion of their time in the trees than on the ground than other great apes. Finally, orangutans are also genetically very distinct from the African great apes and humans, which are grouped together in the *Homininae* subfamily (see Groves, 2017). If further analysis (e.g. on a larger data set) were to confirm that orangutans are in fact less at risk of death as a result of cardiovascular disease, the role that these and many other factors might play in disease risk and aetiopathogenesis would be interesting areas for future research.

### **Manner of death**



Many of the great apes in this study did not display any clinical signs of ill health prior to their death, which was subsequently categorized as being sudden in nature. That is not to say, however, that these apes were truly free of clinical signs or symptoms. The animals might have been experiencing, for example, feelings of light headedness or palpitations, which they were not able to communicate or might even have intentionally masked. It was for this reason, that the definition of sudden death used by Virmani *et al.* (2001), whereby the deceased was last seen in a stable condition less than 24 hours previously, was deemed most appropriate for use in this study.

It is possible, that some very subtle signs of suboptimal cardiac health do exist, an understanding of which requires more in depth study of clinical records assessing for any correlation between ante- and post-mortem findings. However, the question remains; what action a clinician might take if informed of a suspected heart condition in a great ape. Because of their size and dangerous nature, a full health assessment of a great ape requires the animal to be anaesthetised; however, this study identified cardiovascular disease as a risk factor for peri-anaesthetic death. The risk of death is, of course, not a reason to take no action at all but this suggests that the veterinarians, keeping and curatorial staff should be well informed about the potential consequences of carrying out such procedures on these animals. An appreciation for the risk of anaesthetic death must also be considered when anaesthetising any great ape that falls within the subpopulations identified by this study as being at particularly high risk, even in the absence of cardiac symptoms or other cause for concern. Clinicians must, at very least, be knowledgeable about the cardiovascular effects that the anaesthetic drugs they are using can have on the cardiovascular system and be equipped to deal with them should they occur.

### **Cardiomyopathies**

This study implies that the most common pathologies causing cardiovascular disease related mortality among great apes are the cardiomyopathies. Cases of hypertrophic (HCM), dilated (DCM), restrictive (RCM) and arrhythmogenic right ventricular (ARVC) cardiomyopathies were all identified from the post-mortem reports under study. More commonly, however, great apes were reported to be affected by a disorder (often called 'fibrosing cardiomyopathy', FCM), which does not fit into any of these well-recognized categories or diagnoses (Richardson *et al.*, 1996; Davies, 2000; National Heart Lung and Blood Institute, 2016).

The term FCM was first used in 1995 to describe myocardial replacement fibrosis with atrophy and hypertrophy of cardiac myocytes, absent to mild myocardial inflammation, with no apparent aetiology or associated disease condition in 11 captive male Western lowland gorillas (Schulman *et al.*, 1995). FCM has not since been further defined nor characterized in any greater detail. Its association with ante-mortem symptoms and other cardiovascular pathologies, such as atherosclerosis and hypertension, have also been poorly studied. FCM is not a diagnostic term that

is recognized or used in any other clinical or pathological context, whether veterinary or medical. Despite this, influenced by the veterinary literature and as shown by this study, the tendency to diagnose FCM in any fibrosed heart, has become commonplace within the zoo profession. However, myocardial fibrosis is non-specific; it is one of the most common histologic features of the chronically failing heart and has many causes, such as myocardial infarction (Whittaker *et al.*, 1989; Sun & Weber, 2005), hypertension (Díez, 2007) or inflammation (myocarditis) (Kania *et al.*, 2009). Myocardial fibrosis is also a common histopathological feature of dilated and hypertrophic cardiomyopathy (Assomull *et al.*, 2006; Ho, C. Y., *et al.*, 2010; O'Hanlon *et al.*, 2010; Schalla *et al.*, 2010; Ellims *et al.*, 2012; Gulati *et al.*, 2013). The presence of myocardial fibrosis alone is not indicative of a specific disease nor pathological process, which is distinctive to the great ape heart. For this reason, the authors prefer the use of the term idiopathic myocardial fibrosis, which provides a more accurate descriptive diagnosis of an unclassified chronic cardiac-disease process of unknown aetiology.

### **Limitations of the study**

Because this study was a retrospective observational review, it is limited by various factors, including: (1) the authors having little control over raw data collection and recording, and therefore data quality and consistency, (2) missing data and information, and (3) great variation in both the approach to examination and descriptive terminology used in reporting diseases between collections. To minimize any potential impact that this might have upon the results, complete raw data sets (full post-mortem reports) were obtained where possible. These reports were reviewed in detail and further qualitative information was requested when required to assist with clarification. The sample size ( $n = 71$ ) in this study was also small, especially when broken down by taxa, and for this reason the statistical data presented may not be representative of the entire population. This is particularly true for the orangutans, of which only six were represented in this study (from 60 reports reviewed). Therefore, further data collection and longitudinal monitoring are required to substantiate the findings of this study.

### **Implications of the study**

The implications of the findings from this retrospective review of great ape cardiovascular disease epidemiology and pathology are many. Not least, they reiterate the need for a full post-mortem examination to be carried out in the event of every great ape death, and for a detailed report to be generated, stating not only cause of death but also describing all contributing and confounding diseases. Specifically, the inconsistencies and inadequacies in current practices relating to the examination and reporting of great ape cardiovascular lesions highlighted by this study, have the potential to limit the quest for knowledge in this field. Therefore, the authors conclude that there is a critical need for improvements in the consistency and quality of post-mortem examination of the great ape heart to be implemented across Europe, and for dedicated prospective research

investigating great ape cardiovascular aetiopathogenesis to be carried out [for more information, see 'Guidelines for consistent cardiovascular post-mortem examination, sampling and reporting of lesions in European zoo-housed great apes' (Strong *et al.*, 2018)].

As more information becomes available and is analysed, it will hopefully be possible to develop and implement standardized methods for screening, treating and managing cardiac disease in great apes. The findings of this study substantiate reports by others (Lammey *et al.*, 2008; Varki *et al.*, 2009) in demonstrating that great ape cardiovascular associated mortalities are frequently sudden or unexpected. This implies a need for proactive ante-mortem screening to identify at-risk or affected individuals before it is too late (i.e. before death). Findings related to the typically advanced age for deaths resulting from cardiovascular disease, suggest that such screening should, at very least, form part of the routine management and healthcare of the ever-growing elderly great ape population. However, given that fibrosis is suggestive of chronic myocardial damage, it is possible that the onset of disease might precede death by months or even years. It would therefore be prudent to include even young animals in such screening, not least to gather baseline (healthy) information for future reference.

The implementation of routine ante-mortem screening will require a sound understanding of which diagnostic tests are of greatest relevance and practical application. Furthermore, as we increase our knowledge about the effects of various anaesthetic agents on the cardiovascular system of great apes, it should be possible to reduce the risks of cardiovascular disease related peri-anaesthetic mortality. For example, this might involve determining ways in which affected or 'at risk' animals can be identified without the need for anaesthesia, such as training individuals for conscious echocardiography, electrocardiography, blood-pressure assessment, sample (blood, urine, saliva) collection or continual electrocardiogram monitoring using implantable loop recorders.

The study presented here provides indications that there are several potential risk factors involved in great ape cardiovascular disease epidemiology and pathogenesis, all of which warrant further exploration. This study did not assess for any patterns of inheritance nor explore specific genetic factors, which might be involved in great ape cardiovascular disease. Given that breeding in zoo-housed great apes is tightly managed as part of international breeding programmes, and that cardiovascular disorders (e.g. ARVC) with a strong familial basis have been identified (Tong *et al.*, 2014; this study), such investigations would be important next steps.

The findings hereby presented are a valuable addition to the growing body of literature aimed at improving our understanding of the causes and effects of cardiac disease in great apes. Whilst demonstrating that knowledge about this topic remains in its infancy, this study also highlights the

potential positive impact that taking an internationally collaborative and standardized approach to future investigation could have on expanding our understanding in this field.

#### PRODUCTS MENTIONED IN THE TEXT

**GraphPad Prism7 for MacOS X:** statistical analyses software, produced by GraphPad Software, Inc., La Jolla, CA 92037, USA.

**Microsoft, 2010:** computer software (Microsoft Excel, Microsoft Office), version 14.0.7147.5001, produced by Microsoft, Redmond, WA 98052, USA.

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#### **CAPTION**

**Fig. 1. Survival graph showing age at death as a result of cardiovascular disease across Bonobos *Pan paniscus* ( $n = 13$ ), Chimpanzees *Pan troglodytes* ( $n = 37$ ), Western lowland gorillas *Gorilla gorilla gorilla* ( $n = 15$ ), and Bornean orangutans *Pongo pygmaeus* and Sumatran orangutans *Pongo abelii* ( $n = 6$ ) (total  $n = 71$  individuals). Chimpanzees appeared to succumb to cardiovascular disease at a younger age and orangutans later in life when compared with the other taxa.**