

Research article

What necropsy reports can tell us about menopausal and age-related changes in western lowland gorillas (*Gorilla gorilla gorilla*)

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Abstract

This paper explores age-related post-mortem changes in zoo-housed gorillas. Our previous research examined hormonal changes in zoo-housed ageing western lowland gorilla (*Gorilla gorilla gorilla*) females in order to assess whether they experienced hormonal menopause. We had the opportunity to investigate whether these females showed post-mortem changes similar to those seen in ageing human females, and whether or not these changes are associated with general patterns of ageing, or hormone-mediated changes, or both. We reviewed necropsy reports for 14 females, ranging in age from 30 to 56 years at time of death. We evaluated all females for cardiovascular and reproductive tract anomalies. There were no significant differences in occurrence of cardiovascular disease ($P = 0.256$) or reproductive tract abnormalities ($P = 1.00$) between females considered to be menopausal at time of death and those for whom we could not definitively ascertain reproductive status. Females over 45 years of age were significantly more likely to exhibit reproductive tract pathologies ($P = 0.031$) than were females 45 and younger. To our knowledge, this is the first study to report on post-mortem changes in the reproductive tracts in aged gorillas. These findings highlight the importance of long-term monitoring and post-mortem follow-up to more clearly discern patterns in older females and to shed light for comparisons between taxa.

Introduction

Menopause is defined as the complete cessation of menstruation as a result of the decline and loss of ovarian follicular function (Burger et al. 1995, 2007). It is often described as a uniquely human phenomenon because of the associated extended post-reproductive lifespan in women (Pavelka and Fedigan 1991; Hill and Hutardo 1991). Although reproductive cessation may occur in other species, it is generally assumed that it is part of the process of somatic ageing with timing so close to death that an extended post-reproductive lifespan is rarely observed (Caro et al. 1995; Hawkes et al. 1998). Indeed, a long post-reproductive lifespan is rare in wild populations of non-human primates as females do not live long enough to reach a post-reproductive period (Borries and Koenig 2008; Nishida et al. 2003; Alberts et al. 2013). Non-human primates

in zoos, however, are more likely to reach ages characteristic of a species' maximum longevity (Austad and Fischer 1992). Reporting on maximum lifespans for seven primate taxa, including mountain gorillas, Bronikowski et al. (2011) noted that the oldest confirmed gorilla in the wild was 38–39 years old. In contrast, de Magalhaes and Costa (2009) report that the oldest gorilla in captivity died at 55.4 years of age (The Animal Ageing and Longevity Database, Tacutu et al. 2013) and the oldest living gorilla female in captivity is 59 years of age (Wilson 2015). If an extended post-reproductive lifespan is to be observed, it is in the zoo environment that we should see it (Austad and Fischer 1992). Previously, we explored hormonal changes in zoo-housed ageing gorilla females in order to assess whether they experienced hormonal menopause (Atsalis et al. 2004; Atsalis and Margulis 2006; Margulis and Atsalis 2006) or perimenopause (Atsalis and Margulis 2008). Briefly, we

Table 1. Summary of changes in reproductive tract and cardiovascular system in 14 gorilla females based on necropsy results. Necropsy notes are summarized based on findings related to abnormalities of the reproductive tract (in column "Repro Tract"), and cardiovascular system (in column "Cardio"). Date of last sampling indicates year of last hormonal evaluation. "Interval" is the time elapsed between last hormonal evaluation and death. Y=yes; N=no.

Subject	Age at death (yrs)	Summary of necropsy findings	Date of last hormonal sampling	Interval, last hormonal sampling → death (yrs)	Hormonal status (cycling: Y/N)	Necropsy findings: Repro tract	Necropsy findings: Cardio-vascular
1	30	<i>Reproductive tract:</i> none noted <i>Cardiovascular:</i> coronary arteriolar arteriosclerosis distributed sporadically; mild, multifocal arteriosclerosis involving the aorta; mild myocardial fibrosis	2004	0.2	N	N	Y
2	34	<i>Reproductive tract:</i> chronic abscess of uncertain origin involving right ovary and uterus <i>Cardiovascular:</i> hypertension; mild aortic aneurism; hypertension caused encephalopathy; left ventricular hypertrophy; hyperplastic arteriosclerosis	2004	5	N	Y	Y
3	38	<i>Reproductive tract:</i> none noted <i>Cardiovascular:</i> atherosclerosis in meninges; congestive heart failure	2004	6	N	N	Y
4	40	<i>Reproductive tract:</i> none noted <i>Cardiovascular:</i> fibrosis left AV valve (mild fibrosis of heart); marked cardiac fiber hypertrophy; atherosclerosis; cerebral atrophy	2006	1	Y	N	Y
5	42	<i>Reproductive tract:</i> uterine adenocarcinoma (endometrial; indirect cause of death); uterine adenocarcinoma metastases to colon <i>Cardiovascular:</i> atherosclerosis	2006	3	N	Y	Y
6	43	<i>Reproductive tract:</i> none noted <i>Cardiovascular:</i> none noted	2004	5	Y	N	N
7	45	<i>Reproductive tract:</i> calcification of tunica media; athero- and arteriosclerosis involving arteries of ovaries; multifocal leiomyomas, polypoid endometrial metaplasia; vaginal mucosa endometriosis <i>Cardiovascular:</i> chronic cardiomyopathy; interstitial fibrosis; cardiomyotic hypertrophy; presumptive vascular thrombosis; atherosclerosis; arteriosclerosis	2006	4	N	Y	Y
8	45	<i>Reproductive tract:</i> none noted <i>Cardiovascular:</i> aortic dissection; arteriosclerosis and mild myocardial fibrosis	2006	2	Y	N	Y
9	46	<i>Reproductive tract:</i> leiomyosarcoma in uterus; rupture of colon into mass; extensive pelvic fibrosis; inflammation within uterus; blockage of ureters led to renal failure <i>Cardiovascular:</i> hypertension; severe myocardial fibrosis	2006	4	N	Y	Y
10	48	<i>Reproductive tract:</i> focal endometrial carcinoma; ovarian adenocarcinoma <i>Cardiovascular:</i> none noted	2002	6	Y	Y	N
11	48	<i>Reproductive tract:</i> leiomyoma in uterus; chronic myometrial abscess; fibrosis adhesions <i>Cardiovascular:</i> aortic atherosclerosis; moderate myocardial fibrosis with myocyte atrophy	2008	1	Y	Y	Y
12	49	<i>Reproductive tract:</i> urocystitis (bladder) endometriosis; extensive adhesions <i>Cardiovascular:</i> none noted	2004	7	Y	Y	N
13	51	<i>Reproductive tract:</i> multifocal, uterine fibroids; adenomyosis, mild.; mild, multifocal, cystic endometrial hyperplasia <i>Cardiovascular:</i> Multifocal, medial hypertrophic arteriolosclerosis; focal, mild interstitial myocardial fibrosis	2006	8	N	Y	Y
14	56	<i>Reproductive tract:</i> cystic hyperplasia, adenomyosis; benign growth of endometrium into uterine mucosa <i>Cardiovascular:</i> none noted	2004	4	Y	Y	N

found that approximately one-fourth of gorillas for whom we had hormonal data were no longer cycling. Approximately one-third showed irregular cycling patterns, suggestive of perimenopause. The relationship with age was less obvious: in one case, a female as young as 38 years of age was menopausal, and a female as old as 48 was still cycling. Here, we expand on our investigation by reviewing necropsy reports from our previous subjects that allow us to evaluate whether zoo-housed ageing gorilla females show post-mortem changes similar to those seen in ageing human females, and whether these changes are associated with general patterns of ageing, are hormone-related, or both.

In 2002, we began a nationwide study of zoo-housed gorillas evaluating cycling patterns through changes in progesterone levels in order to investigate whether and when females experience reproductive ageing (Atsalis et al. 2004; Atsalis and Margulis 2006; Margulis and Atsalis 2006). We examined faecal progestogen concentrations in 24 geriatric females. Based on our investigation, seven of these females were not cycling and another nine showed variable cycling patterns that we characterized as perimenopausal (Atsalis and Margulis 2006, 2008). As in humans, cycling patterns varied greatly, with cessation of cycling as measured by progesterone concentration occurring between 38 and 51 years of

age. One female over the age of 50 was still cycling though she was confirmed to have stopped cycling by 54 years of age (Margulis and Atsalis unpublished data).

In human females, menopause is associated with specific clinical signs, such as hot flushes and vaginal atrophy (Li et al. 2003), and with increased disease risk (Wartko et al. 2013). Although we are not able to test for these clinical signs in gorillas, we are able to evaluate increased disease prevalence based on post-mortem evaluations. Gorillas in zoos accredited by the Association of Zoos and Aquariums (AZA) undergo complete necropsies to confirm cause of death and document specific physiological changes that can inform husbandry practices. We sought to take advantage of this rich resource of data to investigate whether aged female gorillas showed post-mortem signs of pathology similar to those seen in menopausal human females. Specific changes of interest for our investigation included reproductive tract abnormalities, cardiovascular disease, osteoporosis, and breast and endometrial cancer (Dreisler et al. 2009; Garuti et al. 1999; Hulley et al. 1998; Mishra et al. 2003). The latter two are particularly related to age of menopause in humans (Kelsey et al. 1993; Niwa et al. 2000). Based on our previous research on reproductive ageing in gorillas, we can begin to evaluate whether or not these changes are related to the hormonal milieu of the ageing gorilla female. Building on our prior research, the current study aims to examine age-related and hormone-related changes in ageing gorilla females based on standard necropsy reports. Our findings could allow us to address practical management issues associated with ageing female gorillas, as well as determine whether these changes follow a pattern similar to that observed in human females.

Methods

Previously we measured hormonal cycling patterns in 34 western lowland gorillas (*Gorilla gorilla gorilla*), 24 of whom were over thirty years of age, with 22 of these 24 over 35 years of age. We monitored electronic mailing lists, including gorillakeepers@yahoogroups and zoobiology@yahoogroups, for reports of gorilla deaths. In addition, we reviewed the AZA North American Regional Gorilla Studbook, which was up to date through April 2011 (Lukas, personal communication). We identified 15 deceased females who had been part of our original study. Associated zoological institutions were contacted for necropsy reports, which we obtained for 14 of the 15 females. We reviewed necropsy reports for the following: (1) cause of death, (2) pathologies of the reproductive tract, and (3) cardiovascular pathologies. The necropsy reports varied in level of detail; we inferred that lack of any notation regarding anomalies in the cardiovascular or reproductive system implied that no substantive pathology was observed.

For seven of the 14 necropsied females, we had hormonal data current until 2004. Four of these females had been documented as no longer cycling based on pattern of progestogens. Of the remaining seven necropsied females, we had hormonal data current until 2006 (and in one case through 2008) and two of those seven females were confirmed as no longer cycling based on patterns of progestogens (Table 1). The gap between hormonal measurement and death for the seven females who were still cycling at their last hormonal assessment ranged from 0.2 to six years. It was not possible to determine the reproductive state for these females at the time of death.

For the purposes of the current analysis, we separated females into two age categories: older than 45 years of age and less than or equal to 45 years of age. We classified all females based on the presence or absence of reproductive and cardiovascular anomalies. We used a Fisher's exact test to determine if there were significant differences in the frequency of cardiovascular or

reproductive tract abnormalities based on age, or reproductive status at time of death.

Results

Nine of 14 females showed changes in the reproductive tract and nine of 14 also exhibited cardiovascular involvement (Table 1). There were no significant differences in occurrence of cardiovascular disease ($P = 0.256$) or reproductive tract abnormalities ($P = 1.00$) between females considered to be menopausal at time of death, and those for whom we could not definitively ascertain reproductive status (Figure 1). Females over 45 years of age were significantly more likely to exhibit reproductive tract pathologies ($P = 0.031$) than were females 45 and younger (Figure 2). Specifically, only three of eight females 45 years of age and under were found to have reproductive tract abnormalities whereas all six females over 45 exhibited abnormalities. No such differences were evident with respect to cardiovascular disease; half of the females over 45 years of age exhibited evidence of cardiovascular involvement, and three quarters of females 45 and younger showed a similar pattern ($P = 0.58$).

Discussion

We discovered that older gorilla females have a noticeably higher incidence of reproductive tract abnormalities than younger females. Nevertheless, the incidence of reproductive tract abnormalities was not necessarily high in females considered to be non-cycling at their last hormonal assessment. We note, however, that for half of our subjects, cycling status at time of death was unknown because there was a lapse of 0.2 to 8 years between timing of last hormonal assessment and necropsy. Therefore, while it is possible that those females exhibiting reproductive tract abnormalities may in fact have been non-cycling, we are unable to confirm their status. The necropsy data we received from participating zoos varied in terms of quantity of information

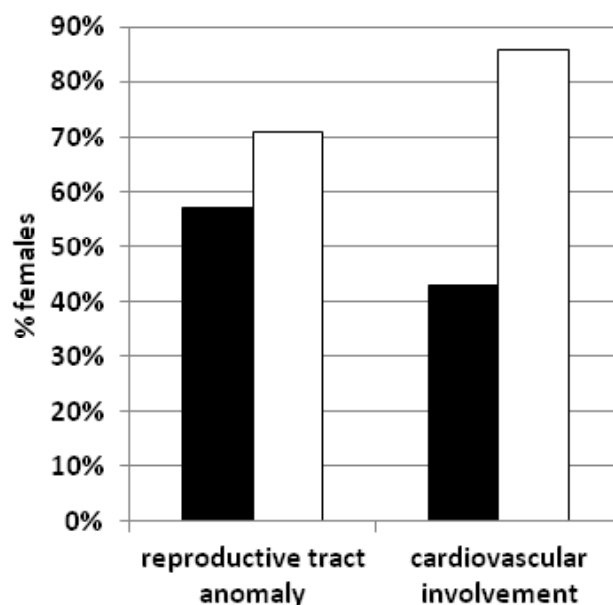


Figure 1. Percentage of females exhibiting abnormalities of the reproductive tract or the cardiovascular system. Solid bars = females confirmed to be non-cycling at time of death ($n = 7$). Open bars = females of unknown cycling status at time of death ($n = 7$).

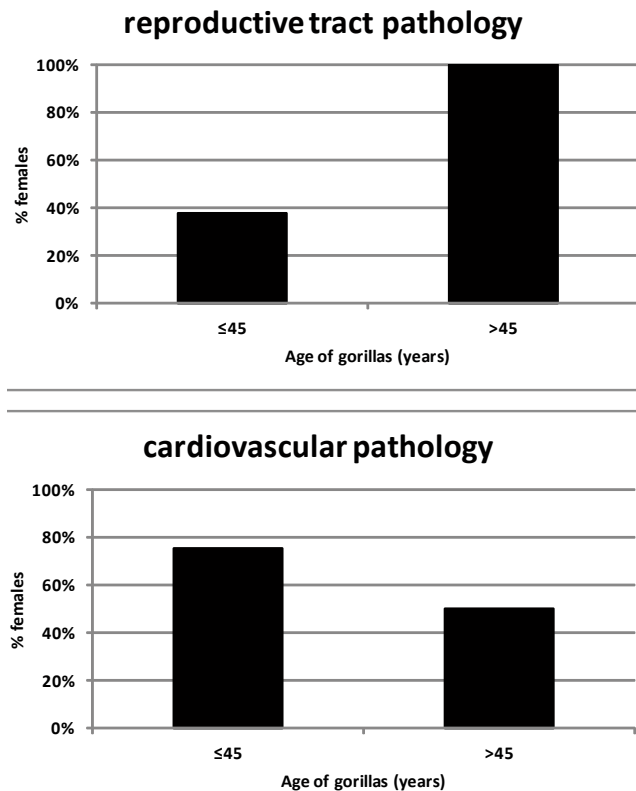


Figure 2. Percentage of 14 females under ($n=8$) and over ($n=6$) 45 years of age that exhibit pathologies of the reproductive tract (upper figure) and cardiovascular system (lower figure).

and level of detail. Given the retrospective nature of this study, we were not able to control the quality of the data. We assumed that the lack of pathological findings could be interpreted as a normal finding for both the reproductive and cardiovascular system. Although the lack of these data present a limitation, our results clearly support age-related changes in reproductive tract health.

Additionally, the necropsy reports suggest that reproductive tract anomalies may be more consistently related to age than are cardiovascular anomalies; whereas all females over the age of 45 exhibited abnormalities of the reproductive tract, there were no age differences found with respect to evidence of cardiovascular involvement. Specifically, although cardiovascular disease was evident in nine of the fourteen animals in our study, there were not any significant differences in the frequency of cardiovascular disease between our two age categories. We note, however, that by conventional standards all animals in our study were considered geriatric.

The Great Ape Heart Project (<https://greatapeheartproject.org/>) represents a multi-institutional effort to explore patterns such as these to more clearly define the extent, scope, and patterns of cardiovascular disease in zoo-housed great apes. Parallel efforts in Europe (the Ape Heart Project, endorsed by the EAZA Ape TAG) echo these efforts. Earlier investigations in other primate species are also informative here. In a large sample ($n = 175$) of laboratory-housed rhesus macaques (*Macaca mulatta*), Uno (1997) noted substantial evidence of disease, most notably with respect to coronary sclerosis and amyloid plaques, with an incidence of 80–100% in the oldest age groups. Incidence of cancer increased from 0–20% in individuals under the age of 30 years to 50% in older individuals. Our small sample size compared to Uno's extensive database may have contributed to the differences in our findings.

Uno did not describe reproductive tract anomalies but noted a relatively low incidence of reproductive tract cancers amongst all females. Cline et al. (2008) and Wilkinson et al. (2008) reported on the incidence of reproductive tract abnormalities in lab- and free-ranging macaque species, indicating an increased incidence of reproductive tract disease in older females.

Through our previous research we discovered females as young as 38 to be non-cycling, and females as old as 51 to be cycling. We were able to confirm duration of individual post-reproductive lifespan for two subjects only: females who were known to be cycling at one sampling time-point, and not cycling at a subsequent time-point. Thus, for these two females, we calculated a post-reproductive lifespan of 2–7% of life, markedly shorter than what is seen in humans, which can be as high as 40% of total lifespan. Moreover, in human females, there is a clear relationship between age, reproductive status and disease risk; the risk of uterine and breast cancers is higher post-menopause, increasing as age at menopause advances (Kelsey et al. 1993; Niwa et al. 2000). Wartko et al. (2013) reported that endometrial cancer is the most common type of gynaecologic cancer, and the prevalence increases after menopause. Risk of cardiovascular disease is also reported to be higher in post-menopausal women, possibly related to age rather than to reproductive status (Barrett-Connor 2013). We too found evidence for pathology in the reproductive tracts of ageing gorillas, with noticeable endometrial involvement. Such anomalies were found in all the subject females that were not cycling during our hormonal study.

Bolton et al. (2015) identified reproductive tract abnormalities in only 7.4% of the 54 gorillas whose reproductive tracts were examined, though these were not old females (all individuals with abnormalities were between the ages of 22 and 33), nor were hormonal data available. It was not clear whether these females were on contraception, or experiencing natural cycling. Several studies have explored cardiovascular disease in gorillas (Kenney et al. 1994; Meehan and Lowenstine 1994; Murphy et al. 2011), but these have focused largely on males. Meehan and Lowenstine (1994) reviewed necropsy reports for 74 gorillas ranging in age from stillbirths to geriatric, and reported that 41% of adults exhibited signs of cardiovascular disease. When broken down by sex, however, 59% of males but only 29% of females fell into this category. Additionally, there was no difference between adult females (seven to 30 years) and geriatric females (greater than 30 years of age) with respect to cardiovascular disease. Three of ten adult (30%) and two of seven geriatric females (29%) presented with cardiovascular pathology. In contrast, six of 12 adult males, age nine to 30 years (50%) and seven of ten (70%) geriatric males showed such signs. Therefore, our findings align with previous surveys suggesting that cardiovascular disease is both less common, and less age-related, in female gorillas than in male gorillas.

To our knowledge, this study is the first to report on post-mortem changes in the reproductive tract in aged gorillas. The data presented offer insights into age-related pathology in female gorillas allowing for some limited comparisons with humans. Our results suggest that there are some similarities between the patterns of reproductive ageing and disease risk in humans and gorillas. These findings highlight the importance of long-term monitoring and post-mortem follow-up to more clearly discern patterns in older females and to shed light for comparisons between taxa. Furthermore, clarity and consistency in the necropsy protocols should facilitate further investigations to help elucidate patterns — age-related and otherwise — associated with cardiovascular and reproductive pathologies. Such coordinated efforts could provide valuable practical knowledge, as well as insights into evolutionary patterns and similarities across the great ape taxa.

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