Chapter 13

Age-Related Changes to the Bony Structure and Musculature of the Shoulder in a Nonhuman Primate Model

Anthony C. Santago II[1], **Johannes F. Plate**[2], **Katherine R. Saul**[3]
[1]*The MITRE Corporation, McLean, VA, United States;* [2]*Department of Orthopaedic Surgery Wake Forest Baptist Health, Winston–Salem, NC, United States;* [3]*Department of Mechanical and Aerospace Engineering North Carolina State University, Raleigh, NC, United States*

INTRODUCTION

Age-related changes to the musculoskeletal system of the upper limb are thought to be associated with progression to disability in humans. The successful completion of activities of daily living (ADLs) is an important marker of the ability to live independently; performance of many ADLs requires strength and coordination in the upper limb (Lundgren-Lindquist and Sperling, 1983), and the reduction in the capability of the upper limb to perform ADLs has been associated with worse outcomes following hospitalization in the elderly (Abizanda et al., 2007).

Age-related pathology of the shoulder including osteoarthritis and rotator cuff tears may lead to marked disability and pain affecting the performance of functional tasks. Approximately 13%–26% of individuals older than 70 years are affected by shoulder pain (Luime et al., 2004). Osteoarthritis in the shoulder has been shown to increase with age (Kobayashi et al., 2014; Mantila Rossa et al., 2012) leading to approximately 30,000 total shoulder arthroplasties performed in the United States in 2006, mainly for the treatment of symptomatic shoulder osteoarthritis (American Academy of Orthopaedic Surgeons, 2008). The shoulder experiences exaggerated declines in strength with aging compared to the elbow and wrist (Vidt et al., 2012) and shoulder strength is a limiting factor in both reaching and pulling tasks (Daly et al., 2013). Rotator cuff tears are a common degenerative shoulder injury resulting in decreased strength and function (Vidt et al., 2016), predominantly affecting older adults (Yamamoto et al., 2010). With increased life expectancy and higher activity levels of the aging population, the prevalence of shoulder pathology including rotator cuff tears and degenerative shoulder disease is expected to increase (Oh et al., 2009), warranting further research of the underlying pathophysiologic mechanisms of aging in the shoulder.

Understanding longitudinal changes to structure, function, and the interplay between the two would lend insight into early predictive factors for future disability that are difficult to assess in a cross-sectional study design. However high cost, long life span, and the need for invasive measurements to fully characterize skeletal muscle make longitudinal studies of the musculoskeletal system difficult to perform in humans. An animal model of upper extremity aging would more easily allow for longitudinal studies by limiting many of the logistical concerns associated with human subjects. Unfortunately, data regarding musculoskeletal degeneration in animals resulting strictly from normal aging are limited (Choi et al., 2013; Hagen et al., 2004; McKiernan et al., 2011; Plate et al., 2014).

Small animals (mouse, rat, and rabbit) have been widely used for shoulder research. The rat has similar anatomic features to humans (Derwin et al., 2007; Edelstein et al., 2011; Soslowsky et al., 1996) and has become an indispensable model for studying shoulder degeneration (Mannava et al., 2011; Soslowsky et al., 2000), including surgically induced rotator cuff tears (Edelstein et al., 2011; Soslowsky et al., 1996; Mannava et al., 2011), tendon to bone healing (Bedi et al., 2010; Plate et al., 2014), muscular changes following injury (Soslowsky et al., 2000; Barton et al., 2005), and biologically enhanced repair strategies (Derwin et al., 2010). However, rat studies limit translation to humans because rats are quadrupedal with weight bearing forelimbs, they have limited overhead and multidirectional shoulder movement, and they are small (Derwin et al., 2007; Gerber et al., 1999; Mannava et al., 2013). Larger animal models, including the rabbit (Derwin et al., 2010; Grumet et al., 2009; Gupta and Lee, 2007; Rowshan et al., 2010; Rubino et al., 2008), dog (Derwin et al., 2007), and sheep (Gerber et al., 2004; Turner, 2007), share pathophysiological features of shoulder degeneration; however, the acromion and the coracoid process are small or not present, which differs from human shoulder anatomy (Derwin et al., 2010). A nonhuman primate model offers a solution that mitigates many of these problems (Table 13.1).

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TABLE 13.1 Comparison of Various Animal Models Utilized for Shoulder Research

	Rat/Mouse	Rabbit	Dog	Sheep/Goat	Nonhuman Primates
Advantages	• Comparable rotator cuff anatomy with supraspinatus tendon translating underneath an enclosed arch • Widely available and inexpensive • Lowest demand (care, facilities) • Large sample size	• Fibrofatty infiltration following injury • Relatively inexpensive • Low demand (care, facilities)	• Assessment of tendon-to-bone healing • Close to human size • Comparable biomechanical loads of the rotator cuff	• Use of standard human repair techniques • Assessment of tendon-to-bone healing • Close to human size	• Similar anatomy • Similar insertional rotator cuff tendon anatomy • Similar age-related degenerative changes of the shoulder • Use of standard human repair techniques • Multidirectional shoulder movement • Assessment of tendon-to-bone healing
Disadvantages	• Limited multidirectional movement of the shoulder • Small scale compared to human • Significant fatty infiltration following surgical rotator cuff injury only in combination with suprascapular nerve transection • Quadrupedal, weight-bearing • No retears following rotator cuff repair	• Limited comparability of anatomy • Use of subscapularis tendon • Quadrupedal, weight-bearing	• Limited multidirectional movement • Different anatomy of acromion and coracoid • Quadrupedal, weight-bearing • Moderate demand (care, facilities) • Expensive	• Limited multidirectional movement • Different anatomy • Use of infraspinatus tendon • Quadrupedal, weight-bearing • High demand (care, facilities) • Expensive	• Semiterrestrial, weight-bearing forelimbs • Highest demand (care, facilities) • Highly expensive for longitudinal studies • Ethical concerns
Chronic rotator cuff tear condition	• Chronic rotator cuff tear partially persists, but spontaneous healing with scar-tissue forming a "pseudo-tendon"	• Chronic condition for muscular changes • Spontaneous healing	• Spontaneous healing with scar tissue	• Spontaneous healing with scar tissue	• Healing response to chronic injury has not been assessed
Outcome measures	• CT, MRI • Gait analysis • Histological analysis • Functional in vivo assessment	• CT, MRI, ultrasound • Gait analysis • Histological analysis	• CT, MRI, ultrasound • Gait analysis • Histological analysis	• CT, MRI, ultrasound • Histological analysis	• CT, MRI, ultrasound • Histological analysis • Assessment of physical activity, walking speed, and functional use of upper extremity and overhead activity
Areas of research	• Pathomechanism of age-related degeneration, intrinsic and extrinsic rotator cuff injury (impingement, overuse) • In vivo functional biomechanic studies • Molecular pathways • Rehabilitation	• Pathomechanism of muscular changes • Biomechanical studies • Tendon-to-bone healing with/without scaffold augmentation	• Tendon-to-bone healing with/without scaffold augmentation • Biomechanical studies • Mechanical strength of repair techniques	• In vivo biomechanical assessment of chronic rotator cuff tears • Mechanical strength of repair techniques	• Pathomechanism of age-related degeneration • In vivo tendon-to-bone healing • Biomechanical studies • Molecular pathways • Mechanical strength of repair techniques
Cost per animal (US Dollars)[a]	CD-1 mouse: $8, Lewis rat: $40	New Zealand white rabbit: $100–$200	Hound: $1000	Sheep/Goat: $1000	$2500–$5000[24]
Approximate per diem rates per animal (US Dollars)[b]	$1	$4	$14	$17	$10

CT, computed tomography; *MRI*, magnetic resonance imaging.

[a] *Mean approximate cost for illustration. Prices may vary by vendor, institution, and type of animal (species, age, strain).*

[b] *Mean per diem rates according to the Animal Resource Program at two U.S. academic institutions as of 10/2012.*

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Reports suggest that the African vervet monkey (*Chlorocebus pygerythrus*) may be a promising species to use as a human surrogate to study age-related musculoskeletal changes. Reductions in muscle fiber force in the vastus lateralis (Choi et al., 2013) and reductions in muscle mass of the hind limb (Kavanagh et al., 2016) similar to human aging have been reported. In addition, measures of physical performance that incorporate the upper limb were diminished in older vervets (Choi et al., 2013; Shively et al., 2012). Recent work has demonstrated that the vervet undergoes age-related structural changes to shoulder similar to what is experienced in humans such as a reduction of glenoid version angle and diminished physiological cross-sectional area (PCSA) of shoulder muscles, which is proportional to strength (Plate et al., 2013; Santago et al., 2015). This chapter outlines the evidence supporting the use of the vervet model as a surrogate for naturally occurring bony and muscular age-related changes to human shoulder.

Vervet Background and Demographics

Two recent studies quantified age-related musculoskeletal degeneration of the shoulder in a cohort of female vervets (Plate et al., 2013; Santago et al., 2015). The adult female vervet monkeys (*C. pygerythrus*) (Table 13.2) were obtained from the Wake Forest Primate Center, a research colony established on St. Kitts Island in the 1970s (Fairbanks and McGuire, 1986; McGuire, 1974). All procedures were conducted in compliance with state and federal laws, standards of the US Department of Health and Human Services, and regulations and guidelines established by the Institutional Animal Care and Use Committee. The institution is accredited by the Association for Assessment and Accreditation of Laboratory Animal Care.

Animals were housed among social groups of approximately 15–40 animals, allowed to roam freely in large, inside/outside pens (30 m^2), and to feed ad libitum. Euthanasia was performed as part of a larger experiment exploring immunologic and physiologic parameters and their relationship to aging. Prior to euthanasia, full-body computed tomography (CT) scans were performed on sedated animals (Ketamine) using a 32-slice CT scanner (Toshiba Aquilion; Toshiba America Medical Systems, Tustin, CA, USA) with 350 μm isotropic resolution and 0.5 mm slices just prior to the end of the study.

Both the left and right upper limb of five middle-aged and six older adult female vervet monkeys were obtained. Vervets aged older than 20 years were categorized as older adults; the 26.4-year-old monkey is the oldest known female vervet in captivity, originating from the original colony (Plate et al., 2013).

Osseous Characteristics

Osteoarthritis in the shoulder has been shown to increase with age (Kobayashi et al., 2014; Mantila Rossa et al., 2012). In a study of five middle-aged and six older vervet shoulders, older vervets demonstrated similar degenerative changes of bony shoulder structures compared with humans based on CT evaluation (Plate et al., 2013). Specifically, prior to euthanasia,

TABLE 13.2 Characteristics of Vervet Specimens

Age (years)	Age Group (MA/OA)	Body Mass (kg)	Arm Length (Right) (mm)	Forearm Length (Right) (mm)
11.76	MA	6.57	119.55	108.80
9.43	MA	4.68	112.15	100.69
11.53	MA	5.87	114.01	105.99
11.63	MA	4.92	108.18	100.17
11.53	MA	7.08	113.99	109.99
21.48	OA	6.14	119.42	109.21
25.75	OA	4.00	107.67	103.71
26.41	OA	4.93	127.48	114.22
23.73	OA	5.51	111.17	108.51
19.86	OA	4.63	113.80	107.99
21.55	OA	5.12	111.46	106.15

MA, middle aged; *OA*, older adult.
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degenerative changes of the glenohumeral joint were evaluated on two-dimensional (2D) coronal CT images and were graded according to the Kellgren and Lawrence (KL) classification system (Kellgren and Lawrence, 1957). Three-dimensional (3D) CT-image reconstructions (AquariusNET; TeraRecon, Foster City, CA, USA) were used to identify glenoid deformity and osteophytes. The joint space was measured on axial 2D CT scans as the shortest distance between the humeral head and the glenoid fossa. The glenoid version angle was assessed from 3D reconstructed images that were resliced to create an axial section. The version angle was measured with a line drawn connecting the anterior and posterior glenoid rim relative to a line tangent to the body of the scapula; negative angles indicating retroversion and positive angles indicating anteversion. Retroversion of the glenoid on CT scans has been found to correspond to degenerative wear of the posterior articular surface or glenoid dysplasia (Walch et al., 1998). The presence of partial and/or full thickness rotator cuff tears as discontinuity of the supraspinatus and/or infraspinatus tendon was assessed on coronal CT images. The acromiohumeral distance (AHD) was measured to assess superior translation of the humeral head using 2D CT image reconstructions, which were standardized by setting the axes parallel to the short and long axes of the scapular body (Lochmuller et al., 1997).

Sixty-seven percent of the older vervets had significant degenerative changes in their shoulders compared to middle-aged animals based on the evaluation of CT images for signs of osteoarthritis. Shoulders in four of six older vervets (eight shoulders) had degenerative changes of the glenoid and humeral head with osteophyte formation on the posterior/inferior glenoid, while no gross degenerative changes were observed in any of the middle-aged animals ($P = .005$) (Fig. 13.1). Two of the eight shoulders were classified as KL Grade 1, three shoulders as Grade 2, one shoulder as Grade 3, and two shoulders in one older vervet as Grade 4 changes with massive osteophyte formation, humeral head deformity, and joint space narrowing.

Glenoid version angle significantly correlated with age, with an increase in glenoid retroversion with increased age. The glenoid of the older vervets was significantly retroverted (mean ± SEM; −2.2 degrees ± 0.5 degrees) compared to middle-aged vervets (mean ± SEM; 2.6 degrees ± 0.5 degrees, $P < .001$, Fig. 13.1). The mean joint space in older vervets (mean ± SEM; 0.55 ± 0.04 mm) was significantly decreased compared to the joint space in middle-aged animals (mean ± SEM; 0.69 ± 0.02 mm, $P = .003$). There was no significant difference in AHD between middle-aged and older adults (mean ± SEM; 5.5 ± 0.73 mm vs. 6.8 ± 2.23 mm, $P = .27$), indicating a normally positioned humeral head. The AHD measurement in the animal with KL Grade 4 was difficult to determine and was increased compared to other animals due to high-grade deformity and osteophyte formation (Fig. 13.1). The glenoid retroversion and significantly smaller joint space in older vervets were similar to age-related degenerative changes observed in osteoarthritis with cartilage wear in human subjects (Walch et al., 1998).

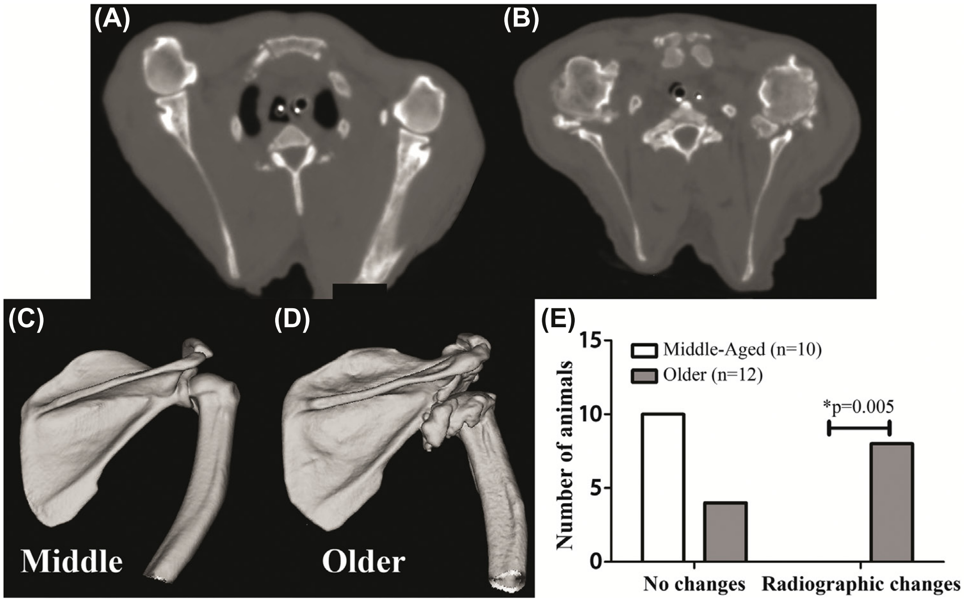

FIGURE 13.1 Representative axial computed tomography (CT) images of a middle aged (A) and older adult (B) vervet monkey shoulder with three-dimensional reconstruction of the middle aged (C) and older adult (D). The older animals exhibited marked glenoid degeneration and increased frequency (E) of shoulder degeneration detectable by CT. Noteworthy are the marked cartilage loss and osteophytic changes in the older adult vervets (D). *(Reprinted from Plate, J.F., et al., 2013. Age-related degenerative functional, radiographic, and histological changes of the shoulder in nonhuman primates. J Shoulder Elbow Surg 22, 1019–1029, with permission from Elsevier.)*

Muscle Density, Histological, and Immunohistochemical Characteristics

Aging and rotator cuff tears can result in alterations to the structure and function of muscle fibers (Vidt et al., 2016; Mendias et al., 2015; Larsson et al., 1997, 1978; Narici and Maffulli, 2010; Narici et al., 2003; Thom et al., 2007; Yu et al., 2007). To determine if there were similar changes in the supraspinatus of the middle aged and older vervets, CT, histology, and immunohistochemical analysis were employed (Plate et al., 2013). Muscle density of both supraspinatus muscles was measured from sagittal 3D reconstructed CT images from a 2 cm × 2 cm region of the supraspinatus muscles in the suprascapular fossa midway along the length of the scapular spine in a plane parallel to the scapular spine in line with the scapular body using the region of interest (ROI) tool embedded in the AquariusNET software (van de Sande et al., 2005). The left supraspinatus muscle specimens were used for histological analysis of muscle fiber cross-sectional area (FCSA) and immunohistochemical analysis of nuclear material content. Specimens were embedded in paraffin, cut into 5-mm-thick cross-sections, placed on glass slides, and stained with hematoxylin and eosin (H&E) or 4,6-diamidino-2-phenylindole (DAPI). Images were obtained at 200× magnification (Zeiss M1 microscope with ImagePro Plus v.6.3; Carl Zeiss, Jena, Germany). Three images per slide of 2 deep and 2 superficial samples were obtained and analyzed for a total of 12 images per specimen. Muscle FCSA was measured as the mean of 56.8 orthogonally cut muscle fascicles per sample by outlining representative muscle fibers with the ROI tool imbedded in ImageJ software (National Institute of Health, Baltimore, MD, USA) (Schneider et al., 2012). A modified counting procedure was used to quantify the fluorescence of nuclei on DAPI-stained images (Mannava et al., 2011; Gupta and Steward, 2003). This method was evaluated for accuracy and precision by comparing it to the manual counting of four randomly chosen images, which yielded a maximum deviation of ±1.2%.

The supraspinatus muscles of older vervets exhibited changes consistent with human aging. The muscles were significantly less dense according to Hounsfield unit measurements on CT-images compared to middle-aged animals (mean ± SEM; 87.0 ± 0.8 vs. 91.5 ± 0.8, $P = .004$). Histological analysis of the supraspinatus muscle in older vervets revealed significantly decreased FCSA in the superficial portion compared to middle-aged animals ($P < .001$) and similar FCSA in the deep portion ($P = .696$). Overall, middle-aged muscle (Fig. 13.2A) appeared more compact and organized on H&E stains compared to older vervets (Fig. 13.2B), whose muscle fibers were disorganized with atrophic changes. Quantification

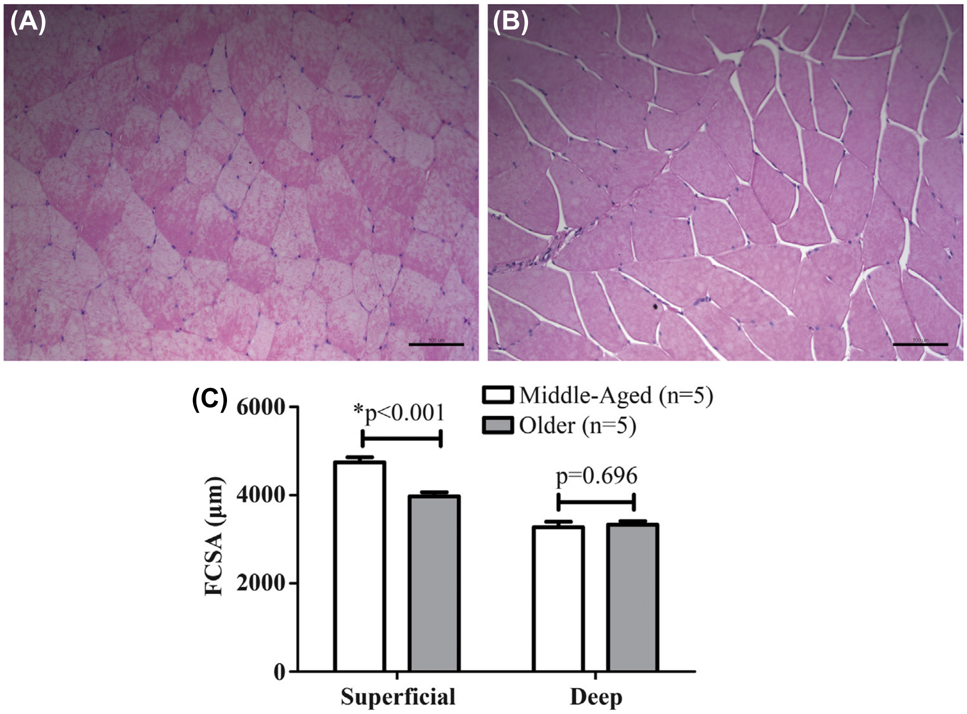

FIGURE 13.2 Representative hematoxylin and eosin (H&E) stained slides at 200 magnification of the superficial layer of the supraspinatus muscle in middle-aged (A) and older (B) animals. Muscle fiber cross-sectional area (FCSA) was measured on the H&E slides. The supraspinatus in middle-aged animals appeared to be more densely packed compared to older vervets, which revealed lower FCSA in the superficial portion of the muscle. In the superficial portion of the supraspinatus muscle, middle-aged animals revealed a greater FCSA compared to older vervets (mean ± SEM; 4740 ± 118.8 mm^2 vs. 3971 ± 98.0 mm^2, $P < .001$) (C). There was no difference in FCSA in the deep portion of the muscle between middle aged and older vervets (mean ± SEM; 3274 ± 123.2 mm^2 vs. 3331 ± 84.2 mm^2, $P = .696$). *(Reprinted from Plate, J.F., et al., 2013. Age-related degenerative functional, radiographic, and histological changes of the shoulder in nonhuman primates. J Shoulder Elbow Surg 22, 1019–1029, with permission from Elsevier.)*

of DAPI fluorescence revealed significantly greater amounts of nuclear material in older vervets in the superficial portion of the supraspinatus muscle compared to middle-aged animals (mean ± SEM; 284.4 ± 13.4 μm^2 vs. 223.2 ± 9.6 μm^2, $P = .001$). However, there was no difference in DAPI fluorescence in the deep portion of the supraspinatus between middle-aged and older vervets (mean ± SEM; 280.9 ± 12.2 μm^2 vs. 313.6 ± 15.7 μm^2, $P = .115$). There was no gross fatty infiltration noted in any of the middle aged or older muscle sections.

Muscle Architecture Characteristics

Multiple cross-sectional studies in human volunteers have demonstrated reduced upper extremity muscle volume in older adults (Vidt et al., 2012; Akagi et al., 2009; Rice et al., 1989). To assess whether similar changes are observed in the vervet, the right upper limb of each vervet was thawed over a period of 24 h, skinned, and fixed in 10% phosphate-buffered formalin for 24 h. Prior to fixation, the limb was placed in a neutral shoulder and wrist posture with 90 of elbow flexion and attached to an aluminum plate via the spine. Each limb was removed from the formalin and placed in a 70% ethanol solution for a minimum of 24 h to preserve the fixation and rinse any excess formalin. Measurements of arm length (acromion to lateral epicondyle) and forearm length (lateral epicondyle to ulnar styloid) were made using digital calipers.

The muscle-tendon units of the four rotator cuff muscles (subscapularis, infraspinatus, supraspinatus, and teres minor), teres major, deltoid, biceps, triceps, coracobrachialis, and brachialis were dissected from the skeleton. Subscapularis, infraspinatus, deltoid, triceps, and biceps were divided into subsections according to previous descriptions of muscle architecture for a total of 18 muscle-tendon units (Table 13.2). Measurements of muscle length and volume were made for each of the 18 muscle-tendon units (Hogfors et al., 1987; Van der Helm and Veenbaas, 1991). The tendon was removed at the muscle-tendon junction; muscle belly length was measured as the distance from the most proximal point to the most distal point and muscle volume was measured with a volume displacement method using ImageJ (Schneider et al., 2012). After fixation and gross muscle measurements, thin strips of muscle fibers were dissected from the interior of the muscle using fine sharp dissection (Langenderfer et al., August 2004), and fiber length l^f was measured using digital calipers. Fibers were dissected from several locations within the muscle belly to ensure the entire muscle belly was represented.

Optimal fiber length l_o^f was calculated using a laser diffraction technique (Murray et al., 2000) for each sarcomere measurement by normalizing the measured sarcomere length by the optimal sarcomere length (2.8 μm) of mammalian muscle (Eq. 13.1) (Lieber et al., 1994). Optimal muscle length l_o^m was calculated in the same manner to normalize muscle belly length. Optimal fiber length (Eq. 13.2) and optimal muscle length (Eq. 13.3) were also calculated for the whole muscle for muscles with multiple sections: where t equals the number of subsections (subscapularis = 3, infraspinatus = 2, deltoid = 3, triceps = 3, biceps = 2). Relative length (Eq. 13.4) of the rotator cuff muscles was calculated to facilitate comparisons between vervet and other animal species.

$$l_o^f = l^f \frac{2.8}{l^s} \tag{13.1}$$

$$l_o^f = \frac{\sum_{j=1}^{t} \mathrm{PCSA}_j \times l_{o\,j}^m}{\sum_{j=1}^{t} \mathrm{PCSA}_j} \tag{13.2}$$

$$l_o^m = \frac{\sum_{j=1}^{t} \mathrm{CSA}_j \times l_{o\,j}^m}{\sum_{j=1}^{t} \mathrm{CSA}_j} \tag{13.3}$$

$$\text{Relative length} = \frac{l_o^f}{l_o^m} \tag{13.4}$$

PCSA was calculated by dividing the muscle volume by optimal fiber length (Murray et al., 2000). A representative cross-sectional area was calculated by dividing muscle volume by optimal muscle length. For muscles with multiple subsections (subscapularis, infraspinatus, deltoid, triceps, and biceps) whole-muscle PCSA was calculated by adding the PCSA from each section (Murray et al., 2000). Total measured PCSA was calculated by adding the PCSA for every muscle.

Older adult vervets had significantly smaller total measured PCSA than the middle-aged vervets ($P = .001$; Table 13.3). Older PCSA was smaller for every individual muscle studied, and 10 of the 18 muscles exhibited significant decreases. The lateral head of the triceps exhibited the largest reduction in PCSA between groups (38.97%), and the supraspinatus exhibited the smallest reduction in PCSA (12.55%).

TABLE 13.3 Mean (Standard Deviation) of Anatomic Properties

	PCSA (cm^2)		Volume (cm^3)		Optimal Fiber Length (mm)		Optimal Muscle Length (mm)	
	OA	MA	OA	MA	OA	MA	OA	MA
Superior subscapularis[a]	2.14 (0.35)[b]	2.66 (0.29)	4.32 (1.15)[b]	5.83 (0.65)	20.37 (3.29)	22.30 (1.86)	62.05 (9.19)	64.74 (11.55)
Middle subscapularis[a,c]	2.62 (0.65)	3.20 (0.33)	4.19 (1.28)[b]	5.87 (0.99)	16.17 (2.84)	18.44 (2.45)	67.53(15.32)	75.95 (8.06)
Inferior subscapularis[a]	1.10 (0.32)	1.35 (0.23)	2.16 (0.65)	2.62 (0.17)	19.79 (2.07)	20.02 (2.65)	71.80 (7.78)	65.13 (3.27)
Subscapularis[a,c]	5.87 (0.60)[b]	7.21 (0.42)	10.67 (2.17)[b]	14.32 (1.59)	18.36 (2.91)	20.07 (1.67)	65.84 (9.66)	68.37 (5.71)
Superior infraspinatus[a]	1.74 (0.27)	2.01 (0.24)	4.47 (0.82)	5.32 (0.61)	26.15 (3.66)	26.97 (2.05)	78.70 (9.65)	82.10 (7.91)
Inferior infraspinatus[a]	1.47 (0.30)	1.81 (0.39)	3.82 (0.92)	4.91 (0.98)	26.40 (2.90)	27.49 (2.97)	81.12 (9.52)	78.07 (13.14)
Infraspinatus[a,c]	3.20 (0.41)	3.82 (0.59)	8.30 (1.44)	10.23 (1.40)	26.22 (3.28)	27.23 (2.36)	79.86 (9.63)	79.66 (9.84)
Supraspinatus[a]	2.42 (0.47)	2.77 (0.55)	6.47 (1.65)	8.12 (1.45)	26.94 (3.36)	29.80 (3.07)	74.22 (4.98)	78.11 (9.96)
Teres minor	0.76 (0.12)[b]	0.98 (0.14)	1.28 (0.14)[b]	1.63 (0.23)	17.27 (2.11)	16.77 (1.40)	44.70 (6.15)	45.89 (3.22)
Anterior deltoid	0.85 (0.18)[b]	1.25 (0.28)	4.70 (0.96)[b]	7.31 (1.26)	56.06 (3.06)	59.86 (5.14)	67.37 (5.39)[b]	77.17 (4.90)
Middle deltoid	1.97 (0.63)[b]	2.91 (0.52)	5.08 (1.50)[b]	7.50 (1.50)	26.45 (2.95)	26.29 (2.09)	50.62 (3.07)	55.22 (6.82)
Posterior deltoid	0.89 (0.20)	1.12 (0.20)	3.02 (0.61)[b]	4.74 (1.36)	34.55 (2.25)[b]	42.65 (8.13)	53.91 (5.54)	62.53 (8.49)
Deltoid[c]	3.71 (0.90)[b]	5.28 (0.76)	12.79 (2.89)[b]	19.55 (3.62)	35.13 (2.29)	37.48 (1.81)	56.36 (1.66)[b]	63.53 (3.97)
Teres major	1.64 (0.37)[b]	2.15 (0.21)	6.29 (1.11)[b]	8.98 (1.80)	39.10 (3.96)	42.41 (6.88)	74.50 (6.67)	79.00 (12.19)
Long triceps	5.59 (0.71)[b]	8.66 (0.97)	16.88 (1.99)[b]	24.72 (3.73)	30.68 (1.35)	29.14 (2.83)	120.85 (8.52)[b]	109.39 (4.48)
Lateral triceps	2.83 (0.43)[b]	4.63 (0.89)	11.96 (1.92)[b]	17.30 (2.59)	42.91 (3.47)	38.32 (4.03)	112.79 (8.10)	104.50 (7.68)
Medial triceps	2.18 (0.42)	2.71 (0.77)	7.52 (1.14)	9.05 (2.10)	35.25 (1.68)	34.41 (4.58)	108.82 (3.33)	108.55 (10.65)
Triceps[c]	10.59 (1.39)[b]	16.00 (2.35)	36.36 (4.55)[b]	51.06 (8.29)	34.85 (1.66)	32.52 (2.93)	115.35 (6.01)[b]	107.26 (4.45)
Long biceps	1.92 (0.42)[b]	2.46 (0.46)	9.03 (2.01)	11.61 (2.10)	47.34 (2.41)	47.41 (4.59)	90.08 (3.73)	93.00 (11.75)
Short biceps	0.59 (0.05)[b]	0.88 (0.19)	3.12 (0.36)[b]	4.81 (1.14)	53.22 (3.91)	54.86 (6.13)	90.81 (3.01)	93.47 (12.85)
Biceps[c]	2.52 (0.44)[b]	3.34 (0.35)	12.15 (2.27)[b]	16.42 (2.87)	48.68 (2.43)	49.36 (4.88)	90.25 (3.43)	93.17 (11.40)
Coracobrachialis	0.36 (0.12)	0.47 (0.14)	0.60 (0.20)	0.80 (0.23)	17.32 (2.31)	17.35 (1.14)	54.36 (10.55)	61.86 (11.15)
Brachialis	1.47 (0.25)[b]	1.81 (0.25)	4.82 (1.02)	5.86 (0.95)	33.17 (2.29)	32.78 (3.32)	71.74 (2.79)	69.35 (9.11)

[a] *Indicates a rotator cuff muscle.*

[b] *Statistically significant differences ($P < .05$) between groups.*

[c] *PCSA and volume were calculated from the summation of PCSA and volume from the subsections. Optimal fiber length and optimal muscle length were calculated from Eqs. (13.2) and (13.3).*

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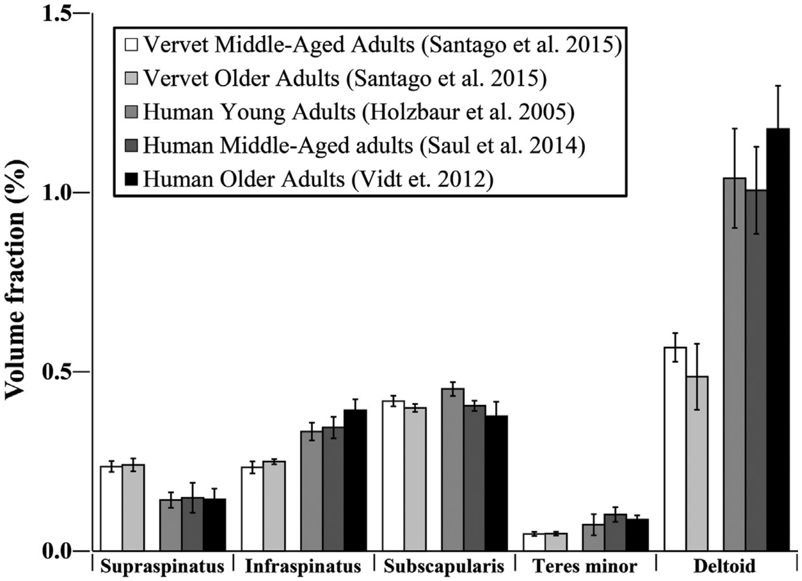

FIGURE 13.3 Volume fraction for human female young adults, vervet and human female middle-aged adults, and vervet and human female older adults as determined by a percentage of the total rotator cuff volume (Vidt et al., 2012; Santago et al., 2015; Holzbaur et al., 2007; Saul et al., 2015). Error bars represent ±1 std. There were no statistical differences between the older adult and middle-aged vervet volume fractions for any muscle. When combined, the vervet supraspinatus volume fraction (24%) was larger than the humans (14%), and the vervet deltoid volume fraction (52%) was smaller than the humans (109%). The range bars indicate the standard deviation. *(Reprinted from Santago, A.C., et al., 2015. Age-related structural changes in upper extremity muscle tissue in a nonhuman primate model. J Shoulder Elbow Surg 24, 1660–1668, with permission from Elsevier.)*

Mean muscle volume in the older adults was numerically smaller for every muscle studied and was statistically different in 10 of the 18 muscles (Table 13.3). The posterior portion of the deltoid (36.25%) and the superior portion of the infraspinatus (15.88%) exhibited the largest and smallest volumes reductions, respectively. Optimal fiber length for the posterior portion of the deltoid was significantly shorter for the older vervets due to a decrease in measured fiber length; no other muscles exhibited a significant difference in optimal fiber length.

Despite significant differences in total rotator cuff (supraspinatus, infraspinatus, subscapularis, and teres minor) PCSA ($P=.008$), there were no significant differences in the rotator cuff PCSA fraction between the older and middle-aged vervets for any muscle. The same was true for volume fraction (Fig. 13.3). The subscapularis made up the largest proportion of the rotator cuff PCSA for the older (mean ± std; 48.03 ± 3.75%) and middle-aged vervets (mean ± std; 48.96 ± 3.39%), and the teres minor made up the smallest (mean ± std; older: 6.22 ± 0.84%; middle-aged: 6.70 ± 1.04%). The deltoid measured (mean ± std) 30.11 ± 4.94% and 35.64 ± 2.34% of the rotator cuff PCSA for the older and middle-aged vervets, respectively. There were no significant differences in body mass, right upper arm, and right forearm length between the middle-aged and older vervets.

Rotator Cuff Tears

The prevalence of rotator cuff tears in humans increases with advancing age, with the incidence reaching 50% in adults aged older than 70 (Yamamoto et al., 2010). Thus, vervets were macroscopically evaluated for the presence of a rotator cuff tear on both the articular and bursal sides of both left and right cadaveric shoulder specimens. Despite vervet monkeys using the supraspinatus, the most commonly torn rotator cuff muscle-tendon unit (Sano et al., 1999), as a dynamic stabilizer similar to humans (Larson and Stern, 1989), older vervets presented with no grossly detectable full or partial thickness rotator cuff tears. Unlike hominoids, such as humans, chimpanzees, and orangutans, the vervets do not have a "true" rotator cuff in which the supraspinatus, infraspinatus, subscapularis, and teres minor share a common insertion site (Sonnabend and Young, 2009).

There are several possible explanations for this. AHD was similar in both middle aged and older vervets, demonstrating that age-related microscopic and macroscopic degeneration, as quantified by decreases in FCSA and density, did not lead to superior translation of the humeral head in these animals. The decrease in FCSA in the superficial portion of the supraspinatus muscle in older vervets is consistent with decreased contractile elements and muscle fiber atrophy in humans (Verdijk et al., 2010). The vervet supraspinatus (24%) and deltoid (52%) represent a larger and smaller proportion, respectively, of the total rotator cuff volume than a human supraspinatus (14%) and deltoid (109%) (Vidt et al., 2012; Holzbaur et al., 2007) (Fig. 13.3). In humans, a lifetime of increased demand on a proportionally smaller supraspinatus from the action of a proportionally larger deltoid may predispose the supraspinatus to age-related tearing not experienced by the vervets. Owing to the lack of naturally occurring rotator cuff tears, it would be necessary to inflict a tear in a vervet model when used to study rotator cuff injury, as is done in other animal models, such as the rat (Mannava et al., 2011). However, the vervet may be a useful model to study atrophy, increases in intramuscular fat, and fat clustering, common muscle changes associated with rotator cuff tears (Melis et al., 2009; Santago et al., 2016) because these changes may be exaggerated and occur more quickly in the supraspinatus due to its large PCSA and subsequently increased role in movement.

Physical Function and Relationship to Osseous and Muscle Degeneration

In humans, functional capacity of the upper limb declines over time (Cooke et al., 1989) and is an important marker of musculoskeletal health and independence (Lundgren-Lindquist and Sperling, 1983). To evaluate whether vervets display similar age-related declines in upper limb function, functional mobility assessments were taken prior to euthanasia, while the vervets were voluntarily moving inside the pen in a standard manner (Shively et al., 2012; Plate et al., 2013). Walking speed was recorded as the time necessary to walk a defined distance on various structures inside the pen. The time spent climbing and hanging was observed during 15-min focal observation on four separate days for each animal and expressed as frequency per hour. Older vervets exhibited decreases in physical mobility and function. Walking speed ($P = .129$) and the time spent climbing ($P = .076$) and hanging ($P = .187$) tended to be reduced in older vervets compared to middle-aged animals.

In humans, age-related reductions in the functional capability of the upper limb may be driven by discomfort and/or a reduction in strength below what is required to complete the functional task of interest. Physical mobility and shoulder function were significantly correlated with glenoid version angle (Walking speed $r^2 = .668$ $P < .001$; Climbing $r^2 = .509$ $P = .016$; Hanging $r^2 = .568$, $P = .006$) highlighting glenoid retroversion as a potential determinant of physical function in the upper limb. Vervets with glenoid retroversion as a marker of osteoarthritic degeneration were less mobile and physically active regardless of age.

Conversely, the total measured PCSA was not significantly correlated with walking speed ($r^2 = .0843$, $P = .3863$), percentage of time hanging ($r^2 = .0247$, $P = .644$), and percentage of time climbing ($r^2 = .0736$, $P = .420$) within either age group or when all vervets were considered together. Due to the relationship between joint strength and function, one might expect that a reduction in PCSA, which is proportional to force-generating capacity (Lieber, 2002), would be associated with a reduction in functional performance. However, in humans, small reductions in strength have been reported to result in large functional declines only when strength falls below the minimum required strength to perform a task and reserve strength is zero (Buchner et al., 1996). Recent work has demonstrated that older adults with and without a rotator cuff tear have sufficient reserve strength necessary to complete upper limb functional tasks (Santago et al., 2017). Thus, despite the substantial reduction in PCSA, the older adult vervets probably retained reserve strength above strength requirements of the measured functional tasks. Taken together with the relationship between bony degeneration and functional capability, these results suggest that the age-related reduction in functional capability experienced by vervets is predominated by discomfort due to bony degeneration and not limited by a lack of strength.

DISCUSSION

In summary, vervets demonstrate changes to both bone and muscle structures consistent with human aging. Older vervets had degenerative changes of the glenoid and humeral head with osteophyte formation on the posterior/inferior glenoid, while no gross degenerative changes were observed in any of the middle-aged animals. Glenoid version angle significantly correlated with age, with an increase in glenoid retroversion with increased age. At the muscle tissue level, older muscles were significantly less dense, had decreased fiber cross-sectional area, more disorganized fiber with atrophic changes, and greater nuclear material. At the whole muscle level, older vervets had significantly smaller PCSA and muscle volumes than the middle-aged vervets, despite similarities in body mass and arm length. Similar trends are experienced by humans throughout their life span (Vidt et al., 2012; Holzbaur et al., 2007; Saul et al., 2015). Reduced PCSA was driven by an overall loss of muscle volume rather than by changes in optimal fiber length, which were not observed. Despite significant differences in total rotator cuff (supraspinatus, infraspinatus, subscapularis, and teres minor) PCSA, there were no significant differences in the rotator cuff PCSA fraction between the older and middle-aged vervets for any muscle. Older vervets also exhibited decreases in physical mobility and function, which were significantly associated with the osseous changes rather than muscular changes. However, unlike human aging, there was no gross fatty infiltration noted in any of the middle-aged or older muscles, and there was no evidence of partial or full thickness rotator cuff tears.

Previous architectural analyses suggest that chimpanzee (*Pan troglodytes*) and capuchin (*Cebus apella*) have rotator cuff muscle architecture more similar to the human rotator cuff than that of large and small quadrupedal animals such as the rat (Mathewson et al., 2014). Specifically, the volume fraction of the muscles of the rotator cuff and the relative length of the muscles (Eq. 13.4) were similar to that of humans. The same parameters for the vervet rotator cuff muscles in the studies by Plate et al. (2013) and Santago et al. (2015) are similar. However, the relative deltoid PCSA was not determined for the capuchin or the chimpanzee in (Mathewson et al., 2014), which may be an important factor for establishing the appropriateness of a rotator cuff model with regard to tear propensity. Further, it should be noted that the vervet is an Old World monkey and that the capuchin and chimpanzee are considered New World monkeys and advanced primates, respectively. New World monkeys and advanced primates exhibit a tendinous connection between rotator cuff tendons, whereas the vervet and other Old World monkeys do not (Sonnabend and Young, 2009). This suggests that other factors beyond architectural parameters should be taken into consideration when considering an animal model for the rotator cuff.

Many age-related changes to muscle tissue limit muscle moment generation and function, such as preferential atrophy of type II muscle fibers (Larsson et al., 1978; Narici and Maffulli, 2010; Lieber, 2002) decreased maximum shortening velocity and specific tension (Larsson et al., 1997; Yu et al., 2007) and increases in intramuscular fat (Narici and Maffulli, 2010; Rice et al., 1989; Ashry et al., 2007; Forsberg et al., 1991; Overend et al., 1992; Visser et al., 2005). Common neurological disorders such as Parkinson's disease and stroke, which are highly related to increasing in age (Sacco et al., 1997; Van Den Eeden et al., 2003), can also result in muscle weakness in upper limb (David et al., 2012; Ekstrand et al., 2016). Measures of muscle architectural characteristics, such as the ones measured here, as well as other biological assessments of tissue composition and gene expression, are more easily obtained in an animal model than in humans. Ethical concerns and the high cost of the nonhuman primate model, specifically for long-term aging studies, need to be considered when contemplating its use for shoulder research. However, the vervet provides an excellent model to investigate the underpinnings of age-related biological changes to shoulder and explore potential orthopaedic, rehabilitative, and pharmacological interventions to limit these changes.

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