TITLE: Prevalence and diagnostic characteristics of non-clinical mitral regurgitation murmurs in North American Whippets

AUTHORS: R.L. Stepien, H.B. Kellihan, V. Luis Fuentes

JOURNAL: Journal of Veterinary Cardiology

PUBLISHER: Elsevier, for the European Society of Veterinary Cardiology

PUBLICATION DATE: 27 June 2017 (online)

DOI: 10.1016/j.jvc.2017.04.004

Prevalence and diagnostic characteristics of non-clinical mitral regurgitation murmurs in North American whippets

Rebecca L. Stepien DVM, MS[a*]

Heidi B. Kellihan DVM[a]

Virginia Luis Fuentes VetMB, PhD[b]

[a]Department of Medical Sciences, University of Wisconsin School of Veterinary Medicine, 2015 Linden Drive, Madison, WI, 53706, USA

[b]Department of Clinical Science and Services, Royal Veterinary College, Hawkshead Lane, North Mymms, Hatfield, Hertfordshire AL9 7TA, UK

*Corresponding author: Rebecca L. Stepien, rebecca.stepien@wisc.edu

Running Head: Mitral regurgitation in whippets

A portion of this information was previously presented: Stepien RL, Kellihan H, Luis Fuentes V. Accuracy of auscultation alone to identify mitral insufficiency in adult whippets (abstract). J Vet Intern Med 2011;25:1480.

Acknowledgements:

This research was partially supported by The Whippet Health Foundation and The American Kennel Club. Lisa Wenholz CVT provided organizational and technical assistance.

Abstract

Objectives: Assess the prevalence of functional ejection murmurs and murmurs of mitral regurgitation (MR) due to myxomatous mitral valve disease (MMVD) in healthy whippets; assess the diagnostic value of auscultation to detect MR; and investigate the relationship between age and presence of echocardiographically-documented MR (MR_{echo}).

Animals: 200 healthy client-owned whippets, recruited at national shows between 2005-2009.

Methods: Cross-sectional study. Dogs were examined by auscultation and Doppler-echocardiography by two independent examiners and results compared. Prevalence of murmurs types and of MR_{echo} were calculated and correlated to age. Accuracy of auscultation to predict MR_{echo} was calculated.

Results: 185/200 (93%) of dogs had left-sided systolic heart murmurs. Left apical systolic murmurs (L_{apic}) were detected in 57/200 (29%); left basilar systolic murmurs (L_{base}) in 128/200 (64%). 76/200 (38%) dogs had MR_{echo}. Prevalence MR_{echo} was correlated with age ($r=0.96$, $p=0.0028$). MR_{echo} was present in 12/78 (15%) of dogs ≤ 2 years of age and in 59% of dogs at 7-8 years old. Detection of L_{apic} predicted MR_{echo} with Se 65%, Sp 94%, PPV 86% and NPV 81%; and accuracy improved when only dogs with more intense L_{apic} (grade ≥ 3/6) were considered.

Conclusions: Systolic murmurs are common in North American whippets and this breed exhibits a high prevalence of MR_{echo}, which may be documented at a relatively early age. Whippets with non-clinical MR_{echo} may not be identifiable by auscultation alone; echocardiographic examination may be required to exclude a diagnosis of MR. Detection of L_{apic} grade ≥ 3/6 increases accuracy of MR_{echo} prediction in this population.

Key Words

Dogs, functional murmur, athletic, physiologic murmur, myxomatous mitral valve disease

Abbreviations

L_{apic}	left apical systolic murmur
L_{base}	left basilar systolic murmur
LA	left atrium
MMVD	myxomatous mitral valve disease
MR	mitral valve regurgitation
MR_{echo}	mitral valve regurgitation detected by echocardiography
MV	mitral valve

Introduction

Adult onset myxomatous mitral valvular heart disease (MMVD) resulting in valvular regurgitation is the most common form of heart disease in dogs and may account for up to 75-80% of canine heart disease cases[1]. This type of heart disease is more prevalent in some breeds, suggesting a heritable component. Genetic tests are currently lacking in these breeds, and "screening" for this adult onset disease in breeding animals at risk is currently focused on detection of suggestive heart murmurs by auscultation, sometimes with additional testing by echocardiography or Doppler-echocardiography[1-4].

"Athletic" or "functional" heart murmurs (also called "flow", "physiologic", non-pathological" or "innocent" murmurs) are associated with ejection of blood through normal valves and vessels. These murmurs are noted to be more common in healthy sighthounds and in other athletic breeds in some circumstances[c][5-7]. Functional murmurs are typically loudest over the left thorax, and may be confused with murmurs of mitral regurgitation (MR)[8]. As a breed, whippets are noted to be both at increased risk of MMVD[9] and to commonly have functional heart murmurs[10].

The aims of this prospective cross-sectional study were to assess the prevalence of functional ejection murmurs and of MR due to MMVD in a population of healthy North American whippets, to assess the diagnostic value of auscultation to detect MR in this population and to investigate the relationship between age and presence of MR.

Animals, Materials and Methods

Dogs were prospectively recruited from a healthy population attending the American Whippet Club National Specialty between 2005 and 2009. Dogs were submitted for examination by their owners and enrolled without regard to age, breeding status or athletic condition. Dogs with known systemic disease conditions were excluded. All dogs were without clinical signs of heart disease at the time of examination, based on owner history. Each dog contributed data from a single examination. This study was approved by the University of Wisconsin School of Veterinary Medicine Animal Care and Use Committee.

Physical Examination

Cardiac auscultation was performed by one observer (RLS) blinded to any previous cardiac information known by the owner. Dogs stood at rest with their owners/handlers for auscultation, during which heart rate and presence of any heart murmurs were recorded. The most prominent heart murmur per dog was used for analysis, and murmurs were characterized by timing (systolic vs. diastolic), intensity (grade 1-6 with grade 1 as the lowest detectable intensity murmur and grade 6 as a murmur audible without a stethoscope) and point of maximal intensity (right or left heart base, right or left apex). Auscultatory findings were withheld from the echocardiographer until after the echocardiographic examination.

Echocardiographic Examination

All dogs had echocardiograms recorded[d] by a single operator (VLF). Two-dimensional, M-mode, color- and spectral Doppler images and cine loops were stored on optical discs for later off-line analysis. Echocardiograms were recorded with the dogs gently restrained in right and left lateral recumbency. Images were recorded from the dependent side of the dog, using typical recommended views[11]. Complete echocardiographic examinations were recorded to exclude concurrent anatomic cardiac disease, using two-dimensional, spectral and color-Doppler modalities. All dogs had continuous electrocardiographic tracings during echocardiographic examination. All dogs were imaged in the same sequence, with particular attention to color-flow Doppler images of the mitral valve (MV) and left atrium (LA) from the right parasternal long axis view and 2- or 4 chamber left apical views to identify any MR jets.

Diagnosis of Mitral Regurgitation

Dogs were diagnosed as having echocardiographically-documented mitral regurgitation (MR_{echo}) if an eccentric systolic jet or multiple systolic jets were documented within the LA in the right parasternal long axis 4 chamber view or left apical 3 or 4 chamber views using color Doppler mapping. Single, narrow, central regurgitation jets that extended to less than approximately 10% of the LA were not classified as MR_{echo}. Presence or absence of MR_{echo} was recorded, but no attempt to quantify MV structural changes or MR_{echo} severity was included in this study. The echocardiographic images were reviewed at a separate time point and without knowledge of the dog's identity by a single observer (RLS) blinded to the dog's identity and auscultation results at the time of echocardiographic analysis.

Statistics

Descriptive statistics were used to characterize the total population and a subset representing animals in a breeding age population. Values are presented as median [range]. Age was recorded in months, and reported in years, with < 24 months of age categorized as "1 year old", ≥ 24 months but < 36 months categorized as "2 years old", up to the "12 years old" group. Dogs ≥ 13 years were grouped due to low numbers (13 years, n=4, 14 years, n=3, 15 years, n=3). The prevalence of MR_{echo} was calculated as the number of dogs with MR_{echo} as a proportion of the total number of dogs and by 2-year age grouping. Sensitivity, specificity, positive and negative predictive value and likelihood ratio for the presence of a left apical systolic murmur to identify MR_{echo} and the effect of murmur intensity on these parameters were calculated. Non-parametric test methods were used for all comparisons (Fisher's exact test or Mann-Whitney U test between groups) and data is presented as median [range]. Spearman rank correlation was used to test the relationship between age (2-year groups) and prevalence of MR_{echo}. P values < 0.05 were considered significant.

Results

Two hundred dogs had complete information available for analyses. Median age of all dogs was 4 [1-15] years and median weight was 15 [9-22] kgs. One hundred four dogs out of 200 (52%) were intact or spayed females. Left-sided systolic heart murmurs were detected in 185/200 (92.5%) of dogs examined and no murmur was heard in 15 dogs (7.5%). Left apical systolic murmurs (L_{apic}) were detected in 57/200 (29% overall, 31%

of dogs with murmurs) of dogs and left basilar systolic murmurs (L_{base}) were detected in 128/200 (64% overall, 69% of dogs with murmurs). Median intensity of L_{apic} was 3/6 [1-6/6] and median intensity of L_{base} was 2/6 [1-4/6].

Seventy-six (38%) dogs in this population had MR_{echo} according to the echocardiographic criteria used in this study. Dogs with MR_{echo} were older (8 [1-15] years) than dogs without MR_{echo} (4 [1-15] years, $p<0.0001$, Figure 1). Male/neutered male dogs were more likely to have MR_{echo}, with 50/96 (46%) male dogs affected vs. 32/104 (31%) female dogs ($p=0.03$), but there was no difference in median age between males (4 [1-14] years) and females (2 [1-15] years, $p= 0.043$). Prevalence of MR_{echo} was closely correlated with age by 2 year groups ($r=0.96$, $p=0.0028$, Figure 2); MR_{echo} was present in 15% of dogs ≤ 2 years of age, in 59% of 7-8 year old dogs and in 80% of all dogs aged 13 years or older.

Detection of L_{apic} of any intensity in the population studied (n=200) predicted the presence of MR_{echo} with sensitivity of 65%, specificity of 94%, positive predictive value (PPV) of 86%, negative predictive value (NPV) of 81% and likelihood ratio (LR) of 10.0. Overall concordance of findings (auscultation categorized dogs correctly as either "MR_{echo}" or "no MR_{echo}") was 83%. Fourteen of the 15 dogs (93%) with no murmur were correctly categorized as "no MR_{echo}" by auscultation. Higher intensity L_{apic} (≥ grade 3/6, n=41) predicted MR_{echo} with sensitivity 93%, specificity 84%, PPV 93%, NPV 84% and LR 5.9. Any murmur of greater intensity (≥ grade 3/6) was more likely to be an accurate

detector of presence or absence of MR_{echo}; when all dogs with L_{apic} or L_{base} ≥ grade 3/6 were considered (n=61), concordance improved to 90%.

In order to assess test characteristics in a population likely to be presented for pre-breeding examination, dogs of typical breeding age (2-5 years, n=85) were considered as a subset. Median age in this group was 3 (range: 2-5) years and 46/55 (84%) were female. All animals in this group were intact. Six dogs (7%) did not have a heart murmur detected. Median murmur grade in the remaining dogs (n=79) was grade 2/6 [1-4/6]; 70/79 (89%) of dogs with murmurs had L_{base} (2/6 [1-3/6]) and 9/79 (11%) dogs with murmurs had L_{apic} (3/6 [2-4/6]). MR_{echo} was present in 18/85 dogs (21%). When L_{apic} were compared to no murmur or L_{base} (grouped) to predict MR_{echo}, sensitivity was 35%, specificity 98%, PPV 89%, NPV 80% and LR 21.6. None of the 6 dogs with no murmur had MR_{echo}. Of the dogs with no murmur or L_{base} (n=76), auscultation correctly categorized 61/76 (80%) dogs without MR_{echo}, but miscategorized 15/76 dogs (20%) with MR_{echo}. Detection of L_{apic} correctly categorized 8/9 (89%) of dogs with MR_{echo}. Overall concordance of auscultation and echo findings in this group was 81%.

Discussion

Screening programs for myxomatous mitral valve disease depend on reliable detection of true abnormality in a population at risk, and in the case of MMVD, abnormalities may be detected via auscultation, phonocardiographic examination, Doppler-echocardiographic examination, or some combination of these[4,10,12,13]. The prevalence of the disease in the population is a crucial part of the evaluation, allowing

estimation of the positive and negative predictive value of a test as applied to a specific population, e.g. a specific breed of dog, or a specific age group. Highly sensitive detectors of MR (i.e. phonocardiography, Doppler echocardiography) may lead to overdiagnosis of MMVD when small, central MR jets are documented, but the risk associated with these jets are unknown[12,14]. Higher intensity systolic heart murmurs are more likely to accurately detect MR_{echo}[12,13], but accurate diagnosis via auscultation may be affected by presence of concurrent abnormalities[15], observer experience, environmental noise, circulatory dynamics, ease of auscultation[12], and in some types of dogs, the prevalence of ejection, or non-pathological murmurs[6,10].

The prevalence of left-sided systolic murmurs in this study population was high, with only a small proportion of examined whippets having no heart murmur detected. A previous study of 105 European whippets without MR found a prevalence of “innocent” murmurs of approximately 58%[10]. The prevalence of L_{base} murmurs (64%) in our population was comparable. The overall prevalence of left-sided heart murmurs was higher because we deliberately did not exclude dogs with MR from analysis. Other study population differences that may have had an effect include differences in population size, weight, athletic conditioning or genetic background, since our study dogs were exclusively North American and generally larger than the population previously reported by Bavagems and colleagues in a previous echocardiographic study of a European population[16]. As is the case in other sighthounds[6], the body conformation and general ease of auscultation of whippets may increase the probability of detection of soft murmurs. The finding that left basilar murmurs in this study were

generally of lower intensity than L_{apic} murmurs is in agreement with other studies of physiologic murmurs in dogs[c][6,10,12] and in people, where higher intensity murmurs are more likely to indicate disease-related than functional murmurs[15].

The prevalence of MR_{echo} in this population was 38%. Reported prevalence of MR varies by breed, but few studies have addressed the prevalence of MR documented by echocardiography in larger populations of dogs. In previous studies, prevalence has been expressed as the percentage of dogs with typical murmurs by certain ages; 50% of dachshunds had MR murmurs by 9.4 years of age[2] and in a study of Cavalier King Charles spaniels, 50% had MR murmurs by 7.5 years of age[17]. In the current study, findings were comparable; prevalence of MR_{echo} exceeded 50% (59%) in 7-8 years old dogs and 72% of 9-10 year old dogs studied had MR. Since this was a cross-sectional study and severity of MR_{echo} was not examined, the severity of the MR_{echo} and changes over time were not analyzed. The relationship between male sex and presence of MR_{echo} was significant in the general population and agrees with previous studies[9,17], but the disproportionate number of females in the breeding age population precludes comparison based on age in that group.

Median age of dogs with MR_{echo} was significantly higher than dogs without MR_{echo} and there was a significant and close relationship between age by 2-year group and prevalence MR_{echo} ($r=0.96$, $p=0.0028$). Age is correlated to presence of MR in many breeds, with some breeds prone to development of MV changes at earlier ages[2,17]. In our whippet population, 15% of 78 dogs $\leq$ 2 years old and 21% of the “breeding age”

population had MR_{echo} , suggesting that some dogs have an early onset of MR_{echo} and age alone cannot be used to exclude the possibility of MR in this breed.

Detection of any intensity of L_{apic} murmur predicted had MR_{echo} with sensitivity of 65%, specificity of 94%, positive predictive value of 86% and negative predictive value of 81%. These diagnostic test characteristics are similar to those reported in a human auscultation study, in which MR_{echo} was predicted by the detection of a typical murmur with a sensitivity of 70% and a specificity of 70%[15]. In another human study of both functional and disease-related heart murmurs, the concordance of findings for auscultation and Doppler echocardiography was 77.9%, comparable to our diagnostic concordance of 82.5%[18]. The positive predictive value of L_{apic} murmurs to detect MR_{echo} in our study improved when only more intense murmurs (grade ≥ 3/6) were analyzed, as did concordance of findings. Dogs in the breeding age group had a prevalence of ausculted murmurs (93%) that was similar to the overall prevalence, but the prevalence of L_{base} was much higher at (82%) vs. the general population. Similarly, the prevalence of MR_{echo} was lower in the breeding age population (21% vs. 38% of overall population). In this population of breeding age animals, MR_{echo} is less likely but cannot be excluded on age alone. The low prevalence of MR_{echo} in this group renders a high PPV (89%) when L_{apic} is detected. No attempt was made in this study to quantitate the severity of MR_{echo}, so the clinical importance of any MR_{echo} detected in these dogs remains unknown; it is possible that the 15/23 dogs with MR_{echo} that had L_{base} identified by auscultation (discordant findings) had MR_{echo} that was too mild to be heard by auscultation. If the intention of screening programs for breeding animals is to exclude

dog with *any* degree of MR_{echo}, Doppler-echocardiography would be required to detect all affected animals. When applied to the general population, our findings suggest that absence of any heart murmur is likely to indicate absence of MR_{echo} and left-sided systolic murmurs of ≥3/6 are likely to be localized correctly, whether they indicate the presence of MR_{echo} or the presence of a functional murmur. Further studies are necessary to investigate the severity of MR_{echo} that is clinically important or likely to reflect truly affected animals.

There are limitations in this study. The prevalence of MR_{echo} was determined in a population of clinically-normal whippets that were brought to a national show as show/performance competitors or as companions; this population may not reflect the general whippet population. This is especially important when considering the older age groups – lower numbers of enrollees in these groups may indicate that fewer dogs in the age group are “clinically normal” or considered healthy enough by the owners to be brought to a show. Examination of greater numbers of older dogs may have resulted in a more accurate estimation of MR_{echo} prevalence in these age groups but it remains unknown if prevalence would have be higher or lower.

The "gold standard" for diagnosis of MR in this study was Doppler-echocardiographic findings of an eccentric systolic jet or multiple systolic jets documented within the left atrium. Doppler echocardiography is considered to be highly sensitive for detection of MR[14], but MR jets may be more visible in either the right or left views in a given animal. We attempted to minimize this error by imaging animals from both right and left

views. In people[15] and dogs[12], concern has been expressed that Doppler echocardiography may be too sensitive in detecting small MR jets that may be inconsequential. This concern may be important in whippets in general, a breed often competing in athletic events like lure coursing or agility at national shows, but especially pertinent in the breeding age population, since younger dogs are more likely to be enrolled in highly competitive athletic events. Intensively-trained human athletes have been found to have a higher prevalence of MR_{echo} than matched sedentary subjects[19,20] and these MR jets were significantly smaller (filling less than 20% of LA area) than in control subjects in one study.[20] In the current study, dogs with small, central systolic jets filling less than 10% of the LA were not classified as having MR_{echo} to limit false positive results in this athletic population, since controversy remains regarding the prognostic importance of such jets in athletic dogs with a possible breed predisposition for MMVD. No analysis of valve morphology was included in this study; addition of such information may have improved diagnosis of MV abnormalities, but our aim was to detect regurgitant mitral valve jets rather than anatomic changes that may precede MR[21]. In the setting of "pre-breeding screening", diagnosis of disease in these patients may result in unnecessary restriction of the genetic pool[12]. Conversely, it is unknown if young animals with small, eccentric MR_{echo} jets without visible valve abnormalities are truly affected; thus, our estimates of prevalence must be considered indications of the prevalence of Doppler-echocardiographic abnormalities rather than disease *per se*. The echocardiographic gold standard for diagnosis of MMVD remains undetermined, although various criteria have been suggested[21-23].

Color Doppler mapping is setting-dependent and recognition of regurgitant jets relies on obtaining consistent views and analyzing color mapping images consistently. We attempted to minimize variability by having a single operator obtain all images, and a different single operator analyze all images. Lastly, although ejection murmurs based on blood turbulence in the aortic root may occur whether or not MR_{echo} is present, the accuracy of categorization of dogs in this study may have been hampered by study design. Dogs with any MR_{echo} were considered "positive" for MR, so if the loudest detected murmur was indeed an ejection murmur at the left heart base, and the LA murmur was not the loudest murmur, the dog would have been miscategorized.

The effect of auscultator experience on the accuracy of findings in differentiating disease-related and non-disease related heart murmurs has been explored[12,15,24]. A single, experienced cardiologist performed all auscultations in this study; results may vary with experience and abilities of other examiners in a similar situation[12]. No attempt was made to track or limit intraobserver variability and a "training" effect of the auscultator or variability in auscultation conditions cannot be ruled out.

Murmurs may be miscategorized for multiple reasons: unusual jet direction may cause turbulence to be directed toward and detected at the location of the aorta[15], physiologic murmurs may vary with state of excitement or cardiac output and patients may be difficult to examine based on behavior[12]. Variations in excitement or stress level in dogs affects auscultation findings and echo findings[12,24]. In this study, owners were present to comfort the dogs during both auscultation and

echocardiography, but differences in the dogs' stress level during these two procedures may have caused some variability in murmur grade or MR_{echo} appearance on Doppler examination.

All findings in this study are limited to time of a given dog's individual examination and the effect of findings on prognosis was not studied; longitudinal studies of individual dogs are needed to document the natural history of MMVD changes in whippets.

Conclusions

Systolic murmurs are very common in North American whippets and there is a high prevalence of MR_{echo} with a relatively early onset and close association with age in this breed. Whippets with non-clinical MR_{echo} may not be identifiable by auscultation alone due to the high prevalence of functional systolic murmurs. Auscultation alone may not be sensitive enough to differentiate murmurs indicative of MR_{echo} from functional murmurs with confidence, and Doppler-echocardiographic examination may be required to exclude a diagnosis of MR_{echo} in dogs with low intensity left-sided systolic heart murmurs. Detection of a systolic murmur of grade 3/6 or higher increases the likelihood of accuracy when differentiating murmurs reflecting MR_{echo} from functional murmurs in this population. In a breeding age population, lack of heart murmur or detection of L_{apic} may be considered fairly accurate to rule out or suspect MR_{echo}, but detection of L_{base} in whippets aged 2-5 years does not rule out the possibility of MR_{echo}. The prognostic significance of MR_{echo} jets in young dogs requires further study.

Conflict of Interest Disclosure

None of the authors has any conflict of interest to disclose.

[c]Olsen LH, Hjarback R, Pedersen HD. Physiological flow murmurs in Cavalier King Charles spaniels (abstract). J Vet Intern Med. 2006;20(3):748.

[d]Acuson Cypress™ System, Siemans Medical Solutions USA, Inc., Mountain View, CA 94043, USA

[1] Borgarelli M, Häggström J. Canine degenerative myxomatous mitral valve disease: natural history, clinical presentation and therapy. Vet Clin North Am Small Anim Pract. 2010 Jul;40(4):651–63.

[2] Olsen LH, Fredholm M, Pedersen HD. Epidemiology and inheritance of mitral valve prolapse in dachshunds. J Vet Intern Med. Blackwell Publishing Ltd; 1999 Sep 1;13(5):448–56.

[3] Swenson L, Häggström J, Kvart C, Juneja RK. Relationship between parental cardiac status in Cavalier King Charles spaniels and prevalence and severity of chronic valvular disease in offspring. Journal of the American Veterinary Medical Association. 1996;208:2009–12.

[4] Atkins C, Bonagura J, Ettinger S, Fox P, Gordon S, Häggström J, et al. Guidelines

for the diagnosis and treatment of canine chronic valvular heart disease. J Vet Intern Med. Blackwell Publishing Inc; 2009 Nov;23(6):1142–50.

[5] Stepien RL, Hinchcliff KW, Constable PD, Olson J. Effect of endurance training on cardiac morphology in Alaskan sled dogs. Journal of Applied Physiology. American Physiological Society; 1998 Oct 1;85(4):1368–75.

[6] Fabrizio F, Baumwart R, Iazbik MC, Meurs KM, Couto CG. Left basilar systolic murmur in retired racing greyhounds. J Vet Intern Med. 2006 Jan;20(1):78–82.

[7] Constable PD, Hinchcliff KW, Olson J, Hamlin RL. Athletic heart syndrome in dogs competing in a long-distance sled race. Journal of Applied Physiology. 1994 Jan;76(1):433–8.

[8] Côté E, Edwards NJ, Ettinger SJ, Luis Fuentes V, MacDonald KA, Scansen BA, et al. Management of incidentally detected heart murmurs in dogs and cats. J Vet Cardiol. 2015 Nov 19;17(4):245–61.

[9] Thrusfield MV, Aitken C, Darke P. Observations on breed and sex in relation to canine heart valve incompetence. J Small Anim Pract. Blackwell Publishing Ltd; 1985 Jan 1;26(12):709–17.

[10] Bavegems VC, Duchateau L, Polis IE. Detection of innocent systolic murmurs by auscultation and their relation to hematologic and echocardiographic findings in clinically normal Whippets. J Vet Intern Med. 2011;238(4):468–71.

[11] Moise NS, Fox PR. Echocardiography and Doppler Imaging. In: Fox PR, Sisson

D, Moise NS, editors. Textbook of Canine and Feline Cardiology. 2nd ed. Philadelphia; 1999. pp. 131–71.

[12. Pedersen HD, Häggström J, Falk T, Mow T, Olsen LH, Iversen L, et al. Auscultation in Mild Mitral Regurgitation in Dogs: Observer Variation, Effects of Physical Maneuvers, and Agreement with Color Doppler Echocardiography and Phonocardiography. J Vet Intern Med. Blackwell Publishing Ltd; 1999 Jan 1;13(1):56–64.

[13] Ljungvall I, Ahlstrom C, Höglund K, Hult P, Kvart C, Borgarelli M, et al. Use of signal analysis of heart sounds and murmurs to assess severity of mitral valve regurgitation attributable to myxomatous mitral valve disease in dogs. American Journal of Veterinary Research. 2009 May;70(5):604–13.

[14] Perry GJ, Bouchard A. Doppler echocardiographic evaluation of mitral regurgitation. Cardiol Clin. 1990 May;8(2):265–75.

[15] Jost CA, Turina J, Mayer K, Seifert B. Echocardiography in the evaluation of systolic murmurs of unknown cause. The American journal of Medicine. 2000;108(8):614–20.

[16] Bavegems V, Duchateau L, Sys SU, De Rick A. ECHOCARDIOGRAPHIC REFERENCE VALUES IN WHIPPETS. Veterinary Radiology & Ultrasound. Blackwell Publishing Inc; 2007 Apr 19;48(3):230–8.

[17] Häggström J, Hansson K, Kvart C. Chronic valvular disease in the cavalier King Charles spaniel in Sweden. The Veterinary Record. 1992;:549–53.

[18] Bloch A, Crittin J, Jaussi A. Should functional cardiac murmurs be diagnosed by auscultation or by Doppler echocardiography? Clin Cardiol. 2001 Dec;24(12):767–9.

[19] Macchi C, Catini C, Catini CR, Zito A, Urbano F, Minaiti B, et al. A comparison between the heart of young athletes and of young healthy sedentary subjects: a morphometric and morpho-functional study by echo-color-Doppler method. Ital J Anat Embryo. 2001 Jul 1;106(3):221–31.

[20] Douglas PS, Berman GO, O'Toole ML, Hiller WD, Reichek N. Prevalence of multivalvular regurgitation in athletes. The American Journal of Cardiology. 1989 Jul 15;64(3):209–12.

[21] Olsen LH, Martinussen T, Pedersen HD. Early echocardiographic predictors of myxomatous mitral valve disease in dachshunds. Veterinary Record. 2003 Mar 8;152(10):293–7.

[22] Zoghbi WA, Enriquez-Sarano M, Foster E, Grayburn PA, Kraft CD, Levine RA, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. Vol. 16, Journal of the American Society of Echocardiography. 2003. pp. 777–802.

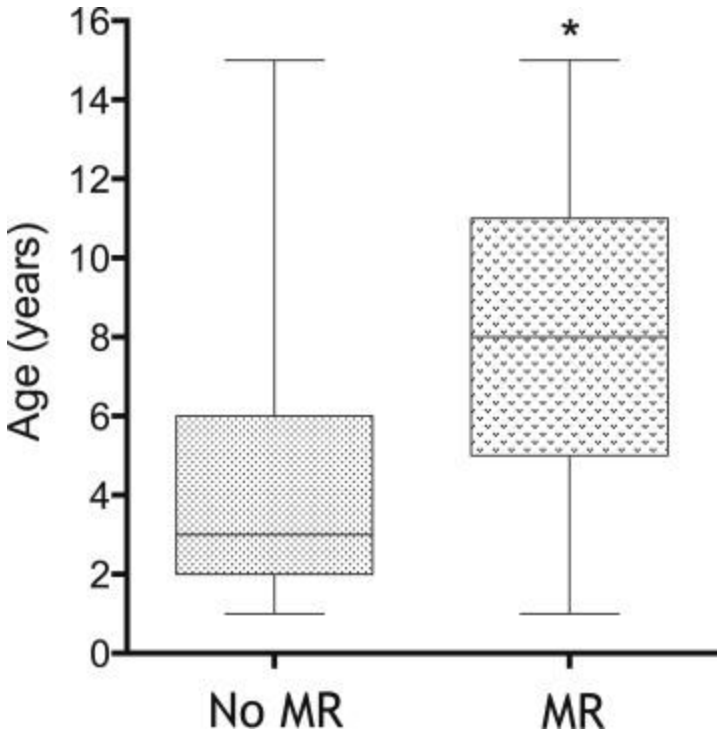
[23] Sargent J, Connolly DJ, Watts V, Mõtsküla P, Volk HA, Lamb CR, et al. Assessment of mitral regurgitation in dogs: comparison of results of echocardiography with magnetic resonance imaging. Journal of Small Animal Practice. 2015 Oct 16;56(11):641–50.

[24] Höglund K, French A, Dukes McEwan J, Häggström J, Smith P, Corcoran B, et al. Low intensity heart murmurs in boxer dogs: inter-observer variation and effects of stress testing. Journal of Small Animal Practice. 2004 Apr;45(4):178–85.

453 Figure 1: Age comparison of dogs with echocardiographically-documented mitral

454 regurgitation (MR_{echo}) versus dogs without MR_{echo}. Median, interquartile range and

455 range are represented. Asterisk denotes significant difference, $p<0.0001$.



456

457

458

Figure 2: Correlation of prevalence of MR_{echo} with age in 200 clinically-healthy North American whippets, by 2 year age groups. Numbers in parentheses indicate the number of dogs in the group. Highest age group, identified as 13 years, contains dogs > 12 years old (13 years (n=4) 14 years (n=3) and 15 years old (n=3).