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1 **Does the computed tomographic appearance of the lung differ between young and old dogs?**

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11 Running head: CT of aged lung

14   **Abstract**

15   In computed tomographic (CT) images of humans, decreased lung attenuation, bronchial

16   dilation and/or thickening, air trapping, cysts, and thickened interlobular septa have been

17   associated with increasing age. To determine if there are differences in the CT appearance of

18   the lungs of young and old dogs that could affect interpretation of diagnostic studies,

19   pulmonary CT images of dogs with conditions unrelated to the thorax were reviewed

20   retrospectively in a case-control study. CT studies of 42 young dogs (range 0.3-4.8 years) and 47

21   old dogs (range 9-15.1 years) were jumbled and reviewed by an observer blinded to dog age. CT

22   was performed under sedation in 62 (70%) dogs and under general anesthesia in 27 (30%).

23   Heterotopic bone was more prevalent (62% versus 14%) in old dogs. Lung collapse was

24   significantly associated with old age, greater body weight, and anesthesia. There were no

25   significant differences in median lung attenuation or occurrence of ground glass pattern, cysts,

26   bronchial thickening, bronchial dilation, or degree of tracheal calcification. No examples of

27   reticular pattern, emphysema, pleural thickening or septal thickening were observed in any

28   dog. Despite previous studies describing age-related changes in the radiographic appearance of

29   the lungs of old dogs, it appears that there are minimal observable differences in CT images.

30   Old dogs are more likely to have visible foci of heterotopic bone and may be more prone to

31   lung lobe collapse than young dogs, but neither of these differences should contribute to

32   misdiagnosis of pulmonary disease.

33   **Introduction**

34   Age-related changes in the morphology of the lung have been described in humans[1], dogs[2,3],

35   and rats.[4] A prominent age-related feature observed in dogs was accumulation of macrophages

36   containing dust and pigment in the respiratory bronchioles and alveolar openings.[2] It was

37   hypothesized that exposure to dust and reduction in function of the mucociliary escalator over

38   time resulted in accumulation of dust and pigment in the lungs,[2] but this was not confirmed.

39   There was also an increase in the relative volume ('volume density') of alveolar ducts,

40   progressive calcification of the bronchial cartilage, and increased size of the bronchial glands.[2]

41   Minimal emphysema was observed and fibrosis was sparse, mainly associated with foci of

42   pneumonitis.[2]

43   Correlations between morphologic changes in the lungs and the radiographic appearance of the

44   lung were described in 100 aged dogs that had no pathologic evidence of pulmonary or

45   cardiovascular disease.[3] Emphysema and alveolar dilatation were reported, but more emphasis

46   was placed on findings of pleural fibrosis and interstitial fibrosis.[3] Accumulation of peribronchial

47   collagen over time causing progressive pulmonary fibrosis has also been emphasized in studies

48   of aging rats.[4] Together with fibrosis, thickening of the alveolar walls and calcification of

49   bronchial cartilage in dogs were associated with radiographic signs including pleural thickening,

50   increased linear markings, and increased opacity of the tracheal and bronchial walls.[3] Foci of

51   heterotopic bone in the lungs of many older dogs produced small nodular opacities in

52   radiographs.[3] Based on these findings, increased lung attenuation, pleural and septal thickening

53   and increased prevalence of heterotopic bone may be expected in computed tomographic (CT)

54   images of the lungs of aged dogs; however, there are no published studies of age-related

55   changes in pulmonary CT images of dogs.

56   Changes associated with normal aging in the lungs of humans have been studied extensively,

57   one aim being to avoid over-diagnosis of age-related changes as signs of clinically significant

58   disease. Age-related changes seen in pulmonary CT images of humans include decreased lung

59   attenuation as a result of dilatation of alveoli and/or emphysema, air-trapping, cysts, a sub-

60   pleural reticular pattern, bronchial dilation, bronchial thickening, and thickening of interlobular

61   septa without inflammation.[5-9] CT signs usually associated with interstitial lung disease may also

62   be seen in healthy elderly humans, and radiologists have been cautioned not to over-interpret

63   such findings in asymptomatic patients.[5]

64   The aim of the present study was to determine if there are differences in the CT appearance of

65   the lungs of young and old dogs that could affect interpretation of diagnostic studies.

66

67   **Method and Materials**

68   Ethical approval was granted by the Clinical Research Ethical Review Board at the Royal

69   Veterinary College. For this retrospective case-control study, the medical records at the Queen

70   Mother Hospital for Animals (QMHA) in the period 2012-2016 were searched for cases that

71   satisfied the following inclusion criteria: dogs that had diagnosis of a non-malignant disease or

72   condition unrelated to the thorax; had non-contrast CT images of the lung acquired using a high

73   resolution (sharp or lung) algorithm; and were either less than 5 years old or more than 9 years

74   old. Dogs with a history of lower respiratory signs or diagnosis of cardiovascular, mediastinal,

75   pleural, bronchial, pulmonary disease, malignant neoplasia or systemic inflammatory disease

76   were not included.

77   For each dog, age at the time of CT, gender, body weight and diagnosis were recorded. On the

78   basis of body weight, dogs were divided in small (<10kg), medium (10-25kg), large (26-40kg),

79   and giant (>40kg) categories. Use of sedation or anesthesia for CT was also recorded. For all

80   sedated dogs, CT images were acquired during free breathing, whereas anaesthetised dogs had

81   brief manual hyperventilation with CT images acquired during the subsequent expiratory pause.

82   As part of the inclusion criteria, all CT images were acquired using the same multi-slice scanner

83   (MX8000 IDT, Phillips Best, The Netherlands). Studies lacking optimal settings for lung

84   examination were excluded. For the purposes of this study, optimal settings were helical

85   acquisition, slice thickness 2mm for small dogs and 3mm for other dogs, matrix 512x512, and

86   high frequency ('sharp' or 'lung enhanced') reconstruction algorithm. All CT images were

87   reviewed by a board-certified radiologist (CRL) without knowledge of the age, breed or history

88   of the subjects. Images were reviewed in a lung window (level -500HU, width 2000HU) using a

89   proprietary Digital Imaging in Communications and Medicine (DICOM) viewer (OsiriX 64-bit,

90   version 5.2.2, Pixmeo, Switzerland). For each dog, the lungs were also examined using

91   maximum- and minimum-intensity projections with slab thickness 5mm for small dogs and

92   8mm for other dogs. Dogs whose CT images were affected by motion blur were excluded.

93   CT images were evaluated for the following features: mean lung attenuation (Hounsfield units,

94   HU) based on the median of three measurements made using a circular region of interest of

95   minimum area 40mm^2 placed in different lung lobes and avoiding bronchi or large vessels;

96   ground glass opacity (absent/present); reticular pattern (absent/present); emphysema

97   (absent/present); pulmonary cysts (absent/present, diameter of largest cyst); visceral pleural

98   thickening (absent, affecting one lobe, affecting multiple lobes); interlobular septal thickening

99   (absent, affecting one lobe, affecting multiple lobes); bronchial thickening (none, slight,

100   marked); bronchial dilation (median of bronchus: pulmonary artery ratio measurements in the

101   right caudal lobe in three adjacent CT slices); degree of tracheal ring calcification (the median of

102   three HU measurements made by placing a point sample on a tracheal cartilage ring

103   immediately cranial to the origin of the lobar bronchi); foci of heterotopic bone (absent,

104   affecting one lobe, affecting multiple lobes); and pulmonary collapse (number of affected lobes

105   and distribution of collapse was recorded: lobe tip only, peripheral, bronchocentric, entire

106   lobe). The term tip is used here to indicate the pointed extremity of a lung lobe in transverse CT

107   images. Diagnosis of heterotopic bone was based on finding pulmonary hyperdense foci ranging

108   from sub-millimeter rounded foci to larger irregularly-shaped densely ossified foci. Diagnosis of

109   lung collapse was based on finding increased lung attenuation accompanied by reduced volume

110   of the affected lung. Terminology followed recommendations for thoracic imaging by the

111   Fleischner Society.[10]

112   Statistical analyses were done by a statistician (Yu-Mei Chang) using a commercial statistical

113   software package (SPSS 22, IBM)   Significance of differences in median lung attenuation,

114   bronchus: pulmonary artery ratio and tracheal calcification between young and old dogs were

115   tested using the Mann-Whitney test. Differences in prevalence of ground glass opacity,

116   bronchial thickening and cysts were tested using Fisher's exact test. Differences in occurrence

117   of heterotopic bone and body weight of dogs were tested using Kendall's tau-c test.

118   Associations between the dependent variable lung collapse and independent variables age,

119   body weight, and anesthesia were tested using binary logistic regression and results

120   summarized as odds ratio (OR) and 95% confidence interval (CI). Differences with p<0.05 were

121   considered significant.

122

123   **Results**

124   CT images of 42 young dogs (age range 0.3-4.8 years) and 47 old dogs (age range 9-15.1 years)

125   were reviewed. All dogs were scanned in sternal recumbency. Characteristics of young and old

126   dog groups are summarized in Table 1. CT features observed in young and old dogs are

127   summarized in Table 2. Heterotopic bone was more prevalent (62% versus 14%; p<0.001) in old

128   dogs.

129   Signs of lung collapse were identified in 40 (46%) dogs. Based on regression analysis,

130   occurrence of lung collapse was significantly associated with age (OR 3.7, CI 1.4-9.5, p=0.007),

131   body weight (OR 1.9, CI 1.1-3.3, p=0.02), and anesthesia (OR 3.1, CI 1.1-8.8, p=0.03). Lung

132   collapse affected the right middle lobe in 22 dogs, left cranial lobe in 21 dogs, right cranial lobe

133   in 18 dogs, left caudal lobe in 7 dogs, accessory lobe in 6 dogs, and right caudal lobe in 4 dogs.

134   Lung collapse affected a single lobe in 21 (24%) dogs and multiple lobes in 19 (22%) dogs. In

135   58/68 (85%) affected lobes collapse was limited to the tip of the lobe, in 7 (1%) lobes it was

136   bronchocentric, and in 3 (5%) lobes it was peripheral (figure 1).

137   There were no significant differences in median lung attenuation or occurrence of ground glass

138   pattern, cysts, bronchial thickening, bronchial dilation, or degree of tracheal calcification

139   between young and old dogs. Cysts were found in 6 (7%) dogs; these were solitary in 3 dogs and

140   multiple (2-9) in 3 dogs, and the largest ranged in size from 2-11mm diameter (figure 2). No

141   examples of reticular pattern, emphysema, pleural thickening or septal thickening were

142   observed in any dog.

143

144   **Discussion**

145   In this study there were minimal observable differences between the lungs of young and old

146   dogs. Heterotopic bone was more prevalent in old dogs, which agrees with previous

147   observations.[3] Lung collapse was also observed more frequently in old dogs, although the

148   underlying reason for this difference cannot be determined by the present study. For

149   physiological reasons, the right middle lobe is most prone to collapse in the dog.[11] In the

150   present study, collapse of the right middle lobe and the right and left cranial lobes occurred

151   with similar frequencies. In the majority of dogs, lung collapse affected only the tip of the lobe.

152   Reduced collateral ventilation because of subclinical disease, such as chronic bronchitis with

153   excessive mucus production, is liable to exacerbate lung collapse.[12,13] The increased tendency

154   for lung collapse in older dogs could reflect an increasing prevalence of subclinical lung disease

155   over their lifetime. The observation that lung collapse was more frequent in dogs that had CT

156   under general anesthesia than in dogs that were sedated could reflect the use of high inspired

157   pO_2 for anesthesia, which has also been associated with a higher prevalence of lung collapse

158   than when using moderate inspired pO_2 ('medical air').[14] It is uncertain why lung collapse was

159   more frequent in larger dogs. It is known that intermittent positive pressure ventilation to

160   minimize lung collapse is required more frequently in large dogs than small dogs or cats[15], and

161   this may reflect the larger gravitational gradient that occurs within the lung of larger patients,

162   as observed in anesthetized horses.[16]

163   There were no significant differences in median lung attenuation or occurrence of ground glass

164   pattern, cysts, bronchial thickening, bronchial dilation, or degree of tracheal calcification

165   between young and old dogs. These results are in contrast with those of a previous study in

166   which the lungs of old dogs had radiographic signs including pleural thickening, increased linear

167   markings, and increased opacity of the tracheal and bronchial walls.[3] Although the results of CT

168   in one group of dogs cannot be compared directly with results of radiography in a different

169   group of dogs, it seems likely that CT would have detected signs of pleural thickening, increased

170   linear markings and increased opacity of the tracheal and bronchial walls had they been

171   present. In fact, based on ability to directly measure lung attenuation using CT and other canine

172   studies that found increased sensitivity of CT for lung lesions[17,18], CT might be expected to

173   reveal more age-related changes than radiography. Therefore, the relative lack of CT signs in

174   the present study could reflect a true difference in the condition of the lungs of the dogs used

175   in these respective studies, possibly reflecting different genetic or environmental factors. If so,

176   this could limit the generalizability of our results, which may not be applicable in other

177   locations.

178   Attenuation measurements of tracheal rings were used in the present study as an indirect

179   indicator of bronchial wall calcification. Tracheal rings were measured instead of bronchial walls

180   because they are normally thicker than bronchial walls, hence any attenuation measurements

181   will be less affected by partial volume artifact.

182 The process of aging occurs over a shorter period of time in dogs than in humans[1], and It is

183 generally accepted that dogs of large and giant breeds age more rapidly than dogs of small or

184 medium breeds. The smaller number of giant breed dogs in the aged group in the present study

185 reflects this phenomenon. Non-contiguous age ranges were used in this study to ensure

186 separation of young and aged dogs, which could intermingle if a heterogeneous sample of dogs

187 were classified using a single calendar age threshold alone.

188 In this study, examination of the CT images included quantitative measurements and search for

189 multiple possible lesions based on previous studies of CT signs in aged humans[5-9]; however, few

190 examples were found of ground glass pattern, bronchial thickening or bronchial dilation, and no

191 signs of reticular pattern, emphysema, pleural thickening or septal thickening were identified in

192 any dog. Hence, finding any of these features in CT images of a dog with respiratory signs

193 suggests the presence of non-age-related lung pathology that is clinically relevant.

194 Cysts were found in 6 (7%) dogs in this study. There is some overlap in use of the terms cyst and

195 bulla, although in humans bulla is used for lesions greater than 1cm, and usually several cm in

196 diameter.[10] Lung cysts (and bullae), which can be subclinical, should be distinguished from both

197 congenital lobar emphysema[19,20] and superficial bullous emphysema, which is associated with

198 non-traumatic ('spontaneous') pneumothorax.[21,22]

199 The main limitation of the present study was the lack of pathologic examination of lungs, which

200 prevents histologic proof of the nature of lesions identified by CT, and allows the possibility that

201 there were age-related lung changes that were undetected by CT. All CT studies reviewed in

202 this study were obtained using settings suitable for clinical assessment of the lung of dogs, but

203 more detailed assessment is possible using thinner (1mm) CT slices[23] or micro-CT[24] with

204   histologic examination of precisely orientated lung sections. Further studies are indicated to

205   better examine imaging-pathologic correlations in the aging canine lung. The number of dogs

206   available for study was limited by the need to avoid including dogs likely to have had pathologic

207   lung lesions. Use of a single observer to review the CT is also a limitation, but this is not

208   considered to be a major problem because of the relatively homogenous nature of the study

209   sample and use of comprehensive, pre-considered assessment criteria based on previous

210   studies of humans.[5-9]

211   In conclusion, despite previous studies describing age-related changes in the radiographic

212   appearance of the lungs of old dogs, it appears that there are minimal observable differences in

213   CT images. Old dogs are more likely to have visible foci of heterotopic bone and may be more

214   prone to lung lobe collapse than young dogs, but neither of these differences should contribute

215   to misdiagnosis of pulmonary disease.

216

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294   Table 1. Characteristics of young and old dog groups

|	Young dogs (n=42)	Old dogs (n=47)
Median (range) age (y)	3 (0.3-4.8)	11 (9.0-15.1)
Males/ females	28 (67%)/ 14 (33%)	31 (66%)/ 16 (34%)
Body weight range		
Small (<10kg)	10 (24%)	12 (25%)
Medium (10-25kg)	15 (36%)	20 (43%)
Large (26-40kg)	12 (28%)	13 (28%)
Giant (>40kg)	5 (12%)	2 (4%)
Diagnostic category		
Upper respiratory	19 (45%)	12 (25%)
Immune-mediated	11 (26%)	1 (2%)
Alimentary	4 (10%)	3 (6%)
Neurologic	4 (10%)	3 (6%)
Orthopedic	2 (5%)	0
Urinary	2 (5%)	2 (4%)
Benign neoplasm	0	17 (36%)
Oral conditions	0	6 (13%)
Endocrinopathy	0	3 (6%)
CT under anesthesia	12 (29%)	15 (32%)

295

296   Table 2. CT features of the lungs of young and old dogs

	Young dogs (n=42)	Old dogs (n=47)
Median (range) lung attenuation (HU)	-788 (-605 to -878)	-793 (-679 to -900)
Ground glass opacity	7 (17%)	8 (17%)
Cysts	1 (2%)	5 (10%)
Bronchial thickening	5 (12%)	5 (11%)
Median (range) bronchus: pulmonary artery ratio	0.66 (0.41-1.06)	0.63 (0.40-1.46)
Median (range) tracheal calcification (HU)	224 (65-577)	236 (107-512)
Heterotopic bone		
In one lobe	3 (7%)	6 (13%)
In multiple lobes	3 (7%)	23 (49%)
Pulmonary collapse		
None	29 (69%)	20 (43%)
One lung lobe affected	9 (21%)	12 (26%)
Multiple lobes affected	4 (10%)	15 (32%)

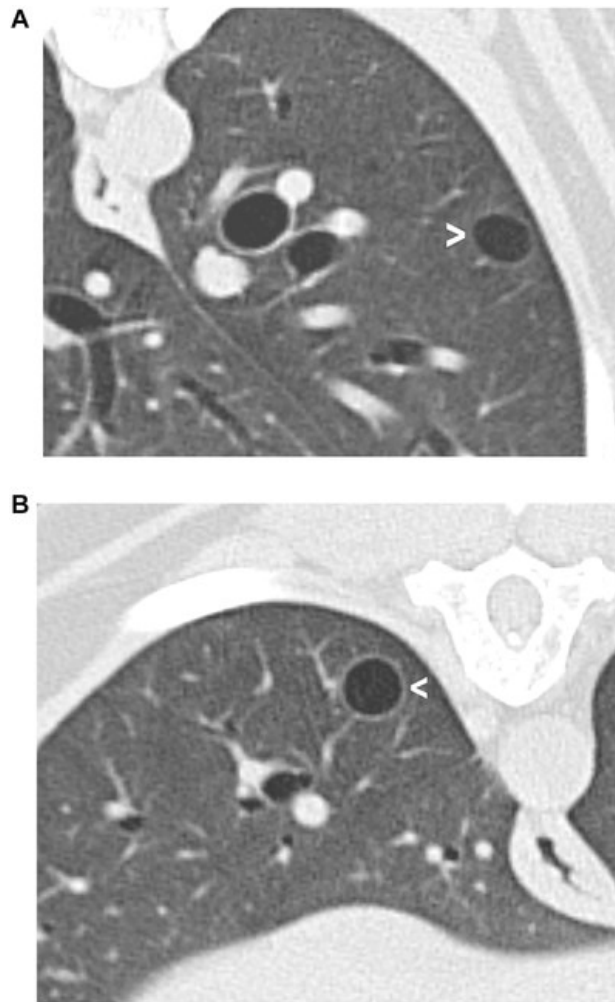297

298   **Legend**

299   Figure 1. Examples of pulmonary collapse. A) Collapse of the ventral tip of the left cranial lobe

300   (arrowhead); B) bronchocentric collapse (arrowhead) affecting the right cranial lobe; C)

301   peripheral pulmonary collapse (arrowheads) affecting the lateral aspect of the left caudal lobe.
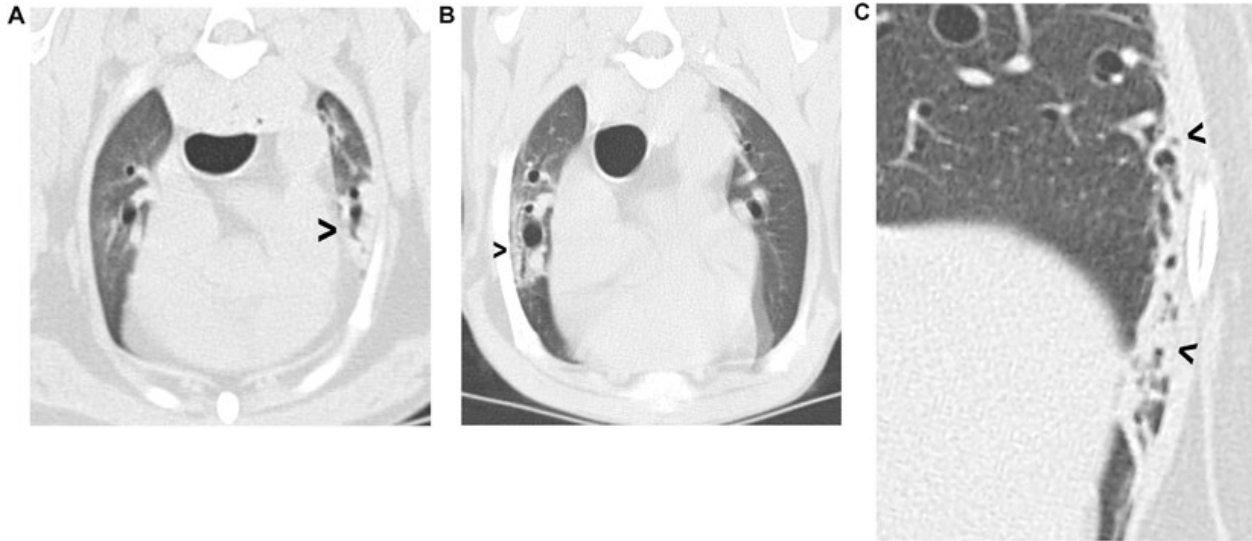
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303

304 Figure 2. Examples of lung cysts. A) 10mm diameter cyst (arrowhead) in the left caudal lobe of a

305 1-year-old golden retriever that had CT as part of the work-up for nasal panniculitis. This was

306 one of 3 pulmonary cysts in this dog; B) 8mm diameter cyst (arrowhead) in the right caudal lobe

307 of a 14-year-old English springer spaniel that had CT as part of the work-up for

308 hyperadrenocorticism.

309