COMPARISON BETWEEN SEDATION AND GENERAL ANESTHESIA FOR HIGH RESOLUTION COMPUTED TOMOGRAPHIC CHARACTERIZATION OF CANINE IDIOPATHIC PULMONARY FIBROSIS IN WEST HIGHLAND WHITE TERRIERS

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Running head: CIPF-HRCT findings, sedation vs. anesthesia

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Abstract

Canine idiopathic pulmonary fibrosis (CIPF) is a progressive interstitial lung disease mainly affecting West Highland white terriers (WHWTs). Thoracic high-resolution computed tomographic (T-HRCT) findings for CIPF acquired under general anesthesia have been described previously. However, the use of general anesthesia may be contraindicated for some affected dogs. Sedation may allow improved speed and safety, but it is unknown whether sedation would yield similar results in identification and grading of CIPF lesions. The aim of this prospective, observational, method-comparison, case-control study was to compare findings from T-HRCT images acquired under sedation versus general anesthesia for WHWTs affected with CIPF (n=11) and age-matched controls (n=9), using the glossary of terms of the Fleischner Society and a scoring system. Ground-glass opacity (GGO) was identified in all affected WHWTs for both sedation and general anesthesia acquisitions, although the GGO extent varied significantly between the two acquisitions (P<0.001). Ground-glass opacity was the sole lesion observed in control dogs (n=6), but was less extensive compared with affected WHWTs. Identification and grading of a mosaic attenuation pattern differed significantly between acquisitions (P<0.001). Identification of lesions such as consolidations, nodules, parenchymal and subpleural bands, bronchial wall thickening, and bronchiectasis did not differ between acquisitions. The present study demonstrated that T-HRCT obtained under sedation may provide different information than T-HRCT obtained under general anesthesia for identification and grading of some CIPF lesions, but not all of them. These differences should be taken into consideration when general anesthesia is contraindicated and sedation is necessary for evaluating WHWTs with CIPF.

Introduction

Canine idiopathic pulmonary fibrosis (CIPF) is a progressive interstitial pulmonary disease affecting mainly old West Highland white terriers (WHWTs).[1] Clinical signs include cough, exercise intolerance, progressive dyspnea and inspiratory crackles on lung auscultation.[2,3] Definitive diagnosis of canine idiopathic pulmonary fibrosis relies on histopathology.[4] However, ante-mortem lung biopsies are not routinely performed in veterinary practice due to the invasiveness of the procedure.[5,6] To further complicate matters, information obtained from focal biopsies may not be representative of the organ as a whole. The present lack of effective therapy for canine idiopathic pulmonary fibrosis is also a poor incentive for such aggressive intervention. Consequently, thoracic high resolution computed tomography (T-HRCT) has become the key modality for the diagnosis of canine idiopathic pulmonary fibrosis.[1,7] Thoracic high-resolution computed tomography findings have previously been described in canine idiopathic pulmonary fibrosis dogs under general anesthesia.[2,7,8] However, general anesthesia may be contraindicated for patients considered at high risk (e.g. pulmonary-diseased patients with concurrent pulmonary hypertension). The use of sedation may offer the opportunity to more safely repeat T-HRCT examinations of West Highland white terriers affected with canine idiopathic pulmonary fibrosis at multiple time-points. This may also help improve understanding of the progression of this disease and effects of new treatments.

It is presently unknown whether T-HRCT obtained under sedation can be interpreted equally as T-HRCT obtained under general anesthesia for the identification and grading of canine idiopathic pulmonary fibrosis lesions. The objective of the present study was thus to compare T-HRCT images obtained under sedation and general anesthesia from canine idiopathic pulmonary fibrosis and control West Highland white terriers. A scoring system was employed to describe canine idiopathic pulmonary fibrosis lesions in a standardized manner

using the glossary of terms of the Fleischner Society[9]. We hypothesized that the different breathing patterns seen with sedation (spontaneous breathing) and general anesthesia (induced apnea following hyperventilation) would provoke differences in some lesions detected in lungs affected by canine idiopathic pulmonary fibrosis on T-HRCT due to the variable content of air present in the alveoli. However, we also hypothesized that some lesions would not differ and therefore the use of sedation would not prevent the diagnosis of canine idiopathic pulmonary fibrosis.

Materials and Methods

Study population

West Highland white terriers affected with canine idiopathic pulmonary fibrosis and age-matched unaffected control West Highland white terriers were prospectively enrolled at the Veterinary Teaching Hospital of the University of Liège during a three-year period from March 2013 to March 2016 under the umbrella of the canine idiopathic pulmonary fibrosis project (see: http://www.caninepulmonaryfibrosis.ulg.ac.be/ accessed 13.09.2016). Among dogs recruited in the canine idiopathic pulmonary fibrosis project, those that prospectively underwent T-HRCT under both sedation and general anesthesia were included in the present observational method-comparison case-control study. The study protocol was approved by the Committee of Experimental Animals of the University of Liège, Belgium (permit number: 1435, date of approval: 14 March 2013). All examinations were performed with the owners' informed consent. Control West Highland white terriers were recruited if they had no history of cardiovascular or pulmonary clinical signs, and a normal cardiopulmonary physical examination. Furthermore, echocardiography was performed in all control dogs to exclude primary cardiac disease. Inclusion criteria for West Highland white terriers affected with

Code de champ modifié

canine idiopathic pulmonary fibrosis comprised history of cough, exercise intolerance and/or dyspnea, the presence of marked inspiratory crackles on lung auscultation, and the exclusion of primary cardiac disease through echocardiography. Additional examinations, including arterial blood gas analysis, 6-minute walking test and endoscopy with bronchoalveolar lavage were performed in the majority of canine idiopathic pulmonary fibrosisaffected dogs. Results of these tests supported the diagnosis of canine idiopathic pulmonary fibrosis in dogs where histopathologic examination of pulmonary tissue was not available.

Thoracic high-resolution computed tomography acquisition

Thoracic high-resolution computed tomography images were acquired under sedation and general anesthesia successively on each dog included at a single occasion. Dogs were maintained in sternal recumbency following premedication and throughout both sets of T-HRCT acquisitions. Sedative agents and dosages were adjusted for each dog according to the recommendations of the anesthetist. Sedated dogs were not provided with supplemental oxygen. After T-HRCT image acquisition under sedation, general anesthesia was induced using intravenous propofol. Following endotracheal intubation, dogs were maintained on isoflurane gas with 100% oxygen. Several gentle lung inflations were performed prior to image acquisition, in order to induce apnea and minimize motion artefact as in previous studies describing T-HRCT findings in canine idiopathic pulmonary fibrosis.[2,7] The same 16 multi-slice CT scanner (Siemens, Somatom 16, Erlangen, Germany) was used to acquire all scans and scans included the entire thorax, sequenced cranially to caudally. Acquisition parameters used were as follows: tube voltage 120 kV, reference tube current 130 mA, and pitch 0.7 – 1.15. Scan tube current was modulated by automatic exposure control (Care Dose, Siemens Medical Solutions, International). Image data sets were reconstructed using

parameters of 200 – 300 mm field of view, 512 x 512 matrix, 1mm slice thickness and B-60 Sharp reconstruction algorithm.

Thoracic high-resolution computed tomography interpretation

Images from both T-HRCT acquisitions were reviewed in a random order on lung window settings (WW 1500 – WL -500) by one veterinary (GB) and two medical (TC and JV) radiologists at the same time to obtain a consensus opinion for each case. Observers were unaware of the dog's group status (canine idiopathic pulmonary fibrosis or control) but were aware of the acquisition status (sedation or general anesthesia) as the endotracheal tube was visible in dogs under general anesthesia. For each scan, overall T-HRCT quality was subjectively graded as good (thoracic walls perfectly sharp and well-defined), moderate (thoracic walls partially blurred, with artefacts present only at the periphery of the lung field) or poor (thoracic walls blurred with artefacts extending significantly into the lung field). Heart and diaphragm motion artefacts were graded as absent, mild (artefacts affecting the diaphragm and/or heart without impacting evaluation of the lung fields), moderate (artefacts inducing blurred margins of the diaphragm and/or the heart that extended slightly over the periphery of the lung fields) or severe (artefacts inducing blurred margins of the diaphragm and/or the heart that extended extensively over the lung fields with several artefactual sequential images of the diaphragm and/or the heart). Characteristics present in T-HRCT images were defined using the glossary of terms established by the Fleischner Society.[9] Four major groupings were used: increased attenuation, decreased attenuation, nodular opacities and linear opacities. Each category was divided into sub-groups corresponding to specific features (Table 1). Each specific feature was assessed independently for each lung lobe. For ground glass opacity (GGO), consolidation and mosaic attenuation pattern features, the following scoring system was applied for each lung lobe: 0 = absent, 1 = present in < 1/3 of

Commentaire [JCJ1]: In random order ? in order of dog name ? in order of date scanned ?

149 the lobe, 2 = present in 1/3 to 2/3 of the lobe, and 3 = present in > 2/3 of the lobe. This
150 grading system was qualitative and applied following detailed review of the available images.
151 Delimitation of each lung lobe was determined in relation to the main bronchial division
152 (right cranial, middle and caudal lung lobes, accessory lung lobe, and left cranial and caudal
153 lung lobes). An overall cumulative score was calculated by adding the individual lobe scores
154 together (0 to 18). The presence or absence of cysts, emphysema, nodules, honeycombing,
155 reticulations, parenchymal and subpleural bands was assessed for each lung lobe. Trachea,
156 bronchi, pleura, blood vessels and lymph nodes were also evaluated. Tracheal shape was
157 subjectively assessed at the level of the 6th cervical vertebrae and was classified as round with
158 a normal or flattened dorsal membrane (no collapse), oval with a flattened dorsal membrane
159 (mild to moderate collapse) or oval with an invaginated dorsal membrane or with a loss of >
160 50% of the tracheal lumen (severe collapse).
161
162 *Statistics*
163 Statistical analyses were performed by one statistician (FR) using commercially
164 available software (Excel, Microsoft Office; and XLStat software; Addinsoft SARL,
165 International). Continuous variables were reported as median and range (minimum and
166 maximum), and categorical data as proportions. Proportions were compared using the Fisher's
167 exact test. Differences between T-HRCT acquisitions under sedation versus general anesthesia
168 for identification or grading of GGO, consolidation and mosaic attenuation patterns in canine
169 idiopathic pulmonary fibrosis dogs were assessed using a permutation test. This allowed us to
170 test the following null-hypothesis: H0 = no difference between acquisitions for the allocation
171 of lung lobe scores. To test this hypothesis we generated permutated datasets by randomly
172 allocating scores to either method (sedation or general anesthesia) for each lung lobe and for
173 each dog. We summed the absolute differences between the two methods over the whole lung

Commentaire [JCJ2]: Please specify who performed statistics.

for each dog to obtain a hypothetical value of the overall absolute difference for each individual (|d|). Absolute values were employed because differences between the 2 methods could vary positively or negatively. Summing individual |d| allowed the calculation of a hypothetical overall difference D between the two methods over the entire sample. By repeating this procedure 1000 times (random allocation of a score for each lung lobe, calculation of |d| and then D) we obtained a distribution of overall differences D for the null hypothesis. By comparing results for the real observed overall difference (Dr) with this generated distribution we could estimate a *P*-value. The percentage of D ≥ to Dr in the distribution allows calculation of the *P*-value associated to the observed Dr. Values of $P \leq 0.05$ were considered statistically significant.

Results

Study population

Over the three-year period of the present study, 15 West Highland white terriers affected with canine idiopathic pulmonary fibrosis were examined at the Veterinary Teaching Hospital of the University of Liège. Among those 15 dogs, 11 were scanned under both sedation and general anesthesia at initial presentation and were included in the present study. The remaining four dogs were excluded due to the absence of one or both acquisitions. Indeed, two dogs were scanned under general anesthesia alone due to severe breathing difficulties and cyanosis induced by sedation requiring a rapid intubation and ventilation, and two were not sedated nor anesthetized due to the presence of a severe pulmonary hypertension in one dog and owner decision in the other dog. Among the included 11 West Highland white terriers affected with canine idiopathic pulmonary fibrosis, there were six males and five females that were aged from 5.2 to 14.5 years (median 11.6 years) and weighed between 7.3 to 16.6 kg (median 9.5 kg). Seven of these affected dogs had a history of both exercise

intolerance and cough, one presented for exercise intolerance alone, and three dogs exhibited only a cough. The duration of clinical signs at diagnosis ranged from 1 month to 3.5 years with a median of 3 months. Crackles were noticed on lung auscultation in all dogs, a mild restrictive dyspnea was present in six dogs and cyanosis was observed in one dog. Echocardiography was performed in all West Highland white terriers affected with canine idiopathic pulmonary fibrosisaffected dogs to confirm the absence of primary cardiac disease. Doppler-echocardiographic evidence of mild pulmonary hypertension was present in two affected canine idiopathic pulmonary fibrosis dogs, with pulmonary systolic pressure gradients estimated at 37.4 and 40.7 mmHg (reference < 31.4)[10]. Arterial blood gas analysis was performed in ten West Highland white terriers affected with canine idiopathic pulmonary fibrosisaffected dogs and revealed hypoxemia in all dogs with a median of 58.9 mmHg (range 50.6 – 65.0) (laboratory reference range: 80 – 100mmHg). The 6-minute walking test was performed in ten affected West Highland white terriers and a decreased walked distance was recorded in seven dogs (median 350m, range 232 – 488) (reference: > 420)[11]. Bronchoscopy was performed in ten affected dogs and identified tracheal collapse (ten dogs), bronchi mucosal irregularity (nine dogs), bronchomalacia (four dogs), bronchiectasis (two dogs), and the presence of a moderate amount of mucus (seven dogs). Bronchoalveolar lavage fluid analysis revealed a moderate increase in the total cell count (median 2305 cells/mm³, range 420 – 9520) (reference: < 500).[12] In six dogs a moderate increase in the percentage of neutrophils was observed (median 16%, range 2 – 76) (reference range: 0 – 10)[12]. Angiostrongylus infection was considered unlikely in all affected West Highland white terriers, based on a negative Bearmann fecal analysis (three dogs), documentation of the absence of improvement of clinical signs following anti-parasitic treatment (five dogs) or a negative antigen test (Idexx Angio Detect, Idexx Laboratories) (three dogs). At the end of the study period, five West Highland white terriers affected with canine idiopathic pulmonary

fibrosis were still alive, one dog was lost to follow-up and five had died or been euthanized for respiratory failure. Lung tissue samples were available in four of these dogs and allowed the histopathologic confirmation of canine idiopathic pulmonary fibrosis.[4]

Nine unaffected West Highland white terriers were recruited during the same period of time as a control group and were all included the study. There were four males and five females that were aged from 5.7 to 15.0 years (median 10.4 years) and weighed between 6.6 to 11.0 kg (median 8.4 kg). Five of the nine control dogs were clinically healthy; the remaining four dogs had presented to the University for unrelated conditions including one dog with bilateral hip luxation surgery, one with a nasal tumor and two for postoperative check-ups following right ear conduct ablation (one dog), or rectal polyp resection (one dog). Control dogs did not have any signs or findings indicating cardiopulmonary disease. Echocardiography was performed to exclude the presence of primary cardiac disease in all control dogs.

Thoracic high-resolution computed tomography acquisition

Dogs were sedated on the CT scan table to minimize stress and time between sedation and image acquisition. For all sedation acquisitions, butorphanol (0.2 – 0.35 mg/kg IV) was used. For some dogs, butorphanol was combined with medetomidine (1 – 5 µg/kg IV) (four of the control dogs) or acepromazine (10 µg/kg IV) (one of the control dogs). When butorphanol alone did not induce sufficient immobilization for some of the dogs, additional gentle restraints were used (e.g. sand bags and Velcro straps) during T-HRCT acquisition. For all general anesthesia acquisitions, dogs were induced with a combination of diazepam (0.2 mg/kg IV) (one dog) or midazolam (0.2 – 0.3 mg/kg IV) (16 dogs) immediately followed by propofol (1.5 – 5 mg/kg IV) (all dogs). Anesthesia was maintained by inhalation of

248 isoflurane gas (1.5 - 2%) with 100% oxygen (all dogs). The median time between sedation
249 and general anesthesia image acquisitions was 6 minutes (range 3 – 23) (Appendix 1).

250

251 *Thoracic high-resolution computed tomography interpretation*

252 Detailed characteristics of T-HRCT findings observed in each sampled dog, including
253 grades for GGO, consolidation, and mosaic attenuation pattern, are provided in Appendix 1.

254 **Comparisons between acquisitions for T-HRCT quality and motion artefacts -**
255 The overall T-HRCT quality was graded as good in 11/20 examinations under sedation and
256 16/20 examinations under general anesthesia (P = 0.176). Poor overall T-HRCT quality was
257 observed under sedation in two affected West Highland white terriers owing to severe
258 respiratory dyspnea-related artefacts. Motion artefacts due to cardiac and/or respiratory
259 movements were present in 18/20 examinations under sedation and 7/20 examinations under
260 general anesthesia (P = 0.001). Thoracic high-resolution computed tomography motion
261 artefacts under sedation were most frequently graded as mild (12/18) rather than moderate
262 (4/18) or severe (2/18). Thoracic high-resolution computed tomography motion artefacts
263 under general anesthesia were graded as mild (5/7) or moderate (2/7).

264 **Comparisons between acquisitions for characterization of T-HRCT pulmonary**
265 **lesions –** A summary of T-HRCT findings identified in affected and control West Highland
266 white terriers for each method of image acquisition is displayed in Fig. 1. Compared with
267 images obtained under general anesthesia, sedation over-graded GGO in three dogs (two
268 affected and one control) and under-graded GGO in one affected dog ($P < 0.001$), while
269 similar overall scores were found between both acquisitions in the remaining 13 dogs (eight
270 affected and five controls) who were displaying this finding (Appendix 1) (Fig. 2A and 2B).
271 Consolidations were found to be absent in two and present in one affected West Highland

white terriers when images acquired under sedation were compared with those acquired under general anesthesia (P = 0.121) (Appendix 1) (Fig. 3A and 3B). Compared with images obtained under general anesthesia, mosaic attenuation pattern was either under-graded or over-graded in respectively two and three canine idiopathic pulmonary fibrosisaffected West Highland white terriersdogs on images acquired under sedation (P < 0.001), while similar overall score was found between both acquisitions in the remaining four canine idiopathic pulmonary fibrosis West Highland white terriers dogs who were displaying this finding (Appendix 1) (Fig. 4A and 4B). Tracheal collapse identification also varied between both acquisitions, being respectively absent or present in three dogs (one CIPFcanine idiopathic pulmonary fibrosisaffected and two controls WHWTsWest Highland white terriers) and four dogs (one CIPFcanine idiopathic pulmonary fibrosis WHWTWest Highland white terrier affected and three controls) when images acquired under sedation were compared with those acquired under general anesthesia, while similarly identified on both acquisitions in four dogs (three CIPFcanine idiopathic pulmonary fibrosis affected and one control WHWTsWest Highland white terriers) (Appendix 1). There was no difference between sedation and general anesthesia acquisitions for the other T-HRCT findings studied including cyst, nodules, subpleural and parenchymal bands, bronchial wall thickening, and bronchiectasis.

Descriptions of specific lung lesions – Ground glass opacity was identified in all West Highland white terriers affected with canine idiopathic pulmonary fibrosis and in 6 controls. In affected dogs, overall GGO score calculated on T-HRCT images acquired under sedation ranged from 6 to 18 with a median of 12, while it ranged from 1 to 6 in controls with a median of 2. Ground glass opacityGO was observed in every lung lobe in all canine idiopathic pulmonary fibrosis affected dogs on T-HRCT images obtained under sedation, and in all except two dogs on T-HRCT images acquired under general anesthesia. In these two dogs, GGO was only observed in the cranial and accessory lung lobes. In controls, GGO was

visualized in the right and/or left cranial lung lobes (three dogs), the accessory lobe (two dog), the right caudal lung lobe (one dog), or in all lung lobes (one dog). Consolidations under sedation and/or general anesthesia were observed in four of 11 West Highland white terriers affected with canine idiopathic pulmonaryaffected dogs fibrosis but in none of the controls dogs. Overall consolidation score was low and ranged from 1 to 6 (range 1.5). There was no lobe predilection for consolidations, which were found either in cranial or caudal lung lobes. A mosaic attenuation pattern under sedation and/or general anesthesia was observed in nine of 11 affected West Highland white terriers affected with canine idiopathic pulmonary fibrosis, without lobe predilection, while it was not observed in any control dogs. Overall mosaic attenuation pattern score calculated on T-HRCT images acquired under sedation ranged from 2 to 18 with a median of 10. but not in any control dogs. A cyst was found in the caudal left lung lobe of one control West Highland white terrier. Single or multiple non-specific nodules were noticed in two and one of 11 affected West Highland white terriers affected with canine idiopathic pulmonary fibrosis respectively but in none of the control dogs. Nodules were localized in the right and/or left caudal lung lobes and had a median size of 4.6 mm (range 3.8 – 7.8). One CIPFcanine idiopathic pulmonary fibrosisaffected dog had evidence of subpleural bands (Fig. 5), and parenchymal bands (Fig. 6) were seen in three canine idiopathic pulmonary fibrosisaffected West Highland white terriers. The subpleural bands were observed in the cranial right lung lobe and the parenchymal bands in right and/or left cranial lung lobes. Bronchial wall thickening was recognized in five of 11 affected West Highland white terriers affected with canine idiopathic pulmonary fibrosis and none of the control dogs. Bronchial wall thickening was observed in all lung lobes in four dogs and in the cranial lobes only in one dog. Varicose bronchiectasis, defined as an irregular bronchial dilatation, was observed in the right middle lobe of one CIPFcanine idiopathic pulmonary fibrosis WHWTWest Highland white terrieraffected dog. Tracheal collapse was observed in six of 11 affected West Highland

white terriers affected with canine idiopathic pulmonary fibrosis and in six of nine control sdogs. The tracheal collapse was considered severe in two West Highland white terriers affected with canine idiopathic pulmonary fibrosisaffected dogs. Emphysema, reticulations, honeycombing were not observed in CIPFaffectedcanine idiopathic pulmonary fibrosis or control dogs. Neither pleural effusion nor pleural thickening were observed. Blood vessel caliber and interface with pulmonary parenchyma were within normal limits in all dogs. Lymph nodes were within normal limits in all dogs, except in one affected WHWTWest Highland white terrier affected with CIPFcanine idiopathic pulmonary fibrosis in which a left cranial mediastinal lymph node appeared slightly enlarged.

Discussion

The present study demonstrated that T-HRCT images obtained under sedation are more frequently affected by motion artefacts and provide non-systematically different information concerning identification and grading of some canine idiopathic pulmonary fibrosis lesions versus T-HRCT images obtained under general anesthesia. However, authors believe that those differences would not preclude the use of sedation for T-HRCT in dogs suspected to have canine idiopathic pulmonary fibrosis when general anesthesia is contraindicated. For example, GGO was observed in all affected West Highland white terriers under sedation, with a wider distribution extent than seen in the control dogs and/or in association with other canine idiopathic pulmonary fibrosis features not identified in control dogs. Among the features studied, GGO, mosaic attenuation pattern, and bronchial wall thickening were found to be the main T-HRCT features observed in West Highland white terriers affected with canine idiopathic pulmonary fibrosis, although they were not necessarily

simultaneously present in all affected dogs. Honeycombing, the major feature of IPF in humans[13], was not observed in dogs in this study.

The differences observed between sedation and general anesthesia for identification and/or grading of some T-HRCT canine idiopathic pulmonary fibrosis findings in the present study were more likely related to different respiratory patterns induced in the dogs by either sedation and/or general anesthesia. Differences in respiratory pattern probably influenced appearance of lesions in one way or another. During sedation, dogs breathed spontaneously; T-HRCT acquisition was consequently obtained either during inspiration or expiration phases or during both phases. During general anesthesia, an end-expiratory pause was artificially induced by providing several lung inflations to induce a transient apnea. Such differences may have had an impact on the evaluation of mosaic attenuation pattern, GGO or consolidations, since all may be influenced by the breathing pattern and the subsequent amount of air remaining in the alveoli.[9,14-16] This explanation is also supported by the fact that the tracheal shape and the appearance of tracheal collapse were discordant in seven included dogs (two WHWTsWest Highland white terriers affected with CIPFcanine idiopathic pulmonary fibrosis affected and five controls). Changes in tracheal dimension during respiratory movements have previously been shown to occur in up to 24% in dogs.[17]

Similar to previously published data about T-HRCT features of canine idiopathic pulmonary fibrosis, the present study also identified the presence of GGO in all West Highland white terriers affected with canine idiopathic pulmonary fibrosis and bronchial changes in 50%.[2,7,8] However, we described for the first time the existence of a mosaic attenuation pattern in affected West Highland white terriers affected with canine idiopathic pulmonary fibrosis and GGO in control West Highland white terrierscontrols, and we observed linear opacities only in a minor proportion of CIPFcanine idiopathic pulmonary fibrosisaffected dogs. The main explanation for the discrepancies observed between previous

studies and the present one is the introduction of a recent nomenclature, the glossary of terms of the Fleischner Society, which has sparsely been employed in veterinary literature until now. According to this nomenclature, the mosaic attenuation pattern may appear in cases of patchy interstitial disease, obliterative small airway disease, or occlusive vascular disease, alone or in combination.[9] In the case of interstitial lung disease, the mosaic attenuation pattern results from hyperattenuated areas of GGO interposed with hypoattenuated areas of normal lung tissue.[9,15] In the case of bronchial or bronchiolar obstruction, the mosaic attenuation pattern consists of regions of hypoattenuation where air trapping has occurred, interspersed with regions of hyperattenuation representing normal ventilation.[14-16] Finally, in the case of occlusive vascular disease, regions of hypoattenuation reflect decreased blood flow and reduced vessel caliber in comparison to regions of hyperattenuation representing normal or excessive vascularization.[15,16] In West Highland white terriers affected with canine idiopathic pulmonary fibrosis, the underlying patchy interstitial disease, but also the concomitant airway involvement may explain the appearance of a mosaic attenuation pattern on CT images. Indeed, in human medicine, the presence of abnormalities of bronchi has proved to be a good indicator that the underlying mosaic attenuation pattern is related to small airway disease and concurrent air trapping.[15] In humans, air trapping is generally accentuated at end-expiration, depends on the respiratory efforts of the patient at the time of image acquisition and may not be reproducible, particularly in dyspneic patients.[16] This may explain why this feature was not present in all canine idiopathic pulmonary fibrosis dogs included in this study. Furthermore, two WHWTsWest Highland white terriers affected with CIPFcanine idiopathic pulmonary fibrosis affected dogs showed signs of pulmonary hypertension on echocardiography, which may also have contributed to the appearance of a mosaic attenuation pattern, despite the absence of difference in the caliber of the vessels between the lucent and the dense part of the lung.[16] Explanations for the presence of GGO in control West Highland white terriers may

relate to a reduction of air in the alveoli due to the modification of the respiratory pattern secondary to sedation or general anesthesia. Another explanation could be that those control dogs were suffering from subclinical or early canine idiopathic pulmonary fibrosis lesions. However, the distribution of GGO in controls was less extensive than in affected West Highland white terriers, except in one dog in which GGO was present in all lung lobes. Lung histopathology or follow-up imaging at regular intervals would be needed to confirm the presence of early canine idiopathic pulmonary fibrosis lesions but were not available. Unlike previous studies, we found linear opacities only occasionally in a minority of affected dogs. A different degree of disease severity among studied populations may be an explanation for those discrepancies. West Highland white terriers from our population may have been less severely affected than dogs included in previous studies. However, in the majority of the affected dogs included clinical signs had been present for several months and five West Highland white terriers died during the study period from respiratory failure (within a median time of 8 months) suggesting that the disease was well established at the time of T-HRCT acquisition.

The main limitation of the present study was the small number of dogs included. A second limitation was that radiologists were not blinded as to the dog's anesthetic status, which did not appear to cause a systematic bias as differences for identification or grading of T-HRCT lesions between sedation and general anesthesia varied either positively or negatively according to individuals (Appendix 1). Further sedative and anesthetic agent dosages among canine idiopathic pulmonary fibrosis dogs were slightly different which could potentially have influenced image interpretation. Using standardized anesthetic dosages for each included dog could possibly have alleviated this limitation, but would not reflect the real clinical practice where anesthetic protocols are adapted for each dog according to their co-morbidity and level of anxiety. A fourth limitation concerns the fact that the order of T-HRCT

acquisitions could not be randomized given that pre-medication is preliminary to induction of general anesthesia. The possibility cannot be excluded that areas of atelectasis could have appeared between the first T-HRCT under sedation and the second T-HRCT under general anesthesia and could have influenced image interpretation. In addition, the use of 100% oxygen has previously been shown to be less effective than medical air containing 40% oxygen for maintaining lung aeration during prolonged anesthesia.[18] However this seems unlikely given the short interval of time between the two acquisitions and the manual ventilation performed prior to T-HRCT image acquisition under general anesthesia. Alleviation of this limitation is also supported by the fact that the two West Highland white terriers affected with canine idiopathic pulmonary fibrosis affected dogs for which the time between sedation and general anesthesia was above 10 minutes were not the ones that displayed consolidations (Appendix 1). It would also have been interesting to use a positive ventilation breath-old protocol to maintain the dogs in forced full inspiration during T-HRCT acquisition under general anesthesia. However, we preferred to induce apnea by providing several lung inflations, such as performed in previously published studies about T-HRCT findings in canine idiopathic pulmonary fibrosis and other parenchymal lung diseases.[2,7,19,20] This technique is considered safer (less risks of barotrauma), easier and more applicable in a daily clinical practice. Finally, streaking artefacts extending from outside the lungs onto the lung field were present on some T-HRCT images caused by photon starvation when crossing the spine and the ribs. The reconstruction process (sharp reconstruction algorithm), the thin slice thickness (1mm) and the data recording have probably magnified this noise. However, none of the radiologists reported that these streaking artifacts interfered with their characterization of canine idiopathic pulmonary fibrosis lesions.

In conclusion, the present study demonstrated that some T-HRCT characteristics of canine idiopathic pulmonary fibrosis differed and others did not for West Highland white

terriers evaluated using sedation versus general anesthesia. These differences should be taken into consideration when general anesthesia is contraindicated and sedation is necessary. Ground-glass opacities, mosaic attenuation pattern and bronchial wall thickening were found to be the main T-HRCT features of canine idiopathic pulmonary fibrosis in West Highland white terriers. Further work comparing T-HRCT features of canine idiopathic pulmonary fibrosis over time according to method acquisition is warranted to improve our knowledge about the natural history of canine idiopathic pulmonary fibrosis and how reliably this disease can be monitored by T-HRCT.

List of Author Contributions

Category 1

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Category 2

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Category 3

(a) Final Approval of the Completed Article: Roels, Couvreur, Farnir, Clercx, Verschakelen, Bolen

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550 **Tables**

551 TABLE 1. Definitions of Thoracic High-Resolution Computed Tomographic Specific Lung

552 Features Studied according to the Fleischner Society.[9]

Major groups	Specific features	Definitions
Increased attenuation	Ground glass opacity	Area of hazy increased lung opacity with preservation of bronchial and vascular margins
	Consolidation	Homogeneous increase in pulmonary parenchymal attenuation that obscures the margins of vessels and airway walls
Decreased attenuation	Mosaic attenuation pattern	Patchwork of regions of differing attenuation that may represent (a) patchy interstitial disease, (b) obliterative small airway disease, or (c) occlusive vascular disease
	Cyst	Round parenchymal lucency or low-attenuating area with a well-defined interface with normal lung
	Emphysema	Focal areas or regions of low attenuation, usually without visible walls
Nodular opacities	Nodules	Rounded or irregular opacity, well or poorly defined
Linear opacities	Reticulation	Collection of small linear opacities that produce an appearance resembling a net
	Parenchymal band	Linear opacity that usually extends to the visceral pleura
	Subpleural band	Linear opacity from and parallel to the pleural surface
	Honeycombing	Clustered cystic air spaces, typically of comparable diameters, usually subpleural and characterized by well-defined walls

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554

555 **Figures legends**

556 FIG. 1. Cumulative bar-charts presenting the frequency of appearance of specific T-HRCT
557 features in West Highland white terriers affected with canine idiopathic pulmonary fibrosis (n
558 = 11) (A) and controls (n = 9) (B) according to the method of image acquisition (sedation or
559 general anesthesia).

560 FIG. 2. Transverse thoracic HRCT image (lung window) of a West Highland white terrier
561 affected with canine idiopathic pulmonary fibrosis (dog 3) under sedation (A) and general
562 anesthesia (B) at the level of the caudal lung lobes showing a lower grade of a generalized
563 ground-glass opacification of the lungs on acquisition performed under sedation in
564 comparison with general anesthesia.

565 FIG. 3. Transverse thoracic HRCT image (lung window) of a West Highland white terrier
566 affected with canine idiopathic pulmonary fibrosis (dog 4) under sedation (A) and general
567 anesthesia (B) at the level of the cranial lung lobes showing consolidations of the right and
568 left cranial lung lobes on general anesthesia acquisition only, in addition to ground-glass
569 opacity visible on both acquisitions.

570 FIG. 4. Transverse thoracic HRCT image (lung window) of a West Highland white terrier
571 affected with canine idiopathic pulmonary fibrosis (dog 5) under sedation (A) and general
572 anesthesia (B) at the level of the caudal lung lobes showing areas of higher (ground-glass
573 opacity) and lower lung attenuation (normal lung parenchyma or air trapping) resulting in a
574 mosaic attenuation pattern visible on sedation acquisition only.

575 FIG. 5. Transverse thoracic HRCT image (lung window) of a West Highland white terrier
576 affected with canine idiopathic pulmonary fibrosis (dog 3) under sedation at the level of the
577 cranial lung lobes showing a sub-pleural band (arrows) in the dorsal part of the right cranial
578 lung lobe in addition to thickening of the bronchial walls and ground-glass opacity.

FIG. 6. Transverse thoracic HRCT image (lung window) of a West Highland white terrier affected with canine idiopathic pulmonary fibrosis (dog 2) under sedation at the level of the cranial lung lobes showing a parenchymal band (arrows) which extend from the visceral pleura into the lung parenchyma in the eft cranial lung lobe in addition to ground-glass opacity.

584 Appendix 1: Specific Thoracic High-Resolution Computed Tomographic Features Obtained Under Sedation and General Anesthesia for Each

585 Dog Included in the Study

Status	Dog number.	Time between acquisitions (min)	Overall GGO score	Overall consolidation score	Overall mosaic attenuation pattern score	Cyst	Nodules	Reticulations	Subpleural bands	Parenchymal bands	Bronchial wall thickening	Bronchiectasis	Tracheal collapse
CIPF	1	9	9	0 / 1	10	-	-	-	-	-	+	-	+
	2	14	6 / 2	0	4 / 0	-	-	-	-	+	-	-	-
	3	4	6 / 12	0	2 / 6	-	+	-	+	-	+	+	++
	4	6	16	0 / 6	0 / 4	-	-	-	-	-	-	-	++
	5	7	13 / 4	1	9 / 0	-	-	-	-	+	+	-	-
	6	5	18	0	18	-	-	-	-	-	+	-	+
	7	23	18	0	18	-	-	-	-	-	-	-	+ / -
	8	6	12	2 / 0	0	-	+	-	-	-	-	-	-
	9	4	18	0	12 / 10	-	+	-	-	-	-	-	-
	10	4	6	0	6	-	-	-	-	+	+	-	-
	11	5	6	0	0	-	-	-	-	-	-	-	- / +
Control	12	9	6	0	0	-	-	-	-	-	-	-	-
	13	6	0	0	0	+	-	-	-	-	-	-	+ / -
	14	8	2	0	0	-	-	-	-	-	-	-	+ / -
	15	3	1 / 0	0	0	-	-	-	-	-	-	-	+
	16	7	0	0	0	-	-	-	-	-	-	-	+ / -
	17	4	1	0	0	-	-	-	-	-	-	-	- / +
	18	10	0	0	0	-	-	-	-	-	-	-	-
	19	9	2	0	0	-	-	-	-	-	-	-	- / +
	20	5	2	0	0	-	-	-	-	-	-	-	-

586 GGO, ground-glass opacity; +, presence; -, absence. Note that when two numbers or symbols are present in a box, the first one corresponds to the
587 result obtained under sedation and the second one to the result obtained under general anesthesia. If there is only one number or symbol in a box,
588 it means that both sedation and general anesthesia yield the same result

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