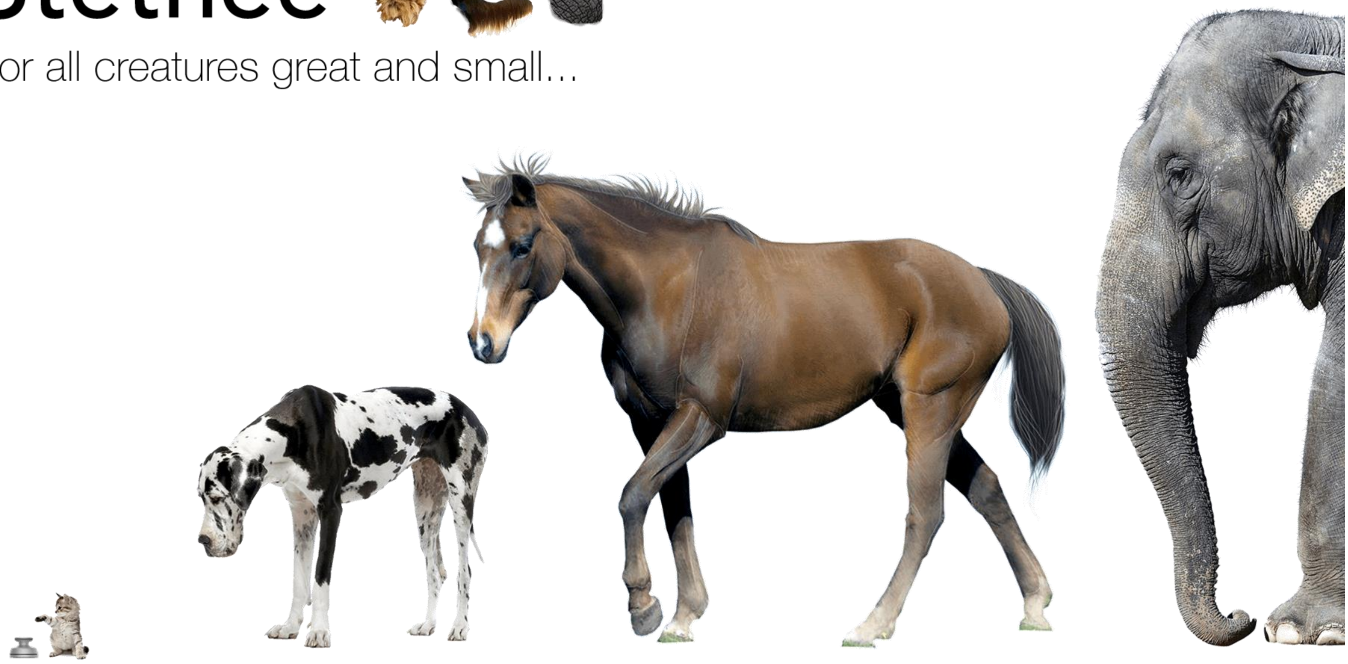
Clinical evaluation of the Stethee stethoscope in dogs presented for cardiac evaluation

Stethee vet
For all creatures great and small...



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ABSTRACT

Approximately 10% of dogs have heart disease, most commonly myxomatous mitral valve disease (MMVD). MMVD is predisposed in certain breeds, especially the Cavalier King Charles Spaniel (CKCS). Detection of a heart murmur by cardiac auscultation is the most common technique to suspect heart disease. It is a quick, inexpensive and non-invasive method and is therefore commonly used by veterinarians.

Digital stethoscopes coupled with artificial intelligence could help the veterinarian to diagnose heart murmurs. In this thesis the use of a wireless electronic stethoscope named Stethee (M3DICINE Pty Ltd (Brisbane, Australia)) is described. It records and stores the heart sounds via Bluetooth using an App called Stethee Vet. The recordings are analysed by an Artificial Intelligence analysing system (Aida), which tries to differ recordings of animals with a normal heart sound from recordings of animals with a heart murmur.

Accuracy of Aida was assessed by comparing auscultatory findings of a veterinary cardiologist to the diagnoses made with Aida in 132 dogs. Also, the interobserver agreement between an inexperienced and experienced observer was assessed in a subset of 86 CKCS. The agreement between Aida and the experienced observer was 89% with a kappa value of 0.77 and a PPV and NPV of 83% and 93% respectively. The interobserver agreement was 88% with a kappa value of 0.70 and a PPV and NPV of 86% and 89% respectively.

The level of interobserver agreement decreased with low intensity heart murmurs, while the levels of agreement involving Aida were constant. Thus, Aida could be helpful in diagnosing low intensity murmurs for general veterinarians.

Keywords: Stethee, Artificial Intelligence, Auscultation, Heart murmur, Heart disease, Myxomatous mitral valve disease, Cavalier King Charles Spaniel, Interobserver agreement

1. Introduction

1.1 Heart disease in dogs

Heart diseases are common in dogs[1], with approximately 10% of the dogs presented to veterinary practices have heart disease[2,3]. Acquired heart diseases are more common than congenital heart diseases and include various cardiomyopathies, pericardial effusion secondary to neoplasia and endocarditis[2]. However, the most common acquired heart disease in dogs is myxomatous mitral valve disease (MMVD)[3,4].

1.1.1 Myxomatous mitral valve disease

The most common acquired heart disease in dogs is myxomatous mitral valve disease (MMVD), also known as endocardiosis and chronic valvular heart disease, representing 75% of the dogs with a heart disease[3,4]. The prevalence of MMVD is higher in small and medium-sized breed dogs, such as Cavalier King Charles Spaniels (CKCS), Dachshunds, miniature Poodles, Cocker Spaniels, Miniature schnauzers, Pomeranians, Chihuahuas, Pekingese, Fox terriers, Boston terriers and Yorkshire Terriers, as well as mixed breed dogs[5-7] . MMVD tends to be a multifactorial, polygenic threshold trait and male dogs have a lower threshold than female dogs [8-10]. Therefore, males are approximately 1.5 times more affected than females at a given age [3,6,7] and the prevalence of the disease is strongly correlated with age[11].
MMVD is caused by a progressive myxomatous degeneration of the atrioventricular valves[4,12]. The left atrioventricular valves (mitral valves) are most commonly affected, although 30% of the cases also involve the right valves (tricuspid valves)[3].
Many dogs developing MMVD show no symptoms for years and some are even asymptomatic for life[13,14]. Nevertheless, severe complications can occur[15-17] and can result in death or euthanasia[1]. As the disease progresses, congestive heart failure occurs and may give the following clinical signs; coughing, tachypnoe, dyspnoe, weakness, exercise intolerance, reduced stamina, ascites, anorexia and syncope[7,9,18,19]. In general, the cough occurs after exercise or excitement and is described as a dry hacking cough[7,9,18,19].

Auscultatory findings in dogs with mitral valve disease
Cardiac auscultation is a quick, inexpensive and non-invasive method that can detect murmurs, systolic clicks and arrhythmias that indicate heart disease[20]. Since small breed dogs are predisposed to develop MMVD, these dogs should be auscultated yearly by the veterinarian as part of routine health care to detect the early stages of the disease[3]. There are also yearly screening events at dog shows or other events that dog owners can participate in[3].

<u>Heart murmur</u>
Early detection and treatment can prolong the B2 stage of MMVD[21] and since the most common first clinical sign of mitral regurgitation is the detection of a soft heart murmur[8-10,18], auscultation is very important in diagnosing MMVD. Soft murmurs are commonly proto- or mid-systolic while loud murmurs are holo-systolic and plateau-shaped[22]. Murmurs caused by mitral regurgitation are mid- to late-systolic. Typical characteristics of a murmur caused by mitral insufficiency are the mixed frequency and the harsh sounding although it can also be high-pitched and musical[22]. The murmur is typically systolic, loudest at the apex of the heart on the left thorax[7]. The intensity of the murmur is strongly correlated with the severity of the valvular thickening and the size of the left cardiac chambers and thus can be used to subjectively evaluate the severity of the disease[8,23]. In dogs with more severe MMVD, the murmur can radiate toward the left heart base and to the right hemithorax[8,23]. Furthermore, the tricuspid valves may get affected in severe cases which also causes a murmur on the right thorax[8,23]. In dogs with severe MMVD a precordial thrill can also be palpable at the apex of the heart on the left side of the thorax[8-10,18].

In some dogs the detection of a systolic click preceded a murmur[7]. A systolic click is often intermittent and it is probably caused by the tensing of the chordae tendinae and rapid deceleration of blood against the leaflets at maximum prolapse into the left atrium[24]. Systolic clicks can occur in dogs with early MMVD, typically in mid or late systole[14,16,22] . They are short, mid- to high-frequency sounds that can vary in occurrence, timing and intensity and they can be best heard at the mitral and tricuspid valve areas[22].

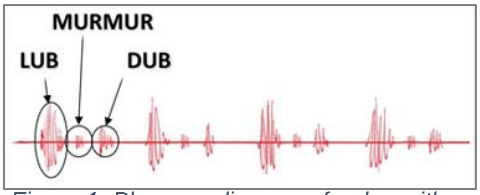

Figure 1. Phonocardiogram of a dog with MMVD[21].

The heart sounds can be recorded and displayed in a phonocardiogram. Murmurs and systolic clicks can be detected as shown in figure 1.

<u>Arrhythmias associated with heart disease</u>
In more advanced forms of the disease, arrhythmias may occur[3,15,25]. In dogs with MMVD more supraventricular arrhythmias are seen in dogs with atrium enlargement[25]. Also, ventricular arrhythmias are more commonly seen in dogs with clinical signs that in asymptomatic dogs diagnosed with MMVD[25].

1.1.2 Myxomatous mitral valve disease in the Cavalier King Charles Spaniel


Figure 2. Four colours of the cavalier King Charles Spaniel. From left to right: Blenheim, Tricolour, Ruby, Black and Tan[26].

The Cavalier King Charles Spaniel (CKCS) descends from toy spaniels that were found in Italy, France and Holland in the 16th, 17th and 18th centuries[26]. They were popular among royal and noble families in Europe and they became favourites of King Charles I when they were brought to England. The Cavalier King Charles Spaniel is a small Toy dog with a soft and silky coat with feathering on the ears, chest, legs and tail. They can have four different colours: Black and Tan (black with tan markings above the eye, on the cheeks, chest, legs, tail and inside the ears), Blenheim (white with red markings), Ruby (red) and Tricolour (white and black with tan markings) (Figure 2). The cavalier is a companion dog and is very friendly, gentle and intelligent, but they can also be very active and energetic. Various diseases are predisposed in CKCS among whilst MMVD[26].

Myxomatous mitral valve disease in the Cavalier King Charles Spaniel

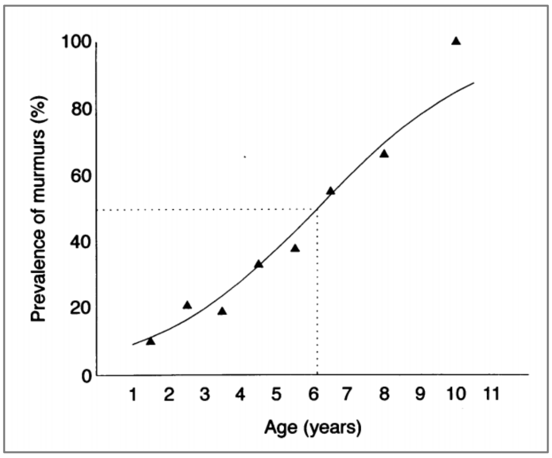

Figure 3. Logistic regression curve illustrating the percentage expected to have a murmur as a function of the age of the dogs. The mean age (6.2 years) is illustrated by the dotted line. The triangles show the observed percentages[30].

<u>Prevalence and onset of the disease</u>

Myxomatous mitral valve disease (MMVD) is a common heart disease in small breeds and several studies revealed that the frequency of MMVD is especially high in CKCS[19,27,28]. Beardow and Buchanan (1993) show a mean age of developing MMVD in CKCS of 6.25 years in contrast to a mean age of 12 years in other breeds[27]. Other studies show similar mean ages in CKCS[29,30]. The prevalence of MMVD increases with age[11,27-32]. The study of Beardow and Buchanan (1993) shows a range in prevalence from 9% in dogs < 1 year old to 100% in dogs ≥ 10 years old and a prevalence of 56% in dogs ≥ 4 years old[27]. Similar results were found in Sweden, Denmark and the United Kingdom (Figure 3)[28-30]. In dogs ≥ 4 years old, respectively 42%, 48% and 59% were found to have a heart murmur and 100% of the dogs > 10 years old had a heart murmur[28-30]. However, in Australia only 25% of the dogs ≥ 4 years old revealed a heart murmur and in dogs older than 10 years old 83% had developed MMVD[31]. This suggests that CKCS in Australia may have a later onset of the disease due to different breeding lines in the different countries[32]. This and the fact that some dog breeds are predisposed to MMVD also suggest that the disease has a strong genetic background[6].

<u>Heritability</u>

The study of Swenson et al. (1996) shows a strong relation between the presence and severity of MMVD in parents and their offspring at a given age[10] and MMVD has been suggested to be inherited as a multifactorial, polygenic threshold trait[10,33]. Lewis et al. stated that dogs with an audible murmur at an age of 4 years can be considered to be affected with severely premature prolapse and they found the premature onset of MMVD to be highly heritable[33]. Research indicates that male dogs have a lower threshold than female dogs resulting in males to be affected approximately 1.5 times more than females[3,6,7,10]. Madsen et al. (2011) identified two loci that are associated with the development of MMVD in CKCS[34]. In the region on CFA 13 (1.68 Mb) and the homologous HSA 4 region there have been annotated twenty protein-coding genes and in the 1.58 Mb CFA 14 region and the homologous HAS 7 region there have been annotated 11 protein-coding genes[34]. Some of these genes play a role in collagen formation, deposition of proteoglycans and hyaluronan and the composition of connective tissue, which is thought to play a role in the developing of MMVD and thus these genes are good candidate genes for the development of MMVD[34].

<u>Breeding programs</u>

Since the highly heritability of MMVD a breeding program would be helpful to reduce the prevalence and early onset of MMVD[33]. In 1996 the Cavalier King Charles Spaniel Club of the United Kingdom held a seminar from which breeding guidelines were developed (Figure 4)[36]. In various countries derivations from 'The MMVD Breeding Protocol' have been designed to reduce the prevalence of MMVD in CKCS[35].

The MMVD Breeding Protocol:

- Every breeding Cavalier King Charles Spaniel should be examined annually by a board certified veterinary cardiologist.
- Do not breed any Cavalier who is diagnosed with an MMVD murmur under the age of 5 years.
- Do not breed any CKCS before age 2.5 years.
- Do not breed any Cavalier under the age of 5 years, unless its parents' hearts were free of MMVD murmurs by age 5 years.

Figure 4. The MMVD Breeding Protocol[35].

Since the introduction of the breeding programs, various studies have been done to determine the effects of the programs[36-39]. In the United Kingdom a significance age increase of murmur incidence associated with MMVD was seen after the application of the MMVD Breeding Protocol in 1996[36]. However, this benefit was only seen in a subgroup because participation in the breeding program by breeders was voluntary and compliance of breeders with this voluntary scheme was poor[36]. In Sweden, a study was done between dogs that were born before the breeding program has started and dogs that were born 2 years after the introduction of the breeding program in 2001[37]. In this program, dogs are not allowed to breed if their parents have a heart murmur before the age of 4. The dogs need a heart auscultation without murmurs within 8 months before mating and are not allowed to breed before the age of 4. However, dogs at an age of 24 months are allowed to breed if the dog and its parents have no murmur and male dogs are allowed to breed without further heart evaluation if their heart auscultation have no murmurs at an age of 7. No decrease of the prevalence of MMVD was seen and they stated that the breeding program might have slow effect on disease prevalence over a longer period[37]. Also Denmark introduced their breeding program in 2001, however, they studied the consequences over an 8-10 year period and the program was different than in Sweden[38,39]. Dogs with an age of 1.5 or older that have a good cardiac health are allowed to breed until the age of 4. After the age of 4 re-examination has to be done to allow further breeding and since 2007, male dogs have to do an additional re-examination at the age of 6. Since 2007, the criteria of the examination are that the murmur can have a maximum of 1 combined with a maximum mitral valve prolapse grade of 2 or a grade 2 murmur combined with a mitral valve prolapse grade of 1 or less. Before 2007, the maximum grade of mitral valve prolapse was 3 combined with a murmur grade of 1 or less. However, physiological flow murmurs are accepted. This study showed a 73% decreased risk of a murmur caused by MMVD using the breeding program in CKCS. A significant decrease was only seen in dogs with parents that were both approved by the breeding program[38,39]. In conclusion, a mandatory breeding program is recommended for CKCS[36,38,39].

Current situation in Australia

In Australia yearly auscultation of CKCS is encouraged, however voluntarily. It is unknown which percentage of the breeding population is tested yearly, and until which age.

1.2 Cardiac auscultation in dogs

Cardiac auscultation is a quick, non-invasive and inexpensive method to perform[20]. Auscultation should be performed in a quiet environment while background noises can obscure the soft heart sounds[22]. Also respiratory noises can disrupt normal heart sound recognition. Therefore, the animal's nares can be held closed shortly when auscultating[22].

Valve areas

It is important to listen to the thorax when heart disease is suspected[22]. There are four traditional areas of auscultation: the mitral, aortic, pulmonic and tricuspid valve areas, as shown in figure 5[40-42]. Auscultation usually begins at the mitral valve area at the left 5th intercostal space and then the pulmonic valve area is auscultated at the 3rd intercostal space on the left hemithorax[22]. The aortic valve area is placed more dorsal at the 4th intercostal space on the left side and at last the tricuspid valve area is listened to at the 3rd to 5th intercostal space on the right side of the thorax[22]. In small dogs and cats the pulmonic and aortic regions overlap, making their separation difficult[22].

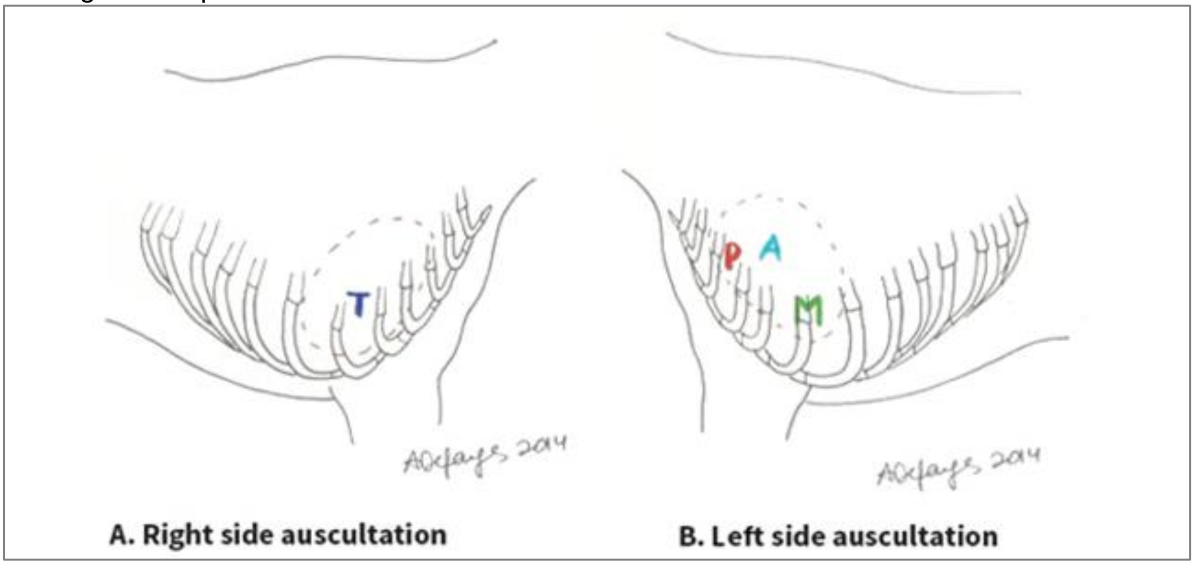

Figure 5. Approximate location of the four valve areas in auscultation in the dog. A. Right side auscultation, T=Tricuspid valve area; B. Left side auscultation, P=Pulmonic valve area, A=Aortic valve area, M=Mitral valve area[40].

Normal heart sounds

In healthy dogs the first and second heart tone are heard as a lub-dub[22,43].

<u>The first heart sound</u>

The first heart sound (S_1) occurs at the onset of ventricular systole and is associated with the palpable apex beat and AV valve closure[41]. S_1 is louder, longer and lower pitched than the second heart sound (S_2)[41]. Therefore, it is best heard at the mitral and tricuspid valve areas[22]. Further, early ventricular muscle contraction, opening of the semilunar valves and rapid acceleration of blood in the ventricles contribute to the sound of S_1[41]. S_1 can have an increased intensity in young, thin animals, in dogs with acquired valvular diseases causing mitral insufficiency (for example MMVD) and in animals with high sympathetic tone, tachycardia, systemic hypertension or anemia[22]. A decreased intensity of S_1 is heard in obese dogs and in animals with pleural or pericardial effusion, diaphragmatic hernia, emphysema, shock, decreased myocardial contractility or prolonged P-R intervals[22].

<u>The second heart sound</u>

The second heart sound (S_2) occurs at the end of ventricular systole and originates from the closing semilunar valves[22]. Contributing vibrations include early muscular relaxation, blood vibration in the great vessels[44]. S_2 is heard as a single sound although the aortic valves close earlier than the pulmonic valves and S_2 is best heard at the aortic and pulmonic valve areas[41,42].

Heart murmurs
A murmur originates from turbulent blood flow caused by disruption of the normal, quiet, laminar flow[22]. Reynold's number describes the relationship of cardiac murmurs to vessel size, flow velocity and blood viscosity:
Reynold's number = (Radius x velocity x density) / Viscosity[22]

<u>The characterization of heart murmurs</u>

Timing
Murmurs can be divided into systolic, diastolic or continuous murmurs based on the timing during the cardiac cycle[22,40]. Systolic murmurs begin with or after S_1 and end with or before S_2. Diastolic murmurs begin with or after S_2 and end with or before S_1[22]. Further modification can be made by using terms such as holo-, pan-, proto-, meso-, tele- and pre- systolic/diastolic[22].

Location
The valve area where the murmur is heard loudest is called the punctum maximum and most of the times that valve is affected[22,40].

Intensity
When there is a murmur, the intensity of the murmur is graded in all valve areas using a classification system as showed in Table 1[22,40].

Table 1. Classification of heart murmurs based on intensity[45]).

Intensity	Grades	Description
Low intensity	Grade 1	A low intensity murmur heard only in quiet surroundings after careful auscultation over a localized cardiac area.
	Grade 2	A low intensity murmur heard immediately when the stethoscope is placed over the point of maximal intensity.
Moderate intensity	Grade 3	A murmur of moderate intensity.
	Grade 4	A high intensity murmur that can be auscultated over several areas without any palpable precordial thrill.
Severe intensity	Grade 5	A high intensity murmur with a precordial thrill.
	Grade 6	A high intensity murmur with a palpable thrill that may even be heard when the stethoscope is slightly lifted off the chest wall.

Shape
The shape of the murmur corresponds to the shape on the phonocardiogram. Murmurs with an equal intensity throughout their duration are called plateau or band-shaped, murmurs with decreasing intensity are called decrescendo and murmurs with increasing intensity crescendo[22]. Diamond-shaped or crescendo-decrescendo murmurs first build to a peak and then gradually diminish[22].

Frequency or Pitch
Murmurs can be high-, medium- or low-pitched or can have a mixed frequency[22]. Sometimes murmurs are described as harsh, blowing or musical[22].

Radiation
Murmurs radiate in the direction of blood flow responsible for the murmur and the pattern of radiation is important in some lesions because the murmur can have a punctum maximum in another place than the area of the affected valve[22].

The stethoscope
Auscultation is performed by a stethoscope and there are different stethoscopes varying in quality of design and sound transmission[22]. The stethoscope should have comfortable ear pieces that fit the ear canals and it should also have a clearly transmission of both normal and

abnormal heart and lung sounds[22,40]. Both single and double tubing transmit the sounds accurately although, double tubing should be superior in theory[22]. The optimal diameter of the tubing is 3 mm and the length should be as short as practical[22]. In most models the chest piece contains a bell and a diaphragm to accentuate both high and low-frequency vibrations[22,40]. When the bell is placed gently on the thorax, the low-frequency sounds are accentuated and when it is placed firmly, the high-frequency sounds are more accentuated[22]. The diaphragm transmits a wider band of frequencies especially higher-frequency sounds[22,40]. If the diaphragm is large, it gathers more sounds of a wider area and thus a large diaphragm is more sensitive than a small one[22]. However, small diaphragms are used to get a better sound localization[22].

Although standard auscultation is very useful, there are some disadvantages[46]. Firstly, the grading of the murmurs is somewhat subjective and veterinarians with different observer experience grade a murmur differently. The level of agreement between a high experienced observer and another observer decreases with a decreasing level of experience. In comparison with phonocardiography the specificity of observers with different experience is high, but the sensitivity decreases with a decreased level of experience. Furthermore, the detection of murmurs is influenced by the difficulty of auscultating the dog and the level of stress during auscultation[46]. Lastly, when auscultating a dog several times over its lifespan, without recording the heart sounds/murmurs, it can be difficult to draw conclusion of progression of murmur intensity. For all these situations, electronic stethoscopes might be of benefit over standard auscultation.

1.2.1 Potential benefits of using Stethee in auscultation

Stethee

Figure 6. The Stethee device.

Stethee (figure 6) is a wireless electronic stethoscope designed and developed by M3DICINE Pty Ltd (Brisbane, Australia)[16,47]. It has an audible bandwidth of 20 to 20,000 Hertz which is a lot wider than the bandwidth of under 1,000 Hertz of a traditional stethoscope[16,47]. This could provide a more accurate representation of the heart sounds. Also, there is no impact of resonance caused by the tube components because the stethoscope is wireless[47]. The heart sounds can be streamed to a phone or headset via Bluetooth[48]. Also, the heartbeat is visualised by a LED ring. The colour of the ring shows whether the heartbeat is within the references or not. Stethee also contains a vibration mechanism, so the heartbeat can be felt by the user of Stethee[48]. Furthermore, the heart sounds can be recorded by Stethee and stored in the cloud via the Stethee Vet App. Figure 7 shows a representation of the Stethee Vet App of a normal heart sound and a heart sound with a murmur.

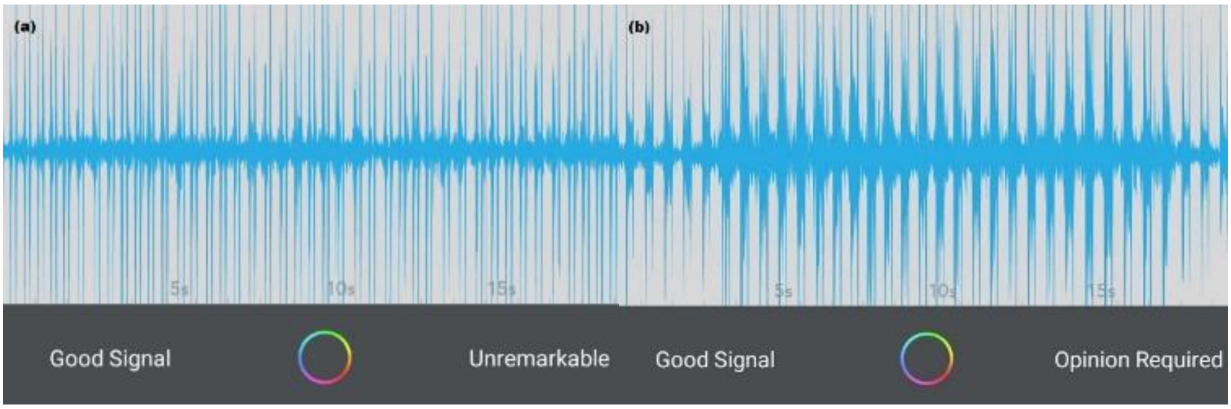

Figure 7. A representation of the Stethee Vet App. (a) recording of a normal heart sound; (b) recording of a heart sound with a systolic heart murmur.

Artificial Intelligence analysis

M3DICINE Pty Ltd (Brisbane, Australia) is developing a system for heart sound classification of recordings captured by Stethee® called Aida[47,49]. It detects S_1, S_2, systole and diastole periods in the cardiac cycle and is able to detect heart murmurs[47,49].

Feature Extraction

First, the system extracts Mel-frequency filterbank features from a digital audio recording to capture the fundamental frequencies of S1 and S2 sounds, while neglecting noisier bands with less relevant information[47].

Feature Projection

The extracted features still contain more information than necessary to discriminate between “Normal” and “Murmur” recordings[49]. Therefore, joint factor analysis (JFA) is applied using the ground-truth labels provided by the veterinary physician to achieve dimensionality reduction and a form of feature projection that maximises the discriminatory features for automatic Normal/Murmur diagnosis[47,49].

Classification

These projected features are used to train a feed-forward deep neural network (DNN) with 5 hidden layers to distinguish “Normal” and “Murmur” recordings[47,49]. Now, the DNN is able to classify audio recordings of an animal’s heart captured with Stethee®[49].

Potential benefits

Stethee is wireless, which allows the pet owner to place the Stethee themselves on their animal while the vet is performing auscultation from a distance[16]. It is also able to store recorded heart sounds in the cloud and the recordings can also be shared via the cloud. This enables the veterinarian to get information about the heart sounds of an animal in a familiar and calm environment and is perfect for animals that are afraid or excited to go to the veterinarian. It also enables the veterinarian to compare murmur intensity, and thus to assess disease severity in animals with MMMVD, if an animal is auscultated regularly. Moreover, if Aida is accurate, pet owners can use Stethee to check their pet’s heart sounds without going to the veterinarian.

2. Aim of the study

The aim of the study is to compare the classification system (Aida) in recordings captured with Stethee to the normal auscultation technique by a cardiologist and a less experienced observer on the presence or absence of a heart murmur to define the accuracy of Aida.

3. Material and Methods

3.1 Experiments

Experiment 1: Comparison of auscultation by an experienced observer and Stethee

Experimental design
132 dogs presented for cardiac evaluation were auscultated by an experienced observer (a veterinary cardiologist) and recorded by another observer with Stethee. First, the microchip number of the animal was estimated with a microchip reader for identification. Then, the animals were first auscultated by the cardiologist and directly after, they were recorded with Stethee. The diagnoses of the cardiologist were documented and the recordings of Stethee were sent to M3DICINE Pty Ltd to be analysed by Aida, blinded to the results of the cardiologist.

Animals
132 dogs of different ages between 0 and 16 years old with a mean age of 4,54 were used. The animals (51 males and 81 females) were presented for cardiac assessment and belonged to owners living in or near Sydney, Australia.

Sub-experiment: Comparison of auscultation by an experienced observer and Stethee in Cavalier King Charles Spaniels

Experimental design
Of the 132 dogs from experiment 1 we isolated the Cavalier King Charles Spaniels (CKCS).

Animals
91 CKCS were used, aging from 0 to 13 years old with a mean age of 5,90.

Experiment 2: Comparison of auscultation by an experienced observer and an inexperienced observer

Experimental design
86 CKCS presented for cardiac evaluation in Sydney were auscultated by an experienced observer (a veterinary cardiologist) and an inexperienced observer (a veterinary student). First, the microchip number of the dog was estimated with a microchip reader for identification. Then the dogs were auscultated in turns by both observers. The observers were unaware of the diagnoses made by the other observer and they have documented their diagnoses independently.

Animals
86 CKCS of different ages between 0 and 12 years old with a mean age of 3,01 were used. The dogs (27 males and 59 females) were presented for cardiac auscultation, mostly for breeding purposes, and belonged to owners living in or near Sydney, Australia.

3.2 Protocols

Cardiac auscultation method
For auscultating the dogs, we let them stand on a table in a quiet environment. The auscultating person was standing diagonally behind the animal and placed both hands on the animal's chest to feel for a precordial thrill. Then the stethoscope (3M™ Littmann® Classic II S.E.) was placed on the different valve areas on the animal's chest to listen for murmurs. When the animal was panting, the nares were held closed to reduce the respiratory noises.

Cardiac recording with Stethee®
As with the normal auscultation, the animals were put on the table. The animals were held by one person to keep the animals standing still and to keep them from panting. The second person placed Stethee on the 5th intercostal space on the left side of the animal's chest and verified if the heartbeats could be heard through the headphones. Then the recording of 20 seconds was started. During the recordings we continued listening to the heartbeats and afterwards we checked for background noises. If there were too many background noises, a new recording was made to optimize the quality of all the recordings.

Analysing of the recordings
The recordings were analysed by Aida developed by M3DICINE Pty Ltd (Brisbane, Australia).

3.3 Statistical analysis

The degree of agreement between the two observers and between the experienced observer and Aida using Stethee® was assessed by calculating the percentage of identically diagnosed animals. Also, a kappa value was calculated to estimate the actual to potential agreement beyond chance[50]. Furthermore, the specificity, sensitivity, positive predictive value (PPV) and negative predictive value (NPV) of the inexperienced observer and of Aida were calculated. The Fisher's exact test was used to evaluate whether the murmur gradings made by the two observers were correlated and whether the murmur gradings made by the experienced observer and Aida were correlated. A P-value of <0.05 was considered as significant.

4. Results

Overview of findings

Experiment 1
40.9 % of the animals had a murmur according to the cardiologist varying from grade 1 to 6. Table 2 shows the distribution of the murmur grades over the dogs. 87.0% of the animals with a murmur suffered from MMVD. Other heart diseases the animals suffered from, and their prevalence are shown in table 3. 5.6% of the animals with a murmur had a physiological murmur and thus were not affected by a heart disease.

Table 2. Distribution of the murmur grades over the animals used in experiment 1

Murmur grades	Quantity	Percentage
0	78	59.1%
Low intensity 1-2	17	12.9%
Moderate intensity 3-4	17	12.9%
Severe intensity 5-6	20	15.2%
Total	132	100%

Table 3. Distribution of the heart diseases found in the animals with a murmur used in experiment 1

Diseases	Quantity	Percentage
Myxomatous mitral valve disease	47	87.0%
Dilated cardiomyopathy	2	3.7%
PDA	1	1.9%
Pulmonary hypertension	1	1.9%
Physiological murmur	3	5.6%
Total	54	100%

The experienced observer found 54 animals with a murmur varying from grade 1 to 6 and 78 without a murmur, while the Artificial Intelligence system of Stethee (Aida) detected a murmur in 59 of the animals (Figure 8a).

Sub-experiment
33.0% of the dogs (29 males and 62 females) had a murmur varying from grade 1 to 6. Table 4 shows the distribution of the murmur grades over the dogs. All dogs with a murmur suffered from MMVD.

Table 4. Distribution of the murmur grades over the dogs used in the sub-experiment

Murmur grades	Quantity	Percentage
0	61	67.0 %
Low intensity	12	13.2 %
Moderate intensity	9	9.9%
High intensity	9	9.9%
Total	91	100 %

Both the experienced observer and Aida found 30 dogs with a murmur and 61 without. However, there were 2 false negative and 2 false positive outcomes. Figure 8b gives an overview of these findings.

Experiment 2
29.1% of the dogs had a murmur varying from grade 1 to 5. Table 5 shows the distribution of the murmur grades over the dogs. All dogs with a murmur suffered from MMVD.

Table 5. Distribution of the murmur grades over the dogs used in experiment 2

Murmur grades	Quantity	Percentage
0	61	70.9 %
Low intensity	11	12.8 %
Moderate intensity	8	9.3%
High intensity	6	7.0%
Total	86	100 %

The experienced observer found 25 dogs without a murmur and 61 with a murmur varying from grade 1 to grade 5, while the inexperienced observer only detected 21 dogs with a murmur (Figure 8c).

(a)

		Experienced observer		
		Murmur	No murmur	Total
Stethee	Murmur	49	10	59
	No murmur	5	68	73
	Total	54	78	132

(b)

		Experienced observer		
		Murmur	No murmur	Total
Stethee	Murmur	28	2	30
	No murmur	2	59	61
	Total	30	61	91

(c)

		Experienced observer		
		Murmur	No murmur	Total
Inexperienced observer	Murmur	18	3	21
	No murmur	7	58	65
	Total	25	61	86

Figure 8. Overview of murmur detection in dogs by Stethee and an inexperienced observer compared to the murmur detection by an experienced observer. (a) Experiment 1; (b) Sub-experiment; (c) Experiment 2

Interobserver agreements

Table 6 shows the percentages of agreement, kappa value, specificity, sensitivity, positive predictive value (PPV) and negative predictive value (NPV) of all three experiments. The agreement between the experienced observer and Aida was 89% with a kappa value of 0.77 in experiment 1, while the agreement in the sub-experiment was significantly higher (96% with a kappa value of 0.90). Also the specificity, sensitivity, PPV and NPV were higher in the sub-experiment (Table 7). The interobserver agreement in experiment 2 was 88% with a kappa value of 0.70. All three experiments show strong correlations between the observers ($P<0.05$). Figure 9 shows the levels of agreement categorized by the intensity of the heart murmurs. Figure 9a and 9b show steady levels of agreement overall while 8c shows an increase in agreement when the intensity of the murmur is higher. Moreover, the agreement is 100% in the severe murmurs, while only 45.5% of the low intensity murmurs are picked up by the inexperienced observer.

Table 6. Percentages of agreement, kappa value, specificity, sensitivity, positive predictive value (PPV) and negative predictive value (NPV)

	Agreement	**Kappa**	**Specificity**	**Sensitivity**	**PPV**	**NPV**
Experiment 1	89%	77%	87%	91%	83%	93%
Sub-experiment	96%	90%	97%	93%	93%	97%
Experiment 2	88%	70%	95%	72%	86%	89%

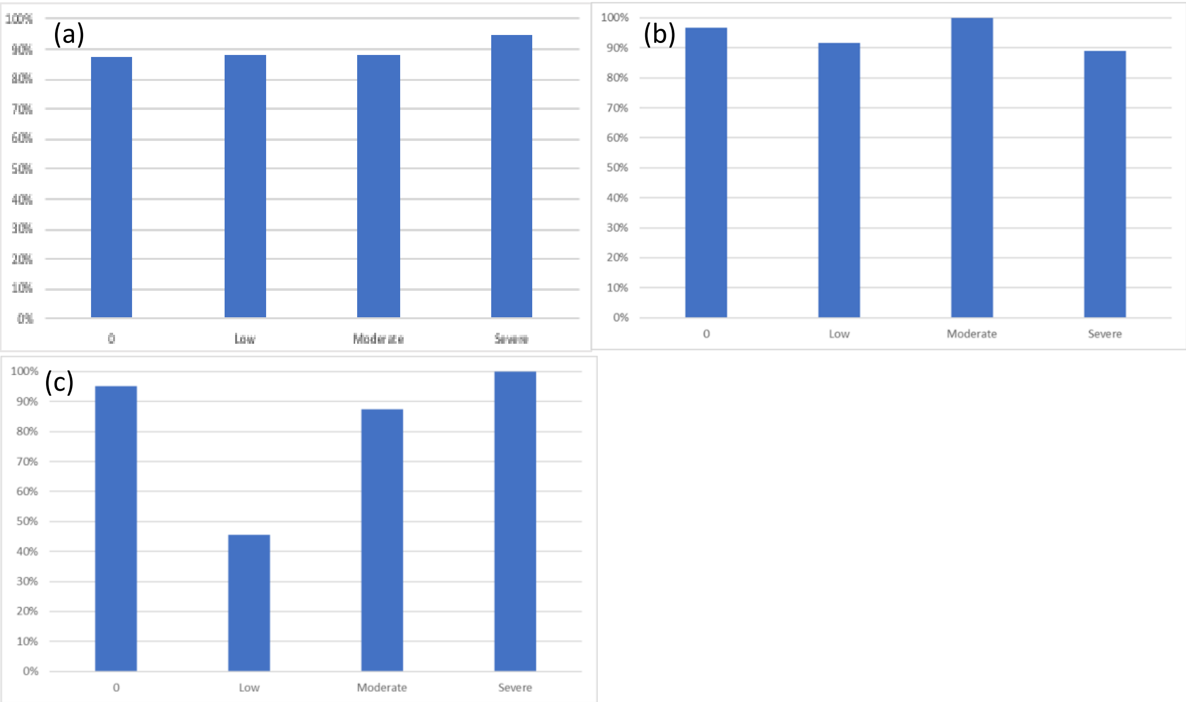

Figure 9. Levels of agreement, whether a murmur was present or not, categorized by the intensity of the heart murmur. (a) Experiment 1; (b) Sub-experiment; (c) Experiment 2

5. Discussion

Evaluation of the results

The fraction of animals with a murmur varied from 29.1% to 43.3% in the present study, which is a high prevalence. This can be explained by the following factors. Firstly, most of the animals that were presented to the veterinary clinic were referred to the cardiologist because the regular veterinarian could hear a murmur or thought that the animal might have a heart disease because of their symptoms. Furthermore, the majority of the animals that were used for this study were Cavalier King Charles Spaniels (CKCS). This breed is known for a high prevalence and early onset of myxomatous mitral valve disease (MMVD)[19,27-30]. These factors make the population of this study more susceptible of a higher prevalence of heart murmurs, which was convenient for this study to compare auscultation findings.

Thereby, a small percentage of the healthy animals has a physiological heart murmur[51]. These murmurs can be induced by stress and an increased heart rate[24,46]. The increased heart rate indicates a sympathetic stimulation of the heart and thus a more vigorous contraction of the heart[52]. This causes an increase in the velocity and flow rate of the blood, which can cause turbulence and thus a murmur[52]. In the present study there were 6 animals that were presented with a physiological murmur.

The results show that an inexperienced observer can pick up all the severe murmurs (100% agreement) while Aida (the Artificial Intelligence system of Stethee) diagnosed some of the severe murmurs as a heart sound without a murmur. This can be caused by the precordial thrill that can be felt on the chest when the murmur is severe[45]. Stethee cannot feel the thrill and is thus rather inclined to diagnose a severe murmur as a normal heart sound. Secondly, it is stated that auscultatory findings in severe mitral regurgitation are less sensitive to several factors, such as circulatory status, observer experience and level of difficulty involved in auscultation, than in mild and moderate mitral regurgitation[46]. Thus, inexperienced observers are inclined to diagnose severe murmurs more often correctly than low intensity murmurs. Aida is significantly better in diagnosing low intensity murmurs and may therefore be very helpful for veterinarians that have little experience in auscultating and also for screening of mild disease.

Aida misdiagnosed 7 animals with a murmur and 13 animals with a normal heart sound according to the cardiologist. False negative results can be explained by background noises that mask the sound of the murmur. Furthermore, murmurs can be intermittent and dynamic. When the heart rate decreases, the velocity and flow rate of the blood decrease and murmurs might disappear[46,48,52]. The false positive diagnoses can be mostly explained by background noises. Noises like breathing, panting, purring, snoring and other background noises can be interpreted as a murmur by Aida and cause the system to label the recording as one with a murmur.

Limitations of the study

The interobserver agreement in diagnosing the presence or absence of left sided murmurs was 88% in the present study (Table 6). However, only one inexperienced observer was compared with one experienced observer, which questions the reliability of the study to some extent[50]. Though, a similar study was performed by Pedersen et al. in 1999 which showed a comparable interobserver agreement of 65%-88%[46]. They also showed that their most experienced observer had an agreement of 91% compared to phonocardiography and 89% compared with echocardiography[46]. In the present study, we used a veterinary cardiologist as the golden standard instead of phonocardiography, which also influences the reliability of the study.

As already stated, mostly CKCS were used in this study. Other than that, they have a high prevalence and early onset of MMVD[19,27-30], they are easy to auscultate. CKCS are small-breed dogs that are narrow chested, which causes the heart to be superficial and easy to auscultate. When auscultating a CKCS, the heartbeat is very clear and murmurs are easy to pick up. In other breeds, such as an English Bulldog, the chest is barrel-shaped which causes the heart to be deeper in the chest and more difficult to auscultate. This may have been influencing the levels of agreement of both experiments.
Furthermore, the present study was not completely blinded which can have caused an observer bias. Also, some of the recordings that were used to train Aida were also used as test recordings, which can also have caused some bias although the system does not memorise the recordings that go through the system.

Research suggestions
Further research with the device and Aida should be done in dogs and cats with different heart diseases and different heart murmurs since this study mostly involved CKCS with MMVD and only included systolic murmurs.
It would also be interesting to compare Aida to diagnoses made with phonocardiography instead of an experienced auscultator.
Until now, Aida only differs between the presence or absence of a murmur. Stethee will be more of use when the analysing system can also implement the different murmur grades and murmur grade progression, since the murmur grade often correlates with the severity of a disease[8,23]. When an animal is auscultated regularly, the progression of the disease can be monitored and eventually the prognosis of individual patients might be implemented in Aida.

Evaluation of the use of Stethee
We have used the Stethee device and Stethee Vet App for a couple of months to perform this study. The Stethee device and App are very easy to understand. With a simple double-click, the device turns on and can connect to the phone via Bluetooth. The recordings can be stored in the cloud, which is very convenient for sharing the recordings. The battery of the Stethee device is very strong and can easily last for a day when using it intensively. However, when recording and storing the recordings, the App uses a lot of battery and when using the App constantly the phone can get overheated which causes the App to stop. Furthermore, sometimes the recordings were not stored correctly and disappeared from the App. This might be due to a disconnection between the Stethee device and the phone. However, the overall experience with the use of Stethee was very positive. It is an easy way to store recordings of heart sounds and it can be very convenient for monitoring individuals over a longer period since it enables veterinarians to compare murmur intensity, and thus to assess disease severity in dogs with MMVD, if an animal is auscultated regularly.

6. Conclusion

Aida is found to be more accurate than an inexperienced observer in diagnosing low intensity murmurs and can therefore be a helpful tool for veterinarians that have little experience in auscultating. However, severe intensity murmurs are better diagnosed by the inexperienced observer, probably due to the precordial thrill. Although more research and developing has to be done to optimize the accuracy of Aida, it is a very promising Artificial Intelligence analysing system.

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