Long-Term Outcome and Use of 6-Minute Walk Test in West Highland White Terriers with Idiopathic Pulmonary Fibrosis

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Background: Idiopathic pulmonary fibrosis (IPF) is an incurable interstitial lung disease occurring mainly in West Highland White Terriers (WHWTs). The effects of IPF on survival and on exercise tolerance in WHWTs are unknown.

Objectives: To evaluate survival, prognostic factors, and exercise tolerance in WHWTs with IPF.

Animals: Privately owned WHWTs; 15 with IPF and 11 healthy controls.

Methods: Prospective case-control study conducted in 2007–2012. For survival, descriptive statistics and Kaplan–Meier (KM) survival curves with Cox proportional hazard ratios were performed. For the prognostic factor study, KM curves, Cox regression analysis, and logistic regression models were used. The 6-minute walk test (6MWT) was used for measurement of exercise tolerance.

Results: The median IPF-specific survival of deceased WHWTs (7/15) with IPF was 32 (range 2–51) months from onset of clinical signs. The risk of death from birth in WHWTs with IPF in age-adjusted Cox model was significantly higher (hazard ratio 4.6; 95% confidence interval 1.05–19.74, $P = .04$) than in control WHWTs. No significant prognostic factors were identified. In 6MWT, WHWTs with IPF walked a shorter distance, median 398 m (range 273–519 m), than healthy controls, median 492 m (420–568 m), $P = .05$, and the partial pressure of oxygen in arterial blood in diseased dogs had a moderate positive correlation with walking distance (Kendall's tau-b = 0.69, $P = .06$).

Conclusion and Clinical Importance: IPF had a negative impact on life expectancy, but individual survival varied considerably. 6MWT proved to be a well-tolerated, noninvasive test to evaluate exercise tolerance.

Key words: Dog; Exercise test; Interstitial lung disease; Prognosis; Survival.

Idiopathic pulmonary fibrosis (IPF) is a disease of unknown etiology that occurs particularly in West Highland White Terriers (WHWTs).[1,2] The disease causes collagenous thickening of the pulmonary interstitium[3,4] and impairs gas exchange.[1] Histologically, IPF in WHWTs shares features of the 2 most common subtypes of human idiopathic interstitial pneumonia, usual interstitial pneumonia (UIP), the pathologic counterpart of IPF, and nonspecific interstitial pneumonia (NSIP).[4] The median survival of WHWTs with IPF has been reported in a retrospective study to be 16 months from onset of clinical signs and 7 months from diagnosis, but speculated not to shorten life expectancy as the disease affects middle-aged to older WHWTs.[2] In humans, median survival of IPF patients from diagnosis is only 2–3 years,[5] whereas fibrotic NSIP has a better prognosis of 6–13.5 years.[6,7]

No studies have reported prognostic factors in any interstitial lung disease in dogs. In human IPF, the search for prognostic factors has been extensive as the

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Abbreviations:

6MWD	6-minute walk distance
6MWT	6-minute walk test
AE	acute exacerbation
BAL	bronchoalveolar lavage
DAD	diffuse alveolar damage
HRCT	high-resolution computed tomography
IPF	idiopathic pulmonary fibrosis
NSIP	nonspecific interstitial pneumonia
UIP	usual interstitial pneumonia
WHWT	West Highland White Terrier

course of the disease can vary greatly among patients, from rapidly to slowly progressive to a step-like process.[6] Several factors have been associated with poor survival in humans, including decreased walking distance in 6-minute walk test (6MWT),[8] increasing grade of interstitial fibrosis on thoracic radiographs,[9] fibrosis score and traction bronchiectasis in thin-section computed tomography,[10] increased bronchoalveolar lavage (BAL) neutrophilia,[11] and presence of pulmonary hypertension.[12] In human IPF with a step-like progression, periods of relative stability are interrupted by acute exacerbations (AEs), which are associated with high mortality and a histopathologic pattern of diffuse alveolar damage (DAD).[6] In WHWTs with IPF, DAD has been demonstrated along with consequent organizing luminal fibrosis, suggesting a more rapid progression of the fibrosis through organizing DAD in some dogs.[4]

The 6MWT is a submaximal exercise test that measures the distance an individual is able to walk over 6 minutes (6MWD)[13] and is widely used in clinical practice to evaluate and monitor human patients with

IPF.[5,14] The 6MWT has been assessed in a limited number of studies with healthy dogs,[a,b,15] dogs with induced congestive heart failure,[16] and dogs with various pulmonary diseases,[15] and has been found to be an easy and reproducible test for screening exercise tolerance.

Our objective here was to describe the clinical course of IPF in WHWTs and assess survival of affected dogs compared with controls. In addition, prognostic factors for the disease, and use of 6MWT in WHWTs were evaluated.

Materials and Methods

Study Population

Fifteen privately owned WHWTs with IPF and 11 healthy privately owned WHWTs were prospectively recruited during 2007–2012 and followed until death or the study endpoint in September 2012, at the Veterinary Teaching Hospital of the University of Helsinki, Finland.

The median age of the WHWTs with IPF (7 intact males, 2 intact females, 1 neutered male, 5 neutered females) at the time of presentation was 12 (range 8–13) years. The median age of the healthy control WHWTs (3 intact males, 1 intact female, 7 neutered females) at the time of presentation was 9 (range 6–13) years. The study protocols were approved by the Committee of Experimental Animals of Western Finland.

WHWTs with IPF—Clinical Information, Diagnosis, and Classification of Causes of Death

The clinical examinations of WHWTs with IPF were performed as described previously.[1] Briefly, the diagnostic evaluation at the time of presentation consisted of history and physical examination (15/15), hematology and serum biochemistry (15/15), fecal examination (14/15), arterial blood gas analysis (15/15), thoracic radiography (15/15), echocardiography (13/15), high-resolution computed tomography (HRCT) (10/15), and bronchoscopy and BAL (9/15). After the initial visit, the dogs were followed in control visits at 3- to 6-month intervals and additionally as needed. At control visits, a physical examination, hematology and serum biochemistry, arterial blood gases, and thoracic radiography were performed. All WHWTs with IPF received individual treatment. The medications used included prednisolone, theophylline, azathioprine, doxycycline, and sildenafil. Two of the WHWTs with IPF had concurrent systemic diseases (pyelonephritis and hyperadrenocorticism) at presentation and were treated accordingly. One dog receiving prednisolone medication developed diabetes mellitus 9 months after IPF diagnosis, and another dog was diagnosed with a mammary tumor 6 months after IPF diagnosis. Ten dogs had allergies and dermatologic problems.

Diagnosis of IPF was confirmed by histopathology in 13 deceased animals, as described in Syrjä et al,[4] and by HRCT in 2 dogs that were still alive at the study endpoint.

The causes of death were divided into IPF-related (defined as euthanasia because of acute dyspnea or severe progression of respiratory symptoms) or non-IPF–related. The onset of clinical signs was defined as the time point when owner first noticed respiratory signs or exercise intolerance.

Control WHWTs—Clinical Information

Similar clinical examinations as for WHWTs with IPF were performed on control dogs. Dogs representing the same age group as WHWTs with IPF, middle age to older, were chosen. The health status of control WHWTs was confirmed with history and physical examination (11/11), hematology and serum biochemistry (11/11), fecal examination (10/11), arterial blood gas analysis (11/11), thoracic radiography (11/11), echocardiography (10/11), HRCT (8/11), and bronchoscopy and BAL (8/11). None of the control WHWTs showed any signs or findings indicative of pulmonary disease. Three dogs had allergies and dermatologic problems. Ten dogs were included in the survival analysis. Follow-up was performed by control visits (3/10) or by contacting the owner by phone after the study endpoint (7/10).

Selection Criteria for Prognostic Variables

Variables representing possible prognostic factors predicting survival of IPF dogs were chosen among the clinical information collected at the time of diagnosis. Only variables that were available for at least 10 diseased animals and that had previously been shown to be altered in WHWTs with IPF[1,17] were chosen. The variables analyzed included partial pressures of oxygen (PaO_2) and carbon dioxide ($PaCO_2$) in arterial blood, alveolar-arterial oxygen gradient ($P(A-a)O_2$), serum endothelin-1 concentration, severity of changes in thoracic radiographs, and HRCT Hounsfield unit values. These variables were analyzed as previously described.[1,17] The radiographs and HRCT images were viewed by one of the authors (A.K.L.). In addition, prognostic value of rate of change in arterial blood gas (PaO_2, $PaCO_2$, and $P(A-a)O_2$) and complete blood cell count values (hemoglobin, hematocrit, erythrocytes, mean corpuscular volume, neutrophils, lymphocytes, eosinophils, monocytes, and thrombocytes) between the first and last available measurement in IPF-related death were analyzed. These analyses were performed for those diseased animals that had at least 1 control visit (12/15) before death or study endpoint.

6MWT

The 6MWT was performed on 6 WHWTs with IPF at the time of diagnosis and on 5 healthy control WHWTs. The test was repeated in 5 WHWTs with IPF during their control visits. The dogs were walked along a quiet 63.5-m straight corridor on a leash at their own pace for 6 minutes. All the dogs were walked by the same exerciser, in the same corridor, and had similar time with respect to feeding. The 6MWD was recorded in meters and heart rate, body temperature, oxygen saturation (SpO_2) by pulse oximetry,[c] and arterial blood gases were measured before and after walking. A pulse oximetry probe suitable for placement underside was placed under the tail base, near the anal orifice.

Statistics

Descriptive statistics are presented as median and range. Both IPF-specific and all-cause survival times were calculated. In the IPF-specific analysis, dogs were censored if they were alive (2 WHWTs) or had died because of a non-IPF–related cause (6 WHWTs). For the all-cause survival analysis, dogs were only censored if they were alive. The all-cause survival of WHWTs with IPF against the control group was compared with Kaplan–Meier (KM) survival curves and estimated together with Cox proportional hazards models. The Cox model was adjusted for the dog's age at the time of diagnosis/study inclusion.

For prognostic factor analysis, KM curves and Cox regression analysis were performed on categorical variables (radiographic values) and Cox regression on continuous variables. The survival

time was calculated from onset of clinical signs. Hazard ratios (HR) with 95% confidence intervals (CIs) were calculated for all of the models. The effects of rate of change in repeated-measure variables from the time of diagnosis to the last available measurement on IPF-related death were assessed with logistic regression models. Odds ratios with 95% CIs were calculated to quantify the results.

For 6MWT results, Mann–Whitney U-test was used to compare differences between control and diseased animals, and Kendall's tau-b correlation coefficient was used for correlations. Wilcoxon signed-rank test was used for all paired samples.

All comparisons were performed as two-tailed. P-values < .05 were considered significant. Statistical analyses were conducted using commercially available statistical programs.[d,e]

Results

Survival

The median follow-up time of IPF WHWTs (15/15) was 15 (range 0–40) months. The median all-cause survival of deceased WHWTs with IPF (13/15) was 160 (123–188) months from birth, 27 (2–51) months from onset of clinical signs, and 13 (0–40) months from time of diagnosis. The median survival of WHWTs with IPF-related death (7/15) was 163 (range 155–170) months from birth, 32 (2–51) months from onset of clinical signs, and 11 (0–40) months from diagnosis. The KM curves for all-cause and IPF-specific survival from onset of clinical signs are presented in Figure 1. The median survival of deceased control WHWTs (3/10) was 172 (range 154–184) months from birth. Median follow-up time of control WHWTs was 35 (6–55) months. Based on the Cox regression model for all-cause survival adjusted for dog's age at study inclusion, the HR for risk of death in WHWTs with IPF from birth compared to control WHWTs was 4.6 (95% CI 1.05–19.74, P = .04) and from study inclusion 4.4 (95% CI 0.94-20.5, P = .06). The HR for age in the multivariate Cox model from birth was 0.66 (95% CI 0.42–1.04, P = .08) and from study inclusion 1.93 (95% CI 1.25–2.98, P = .003). KM curves for survival of WHWTs with IPF and control WHWTs from birth and study inclusion are presented in Figure 2.

Prognostic Factors

No statistically significant prognostic factors were identified (Table 1). In addition, no significant effects of the rate of change in repeated-measure variables on the risk of IPF-related death were detected (Table 2).

Changes in Arterial Blood Gas Values, Body Weight, and Radiographic Pattern

A significant decrease occurred between the first (median 58.9 mmHg, range 50.6–64.0 mmHg) and the last (median 50.0 mmHg, range 44.3–51.5 mmHg) PaO_2 values (P = .04) and an increase between the first (median 54.8 mmHg, range 43.5–67.4 mmHg) and the last (median 70.9 mmHg, range 57.6–
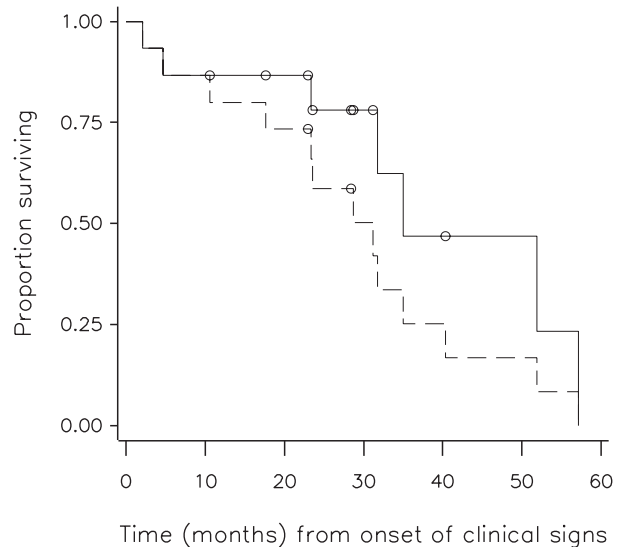

Fig 1. Kaplan–Meier survival curves for all-cause survival (dotted line) and idiopathic pulmonary fibrosis (IPF)-specific survival (solid line) of West Highland White Terriers (WHWTs) with IPF from onset of clinical signs. Censored animals (for all-cause survival WHWTs alive at study endpoint and for IPF-specific survival WHWTs alive and those who died of non-IPF–related causes) are presented as circles.

80.8 mmHg) $P(A-a)O_2$ measurement (P = .04) in 5 IPF WHWTs that died of IPF-related causes and had at least 1 control visit. During the disease course, temporary improvements were noted in PaO_2 values in 7/12 WHWTs with IPF that had at least 1 control visit before death or the study endpoint. Magnitude of these improvements varied from 2.8 mmHg to 19.9 mmHg, with median of 7.9 mmHg. No significant change was noted in body weight of WHWTs with IPF (12) between the first (median 9.9 kg, range 7.8–11.9 kg) and last (median 9.6 kg, range 7.2–11.8 kg) measurement (P = .31). The bronchointerstitial radiographic changes were initially classified as severe in 7/12 animals or moderate in 5/12 animals. In 6 animals, no change in pattern severity was seen, in 3 the classification changed from moderate to severe, and in 3 it changed from severe to moderate during progression of the disease. Three animals had an alveolar pattern at the time of diagnosis, but not at the last control visit, and 5 dogs with no alveolar pattern at the first visit had it at the last control visit.

6MWT

The 6MWD and the variables measured before and after walking in IPF and control WHWTs are presented in Table 3. In diseased animals, PaO_2 seemed to have a moderate positive correlation with 6MWD, although only statistically significant at 10% (Kendall's tau-b = 0.69, P = .06). Nine to 11 months after the first 6MWT, 4 of the 5 WHWTs with IPF had a reduced 6MWD relative to their initial visit. However, difference between 6MWD at the first visit (median 399 m, range
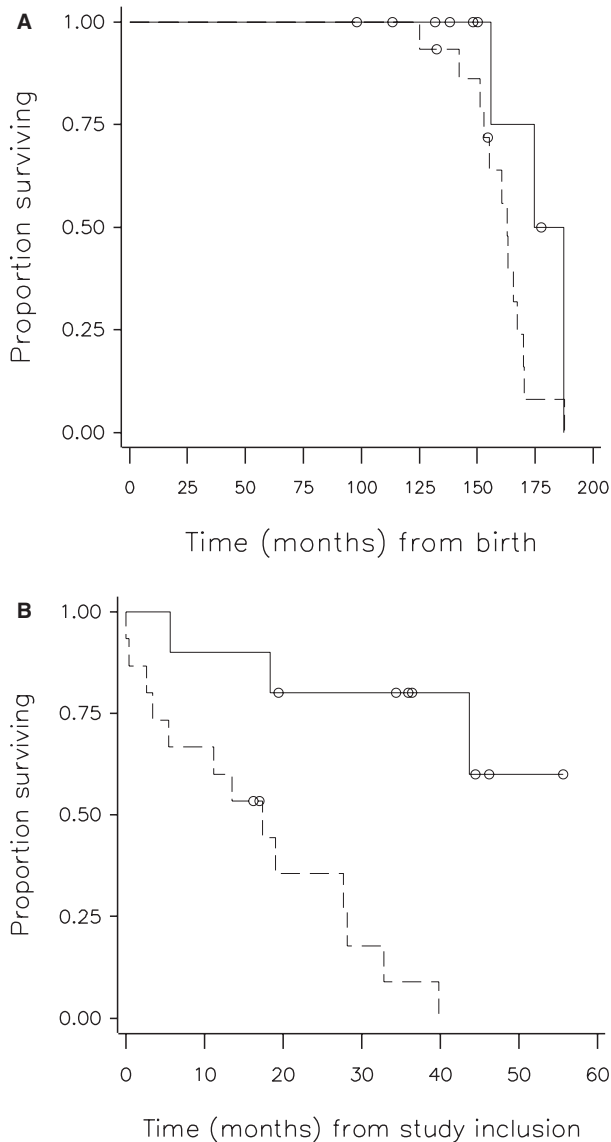
Fig 2. **(A)** Kaplan–Meier (KM) survival curves for all-cause survival of West Highland White Terriers (WHWTs) with idiopathic pulmonary fibrosis (IPF) (dotted line), and control WHWTs (solid line) from birth. Censored animals (WHWTs alive at study endpoint) are presented as circles. **(B)** KM survival curves for all-cause survival of WHWTs with IPF and control WHWTs from study inclusion.

309–519 m) and 6MWD at the control visit (median 375 m, 230–478 m) was statistically significant only at 10% ($P = .08$).

Cause of Death and Related Histopathologic Findings

Seven WHWTs with IPF died of IPF-related causes. Four of the 5 dyspneic dogs showed acute alveolar damage histopathologically. Causes of death or euthanasia in the non-IPF–related death group (6 dogs) were pyelonephritis, metastatic mammary tumor,

drowning, acute uremia, acute vomiting, and hemoabdomen. The dog that drowned also had DAD in the lungs. A detailed description of the histopathologic findings of 9/13 WHWTs with IPF has been reported previously.[4] Three of the control WHWTs were euthanized before the study endpoint. The reasons were dementia in 1 dog, mammary tumor in another, and unknown in the third. None of the control WHWTs had any owner-reported respiratory signs before death or study endpoint.

Discussion

As IPF is a disease occurring in older WHWTs, and the magnitude of its effect on lifespan has been unclear, as no prospective studies with controls have been published previously.[2] In this study, we have shown that IPF has significant negative impact on life expectancy in WHWTs. This finding is supported by both our age-adjusted survival models, risk from birth being 4.6 times higher and from study inclusion 4.4 times higher in diseased animals than in controls. The age alone was a significant predicting factor in multivariate Cox proportional hazards model from study inclusion, emphasizing the importance of using an age-adjusted model in survival comparison. The HR for age in Cox model from birth was, however, less than one, although not significant, implying that age would reduce the risk of death. This unexpected finding is attributable to the different ages of dogs at the time of inclusion when the follow-up time was kept similar, creating an artificially low HR for age in the Cox model from birth.

Even though the median survival time from onset of clinical signs in the IPF-related death group was quite high, being 2.7 years, it varied greatly, from only 2 months to 4.3 years. This variation indicates that IPF in WHWTs may have a rapid or slow disease progression, as also seen in human IPF.[6] However, the time frame for detection of clinical signs is highly owner-dependent and might be delayed for several reasons, eg, reduced exercise tolerance because of aging. The median survival after diagnosis in WHWTs with IPF was 1 year, but some dogs lived up to 3 years. In human IPF patients, the median survival after diagnosis is 2–3 years.[5]

No significant prognostic factors were identified among the chosen variables. However, a slight indication of high PaO_2 having a protective effect on survival and high $P(A-a)O_2$ being a risk factor were noted. This indicative finding further supports the use of arterial blood gas measurement in IPF follow-up. In humans, an increase in $P(A-a)O_2$ is associated with earlier IPF mortality.[18] In addition, we detected no significant effects of change in repeated-measure variables on the risk of IPF-related death. However, some slight indication of a higher risk of IPF-related death can be seen in the increase of hematocrit, hemoglobin, and erythrocyte values. In human IPF, high red cell distribution width (RDW), not available in our study, and an

Table 1. Cox regression analysis of the effects of prognostic variables on IPF-specific/all-cause survival in WHWTs with IPF.

Variable (unit change)	N	IPF-Specific Survival HR (95% CI)	P	All-Cause Survival HR (95% CI)	P
PaO_2 mmHg (10)	15	0.60 (0.21–1.72)	.34	1.20 (0.58–2.46)	.63
$PaCO_2$ mmHg (1)	15	0.96 (0.75–1.23)	.75	1.02 (0.86–1.21)	.78
$P(A-a)O_2$ mmHg (10)	14	1.59 (0.67–3.73)	.29	0.93 (0.51–1.68)	.81
ET1 pg/mL (1)	10	1.11 (0.70–1.75)	.67	0.91 (0.59–1.42)	.69
HU (100)	10	0.71 (0.08–5.98)	.75	0.69 (0.27–1.76)	.44
Severity of radiographic bronchointerstitial pattern (severe)	15	2.68 (0.29–24.4)	.38	0.66 (0.20–2.21)	.50
Presence of radiographic alveolar pattern (yes)	15	1.87 (0.36–9.74)	.46	1.51 (0.46–4.95)	.50

IPF, idiopathic pulmonary fibrosis; WHWT, West Highland White Terrier; HR, hazard ratio; CI, confidence interval; PaO_2, partial pressure of oxygen in arterial blood; $PaCO_2$, partial pressure of carbon dioxide in arterial blood; $P(A-a)O_2$, alveolar-arterial oxygen gradient; ET1, serum endothelin-1 concentration; HU, Hounsfield unit (describing overall density of lung parenchyma in high-resolution computed tomography image).

Table 2. Logistic regression analysis of the effects of change over time in repeated-measure variables on IPF-specific death in 12 WHWTs with IPF.

Variable (unit change)	OR	95% CI
PaO_2 mmHg (1)	0.85	0.62–1.15
$PaCO_2$ mmHg (1)	0.88	0.62–1.24
$P(A-a)O_2$ mmHg (1)	1.15	0.88–1.49
Hematocrit% (1)	1.37	0.78–2.34
Erythrocytes 10^{12}/L (0.1)	1.21	0.89–1.65
Hemoglobin g/L (1)	1.12	0.91–1.40
MCV fL (1)	0.61	0.28–1.36
Neutrophils 10^9/L (1)	1.13	0.82–1.54
Lymphocytes 10^9/L (0.1)	0.96	0.80–1.15
Eosinophils 10^9/L (0.1)	0.72	0.38–1.34
Monocytes 10^9/L (0.1)	0.97	0.64–1.48
Thrombocytes 10^9/L (10)	0.90	0.76–1.07

IPF, idiopathic pulmonary fibrosis; WHWT, West Highland White Terrier; OR, odds ratio; CI, confidence interval; PaO_2, partial pressure of oxygen in arterial blood; $PaCO_2$, partial pressure of carbon dioxide in arterial blood; $P(A-a)O_2$, alveolar-arterial oxygen gradient; MCV, mean corpuscular volume.

Table 3. Pre and postwalking 6MWT characteristics in 6 WHWTs with IPF and 5 control WHWTs, given as median and range.

Characteristic	IPF WHWT	Control WHWT	P
Pre-HR(bpm)	107 (80–120)	114 (92–144)	.13
Post-HR (bpm)	108 (96–146)	126 (112–144)	.18
P-value	**.04**	.32	
Prebody T (°C)	38.7 (38.5–39.9)	39.0 (38.0–39.1)	.93
Postbody T (°C)	38.7 (38.5–39.2)	38.7 (38.3–39.2)	.84
P-value	.47	.58	
Pre-SpO_2 (%)	96 (87–100)	98 (96–98)	.13
Post-SpO_2 (%)	97 (86–100)	98 (93–99)	.79
P-value	.49	.46	
Pre-PaO_2 (mmHg)	56.7 (49.4–64.9)	101.8 (82.0–108.0)	**.01**
Post-PaO_2 (mmHg)	55.8 (37.7–61.8)	86.3 (82.0–110.0)	**.01**
P-value	.08	.47	
Pre-$PaCO_2$ (mmHg)	31.8 (26.1–36.9)	30.4 (27.4–34.0)	1.00
Post-$PaCO_2$ (mmHg)	28.5 (25.3–34.5)	32.7 (27.8–33.9)	.35
P-value	.17	.14	
Pre-$P(A-a)O_2$ (mmHg)	55.7 (45.3–70.0)	14.5 (12.2–23.8)	**.01**
Post-$P(A-a)O_2$ (mmHg)	61.2 (53.8–82.4)	22.6 (7.8–35.3)	**.01**
P-value	.08	.47	
6MWD (m)	398 (273–519)	492 (420–568)	**.05**

6MWT, 6-minute walk test; IPF, idiopathic pulmonary fibrosis; WHWT, West Highland White Terrier; HR, heart rate; SpO_2, oxygen saturation measured by pulse oximetry; PaO_2, partial pressure of oxygen in arterial blood; $PaCO_2$, partial pressure of carbon dioxide in arterial blood; $P(A-a)O_2$, alveolar-arterial oxygen gradient; 6MWD, 6-minute walk distance. Comparisons between diseased and healthy groups using Mann–Whitney U-test; paired pre- and postwalking comparisons using Wilcoxon test. Bolded values indicating $P \leq .05$.

increase in RDW have been suggested to have prognostic value.[19]

We detected a declining trend in PaO_2 values during disease progression. However, in some dogs, temporary increases in arterial oxygenation were noted, and some owners described a temporal improvement in clinical signs. The reason for these improvements remains unknown, but it is unlikely to be connected to the effect of medications on the fibrosis process; at least fibrosis in human IPF is unresponsive to medications used here.[5] Our study design did not allow systematic evaluation of the treatment effect on survival or on clinical signs because of individual treatment protocols. The decrease between the first and last PaO_2 values in dogs that died of IPF-related causes was significant, as was the increase in $P(A-a)O_2$ values. Repeated measurements of arterial blood gas values seemed to be a good

tool for evaluating disease progression, although it should be noted that some animals with very low PaO_2 values survive quite long because of excellent adaptation and slow deterioration in oxygenation capacity.

Our study showed that IPF does not cause weight loss in dogs. Severe malnutrition is also not a feature of human IPF.[19] Based on our findings, thoracic radiographs are not useful in evaluating disease progression, as the radiographic features varied during the disease independently of clinical signs. Evaluation of other possible emerging diseases, such as infections or neoplasms, is also challenging, as changes seen in radiographs already at the time of diagnosis are notable. None of the deceased WHWTs with IPF in our study had primary lung tumors detected postmortem. In humans, bronchogenic carcinoma occurs with increased frequency in lungs affected by IPF.[20]

Exercise intolerance is a common clinical sign in WHWTs with IPF,[1,2] but is difficult to evaluate reliably in older nonathletic pet dogs. Therefore, a noninvasive 6MWT was applied in the study. We showed that 6MWT is an easy and well-tolerated test also in WHWTs with IPF and the 6MWD in diseased animals was reduced relative to that in control dogs. Use of control dogs of same breed and age group is necessary to rule out confounding factors and to have more comparable results of exercise performance between diseased and healthy animals. Oxygen desaturation in 6MWT increases the risk of death in human IPF patients.[21] Previous studies on dogs have reported a difference in oxygen saturation between healthy dogs and dogs with pulmonary disease[15] as well as postwalking oxygen desaturation in a group of old healthy beagles. [a] In our study, we detected no significant difference in SpO_2 between controls and WHWTs with IPF, nor did we find significant postwalking oxygen desaturation. Pulse oximeter seems to be a rather unreliable indicator of a decline in PaO_2 in unanesthetized dogs, and its usefulness in 6MWT in WHWTs with IPF is questionable. In other variables measured pre- and postwalking, the only significant change was a higher postwalking heart rate in WHWTs with IPF; no changes were seen between any pre- and postwalking variables in control dogs. The short delay when taking the postwalking arterial sample may influence the arterial blood sample results. The PaO_2 seemed to correlate positively with 6MWD, and therefore, 6MWD could serve as a noninvasive means of monitoring lung function in WHWTs with IPF. However, this finding needs further verification.

Four of the 5 WHWTs with IPF that were euthanized because of acute dyspnea had DAD in the lungs, in addition to chronic interstitial fibrosis. This finding is in line with human IPF, where DAD is reported as a common terminal histopathologic finding related to AEs.[6] Human IPF patients with AEs have a very poor prognosis despite treatment efforts.[5,6] One dog in the non-IPF–related death group also had DAD, but this is probably explained by the cause of death of this dog being drowning.

The main study limitation was the low number of animals. This is mainly attributable to disease being uncommon and the diagnosis, as well as verification of health, requiring invasive diagnostics. In addition, the median age of the control group was slightly younger, and only three deaths occurred in the control group. However, the median follow-up time was similar in both groups and the age was taken into account in the survival analysis. Because of low sample size, the results of prognostic factor analyses are mainly indicative, and should therefore be interpreted cautiously. In addition, some potentially interesting prognostic factors, such as 6MWD, altered BAL fluid cell counts, and presence of pulmonary hypertension, detected in WHWTs with IPF[1,22] could not be included in the analysis.

In conclusion, the median IPF-specific lifetime expectancy after onset of clinical signs is 2.7 years, but this can vary greatly. IPF in WHWTs may therefore have both a rapid or slow disease progression. The WHWTs with IPF have a significantly higher risk of dying than control WHWTs. Acute worsening of the disease is characterized by dyspnea and is often associated with DAD in the lungs histologically. The 6MWD is an easy and noninvasive parameter to evaluate lung function and level of exercise intolerance in WHWTs with IPF.

Footnotes

Acknowledgments

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