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Thoracic high resolution CT using the modified VetMousetrap (TM) device is a feasible method for diagnosing canine idiopathic pulmonary fibrosis in awake West Highland White Terriers

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**Thoracic high resolution computed tomography in awake
West Highland white terriers with canine idiopathic
pulmonary fibrosis using VetMousetrap™ device**

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Manuscripts

Review

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5 2 **Thoracic high resolution computed tomography in awake West Highland white terriers**
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7 3 **with canine idiopathic pulmonary fibrosis using VetMousetrap™ device**
8

9 4 **Abstract**
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11 5 Canine idiopathic pulmonary fibrosis (CIPF) is a chronic, progressive interstitial lung disease
12 6 particularly prevalent in West Highland white terriers (WHWTs). In the present prospective
13 7 study, we evaluated the feasibility of modified VetMousetrap™ device in high resolution
14 8 computed tomography (HRCT) to detect CIPF in WHWTs. Twelve awake WHWTs with
15 9 CIPF and 24 age matched clinically healthy control WHWTs were scanned using a helical
16 10 dual slice scanner without or with minimal chemical restraint. Three evaluators blindly
17 11 assessed the images for image quality and the presence of CIPF related imaging findings such
18 12 as ground glass opacity (GGO). Additionally, the attenuation of the lung was quantified with
19 13 ImageJ software using histogram analysis of density over the lung fields.
20 14 CT was successfully completed and the motion artefact ranked barely noticeable to mild in all
21 15 dogs. The agreement between HRCT imaging findings and clinical affection status was very
22 16 good with overall κ value 0.91 and percentage of agreement (PA) of 94%. There was also a
23 17 very good intraobserver ($\kappa_{\text{range}} = 0.79 - 0.91$) and interobserver agreement ($\kappa = 0.94$).
24 18 Moderate to severe GGO was present in all dogs with CIPF. In the ImageJ analysis a
25 19 significant difference in the lung attenuation between the study groups was observed. We
26 20 conclude that modified VetMousetrap™ device is applicable in diagnosing CIPF in awake
27 21 WHWTs without the need of chemical restraint avoiding the anesthetic risk in these often
28 22 severely hypoxic patients.
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26 Introduction

27 Idiopathic pulmonary fibrosis (IPF) is an incurable interstitial lung disease that occurs both in
28 dogs and in humans.^{1,2,3,4} In dogs, the disease appears to be breed-specific, seen particularly in
29 middle aged to older West Highland white terriers (WHWTs).^{1,2,3,5} As the disease develops
30 slowly and the clinical signs can be confused with other respiratory or cardiac diseases as well
31 as with normal ageing process, the diagnosis can be challenging to achieve. In humans, the
32 presence of usual interstitial pneumonia (UIP) pattern in high resolution computed
33 tomography (HRCT) images is the golden standard for diagnosis of IPF and lung biopsies are
34 only needed if HRCT is inconclusive.⁴ In dogs, definite diagnosis of canine IPF (CIPF)
35 requires histopathological examination of lung tissue and due to invasiveness of lung
36 biopsies, the diagnosis is often confirmed at necropsy.⁶ HRCT has been shown to be a reliable
37 and useful diagnostic tool also in CIPF.^{3,7,8,9} However, the technique used has required general
38 anesthesia, which in these respiratory compromised patients might be risky. Recently, HRCT
39 imaging findings under general anesthesia and sedation were compared.¹⁰

41 A transparent positioning device, VetMousetrap™ has been designed to enable CT scanning
42 in awake animals.¹¹ It was first used in CT imaging of thorax of awake healthy cats and cats
43 with different thoracic diseases.^{11,12} CT imaging with minimal or no sedation has been
44 described also in dogs with respiratory and abdominal diseases.^{13,14,15} The positioning device
45 could provide a rapid and safe alternative to obtain thoracic CT without need for sedation or
46 general anesthesia.

48 Quantitative computer image analysis approaches, such as ImageJ, have been applied to
49 detect lung pathology in humans.^{16,17} ImageJ is a Java-based open access imaging software
50 used for many biomedical imaging applications and allows the quantitative assessment of the

DICOM images over the whole lung area.¹⁸ This could provide more accurate reflection of diffuse interstitial lung diseases and superior assessment of the severity of the disease when compared to conventional techniques.

The objective of the present prospective study was to evaluate the feasibility of CT studies in diagnosing CIPF in WHWTs using only physical restraint. The hypothesis was that thoracic HRCT imaging of awake animals using modified VetMousetrap™ device could be performed to obtain acceptable image quality. In addition, we analysed the attenuation of the entire lung fields of the dogs with the ImageJ software and hypothesized increased attenuation in CIPF dogs when compared to controls.

Materials and methods

All the WHWTs were privately owned and prospectively recruited. The study protocols were approved by the “Animal Ethics Committee at the State Provincial Office” (permit number 7383/04.10.07/2013, date of approval: 13 November 2013).

The study group consisted of 12 CIPF and 24 healthy age matched WHWTs. The median age of the WHWTs with CIPF (8 males, 4 females) was 12.8 (range 8-14) years and for the clinically healthy controls (10 males, 14 females) 11.2 (range 7-14) years. The clinical status was based on clinical signs, physical examination findings, hematological and serum biochemical analysis, measurement of C-reactive protein, thoracic radiography and arterial blood gas analysis in all dogs. In addition, for 14/36 fecal analysis, 28/36 6-minute walk test, 12/36 echocardiography and 4/36 dogs bronchoscopy and bronchoalveolar lavage (BAL) was performed. The tentative diagnosis of CIPF was based on previously described findings in WHWTs with CIPF, including typical auscultation findings, low partial pressure of arterial

oxygen (PaO_2) values and exclusion of other cardiac and respiratory diseases.³ The mean PaO_2 for the CIPF dogs was 60.7 mmHg (range 49.4-69.1 mmHg) and for the control group 96.1 mmHg (range 86.1-107.0 mmHg). The control WHWTs had no signs or findings of any respiratory disease. Eight of 12 dogs with CIPF died or were euthanized before the study endpoint in October 2015 and histopathological confirmation of CIPF was done from lung tissue biopsies. One healthy WHWT was euthanized due to neurological signs and was diagnosed with brain astrocytoma. As the aim of this study was to evaluate the use of modified VetMousetrapTM in detecting CIPF, patients with suspicion of other respiratory diseases, such as pneumonia or lung neoplasia, were excluded from the study.

Thoracic HRCT was performed using a helical dual slice scanner (Somatom Emotion Duo, Siemens AG, Forchheim, Germany) and modified VetMousetrapTM (Universal Medical Systems, Inc. Cleveland, Ohio, USA) device without anesthesia between August 2014 and February 2015. For CT scanning the dogs were positioned in sternal recumbency on the VetMousetrapTM device and instead of a lid, velcro tapes and foam cushions were used to fix the dog comfortably into the box and to prevent motion. To relieve anxiety, four WHWTs were given butorphanol (Zoetis) 0.2 mg/kg intramuscularly 15 minutes before scanning. Axial HRCT protocol with high spatial resolution image reconstruction algorithm was employed using 1 mm slice thickness with 7.5 mm table movement, 130 kV and 100 mAs, and matrix of 512 x 512. Tube rotation time was 0.8 s.

HRCT image sets were randomized, anonymized and reviewed by three evaluators. Each observer independently evaluated images three times with minimum of one week interval. Two evaluators were veterinary radiologists and one was a veterinary practitioner. The images were viewed using OsiriX imaging software (Pixmeo, Geneva, Switzerland) and reviewed with pulmonary window settings (WL -500, WW 1500). Affection status of each animal was

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3 100 recorded as healthy or CIPF. Left and right cranial, middle and caudal lung fields were
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5 101 separately assessed for presence of ground glass opacity (GGO).^{3,8} The cranial zone was
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7 102 defined as cranial to the bifurcation, the middle zone as five slices caudal to the bifurcation
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9 103 and the caudal zone as caudal to these. The presence of GGO was determined in each of the
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11 104 six zones by the three observers and the extent was scored as mild if present only in one zone,
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13 105 moderate if present in two or three zones and severe if present in four zones or more. Motion
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15 106 artefact was characterized by blurriness of one or more areas of lung fields and loss of sharp
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17 107 edges of pulmonary vessels and airway walls. The image quality for every lung field from the
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19 108 most representative slice was evaluated separately using criteria that addressed the presence
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21 109 of motion artefact as shown in Table 1.
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25 110 Quantitative CT values in Hounsfield units (HU) of the lung fields were measured using Fiji
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27 111 ImageJ 1.50b software by primary author to objectively estimate the attenuation of the lung.
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29 112 For all the lung zones three slices were selected and anatomical lung outlines of each of the
30
31 113 lung segments of both the left and right lung were depicted as regions of interest (ROI)
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33 114 (Figure 1). The pixel values were measured representing the average global attenuation value
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35 115 of the ROIs as HUs.
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39 116 Descriptive statistics are presented as mean $\pm$ standard deviation (SD) and 95% confidence
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41 117 interval for mean or percentages for continuous and normally distributed variables as median
42
43 118 and range for noncontinuous variables. For quantitative analysis, normality of the data
44
45 119 distribution was tested with the use of the Kolmogorov–Smirnov and Shapiro-Wilk –tests.
46
47 120 For affection status, the agreement between clinical and CT findings was evaluated by
48
49 121 Cohen's kappa (κ) statistics and percentage of agreement (PA). Intra- and interobserver
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51 122 variabilities were analysed using κ statistics. Agreement was classified as “very good”
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53 123 ($\kappa > 0.8$), “good” ($\kappa = 0.61–0.8$), “moderate” ($\kappa = 0.41–0.6$), “fair” ($\kappa = 0.21–0.4$), or “poor” ($\kappa \leq$
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0.2).¹⁹ To describe the certainty of the coefficient, 95% confidence intervals for the κ coefficients were computed.

To assess CT imaging findings and motion artefacts, frequency tables were computed by lung field and observer. Between the three observation rounds the mode value was chosen or in case every result was different, the median was chosen, first for every rater over lung fields, and finally over raters to obtain the overall score. The motion artefacts and attenuation between the two study groups were compared by the use of Student's *t*-test. To compare the lung fields a cumulative logistic regression model was fitted and the probability of higher values for motion artefact was modelled using area as a fixed effect in the model and dog and rater as random effects. Data was analysed with commercially available software SAS® System for Windows, version 9.2 (SAS Institute Inc., Cary, NC, USA). P-values, describing the difference from zero, were calculated. Values of $P < 0.05$ were considered significant.

136

137 Results

The agreement between HRCT imaging findings and clinical affection status was very good with overall κ value of all observers and all rounds being 0.91 ($P < 0.0001$). κ values varied from 0.61 to 1.00. The mean overall PA was 94% (range 83% -100%). With observer 1 the most disagreement with clinical data and the HRCT imaging results was found with the first round, with observer 2 with the third round and with observer 3 with the second and third round (Table 2).

144

The κ values for intraobserver agreement were very good, except in one case where the κ value was 0.79 (good), in diagnosing CIPF between the observation rounds for all observers (Table 3). As for overall interobserver agreement, κ values indicated a very good agreement

148 between the observers. When the most common interpretation per observation for each
149 observer was chosen, the overall interobserver agreement was $\kappa = 0.94$ ($P < 0.0001$). Two of
150 the raters (observers 2 and 3) resulted to a complete agreement and agreement with the third
151 rater (observer 1) was found very good ($\kappa = 0.86$) when interobserver agreement between
152 pairs of observers was calculated (Table 4).

153

154 Motion artefact was found none to mild in all images chosen for evaluation. No significant
155 difference was found in the motion artefact between different lung fields ($P = 0.71$) or
156 between the two study groups ($P = 0.97$).

157

158 Moderate (1/12) to severe (11/12) GGO was detected in all CIPF dogs. In all 12 CIPF dogs
159 the abnormalities seen on HRCT were patchily distributed over the lung area. In 6/24
160 clinically healthy WHWTs mild and in one clinically healthy WHWT moderate GGO was
161 observed. A parenchymal band was detected in the right cranial lobe of one control dog. Other
162 CT findings were not detected in the controls. Examples of HRCT images obtained are
163 illustrated in Figures 2 and 3.

164

165 ImageJ analysis showed a significant difference in mean lung attenuation between the two
166 study groups. In quantitative analysis the HU values of lung fields were significantly higher in
167 CIPF dogs when compared with controls (group mean $\pm$ SD: healthy dogs -708 ± 55.8 HU,
168 95% confidence interval for mean -732 to -685 HU; CIPF dogs -495 ± 66.8 HU, 95%
169 confidence interval for mean: -538 to -453 HU, $P < 0.0005$).

170

171 All dogs were cooperative during scanning. Patient preparation time was less than 5 minutes.

172 No complications were noticed.

173

174 Discussion

175 The aim of the present study was to evaluate the feasibility of modified VetMousetrap™
176 device in HRCT scanning in detecting CIPF in WHWTs. In the absence of lung biopsies,
177 thoracic HRCT is an important diagnostic tool for diagnosis of CIPF.⁶ However, general
178 anesthesia is usually required to obtain thoracic HRCT scans in animals and CIPF dogs
179 commonly have substantial hypoxemia possessing an increased anesthetic risk.³ The
180 positioning device enabling thoracic CT imaging without general anesthesia or sedation, such
181 as VetMousetrap™ could offer a rapid and safe alternative. In our study, we used no or
182 minimal sedation during scanning. The four dogs receiving butorphanol all remained fully
183 conscious and ambulatory.

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185 In human pediatric radiology, HRCT scanning is often performed without general
186 anesthesia.²⁰ In previous studies where VetMousetrap™ device has been used to scan awake
187 or mildly sedated animals, image quality has been adequate for diagnosis of airway diseases
188 including dogs with primary laryngeal and tracheal airway obstruction,¹³ pulmonary
189 thromboembolism,¹⁵ cats with upper airway obstruction and allergic asthma,²¹⁻²³ and dogs
190 with abdominal diseases and traumatic pelvic fractures.^{14,24} Motion artefact has been
191 considered absent or mild in majority of examinations,^{11,12,14} as was the case also in our study.
192 Image quality was considered adequate for diagnosis in spite of the scan acquisition with the
193 animals awake and without a respiratory pause.

194

195 The patient movement and respiratory motion in awake animals during scanning can cause
196 artefacts which impair the image quality. However, motion artefacts can be minimized with
197 the patient immobilization and imaging techniques. Fastest available gantry rotation time is

198 used to reduce the scanning time. Multidetector-row spiral scanners (MDCT) would be
199 optimal for the method in question as they allow even shorter scanning times and less motion
200 artefact.²⁵ Spiral scanning with MDCT would allow complete visualization of all parts of the
201 lungs and enable the generation of multiplanar reformation images. In our study, no
202 statistically significant differences in motion artefact were identified between cranial, middle
203 and caudal parts of the lung. Moreover, scanning under general anesthesia often causes
204 varying degrees of hypostatic congestion and dependent atelectasis which may mimic
205 pathological changes eliciting the need for additional scans in different postures.^{26,27}

206
207 Correlation between the clinical workup and CT diagnosis was high with overall κ value 0.91
208 and PA 94%. The κ value range is 0–1, with 0 indicating only chance agreement and 1 perfect
209 agreement.²⁸ The diagnostic accuracy obtained is consistent with previous studies of thoracic
210 CT in anesthetized dogs.^{8,29} In humans, HRCT performs well in diagnosing UIP using
211 histopathology as the reference standard with an accuracy of 80% to 90% when UIP is the
212 first diagnosis based on imaging findings.³⁰⁻³² Both intra- and interobserver agreements were
213 also very good in our study. In human studies inter-observer agreement for the diagnosis of
214 IPF has been fair to moderate.^{33,34} However, in these studies the different interstitial lung
215 disease patterns were evaluated separately which makes accuracy of diagnosis more
216 challenging. In our study, the study design (observers knew that the dogs were either
217 clinically healthy or had IPF) could have had an effect on good correlation between clinical
218 workup and CT diagnosis and also between intra- and interobserver agreement.

219
220 Moderate to severe GGO, which has previously been described as the hallmark of the
221 CIPF,^{3,7,8} was present in all of the dogs with CIPF. The differences between thoracic HRCT
222 imaging findings for CIPF under general anesthesia and sedation have been recently described

223 stating that different information in terms of extent of GGO and grading of mosaic pattern
224 may be observed between the two methods.¹⁰ Inability to obtain images during specific
225 respiration phase may cause secondary artefactual changes for example due to underinflation
226 of the lungs during expiration,⁸ and motion artefacts could potentially influence on the
227 estimations of these parenchymal lesions. In our study, especially in the most caudal images
228 near the diaphragm, severe motion artefact was common. However, in every case at least one
229 image was representative and diagnosis of GGO was possible. Because of the possible
230 influence of the motion artefacts, we did not evaluate the images for more local abnormalities
231 such as parenchymal bands and subpleural thickening. In a recent study it was demonstrated
232 that identification of this kind of lesions did not differ between acquisition of thoracic HRCT
233 under general anesthesia and sedation.¹⁰

234

235 With ImageJ software, histogram analysis of density in pixels can be performed to
236 differentiate normal and fibrotic lung parenchyma. ImageJ CT image analysis was able to
237 quantify the difference in attenuation over the lung fields between CIPF and healthy WHWTs
238 and detect distinctly CIPF from healthy dogs. In our study the HU values of both healthy and
239 CIPF dogs were higher than in the previous studies where the difference in the lung
240 attenuation of CIPF and healthy WHWTs under general anesthesia were assessed.^{3,9} This
241 could be due to mechanical inflation of the lungs under general anesthesia. Another possible
242 cause might have been inclusion of fat or other tissues than lung tissue in the ROIs, which
243 could be overcome by adding upper HU limit to CT number range but was not implemented
244 as severe pulmonary changes could be missed.³⁵ Since in IPF mosaic pattern with patchily
245 distributed high-attenuation areas is often recognized.³⁶ ImageJ analysis could provide more
246 objective evaluation of the overall lung attenuation. This computer image analysis approach

247 has potential in the assessment of canine interstitial lung diseases for clinical and research
248 purposes.

250 Imaging without anesthesia appeared acceptable to the owners as all approved CT imaging
251 without chemical restraint. Some owners refused conventional HRCT under general
252 anesthesia, but agreed thoracic HRCT study using modified VetMousetrap™ device.

254 Limitations of this study include relatively small number of dogs and lack of
255 histopathological confirmation of affection status for all of the dogs. However, histopathology
256 was available in majority of diseased WHWTs and pathological results verified diagnosis
257 achieved by HRCT. In six clinically healthy control dogs there was mild and in one moderate
258 GGO in HRCT images. These patients were free of respiratory signs and had normal oxygen
259 level in arterial blood. In these patients, follow-up examinations with CT imaging would be
260 recommended to evaluate if these changes represent the early signs of CIPF. Although our
261 study was performed with a dual slice scanner the results for detecting CIPF was good.
262 MDCT scanners that are faster and have more detectors are widely available for clinical use
263 and they could be used to find more subtle changes.

265 In conclusion, CT imaging with modified VetMousetrap™ device was feasible in diagnosing
266 CIPF in awake WHWTs without the need of chemical restraint. Since anesthesia and sedation
267 is often avoided in these often severely hypoxic patients in order to prevent further respiratory
268 compromise, this would provide a valuable alternative in the clinical setting. Image quality
269 was adequate for assessment of the existence of the disease with very good intra- and
270 interobserver accuracy. Quantitative computer image approaches such as ImageJ analysis
271 could be applicable in assessment of CIPF.

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For Peer Review

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370 **Tables**

371 Table 1. The score for evaluation of motion artefact

Score	Quality	Definition
1	Good	None or mild motion artefact, good/very good for interpretation
2	Moderate	Moderate motion artefact, adequate for interpretation
3	Poor	Severe motion artefact, nonacceptable for interpretation

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Table 2. The agreement between high resolution computed tomography imaging findings and clinical affection status* for three observers

Observer	Round	Kappa (SD)	95% CI	p-value
Overall (1-3)	1-3	0.910 (0.096)	(0.721 - 1.000)	<.0001
1	1	0.609 (0.143)	(0.329 - 0.889)	0.0002
	2	0.800 (0.108)	(0.588 - 1.000)	<.0001
	3	0.745 (0.117)	(0.516 - 0.973)	<.0001
2	1	1.000 (0.000)	(1.000 - 1.000)	<.0001
	2	0.936 (0.063)	(0.813 - 1.000)	<.0001
	3	0.870 (0.089)	(0.695 - 1.000)	<.0001
3	1	0.936 (0.063)	(0.813 - 1.000)	<.0001
	2	0.875 (0.086)	(0.707 - 1.000)	<.0001
	3	0.875 (0.086)	(0.707 - 1.000)	<.0001

*healthy vs. diseased status based on history, clinical examination, blood samples including hematology, C-reactive protein, serum biochemistry and arterial blood gas analysis, thoracic radiographs and 6-minute walk test

Table 3. Intraobserver agreement between high resolution computed tomography imaging findings and clinical affection status in diagnosing canine idiopathic pulmonary fibrosis

Observer	Kappa (SD)	95% CI	p-value
1	0.848 (0.096)	(0.659 - 1.000)	<.0001
2	0.913 (0.096)	(0.724 - 1.000)	<.0001
3	0.792 (0.096)	(0.603 - 1.000)	<.0001

Table 4. Interobserver agreement between high resolution computed tomography imaging findings and clinical affection status in diagnosing canine idiopathic pulmonary fibrosis

Observer	Kappa (SD)	95% CI	p-value
Overall	0.936 (0.063)	(0.813 - 1.000)	<.0001
1 vs 2	0.862 (0.094)	(0.678 - 1.000)	<.0001
1 vs 3	0.862 (0.094)	(0.678 - 1.000)	<.0001
2 vs 3	1.000 (0.000)	(1.000 - 1.000)	<.0001

Figure legends

Figure 1. Measurement of lung attenuation of the left caudal field of the lung in a healthy West Highland white terrier. Regions of interest (ROI) were manually placed for cranial, middle and caudal lung areas of both lungs for the measurement of mean lung density in Hounsfield units for each ROI using Fiji ImageJ 1.50b software.

Figure 2. Transverse high resolution computed tomographic image of the middle thorax in a healthy West Highland white terrier under general anesthesia (A) and using VetMousetrap™ device (B).

Figure 3. Transverse high resolution computed tomographic image using VetMousetrap™ device of a dog with canine idiopathic pulmonary fibrosis with severe ground glass opacity.

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Figure 2. Transverse high-resolution computed tomographic image of the middle thorax in a healthy West Highland white terrier under general anesthesia (A) and using VetMousetrap™ device (B)

84x68mm (300 x 300 DPI)

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