UNIVERSITI PUTRA MALAYSIA

IMPACT OF COUGHING ON THE DYNAMIC CHANGES OF TRACHEA IN CARDIAC PATIENTS

CHENG LIN QIAN

IMPACT OF COUGHING ON THE DYNAMIC CHANGES OF TRACHEA IN CARDIAC PATIENTS

CHENG LIN QIAN

A project paper submitted to the

Faculty of Veterinary Medicine, Universiti Putra Malaysia

In partial fulfilment of the requirement for the

DEGREE OF DOCTOR OF VETERINARY MEDICINE

Universiti Putra Malaysia

Serdang, Selangor Darul Ehsan.

2020/2021

CERTIFICATION

It is hereby certified that we have read this project paper entitled "Impact of Coughing on the Dynamic Changes of Trachea in Cardiac Patients" by Cheng Lin Qian and in our opinion, it is satisfactory in terms of scope, quality and presentation as partial fulfilment of the requirement for the course VPD 4999 – Final Year Project (FYP).

ASSOC PROF DR. LAU SENG FONG

DVM (UPM), PhD (UU)

Associate Professor

Faculty of Veterinary Medicine

Universiti Putra Malaysia

(Supervisor)

PROF GOH YONG MENG

RLATG, DVM (UPM), PhD (UPM),

Professor

Faculty of Veterinary Medicine

Universiti Putra Malaysia

(Co-supervisor)

DR KHOR KUAN HUA

DVM (UPM), PhD (UQ)

Senior Lecturer

Faculty of Veterinary Medicine

Universiti Putra Malaysia

(Co-supervisor)

DEDICATION

This thesis is wholeheartedly dedicated to my family, who continually provide mental, spiritual, emotional and financial support.

To my friends who shared their words of advice and encouragement to finish this study.

And lastly, my supervisors for their guidance and support.

ACKNOWLEDGEMENT

First and foremost, praises and thanks to the God, the Almighty, for His showers of blessings throughout my research work to complete this project successfully.

I would like to express my greatest gratitude to my project supervisor, Assoc Prof Dr. Lau Seng Fong for providing me invaluable guidance throughout this study. Thank you, Dr. Lau for your patience, continuous support and motivation. You had definitely inspired me to do my best for this study.

Next, I would like to extend my gratitude to my co-supervisors, Prof Dr. Goh Yong Meng for his assistance, and Dr. Khor Kuan Hua for helping in recruiting patients for my study besides sharing vast knowledge with me. I would also like to thank Dr. Ikhwan and staffs from Radiology Unit, UVH for helping me in carrying out fluoroscopy. It has been a pleasure working with them throughout this period.

I am extremely grateful to my parents for their love, caring and supports in various ways, which equipped me to carry out this project. To my sister, who gave me mental support and advices, thank you.

Last but not least, special thanks to Nicole, who gave me constructive advices and mental support, and everyone who directly and indirectly assisted me in this project. Any omission in this brief acknowledgement does not mean lack of gratitude. This project would not be a success without each and every one of them.

CONTENT

LIST OF FIGURES

LISTS OF ABBREVIATIONS

ACE	Angiotension-converting-enzyme
ACVIM	American College of Veterinary Internal Medicine
CDVD	Chronic degenerative valvular disease
CLH	Cervical lung herniation
COPD	Chronic obstructive pulmonary disease
CT	Computed tomography
DCR	Dynamic chest radiograph
ECAC	Expiratory central airway collapse
EDAC	Excessive dynamic airway collapse
ER	Expiratory reflex
HCM	Hypertrophic cardiomyopathy
MMVD	Myxomatous mitral valve degeneration
TBM	Tracheobronchomalacia
TC	Tracheal collapse
VHS	Vertebral heart size

ABSTRAK

Abstrak kajian projek yang dikemukakan kepada Fakulti Perubatan Veterinar, Universiti Putra Malaysia sebagai memenuhi sebahagian daripada keperluan kursus VPD 4999 – Projek Tahun Akhir

IMPAK BATUK TERHADAP PERUBAHAN DIAMETER TRAKEA DALAM PESAKIT JANTUNG ANJING

Oleh

Cheng Lin Qian

2020

Penyelia: Assoc Prof Dr. Lau Seng Fong

Batuk adalah satu simptom yang boleh disebabkan oleh pelbagai faktor and simptom ini berkemungkinan berasal daripada sistem jantung atau sistem penafasan. Batuk asal penyakit jantung boleh diperhati dalam pesakit jantung yang mempunyai kardiomegali, terutamanya pembesaran atrium kiri and melibatkan pemampatan sistem bronkus, menyebabkan batuk and keruntuhan trakea. Banyak kajian melaporkan komplikasi daripada batuk sakit jantung terhadap trakea, tetapi etiologi keruntuhan trakea adalah tidak terang. Oleh itu, kajian ini adalah untuk mengajian impak batuk terhadap perubahan diameter trakea dalam pesakit jantung anjing. Tiga belas pesakit jantung anjing and tiga anjing sihat telah dilibatkan dalam kajian ini. Fluoroskopi telah dijalankan untuk setiap subjek dekat bahagian leher sampai bahagian toraks. Pesakit-pesakit adalah berdiri semasa fluoroskopi ditangkap. Bahagian yang diperhatikan adalah bahagian cervical, thoracic inlet, intratoraks and carina. Peratusan perubahan dalam diameter trakea telah diukurkan dan dibahagikan. Keputusan daripada kajian ini menunjukkan bahawa keruntuhan trakea adalah lebih serius dalam kalangan pesakit jantung yang membatuk. Purata peratusan perubahan diameter trakea dalam kalangan pesakit jantung yang membatuk adalah Gred IV (98.31%) di carina, Grad II (48.24%) di intratoraks, Gred II (32.91%) di thoracic inlet, dan Gred I (8.31%) di bahagian leher. Manakala bagi pesakit jantung yang tidak membatuk, purata peratusan perubahan diameter trakea adalah Gred II (26.44%) di carina, Gred I (14.57%) di thoracic inlet, Grade I (6.17%) di intratoraks, and Gred I (5.96%) di bahagian leher. Herniasi paru-paru cervikal telah didapti daripada tiga pesakit yang membatuk and satu pesakit yang tidak membatuk. Tracheobronchomalacia telah didapati dalam satu pesakit. Konklusinya, dinamic perubahan diameter trakea dalam kalangan pesakit adalah disebabkan oleh batuk.

Keywords: *keruntuhuan trakea, batuk, fluoroscopi*.

ABSTRACT

IMPACT OF COUGHING ON THE DYNAMIC CHANGES OF TRACHEA IN CARDIAC PATIENTS

By

Cheng Lin Qian

2020

Supervisor: Assoc Prof Dr. Lau Seng Fong

Coughing is a multifactorial symptom which could be cardiogenic or non-cardiogenic in origin. Cardiac cough is a condition seen in cardiac patients with cardiomegaly where the left atrial enlargement and compression of the main stem bronchus result in cough and subsequently tracheal collapse (TC). Numerous researchers reported cough-induced complications affecting the trachea but the aetiology of TC is poorly understood. Hence, this study aimed to study the impact of coughing on the dynamic changes of the trachea in cardiac patients. Thirteen cardiac patients and three healthy dogs were recruited in this study. Fluoroscopic examination was performed in each patient at cervical to thoracic region in standing position and the fluoroscopic images were evaluated to identify the dynamic changes of the trachea at cervical, thoracic inlet, intrathoracic and carinal regions. The percentage change of the tracheal diameter was calculated and graded. The result showed that a more severe TC was observed in coughing cardiac patients (n=5) compared to non-coughing cardiac patients (n=8). In coughing cardiac patients, the mean grade of TC was Grade IV (98.31%) at carina, Grade II (48.24%) at intrathoracic, Grade II (32.91%) at thoracic inlet and Grade I (8.31%) at cervical region. While in non-coughing cardiac patients, the mean grade of TC was Grade II (26.44%) at carina, Grade I (14.57%) at thoracic inlet, Grade I (6.17%) at intrathoraic, and Grade I (5.96%) at cervical region. Cervical lung herniation (CLH) was observed in 3 coughing patients and 1 non-coughing patient, and

tracheobronchomalacia was observed in one patient. In conclusion, the dynamic changes of trachea are influenced by coughing in cardiac patients.

Keywords: *tracheal collapse, cough, cardiac cough, fluoroscopy*.

1.0 INTRODUCTION

Tracheal or airway collapse is a progressive disease that commonly affects middle-aged to older small and toy breed dogs (Tappin, 2016) and is a common cause of cough in dogs (Maggiore, 2014). It is a complex disease which the dog will be presented with a range of clinical signs and potential comorbidities (Culp and O'Donnell, 2015).

Tracheal collapse (TC) is a condition associated with softening of tracheal cartilage as a result of numerous microscopic and subsequent macroscopic changes in trachea cartilage (Maggiore, 2014; Culp and O'Donnell, 2015). TC occurs when there is reduction of glycosaminoglycan and chondroitin sulfate which then impede water retention in the matrix, thus weakening the rigidity and structure of the cartilage (Maggiore, 2014; White and Williams, 1994; Dallman, 1982; Dallman and Brown, 1979). TC in dogs is similar to tracheomalacia described in human which involves the process of weakening and softening of tracheal cartilage (Culp and O'Donnell, 2015).

However, many dogs with anatomic predisposition to TC remain asymptomatic unless being triggered by other factors and start to become symptomatic in later life. The factors that are linked to onset of clinical signs includes cardiomegaly, pulmonary oedema, respiratory infection, presence of smokers in household, allergic respiratory disease and obesity (White and Williams, 1994).

Cardiac cough is associated with cardiac diseases, but cardiac cough and cardiac diseases do not complement each other necessarily. Cardiac cough is cited to be caused by cardiomegaly with marked left atrial enlargement and compression of the main stem bronchus. However, the two are not sufficient to cause cardiac cough without the underlying tracheobronchial disease. Cough is more frequently triggered in small breed dogs with cardiomegaly when there are airway diseases such as TC, chronic bronchitis and bronchomalacia. However, chronic bronchitis is often the leading cause of cough in medium to large breed dogs (Ferasin and Linney, 2019).

The condition is further perpetuated by the cycle of chronic inflammation of the trachea mucosa which in turn exacerbated by the cough (White and Williams, 1994). The vicious cycle continues as additional inflammation, tracheal edema, alterations or failure in the mucociliary apparatus, increased mucus secretion, and mucus trapping within the airways (Maggiore, 2014). Persistent inflammation of the mucosa in trachea results in epithelium loss, fibrinous membrane formation and eventually squamous metaplasia or polypoid proliferation in advanced cases (O'Brien *et al.,* 1966). The metaplastic change in the mucosa reduce the ciliated cells population. The hyperplastic subepithelial glands will secrete highly viscid mucus. The impaired ciliary function is gradually replaced by cough as the major tracheobronchial clearing mechanism (Suterp, 1984). The impaired clearance of mucus will increase the risk of respiratory infections (Al-Qadi *et al*., 2013). Therefore, suppression of the exciting factors should be indicated as therapeutic priority (White and Williams, 1994).

According to Tangner and Hobson (1982), tracheal collapse is classified into four grades. By determining the decrease in luminal diameter, tracheal collapse is graded as 0%-25% (Grade I), 25%-50% (Grade II), 50%-75% (Grade III), and greater than 75% (Grade IV).

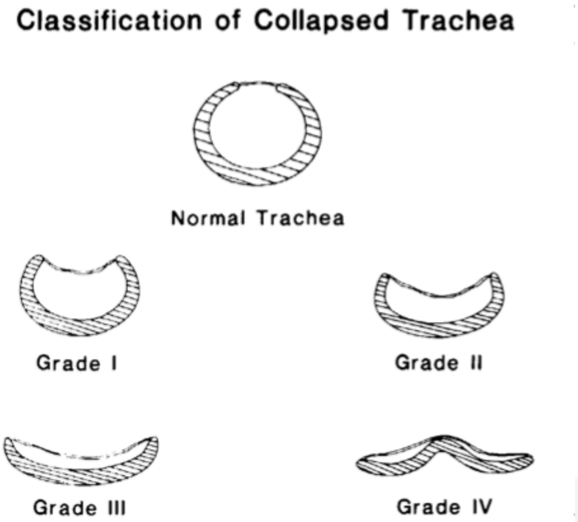

Figure 1: Classification system with four grades of collapsed trachea. (From Tangner, C. H., & Hobson, H. P. (1982). A Retrospective Study of 20 Surgically Managed Cases of Collapsed Trachea. Veterinary Surgery, 11(4), 146–149. doi:10.1111/j.1532-950x.1982.tb0069)

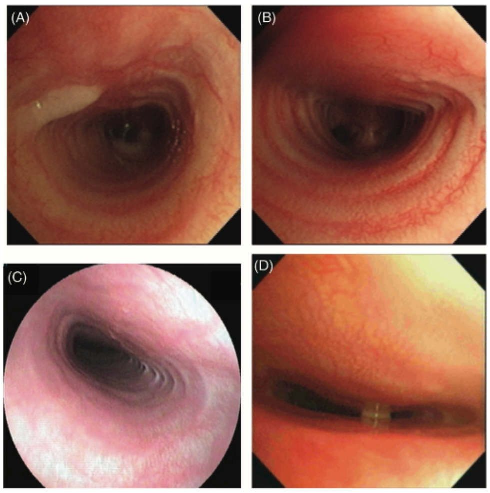

Figure 2 Bronchoscopic images of tracheal collapse. (From Tappin, S. W. (2016). Canine tracheal collapse. Journal of Small Animal Practice, 57(1), 9–17. doi:10.1111/jsap.12436

1.1 OBJECTIVE

To study the impact of coughing on the dynamic changes of the trachea in cardiac patients.

1.2 JUSTIFICATION

Coughing is shown to cause tracheal collapse in human patient. However, the aetiological pathway of coughing in non-tracheal hypoplasia canine patients with cardiac dysfunction is uncertain. Thus, this study was proposed to determine if coughing can lead to tracheal collapse in cardiac patient.

1.3 HYPOTHESIS

H_O = Dynamic tracheal collapse is not present in coughing patient.

H_A = Dynamic tracheal collapse is present in coughing patient.

2.0 LITERATURE REVIEW

2.1 COUGH

Cough is a multifactorial clinical signs that is cardiogenic or non-cardiogenic in origin. Cardiogenic cough involves cardiac diseases which normally present with cardiomegaly, signs of heart murmur, pulmonary oedema and pericardial effusion. Non-cardiogenic cough involves upper airway disorders such as post-nasal drips, laryngeal paralysis and bronchomalacia, and lower airway and pulmonary parenchymal diseases such as chronic bronchitis, eosinophilic bronchopneumopathy, aspiration pneumonia and etc. (Martin and Pereira, 2013). It is a symptom frequently been neglected in cardiovascular disease as it is not a definitive symptom unlike other symptoms of cardiovascular disease (Currens and White, 1949). In human, cough has been associated with environmental irritants such as smoking which causes chronic and persistent coughing. Infectious type of respiratory disease such as viral infection usually causes acute signs. When the coughing reflex is triggered, the mechanism of cough is started with a deep inhalation and then followed by contraction of respiratory muscles which produce an explosive flow of air. This produces a high intrathoracic pressure which will exceed the intraluminal pressure, causing the large respiratory tract to collapse (Irwin, 1977).

Diagnosis of causes of cough always start with thorough history taking and routine physical examination. Complementary diagnostics such as radiography, fluoroscopy, bronchoscopy, computed tomography (CT) scan and tracheobronchial lavage can be carried out to better diagnose the cause (Irwin, 1977). Bronchoscopy is the gold standard in diagnosing tracheal collapse, but anaesthesia is required to carry out the procedure. Radiography tends to underestimate the grades of tracheal collapse as compared to fluoroscopy. Fluoroscopy allows better evaluation of the tracheal collapse in dogs in terms of severity and location (Macready *et al*., 2007).

Treatment of cough depends on the definitive diagnosis of the cause. Palliative treatment is opted only when the cause of cough is unknown and the complications are affecting the quality of life (Irwin, 1977). Tracheal stent is one of the surgical treatment for tracheal collapse especially when life threatening dyspnoea is present. Bronchodilators, steroids and cough suppressants are normally prescribed for bronchomalacia and bronchitis patients (Martin and Pereira, 2013)

2.2 CAUSE OF TRACHEAL COLLAPSE

TC is a complex and multifactorial disease that could be developed congenitally due to primary softening of tracheal cartilage or acquired by secondary factors which play a role in triggering and progression of the disease (Maggiore, 2014; Tappin, 2016). Therefore, identifying and eliminating the cause of tracheal collapse are the therapeutic priority.

Tracheal cartilage is made up of glycosaminoglycan and chondroitin sulfate which provide rigidity to the matrix of tracheal rings. Congenital reduction of these microscopic contents of the cartilage causes inability of the matrix to retain water thus leading to weakness and flattening of the tracheal cartilage (Dallman, 1982; Dallman and Brown, 1979). This medical condition involving trachea and mainstem bronchus is termed as tracheobronchomalacia (TBM). Onset of clinical signs during puppyhood suggests disease of congenital origin (White and Williams, 1994).

A paroxysmal ‘goose-honking’ coughing is the typical clinical sign of respiratory distress and dyspnoea as a result of dynamic airway collapse. Many small breed dogs with anatomic predisposition to tracheal collapse are asymptomatic and only show signs in later life, suggesting that secondary factors are necessary to initiate clinical disease. Secondary factors that are linked to onset of clinical signs include cardiomegaly, pulmonary oedema, respiratory infection, chronic bronchitis, endotracheal intubation, the presence of a smoker in the household, airway irritants and obesity (Maggiore, 2014; White and Williams, 1994). The condition is further exacerbated by vicious cycle of cough which leads to chronic airway inflammation and vice versa (White and Williams, 1994). TC could also be acquired secondary to chronic inflammation (Singh *et al*., 2012).

Middle-aged and small breed dogs such as Pomeranians, Yorkshire terriers, Chihuahuas, Pugs, Shih Tzus, and Miniature/ Toy Poodles are over re-presented with TC (Maggiore, 2014; Macready *et al*., 2007; White and Williams, 1994; Johnson *et al*., 2015; Tangner and Hobson, 1982; Johnson, 2000). No gender predilection has been reported yet (Tappin, 2016; Culp and O’Donnell, 2015). TC is rare in cats and large breed dogs (Tappin, 2016).

Persistent inflammation of the mucosa in trachea results in epithelium loss, fibrinous membrane formation and eventually squamous metaplasia or polypoid proliferation in advanced cases (O’Brien *et al*., 1966). The metaplastic change in the mucosa reduce the ciliated cells population. The hyperplastic subepithelial glands will secrete highly viscid mucus. The impaired ciliary function is gradually replaced by cough as the major tracheobronchial clearing mechanism (Suterp, 1984). Furthermore, pulmonary oedema developed through congestive heart failure may exacerbate the load on tracheobronchial clearing system. Cardiac enlargement and/or pulmonary oedema have been detected in 31 percent of dogs with tracheal collapse in one previous study (White and Williams, 1994). Johnson (2000) reported that concurrent cardiopulmonary disease such as enlarging left atrium or pulmonary oedema can worsen the clinical signs in predisposed dogs with TC. The same author also reported that about one third or more dogs with tracheal collapse suffers systolic heart murmur at left apex.

2.3 DIAGNOSIS

Human with excessive dynamic airway collapse (EDAC) or tracheobronchomalacia (TBM) often presented with clinical signs such as cough during deep inspiration and exhalation, wheeze with forced exhalation, and truncation of expiratory flow during forced exhalation. However, these manifestations are non-specific and definite diagnosis could be difficult to be made. When high suspicion index is held, even when the patients do not present with the typical signs, the diagnosis should not be excluded (Hammond *et al*., 2018).

A dynamic CT scan during hold inspiration and exhalation in human could be utilised to compare the diameter changes (Hammond *et al*., 2018). This method is highly sensitive (Carden *et al.,* 2005) and is frequently used as it provides comprehensive visualization of the adjacent anatomical structures. Hence, CT scan can detect any possible impingement that can worsen the respiratory abnormality and it is useful in surgery planning (Hammond *et al*., 2018; Austin and Ali, 2003). In veterinary practice, CT scan provides non-invasive and excellent cross-sectional visualization of airways. However, it is best carried out in patients with anesthesia to avoid motion artefact. Requirement of anaesthesia in CT scan is not an ideal diagnostic method as it prolonged recovery period which could lead to further complications in respiratory distressed patients (Macready *et al.,* 2007).

Dynamic bronchoscopy is the gold standard in confirming the diagnosis of EDAC or TBM in human patients as well as pediatric populations. This method requires moderate sedation to visualize spontaneous ventilation (Hammond *et al*., 2018; Carden *et al.,* 2005; Austin and Ali, 2003). Dynamic collapse of the airways could be assessed when anaesthesia lightens and patients start to cough (Morehead and Parsons, 1993). Deep sedation should be avoided as airway collapse could be missed. Spirometry or pulmonary function test is used to assess pulmonary function rather than diagnosing the collapse in human medical practice (Austin and Ali, 2003). It has no diagnostic value to in diagnosing tracheobronchomalacia (Wright, 2018).

In veterinary practice, Radiograph tends to underestimate the degree of intrathoracic tracheal collapse (White and Williams, 1994; Johnson, 2000). One study reveals that collapse diagnosed via radiograph is only 15% of accuracy as compared to fluoroscopy assuming collapse diagnosed via fluoroscopy is 100% accurate (Macready *et al*., 2007). As most of the chest radiograph is taken when animals are taking maximum inspiration, it is likely to underdiagnose tracheal collapse on expiration.

Bronchoscopy allows assessment of the degree and location of tracheal collapse, and associated injury in the airway in dogs (Macready *et al.*, 2007; Tappin, 2016). However, in dogs with airway collapse, bronchoscopy might not be a suitable imaging method as it requires anaesthesia. The dogs may have difficulty recovering from anaesthesia as a result of increased respiratory effort (Macready *et al).* Furthermore, endotracheal intubation may trigger the vicious cycle of irritation, cough and inflammation (Macready *et al, 2007;* White and Williams, 1994).

Fluoroscopy is a relatively non-invasive method alternative to bronchoscopy. Fluoroscopy allows dynamic and real-time assessment of the trachea during inspiration, exhalation and during coughing episodes. Fluoroscopy is able to diagnose the location and degree of collapse in trachea more accurately than radiograph (Tappin, 2016).

2.4 TREATMENT

Medical treatment is the ideal approach and should first be considered in dogs with tracheal collapse. Generally, weight reduction is recommended if possible as obesity is one of the factors causing respiration difficulty. Respiratory irritation that could cause exaggeration of coughing should be eliminated. In tracheal collapse patients with concurrent cardiac or pulmonary disease, treatment should also be precis (Culp and O'Donnell, 2015).

Antitussives such as co-phenotrope (diphenoxylate hydrochloride and atropine sulfate), hydrocodone, and butorphanol are commonly used (Tappin, 2016; Culp and O'Donnell, 2015). Antitussives can help to suppress cough which consequently reduce inflammation in trachea mucosa. The vicious cycle of cough and inflammation can thus be reduced and further minimize the adverse effects on the tracheal mucosa (White and Williams, 1994; Tappin, 2016). Sedatives such as acepromazine can help to calm the dogs during excited episode.

Bronchodilators such as theophylline (Methyxanthine-based bronchodilator), terbutaline (B_2-adrenergic bronchodilator) and albuterol are used to dilate the trachea and to reduce intrathoracic pressure, preventing collapse of the airway (Tappin, 2016; Culp and O'Donnell, 2015).

Glucocorticoids could be administered by inhalation or orally to reduce the inflammation of the respiratory tissue. This is useful in minimizing the adverse effects of inflammation in the episodes of cough in tracheal collapse provided the usage is judged carefully (Tappin, 2016; Culp and O'Donnell, 2015) as it may also depress the immune system of the patients. A recent research in 2010 by Pardali and Adamama-Moraitou, suggested the use of stanozolol (anabolic androgenic steroid) in tracheal collapse patients as it provides beneficial effect in strengthening the cartilage of trachea.

As for cardiac patients, diuretics such as furosemide is used to treat congestive cardiomyopathy, pulmonary oedema, and occasionally as anti-hypertensive agent. It increases renal excretion of water, sodium, potassium, chloride, calcium, magnesium, hydrogen, ammonium, and bicarbonate. Secondly, angiotensin converting enzyme (ACE) inhibitor is medication to treat high blood pressure and heart failure. Pimobendan is a calcium sensitizer and a selective inhibitor of phosphodiesterase 3 with positive inotropic and vasodilator effects (Plumb's, 2008)

The primary goal of surgical intervention such as extraluminal ring prosthetics and intraluminal tracheal stent for tracheal collapse is to restore normal tracheal diameter without damaging the mucociliary flow. Surgical treatment is invasive and is often indicated when medical treatment has failed to control the clinical signs. The suitable candidates for surgical intervention are those with severe tracheal collapse with Grade II to Grade IV (Tappin, 2016).

Extraluminal ring prosthetics is currently the most commonly utilized surgical treatment for tracheal collapse in dogs. This method includes total ring prosthesis, pliable total ring prosthesis, and spiral ring prosthesis. These prostheses are available commercially or it can be formed from polypropylene syringe casings. Total ring prostheses implantation is effective in managing collapsed trachea in most dogs as it allows restoration of normal trachea lumen without the mucociliary apparatus being disrupted (Chisnell and Pardo, 2014).

Intraluminal tracheal stent has recently been advocated as the interventional treatment alternative to surgery for its minimal invasiveness. It is employed depending on the location of collapse. However, this method of restoring trachea lumen is not curative but it can help improve the quality of life of the patients (Culp and O'Donnell, 2015).

3.0 **MATERIALS AND METHODS**

Thirteen canine cardiac patients and three healthy dogs were recruited in this study. The medical records including age, sex, breed, reproductive status, and the condition of heart disease for each case were reviewed. The history details on duration of cough and current coughing status were recorded. The recruited canine patients were patients with history of cough and congestive heart failure as diagnosed by echocardiogram.

The machine used was Fidex, Animage manufactured in Pleasanton, California. The fluoroscopic settings were 100.0 kV, 0.20 mAs and 10 to 30 fps. Each dog was evaluated with fluoroscopy without being anesthetized. They were restrained in standing position and lateral fluoroscopic images were taken at neck and thoracic region.

Fluoroscopic recordings were taken from cervical to thoracic region during normal respiration and inducible coughing episode. The inducible coughing episode was done by stimulating the trachea digitally. The images were taken for at least a breathing cycle at each region so that the change in tracheal diameter. Then, the fluoroscopic recordings from cervical, thoracic inlet, intrathoracic and carinal regions of the trachea were evaluated for evidence of collapse during respiration and coughing episode.

The measurement of tracheal diameter at each region was taken 3 times and the average was recorded. The change of tracheal diameter is determined by measuring the luminal diameter at full inspiration and exhalation, and cough. The degree of collapse is approximated by adopting the grading scheme proposed by Tangner and Hobson (1982).

Grade	Criteria
I	Minor protrusion of the dorsal tracheal membrane into the airway lumen. Tracheal diameter is reduced by less than 25%.
II	Tracheal rings are elongated and mildly flattened. Tracheal diameter is reduced by 50%.
III	Tracheal rings are markedly flattened. The tracheal lumen is reduced by 75%.
IV	The tracheal lumen is obliterated.

The percentage change of the tracheal diameter change was measure using the formula below (Scherf *et al*., 2020):

$$\text{Percentage of tracheal diameter change (\%)} = \frac{\left[\text{Maximal tracheal diameter at inspiration} - \text{Minimal tracheal diameter at expiration}\right]}{\text{Maximal tracheal diameter at inspiration}} \times 100$$

The recorded data was then statistically analysed using Kolmorogov-Smirnov and Shapiro-Wilk test.

4.0 RESULTS

Thirteen client-owned dogs with cardiac diseases and 3 healthy dogs were recruited in this study and fluoroscopy examination was performed. There were 10 breeds involved in this study, with the most being Shihtzu (n=4), followed by Maltese (n=1), Pekingese (n=1), Chihuahua (n=1), Schnauzer (n=1), Cavelier King Charles Spaniel (n=1), Poodle (n=1), Jack Russel Terrier (n=1), Miniature Pinscher (n=1), and Mix breed (n=1). The average age was 9.62 ± 2.63 years old (range, 5.5 to 14 years old). 7 females (53.85%) and 5 males (38.46%) were included in this study.

The signalments of the recruited patients were listed in Table 1. Of these 13 dogs, 7 dogs were having history of chronic coughing while 6 dogs had resolved during presentation to UVH. 5 of the 7 chronic coughing dogs coughed during fluoroscopy upon tracheal stimulation while all 6 dogs with resolved coughing status did not cough during fluoroscopy. The type of cardiac diseases that had been diagnosed in these subjects were mostly chronic degenerative valvular disease (CDVD) [n=9], myxomatous mitral valve degeneration (MMVD) [n=4], and one case of hypertrophic cardiomyopathy (HCM) diagnosed concurrently with CDVD in one patient.

Case no.	Sex	Age	Breed	Coughing status	Cough on fluoroscopy	Type of cardiac disease	Heart size (VHS)	Pulmonary oedema	Part of heart enlarged
1	M	7	Maltese	Chronic	No	CDVD	11	yes	Left atrium
2	M	5.5	Shihtzu	Chronic	No	CDVD	10	yes	-
3	M	9	Shihtzu	Chronic	Yes	CDVD	9.5	No	Right ventricle
4	F	6	Shihtzu	Chronic	Yes	MMVD	-	No	Left atrium
5	CM	14	Poodle	Chronic	Yes	MMVD	10.5	Yes	Right ventricle

6	SF	8	Shihtzu	Chronic	Yes	MMVD	9.5	Yes	Left atrium
7	F	12	Miniature pinscher	Chronic	Yes	MMVD	12.5	Yes	Left atrium
8	SF	9	Pekingese	Resolved	No	CDVD	-	Yes	Right ventricle
9	M	9	Chihuahua	Resolved	No	CDVD	11.5	Yes	Left atrium
10	F	12	Schnauzer	Resolved	No	CDVD		No	-
11	F	8	Cavalier King Charles Spaniel	Resolved	No	CDVD	12	No	-
12	F	11.6	Jack Russel	Resolved	No	CDVD + HCM	11	Yes	Right ventricle
13	F	13	Mix	Resolved	No	CDVD	10.5	No	-

Table1 Patient signalments. CDVD, Chronic degenerative valve disease; MMVD, Myxomatous mitral valve degeneration; HCM, Hypertrophic cardiomyopathy.

Fluoroscopic examination was performed in each dog. The dynamic change of tracheal diameter was measured by taking the difference of the maximal tracheal diameter at dull inspiration and minimal diameter at exhalation. The percentage change of the tracheal diameter change was measure using the formula below (Scherf *et al*., 2020):

$$\text{Percentage of tracheal diameter change (\%)} = \frac{\left[\text{Maximal tracheal diameter at inspiration} - \text{Minimal tracheal diameter at}\right]}{\text{Maximal tracheal diameter at inspiration}} \text{ X100}$$

For the control group, there was no coughing despite being induced at the trachea. The 3 healthy dogs had a mean degree of tracheal diameter change of 2.08%, 4.27%, 5.26% and 6.97% at cervical, thoracic inlet, intrathoracic and carina respectively. These dogs had tracheal diameter change of less than 10% and the findings were too mild to be considered as tracheal collapse and therefore not graded. The fluoroscopic evaluation of the healthy dogs revealed non-significant change in the tracheal diameter at normal respiration. The boxplot of the percentage change in tracheal collapse of control is as shown in Figure 3.

Upon fluoroscopic examination, 5 out of 13 cardiac patients coughed upon tracheal stimulation. They were grouped into coughing cardiac patients (n=5) and the rest were grouped into non-coughing cardiac patients (n=8).

For the group of non-coughing cardiac patients, the most prominent tracheal collapse occurred at carina, followed by thoracic inlet, intrathoracic and cervical region. Adopting the grading system for tracheal collapse by Tangner and Hobson (1982), the mean grade of tracheal collapse at different regions in non-coughing cardiac patients was Grade II (26.44%) at carina, Grade I (14.57%) at thoracic inlet, Grade I (6.17%) at intrathoraic, and Grade I (5.96%) at cervical region. The boxplot of the percentage change in tracheal collapse of non-coughing cardiac patients is as shown in Figure 4.

As for cardiac patients that coughed on fluoroscopy, the most prominent tracheal collapse during the episodes of cough was observed at carina, followed by intrathoracic, thoracic inlet and cervical region. The mean grade of tracheal collapse from the most severe was Grade IV (98.31%) at carina, Grade II (48.24%) at intrathoracic, Grade II (32.91%) at thoracic inlet and Grade I (8.31%) at cervical region. The boxplot of the percentage change in tracheal collapse of coughing cardiac patients is as shown in Figure 5. Among the 5 coughing cardiac patients, 2 were observed to be having total carina collapse due to compression of carina by enlarged left atrium, as shown in Figure 6.

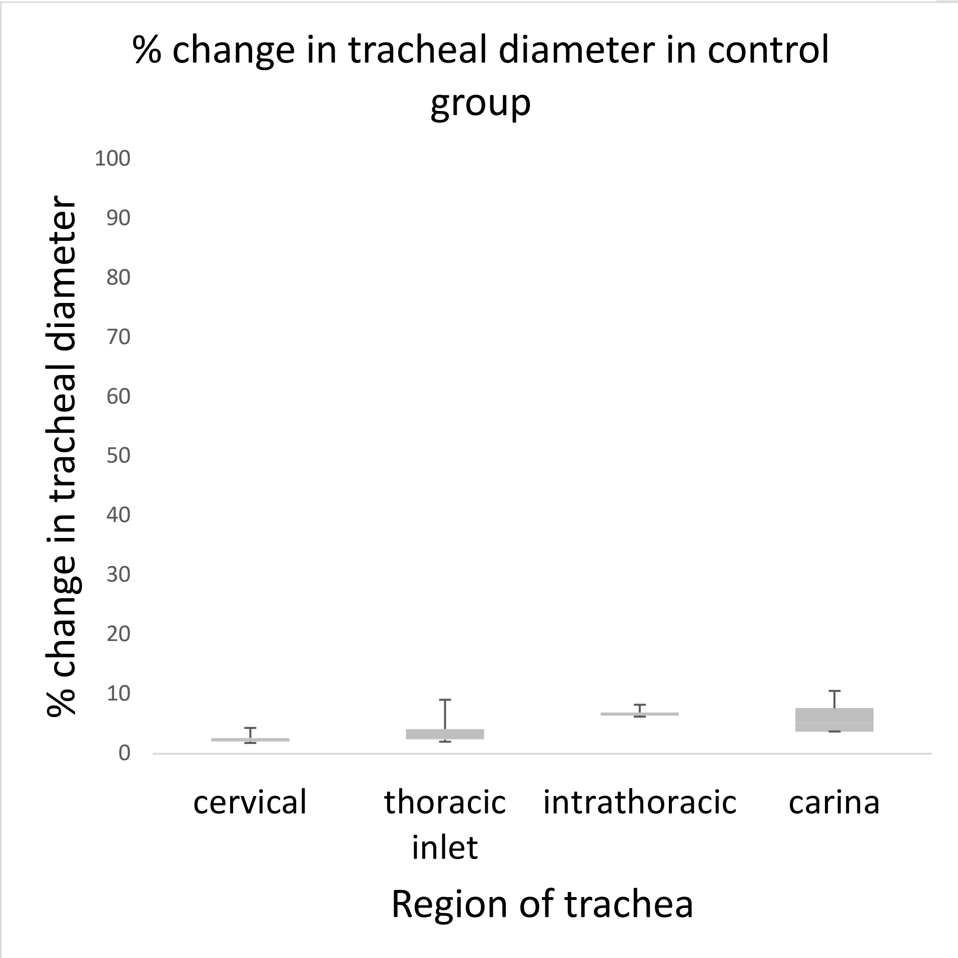

Figure 3 Percentage change in tracheal diameter in healthy dogs

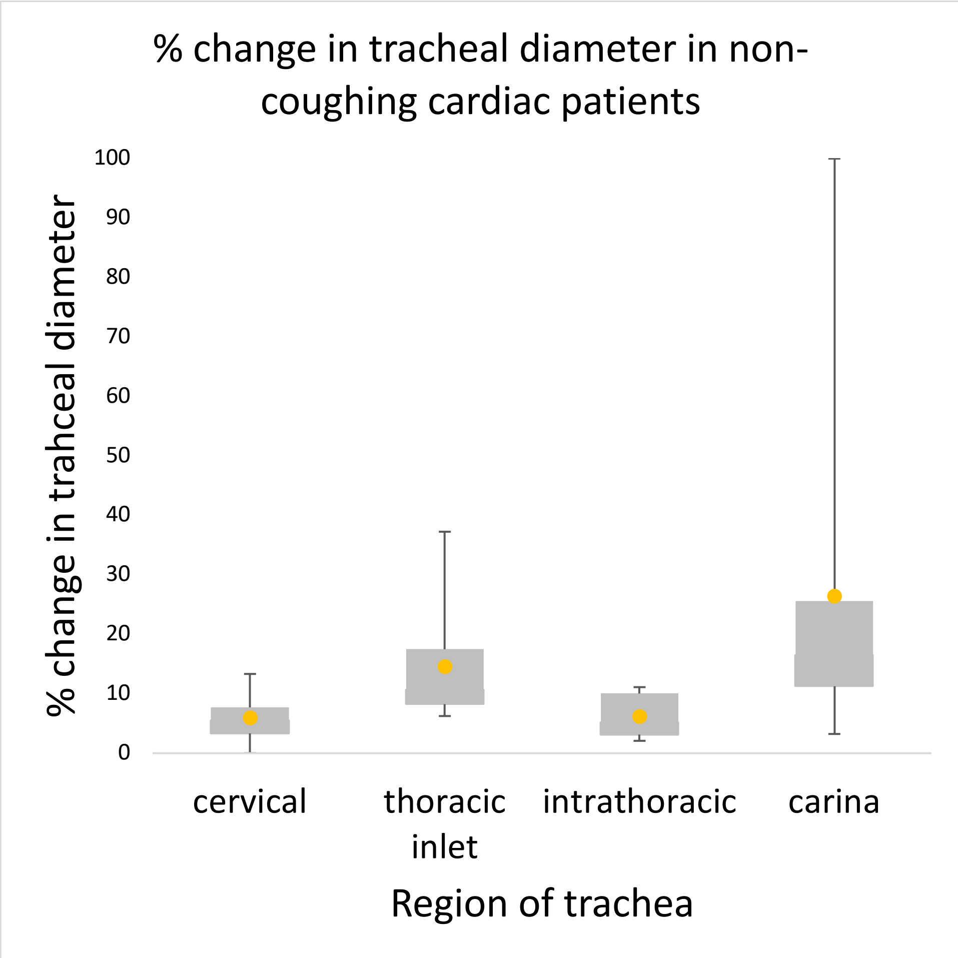

Figure 4 Percentage change in tracheal diameter in non-coughing cardiac patients

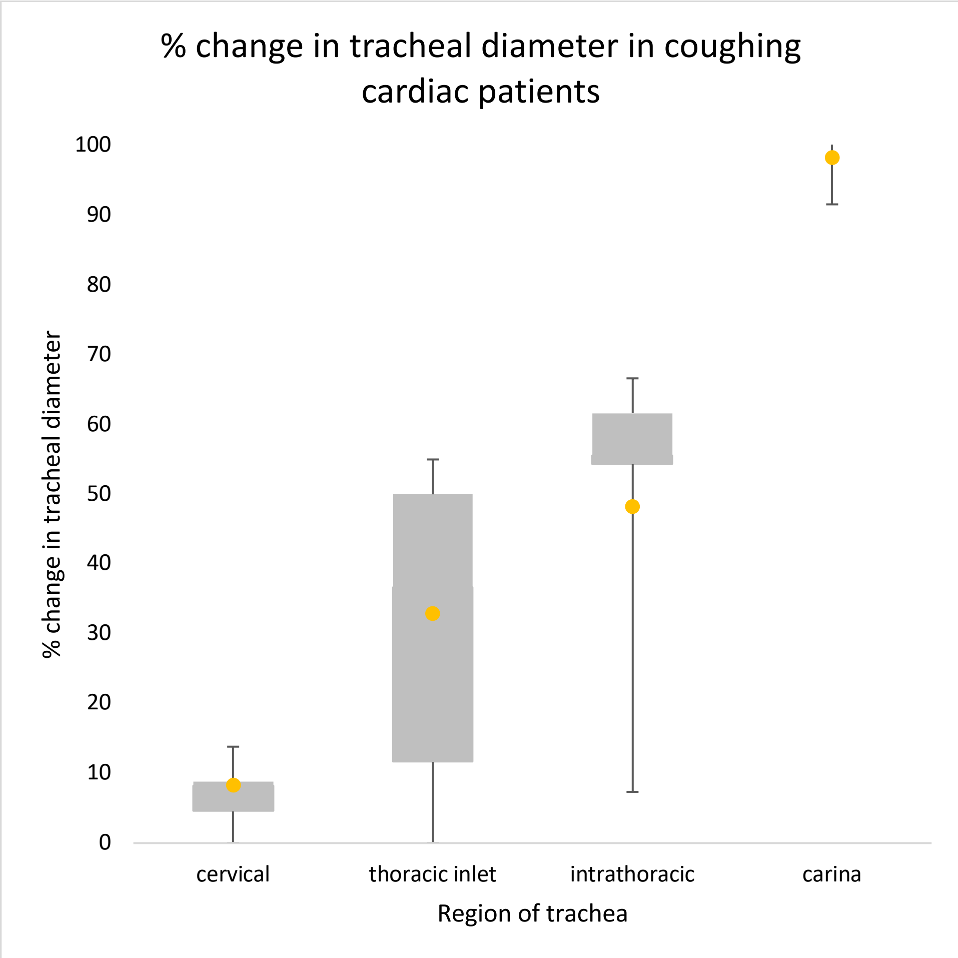

Figure 5: Percentage change in tracheal diameter in coughing cardiac patients

There was one patient that did not cough but total carinal collapse was observed at expiration. This patient had true airway disease termed tracheobronchomalacia that caused tracheal collapse. The trachea at carinal region was observed to experience collapse at expiratory phase during normal breathing as shown in Figure 7.

Cervical lung herniation (CLH) was observed in 4 cardiac patients during fluoroscopy, where 3 out of the 4 dogs were coughing cardiac patients and they had total carinal collapse (Grade IV) during coughing episodes at expiratory phase. The fluoroscopic image of the patient revealed protrusion of cranial lung lobe out of thoracic cavity is as shown in Figure 8.

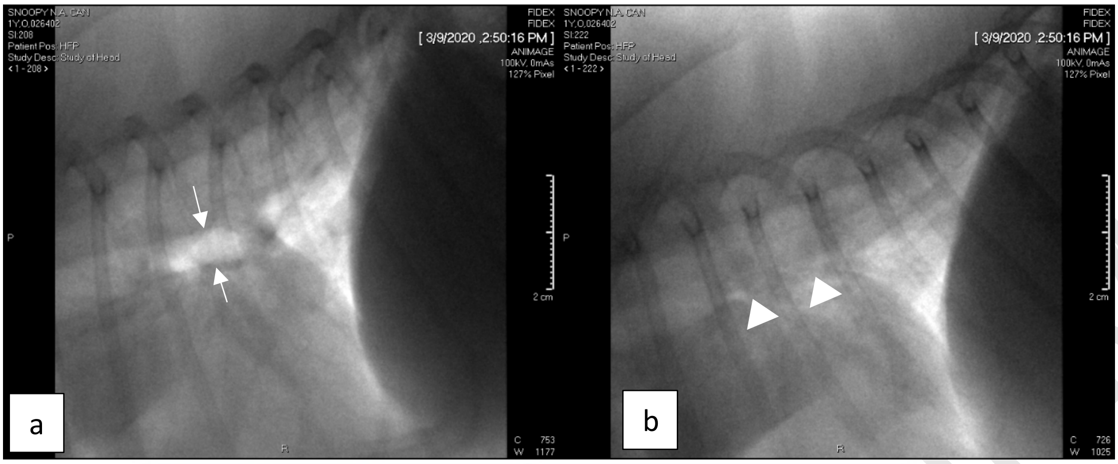

Figure 6: Carina pushed by enlarged left atrium in total carina collapse during expiratory coughing episode. Carina (arrow) at inspiratory phase (a) and carina being pushed by enlarged left atrium (triangle) at expiratory phase of cough (b).

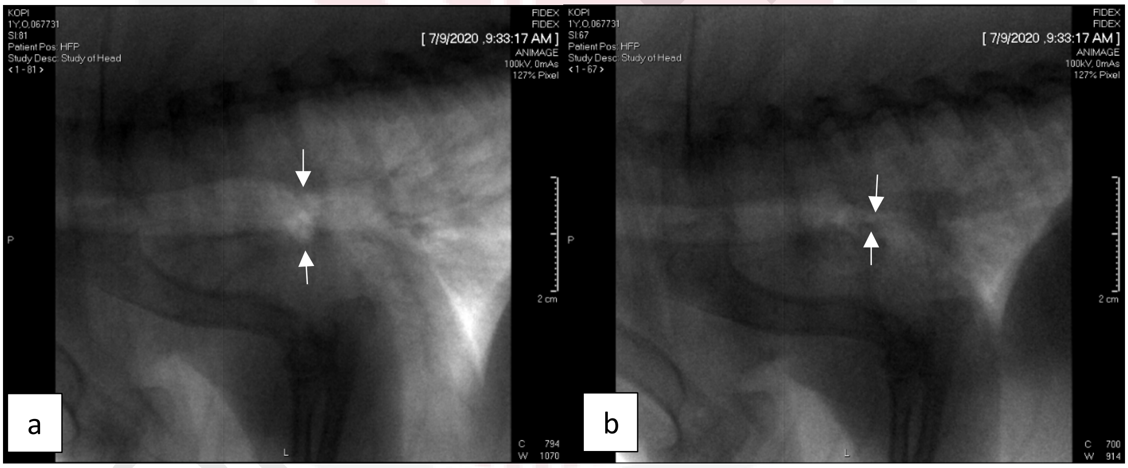

Figure 7: Carinal collapse in patient having tracheobronchomalacia. Carina at inspiratory phase (a) and carina collapse at expiratory phase (b)

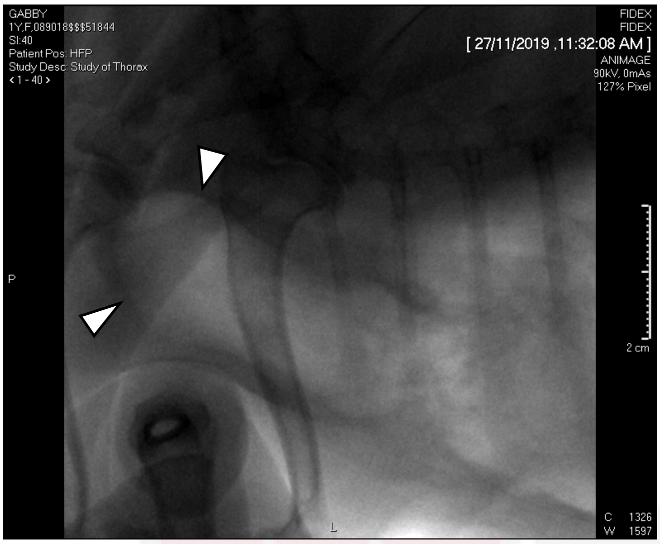

Figure 8: Cervical lung herniation

The statistical results show significant findings for coughing cardiac patients at carina (p<0.05). This reject the null hypothesis that dynamic collapse is not present in coughing cardiac patients.

5.0 DISCUSSION

This study evaluated the dynamic changes of trachea in cardiac patients that coughed upon examination on fluoroscopy. The typical coughing reflex is characterized by an initial deep inspiration and then followed by a forceful expiration that acts against the closed glottis. The nasopharynx closed and the forceful expiration through the mouth accompanied with the vibration of the vocal cords produced the cough. The forceful expulsion promotes clearance of mucus and foreign materials in the trachea and bronchi. True cough always started with a deep inspiration as opposed to expiratory reflex (ER), which does not involve a deep inspiration. This could be seen when larynx is stimulated. This is because upper respiratory tract is more sensitive to mechanical stimulation while lower respiratory tract is more chemosensitive (Ferasin and Linney, 2018).

In this study, 13 patients with history of cough were recruited. 6 out of 13 had resolved coughing status and 7 had chronic coughing status. Among the 7 patients with chronic coughing status, inducible cough by tracheal stimulation during fluoroscopy was successfully stimulated in 5 patients. All patients recruited in this study were on continuing medications for cardiac diseases such as diuretics, angiotensin-converting enzyme (ACE) inhibitor, and pimobendan. Diuretics such as furosemide was given at 1.1 mg/kg PO every other day in mild heart failure to 4.4mg/kg PO q8h for severe heart failure to treat congestive cardiomyopathy, pulmonary oedema, and occasionally as anti-hypertensive agent. It increases renal excretion of water, sodium, potassium, chloride, calcium, magnesium, hydrogen, ammonium, and bicarbonate. ACE inhibitor such as benazepril was given at 0.25mg/kg, SID, PO to treat high blood pressure and heart failure. Pimobendan was given as calcium sensitizer and a selective inhibitor of phosphodiesterase 3 with positive inotropic and vasodilator effects. The 8 patients that did not cough upon tracheal stimulation were medically controlled and therefore cough was not able to be induced upon stimulation.

Among the 5 coughing cardiac patients, 2 were having enlarged left atrium with vertebral heart size (VHS) of more than 10 on radiograph. When the dog coughed, the enlarged left atrium was observed to be pushing the carina cranially, causing total collapse at carina in this dog during expiratory coughing episode. This phenomenon was termed cardiac cough. Cardiac cough is defined as coughing associated with cardiac diseases. According to Ferasin and Linney (2019), cardiac cough is caused by cardiomegaly with marked left atrial enlargement and compression of the main stem bronchus. However, it is believed that cardiac cough often occurs when there is underlying tracheobronchial disease. Cough is more frequently triggered in small breed dogs with cardiomegaly when there are airway diseases such as tracheal collapse, chronic bronchitis and bronchomalacia (Johnson and Pollard, 2010; Ferasin *et al*. 2013). Tracheal collapse is a multifactorial disease commonly seen in middle to old-aged small breed dogs (Maggiore, 2014; Macready *et al*, 2007; White and Williams, 1994). The primary factory can be congenital loss of cartilage matrix and it can be further exacerbated by secondary factors such as cardiomegaly, pulmonary oedema, respiratory tract infection, chronic inflammation, presence of airway irritants and obesity (Singh *et al*., 2012).

The medical treatment in cardiac patients with total carinal collapse due to left atrial enlargement should aim at decreasing the left atrial volume. The management of dogs in ACVIM Stage C usually consists of furosemide to provide diuresis, ACE inhibitor and spironolactone to counteract renin-angiotensin-aldosterone system activation, and pimobendane to enhance forward stroke volume. Since cough is present in these patients, it may exacerbate the tracheal collapse in this these patients and affect the quality of life. Cough suppressants and bronchodilators are indicated to control the coughing (Menciotti and Borgarelli, 2017). Surgical intervention for mitral valve repair or mitral valve replacement is the ideal choice of treatment for more severely affected patients but this technique is currently unavailable (Borgarelli and Haggstrom, 2010).

In this study, fluoroscopy was adopted to evaluate the dynamic change of tracheal collapse in canine cardiac patients. Fluoroscopy is non-invasive and does not require general anesthesia. It can be done in real time and dynamic disorders could be identified by eliciting a cough by tracheal palpation (Scherf *et al*., 2020). Fluoroscopy is more sensitive in detecting tracheal collapse especially of intrathoracic portion of the trachea compared radiography (Macready, 2007). Bronchoscopy is the gold standard in diagnosing respiratory tract diseases in veterinary practice as it provides excellent visualization of the lumen of trachea, mainstem bronchi, and lobar bronchi (Scherf *et al*., 2020). It allows assessment of the extend of tracheal collapse and degree of injury in the tract (Macready, 2007). However, it requires general anaesthesia and it was not opted in this study considering the risk of respiratory distress to the cardiac patients and prolonged recovery in tracheal collapse patients (Macready, 2007). Radiography despite being non-invasive and commonly practiced in evaluating lungs and trachea, it tends to underestimate the degree of tracheal collapse (Macready, 2007). Therefore, radiographic images were recommended to be taken at both inspiratory and expiratory phases as extrathoracic airways are more likely to collapse on inspiration and intrathoracic airways tend to collapse on expiration and (Scherf *et al*., 2020). Computed tomography (CT) provides non-invasive and excellent cross-sectional visualization of airways. However, it is best carried out in patients with anesthesia to avoid motion artefact.

In human medicine, dynamic chest radiography (DCR) is a recommended diagnostic equipment to evaluate tracheal narrowing such as in expiratory central airway collapse (ECAC), in other words, excessive airway collapse during expiration. DCR is utilized to observe the dynamic structure of the chest using continuous pulse fluoroscopy irradiation. ECAC is known to be described in two pathophysiologic entities, which are tracheobronchomalacia (TBM) and excessive dynamic airway collapse (EDAC). ECAC could be acquired idiopathically or secondary to chronic dynamic pulmonary disease (COPD), asthma, and other obstructive ventilation disorders. In COPD patients, there will be various degree of tracheal narrowing. To be able to visualize the real-time changes of the dynamic changes effectively, a new research recommended DCR as it might lead to a new insight to relationship of the degree of tracheal narrowing and symptoms for subjects with obstructive ventilation disorders. (Watase *et al*.,2020).

This study adopted the grading scheme proposed by Tangner and Hobson (1982) to describe the severity of tracheal collapse in the cardiac patients. Grading of tracheal collapse is essential in determining the disease progression and appropriate treatment to be given. Intervention at the earliest possible detection could prevent further degenerative changes in the trachea (Fingland *et al*., 1987). Medical treatment alone often successful when diseases were detected earlier and surgical intervention was reserved for cases that were refractory to medical treatment (White and Williams, 1994). Study by Sun et al. 2008 suggested that dogs with severe collapse (Grade II and higher) should be considered surgical candidates.

Cervical lung herniation (CLH) was observed in 4 cardiac patients, where 3 out of 4 were coughing cardiac patients. CLH is strongly associated with history of cough, intrathoracic tracheal collapse, tracheal kinking, and age. Weakening of the muscles from aging is an important factor that leads to CLH. Furthermore, CLH is also associated with TC as the collapsed airway impedes the air flow and increased intrapleural pressure causes the cranial part of the lungs to protrude out of the thoracic cavity (Lee *et al*., 2017).

One patient that was observed to be having tracheal collapse at normal expiration was suspected to be having tracheobronchomalacia, which is a tracheal collapse of respiratory origin due to congenital loss of glucosaminoglycan and chondroitin sulfate in the cartilage matrix (Maggiore, 2014; White and Williams, 1994; Dallman, 1982; Dallman and Brown, 1979).

6.0 CONCLUSION

In conclusion, the dynamic tracheal collapse is present in coughing cardiac patient. The tracheal collapse occurs significantly at the carinal region as this is associated with the left atrial enlargement that pushed the carina cranially. Cervical lung herniation (CLH) and tracheobronchomalacia which are associated with history of coughing were presented in this study.

7.0 RECOMMENDATIONS

A larger sample size is recommended for a more comprehensive study on the effect of coughing on dynamic change of tracheal diameter. Cardiac patients with similar stages of MMVD are recommended in future study for a more focused community. Thoracic radiograph is recommended to be taken for all patients to determine whether respiratory disease is the cause of cough in cardiac patients.

REFERENCES

Al-Qadi, M. O., Artenstein, A. W., & Braman, S. S. (2013). The "forgotten zone": Acquired disorders of the trachea in adults. *Respiratory Medicine*, 107(9), 1301–1313. doi:10.1016/j.rmed.2013.03.017

Austin, J., & Ali, T. (2003). Tracheomalacia and bronchomalacia in children: pathophysiology, assessment, treatment and anaesthesia management. *Pediatric Anesthesia*, 13(1), 3–11. doi:10.1046/j.1460-9592.2003.00802.x

Borgarelli, M., & Haggstrom, J. (2010). *Canine Degenerative Myxomatous Mitral Valve Disease: Natural History, Clinical Presentation and Therapy. Veterinary Clinics of North America: Small Animal Practice, 40(4), 651–663*. doi:10.1016/j.cvsm.2010.03.008

Carden, K. A., Boiselle, P. M., Waltz, D. A., & Ernst, A. (2005). Tracheomalacia and Tracheobronchomalacia in Children and Adults. Chest, 127(3), 984–1005. doi:10.1378/chest.127.3.984

Chisnell, H. K., & Pardo, A. D. (2014). Long-Term Outcome, Complications and Disease Progression in 23 Dogs After Placement of Tracheal Ring Prostheses for Treatment of Extrathoracic Tracheal Collapse. Veterinary Surgery, n/a–n/a. doi:10.1111/j.1532-950x.2014.12206.x

Culp, W. T. N., & O'Donnell, M. D. (2015). Upper Airway Disease: Tracheal Collapse. *Small Animal Surgical Emergencies*, 289–296. doi:10.1002/9781118487181.ch28

Currens, J. H., & White, P. D. (1949). Cough as a symptom of cardiovascular disease. *Annals of internal medicine*, 30(3), 528-543.

Dallman, M.J. (1982) Normal and collapsed tracheas: a histo- chemical, scanning electron microscopic and statistical study. *Dissertations Abstractions International*42, 3531

Dallmamn., J. & BROWN,E. M. (1979) Structural considerations in tracheal disease. *American Journal of Veterinary Research* 40, 555-260

Ferasin, L., & Linney, C. (2019). Coughing in dogs: what is the evidence for and against a cardiac cough*? Journal of Small Animal Practice*. doi:10.1111/jsap.12976

Ferasin, L., Crews, L., Biller, D. S., Lamb, K. E., & Borgarelli, M. (2013). Risk Factors for Coughing in Dogs with Naturally Acquired Myxomatous Mitral Valve Disease. *Journal of Veterinary Internal Medicine*, 27(2), 286–292. doi:10.1111/jvim.12039

Fingland, R. B., DeHoff, W. D., & Birchard, S. J. (1987). Surgical management of cervical and thoracic tracheal collapse in dogs using extraluminal spiral prostheses. *The Journal of the American Animal Hospital Association (USA)*.

Hammond, K., Ghori, U. K., & Musani, A. I. (2018). Tracheobronchomalacia and Excessive Dynamic Airway Collapse. *Clinics in Chest Medicine*, 39(1), 223–228. doi:10.1016/j.ccm.2017.11.015

Irwin, R. S. (1977). Cough. *Archives of Internal Medicine*, 137(9), 1186. doi:10.1001/archinte.1977.03630210060019

Johnson, L. (2000). Tracheal Collapse. Veterinary Clinics of North America: Small Animal Practice, 30(6), 1253–1266. doi:10.1016/s0195-5616(00)06005-8

Johnson, L. R., Singh, M. K., & Pollard, R. E. (2015). Agreement Among Radiographs, Fluoroscopy and Bronchoscopy in Documentation of Airway Collapse in Dogs. *Journal of Veterinary Internal Medicine*, 29(6), 1619–1626. doi:10.1111/jvim.13612

Lee, J., Yun, S., Lee, I., Choi, M., & Yoon, J. (2017). Fluoroscopic characteristics of tracheal collapse and cervical lung herniation in dogs: 222 cases (2012–2015). Journal of Veterinary Science, 18(4), 499. doi:10.4142/jvs.2017.18.4.499

Macready, D. M., Johnson, L. R., & Pollard, R. E. (2007). Fluoroscopic and radiographic evaluation of tracheal collapse in dogs: 62 cases (2001–2006). *Journal of the American Veterinary Medical Association,* 230(12), 1870–1876. doi:10.2460/javma.230.12.1870

Maggiore, A. D. (2014). *Tracheal and Airway Collapse in Dogs*. *Veterinary Clinics of North America: Small Animal Practice*, 44(1), 117–127

Martin, M., & Pereira, Y. M. (2013). Approach to the coughing dog. In Practice, 35(9), 503–517. doi:10.1136/inp.f5838

Menciotti, G., & Borgarelli, M. (2017). *Review of Diagnostic and Therapeutic Approach to Canine Myxomatous Mitral Valve Disease. Veterinary Sciences, 4(4), 47*. doi:10.3390/vetsci4040047

Morehead, J. M., & Parsons, D. S. (1993). Tracheobronchomalacia in Hunter's syndrome. *International Journal of Pediatric Otorhinolaryngology*, 26(3), 255–261. doi:10.1016/0165-5876(93)90096-l

O'brien, J. A., Buchanan, J. W. & Kelly,D. E. (1966) Tracheal collapse in the dog. *Journal of the American Veterinary Radiology Societ*y 7,12-20

Pardali, D., & Adamama-Moraitou, A. K. (2010). Tracheal Collapse in the dog: step by step from pathophysiology to management. *Journal of the Hellenic Veterinary Medical Society*, 61(3), 253-266.

Plumb's, D. C. (2011). Plumb's Veterinary Drug Handbook. *Ames, Stockholm, Wis*.

Scherf G, Masseau I, Bua AS, Beauchamp G, Dunn ME. Fluoroscopic and radiographic assessment of variations in tracheal height during inspiration and expiration in healthy adult small-breed dogs. Can J Vet Res. 2020 Jan;84(1):24-32. PMID: 31949326; PMCID: PMC6921987.

Singh, M. K., Johnson, L. R., Kittleson, M. D., & Pollard, R. E. (2012). Bronchomalacia in Dogs with Myxomatous Mitral Valve Degeneration. *Journal of Veterinary Internal Medicine,* 26(2), 312–319. doi:10.1111/j.1939-1676.2012.00887.x

Suterp, . F. (Ed) (1984) Diseases of the nasal cavity, larynx and trachea. In: Thoracic Radiology - A Text Atlas of Thoracic Disease of the Dog and Cat. Wettswil, Switzer- land. pp 243-249

Tangner, C. H., & Hobson, H. P. (1982). A Retrospective Study of 20 Surgically Managed Cases of Collapsed Trachea. *Veterinary Surgery*, 11(4), 146–149. doi:10.1111/j.1532-950x.1982.tb00691.x

Tappin, S. W. (2016). Canine tracheal collapse. *Journal of Small Animal Practice*, 57(1), 9–17. doi:10.1111/jsap.12436

Watase, S., Sonoda, A., Matsutani, N., Muraoka, S., Hanaoka, J., Nitta, N., & Watanabe, Y. (2020). Evaluation of intrathoracic tracheal narrowing in patients with obstructive ventilatory impairment using dynamic chest radiography: A preliminary study. *European Journal of Radiology*, 129, 109141. doi:10.1016/j.ejrad.2020.109141

White, R. A. S., & Williams, J. M. (1994). Tracheal collapse in the dog - is there really a role for surgery? A survey of 100 cases. *Journal of Small Animal Practice*, 35(4), 191–196. doi:10.1111/j.1748-5827.1994.tb01685.x

Wright, C. D. (2018). Tracheobronchomalacia and Expiratory Collapse of Central Airways. Thoracic Surgery Clinics, 28(2), 163–166. doi:10.1016/j.thorsurg.2018.01.006