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Published in:
Journal of Small Animal Practice

DOI:
10.1111/jsap.13472

Publication date:
2022

Document version:
Accepted manuscript

Citation for published version (APA):

Go to publication entry in University of Southern Denmark's Research Portal

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Download date: 15. Sep. 2023
Original Article

Epidemiology of Heart Disease in English Bull Terriers and Echocardiographic Characteristics of Mitral Valve Abnormalities

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The study was approved by the Ethical Committee (EAU 2017-13), and written owner consent was obtained for all dogs.

Acknowledgments

This study was financially supported by the Department of Veterinary Clinical Sciences, Faculty of Health and Medical Sciences, University of Copenhagen, Frederiksberg, Denmark, the Faculty of Veterinary Sciences, Mahasarakham University, Maha sarakham, Thailand, and the English Bull Terrier club in Denmark. The authors would like to thank veterinary technicians Elinor Aili Rikovitz

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/jsap.13472

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OBJECTIVES: To present the prevalence and distribution of heart disease as well as echocardiographic findings in English Bull Terriers (BT).

MATERIALS AND METHODS: One-hundred-and-one BT were retrospectively included to evaluate the prevalence and distribution of heart disease. Secondly, a retrospective study on mitral valve abnormalities was performed on 3 groups: a control group (N=120, 19 breeds) used to establish reference intervals for mean transmirtal gradient (MTG); a healthy BT group (N=25) and a BT group with mitral valve abnormalities (N=18). Healthy BT for which mitral inflow parameters were not obtainable and BT with other types of heart disease were excluded.

RESULTS: The prevalence of heart disease in BT was 66% (66/101), with mitral valve abnormalities (47%, 47/101) and aortic stenosis (29%, 29/101) being most common. The cut-off value for normal MTG was 3.5 mmHg in the control group. Healthy BT had a smaller mitral valve area (MVA) and mitral annulus diameter compared with dogs with a similar body surface area.

CLINICAL SIGNIFICANCE: Two-thirds of BT had heart disease, in particular mitral valve abnormalities and aortic stenosis. The MTG for healthy BT was higher than for other dog breeds. The small MVA and mitral annulus diameter in healthy BT indicate that all BT have some degree of mitral stenosis. A high heart rate, smaller MVA, mitral
regurgitation, and volume overload are associated with increased MTG in BT with mitral valve abnormalities. We suggest that MVA, mitral annulus diameter, and MTG measurements should be included in the echocardiographic protocol for BT.
Introduction

The English Bull Terrier (BT) is predisposed to severe heart disease (O'Leary and Wilkie 2009). A complex cardiac phenotype including mitral valve abnormalities (McEwan 1995, O'Leary and Wilkie 2009, O'Leary et al. 2005), aortic stenosis (McEwan 1995, O'Leary and Wilkie 2009), myocarditis and extensive early-onset arteriosclerosis and fibrosis of the cardiac conduction system (O'Leary and Wilkie 2009) is often found in BT. Mitral valve abnormalities reported in BT have been described as a familial, early-onset myxomatous mitral valve degeneration (MMVD) (O'Leary and Wilkie 2009) or congenital mitral dysplasia (Atwell 1979, Malik and Church 1988, McEwan 1995) with or without mitral stenosis (MS) (Lehmkuhl et al. 1994, McEwan 1995, Tidholm et al. 2004).

Mitral dysplasia is a congenital abnormality of the mitral valve apparatus that may involve mitral valve leaflets, mitral annulus, chordae tendineae, and papillary muscle (McEwan 1995). It has been described in several studies in young BT (Atwell 1979, Malik and Church 1988, O'Leary et al. 2005), however, the same studies also reported that some of the cases of mitral valve abnormalities may be acquired due to the early-onset of MMVD seen in this breed (Malik and Church 1988, O'Leary and Wilkie 2009, O'Leary et al. 2005).

Early-onset MMVD was reported in 25 BT with a median age of 17 months (range: 2.0–116.0 months) in a pathology study (O'Leary and Wilkie 2009). The mitral valve changes were characterized by disorganized collagen structure and accumulation of mucopolysaccharides. Gross examination of the mitral valve in affected BT revealed short, dense, and white leaflets with multiple firm nodules, while BT with MS had stiff mitral valve leaflets and commissural fusion of the mitral valve. Furthermore, papillary muscles were thickened, and chordae tendineae were short, thick, and fused (O'Leary and Wilkie 2009).

A combination of various abnormalities of the mitral valve apparatus in BT usually results in mitral regurgitation (MR) without MS (Malik and Church 1988, McEwan 1995).
Currently, however, the diagnosis MS is difficult in dogs because the mitral valve area (MVA) and mean transmirtal gradient (MTG) cut-off values have not yet been firmly established. According to guidelines in human cardiology, mild MS is defined as MVA planimetry using two-dimensional echocardiography (MVA2D) > 1.5 cm² and MTG < 5.0 mmHg (Baumgartner et al. 2009).

Based on a recent publication both MVA2D and MVA planimetry using three-dimensional echocardiography (MVA3D) can be used to diagnose MS in BT – however, MVA3D is the preferred method for estimating the narrowest orifice area (XXX 2021).

The distribution and echocardiographic characteristics of heart disease, especially mitral valve abnormalities, in BT are unknown. Therefore, the aims of this study were to 1) assess the prevalence and distribution of heart disease in a cohort of BT; 2) describe the echocardiographic characteristics in healthy BT and BT with mitral valve abnormalities.

Materials and methods

Animals

This retrospective study included 101 BT presented by their owners for cardiac screening during an 11-year period (2007–2018) and consisted of a cross-sectional study evaluating the prevalence and distribution of heart disease in BT and a sub-study evaluating the characteristics of mitral valve abnormalities in BT. No dogs with known cardiac status were actively recruited for the study. A small subpopulation of the dogs in this study has been used in our previous study. However, only data used to compare MVA by either transthoracic two or three-dimensional echocardiography were published (XXX 2021). Only dogs with an age > 1 year old and with enough clinical data to diagnose heart disease were included. Dogs referred with known heart disease or presented outside of the screening program were not included in the study population.
All dogs included underwent a thorough clinical examination as well as electrocardiography and conventional transthoracic echocardiography.

The sub-study, evaluating the characteristics of mitral valve abnormalities in BT, included 3 groups. The first group served as a reference control group and consisted of 120 dogs of 19 different breeds. These dogs were classified as healthy if the physical examination was unremarkable, the dogs were normotensive and had a normal ECG and echocardiographic examination without flow abnormalities. The 19 different breeds included: Australian Shepherd (n=1), Bernese Mountain Dog (n=3), Border Terrier (n=10), Boxer (n=10), Cavalier King Charles Spaniel (n=10), Chihuahua (n=9), Dachshund (n=5), Dalmatian (n=10), Danish Mastiff (n=1), German Shepherd (n=1), Great Dane (n=8), Greyhound (n=7), Irish Wolfhound (n=5), Labrador Retriever (n=10), Newfoundland (n=10), Parson Russel Terrier (n=1), Petit Basset Griffon Vendeen (n=10), Spanish Greyhound (n=1), and Whippet (n=8). This group of dogs was used to establish reference intervals for the peak velocity of early diastolic transmitral flow and MTG across a range of breeds and heart rate.

The second group consisted of healthy BT, and the third group consisted of BT with mitral valve abnormalities. All dogs in the sub-study had adequate echocardiograms and were not undergoing medical therapy with cardio-active drugs at the time of data acquisition. Exclusion criteria in this sub-study included other types of cardiac disease or non-cardiac systemic diseases as well as persistent non-sinus arrhythmias such as atrial fibrillation. Finally, dogs with echocardiographic data but without simultaneous electrocardiography or mitral inflow parameters using continuous-wave Doppler (CW) were excluded.

The study was approved by the Ethical Committee (XXX), and written owner consent was obtained for all dogs.

**Echocardiography**
Echocardiography was performed by a single experienced operator using a Vivid 7 ultrasonographic system (GE Healthcare) equipped with a 4M MHz and a 5S MHz phased-array transducer and a GE Vivid E9 ultrasonographic system with 6S MHz, M5Sc MHz, and 4V MHz phased-array transducers. The echocardiographic examinations were stored as raw data for subsequent offline analysis using the EchoPAC version 113 for the PC (GE Healthcare).

All dogs were examined without sedation under gentle manual restraint in both right and left lateral recumbency. The protocol included transthoracic two-dimensional, M-mode, spectral, and color-flow Doppler echocardiography with electrocardiography recorded continuously according to the recommendations (Quiñones et al. 2002, Thomas et al. 1993). The mitral annulus diameter was measured from the left apical four-chamber view during end-systole by measuring the distance between mitral valve hinge points.

Mitral inflow was assessed at a position that ensured optimal parallel alignment with the flow using CW (Fig. 1) and at the tips of the mitral valve leaflets using pulsed-wave Doppler (PW) from the apical four-chamber view (Quiñones et al. 2002). The peak velocity of early diastolic transmitral flow, the peak transmitral gradients, and MTG were calculated automatically by tracing the dense outline of transmitral inflow. The transmitral gradients were calculated using the simplified Bernoulli equation (Heys et al. 2010). Fused mitral inflow waves were not included in statistical analysis for the peak velocity of early diastolic transmitral flow.

The MVA planimetry using three-dimensional echocardiography (MVA3D) was measured using four-dimensional preparation. The four-dimensional zoom prepare mode was applied to the left apical two- and four-chamber views. A full-volume image of the mitral valve was obtained, and a four-dimensional construction was then prepared. During offline analysis, the three-dimensional Flexi Slice mode was applied to multiplanar reconstruct for
the narrowest cross-sectional opening of the mitral orifice during early diastole. The edge of the mitral valve orifice was then traced using a two-dimensional image. The MVA\textsubscript{3D} was used only for the diagnosis of MS.

The MVA\textsubscript{2D} was measured in the right parasternal short-axis view during early diastole when the valve was maximally open (Fig. 1). A transducer was adjusted to obtain the optimal image crossing the mitral leaflet tips and parallel to the mitral valve orifice. The entire circumference of the MVA was traced with optimized gain.

Left atrial (LA) volumes were measured using the single-plane area-length method from the left apical four-chamber view (Höllmer \textit{et al.} 2013), while left ventricular (LV) volumes were measured using the Simpson’s method of discs (Wess \textit{et al.} 2010).

Heart rate was recorded for each frame used for the mitral inflow parameter measurement. The body surface area was calculated as $0.10 \times \text{kg}^{0.667}$ (Wess \textit{et al.} 2010). The normalized LV internal dimension at end-diastole was calculated as the LV internal dimension at end-diastole (cm) per body weight (kg) raised to the power of 0.294, while the normalized LV internal dimension at end-systole was calculated as the LV internal dimension at end-systole (cm) per body weight (kg) raised to the power of 0.315 (Cornell \textit{et al.} 2004). Three cardiac cycles were used to measure all echocardiographic parameters. The data were averaged and used in the statistical analysis.

Dogs with mitral valve abnormalities were subdivided into two categories, depending on the present of MS. Mitral valve abnormalities without MS were defined as the presence of thickened mitral leaflets, thickened papillary muscles or chordae tendineae, increased E-point to septal separation (EPSS) (Lehmkuhl \textit{et al.} 1994, McEwan 1995, O’Leary and Wilkie 2009, Tidholm \textit{et al.} 2004), MR or mitral valve prolapse (Tidholm \textit{et al.} 2019). Thickened mitral leaflets were defined by an anterior mitral valve width that is higher than the reference interval based on body weight (Wesselowski \textit{et al.} 2015) or severely thickened mitral leaflets.
identified using two-dimensional echocardiography. Myxomatous mitral valve degeneration with or without MR was defined as the presence of thickened mitral leaflets and/or thickened and fused chordae tendineae (O'Leary and Wilkie 2009). In addition, MS was defined as the MVA_{3D} measurements < 1.8 cm² or MVA_{2D} measurements < 2.1 cm² (XXX 2021). Mitral stenosis was considered clinically significant when the MTG was above the upper limit of the reference interval for the MTG from the control group, in addition to thickened mitral leaflets, and mitral valve motion characteristic of valve stenosis on the two-dimensional image including incomplete diastolic leaflet separation and restricted diastolic movements. Aortic stenosis was diagnosed in dogs with or without visible obstruction, with a peak LV outflow and aortic velocity from the subcostal transhepatic view >2.4 m/s (Jenni et al. 2009). Pulmonic stenosis was diagnosed when peak pulmonic velocity was >1.8 m/s (Jenni et al. 2009, Kander et al. 2015), with or without visible obstruction. Dilated cardiomyopathy was diagnosed based on previously reported guidelines (Dukes-McEwan et al. 2003), with the main criteria including increased LV dimension/volume and decreased fractional shortening or LV ejection fraction. Mitral regurgitation was assessed using Proximal Isovelocity Surface Area method (Gouni et al. 2007, Lambert 2007) and LA volume.

**Statistical methods**

Statistical analysis was performed using commercially available software (IBM SPSS Statistics version 25, IBM, and MedCalc Statistical software version 19.0.7). The outliers were detected using values outside the interval “upper/lower quartile ± triple interquartile range” (Heumann et al. 2017). Normal distribution was visually assessed using histograms and Q-Q plot. Data was reported as median with range for non-normally distributed variables. The 95% reference intervals for the peak velocity of early diastolic transmitral flow, MTG, and heart rate were calculated following Clinical and Laboratory Standards Institute guidelines for nonparametric percentiles (Wayne 2008). The lower and upper reference limits
were the 2.5<sup>th</sup> and 97.5<sup>th</sup> percentiles, respectively. The percentiles are calculated as the observations corresponding to rank \( r = p \cdot (n + 1) \) and 90% confidence intervals around these limits were determined. The upper limit of the reference interval for MTG from the control group consisting of 19 different dog breeds was used to distinguish between normal and increased MTG. In the healthy BT group, multivariate generalized linear models with Gamma as the distribution of response and log as the link function was performed to evaluate the association between MTG and heart rate, MVA<sub>2D</sub> and LA end-diastolic volume indexed to body weight (LAEDV:kg). The echocardiographic variables were compared between BT groups, and the MTG and heart rate were compared between the control group and the healthy BT group, using the Mann-Whitney U test. A significance level of 5% (\( P < 0.05 \)) was used for all analyses.

**Results**

The cross-sectional study included 101 BT, distributed as 45 male (44.6%) and 56 female (55.4%) BT. The median age was 36 months (range: 12–155 months), and the median body weight was 27.0 kg (range: 21.0–40.0 kg). Heart disease was identified in 66% (66/101) of the included BT, with mitral valve abnormalities (47%, 47/101) and aortic stenosis (29%, 29/101) as the most common phenotypes. The frequency of mitral valve abnormalities with MS among all BT was 10% (10/101), while 21% BT with mitral valve abnormalities had MS (10/47). The full distribution of cardiac abnormalities is shown in Table 1.

Echocardiographic findings of mitral valve abnormalities in the 47 BT from the cross-sectional study are shown in Table 2. The most predominant findings were mitral regurgitation, thickening of mitral valve and restrictions of mitral valve movement with fusion of mitral valve leaflets and restricted anterior mitral leaflet (Fig. 2). Of the 36 BT with MR, a total of 32 were classified as mild with a proximal isovelocity surface area radius < 4 mm (aliasing velocity 35.0 cm/s) and LAEDV:kg < 1.2 ml/kg, while 4 BT were classified as
severe MR with a proximal isovelocity surface area radius >7 mm (aliasing velocity 35.0 cm/s) and a median LAEDV:kg of 2.4 ml/kg, range 2.0-2.8 ml/kg.

In the sub-study evaluating the characteristics of mitral valve abnormalities in BT, 120 healthy dogs were used to establish the reference intervals for the peak velocity of early diastolic transmitral flow and MTG, shown in Table 3. The cut-off value for normal MTG using CW was 3.5 mmHg at a median heart rate of 110 beats per minute (bpm; range 55–167 bpm).

Twenty-five healthy BT and 18 BT with mitral valve abnormalities were included in this sub-study, as 10 BT without available CW of the mitral inflow and 48 BT with other types of heart disease were excluded. Demographic data and selected conventional echocardiographic variables from the BT groups are shown in Table 4.

The healthy BT group had a median MTG of 2.8 mmHg, which was significantly higher than the median MTG of 1.5 mmHg found in the control group (P<0.001).

The median EPSS and fractional shortening in BT with mitral valve abnormalities was significantly higher than for the healthy BT group (P<0.001).

The median heart rate for the control group was significantly lower than for the healthy BT group (P<0.001). Also, the median heart rate for the groups of BT with mitral valve abnormalities was significantly higher than for the healthy BT group (P= 0.042). The multivariate generalized linear models showed that heart rate was the highest contributing predictor for MTG (β: 0.012, 95% confidence interval (CI) of β: 0.007–0.017, P<0.001), followed by LAEDV:kg (β: 0.979, 95% CI of β: 0.066–1.893, P= 0.036), while MVA2D was not associated with MTG in the healthy BT group (table 5).

There was a significant difference in cardiac dimension and volume parameters as well as mitral inflow parameters (P<0.05) between healthy BT and BT with mitral valve abnormalities, including LV internal dimension at end-diastole, normalized LV internal
dimension at end-diastole, LV internal dimension at end-systole, normalized LV internal
dimension at end-systole, LA diameter, the ratio of LA dimension to aortic annulus
dimension, LV end-diastolic volume indexed to body surface area, LV end-systolic volume
indexed to body surface area, LAEDV:kg, LA end-systolic volume indexed to body weight,
the peak velocity of early diastolic transmitral flow, the peak transmitral gradients, and MTG
(table 4).

Systolic dysfunction was found in 7 out of 18 BT with mitral valve abnormalities with
increased LV internal dimension at end-systole, normalized LV internal dimension at end-
systole, LV end-systolic volume indexed to body surface area, EPSS, decreased fractional
shortening and decreased ejection fraction.

Discussion

In the present study, mitral valve abnormalities and aortic stenosis were the most
common findings (47.0% and 29.0%, respectively). The prevalence of BT with mitral valve
abnormalities was similar to an earlier report of 44.1% (McEwan 1995) and slightly higher than
the 39% reported by O’Leary et al. (O’Leary et al. 2005). The prevalence of BT with aortic
stenosis, however, has been more varied with 29% detected in the present study and previous
studies ranging from 3.3-53.0% (O’Leary et al. 2005). The prevalence of mitral valve
abnormalities with MS was 10.0 % in our study (corresponding to 21.0% of the dogs with mitral
valve abnormalities). As such, the reported disease prevalences should be interpreted in light
of the sample population and the diagnostic method applied. In general, MS is a rare congenital
heart disease in dogs (Lehmkuhl et al. 1994) whereas BT seems predisposed (Fox et al. 1992,
Lehmkuhl et al. 1994). Thus, one study found that 4 of 15 dogs with MS were BT (Lehmkuhl
et al. 1994), and the prevalence of MS in the McEwan study was 2.2% (McEwan 1995).

Mitral valve abnormalities in BT have been described as either a congenital or
acquired heart disease. Several studies reported mitral valve abnormalities as a congenital
malformation and described it as mitral valve dysplasia (Atwell 1979, Malik and Church 1988, McEwan 1995, O'Leary et al. 2005) with the youngest affected dog being only 2 months old (O'Leary and Wilkie 2009). However, MMVD with an early onset has also been suggested, although some dogs developed clinical signs as late as 13 years of age. In a follow-up study of 10 BT, mitral valve abnormalities in 2 dogs were only detected at the second examination one year later (O'Leary 2002). The present study found that clinically significant MS was only seen in adult BT. Based on these findings, our study supports that acquired MMVD with or without MS is the most common causative factor for developing symptomatic heart disease in BT.

The severity of MMVD in BT increases with age (O'Leary et al. 2005), which is similar to MMVD in Cavalier King Charles Spaniels (Häggström et al. 1992). However, significant differences exist between the two breeds as Cavalier King Charles Spaniels have MMVD with mitral valve prolapse and without a complex cardiac phenotype or MS (Häggström et al. 1992).

Mitral valve abnormalities in the present study included thickening of the mitral valve, a hockey-stick appearance of the anterior mitral leaflet, restricted valve movement, thickened chordae tendineae, and fusion of the mitral valve leaflets. These findings were similar to those described in case reports on BT with MS (Fox et al. 1992, Tidholm et al. 2004), a study including 15 dogs with MS (Lehmkuhl et al. 1994) and the McEwan study (McEwan 1995).

MVA planimetry is the reference method for diagnosis of MS in humans (Baumgartner et al. 2009). In the sub-study evaluating the characteristics of mitral valve abnormalities in BT, healthy BT had a smaller range of MVA\(_{2D}\) (2.1–3.6 cm\(^2\)) compared with other dog breeds with the same range of body surface area (4.1–5.7 cm\(^2\)), as given by the regression equation reported by O'Grady et al. (1986). Similarly, the median mitral annulus diameter of 21.7 mm in healthy BT in the present study was lower than that reported in other
dog breeds. Wesselowski et al. (2015) found that dogs with a body weight of 25–30 kg had a median mitral annulus diameter of 29.6–31.7 mm. Moreover, the median MTG of 2.8 mmHg in the group of healthy BT was significantly higher than the median MTG of 1.5 mmHg found in the control group, corresponding to BT having a higher MTG than other dog breeds. BT have a relatively smaller MVA and mitral annulus diameter compared to other dog breeds which is associated with increased MTG. Thus, it appears that all BT might have some degree of MS. As no cardiac remodeling was seen in BT with MVD and MTG < 6.3 mmHg (without other concurrent heart diseases), and as mild MS in humans are defined using a MTG < 5 mmHg, applying a diagnostic criterion of > 5 or 6 mmHg for clinically significant MS in BT may be valid.

In addition to anatomical disease, several other factors can increase the MTG, including heart rate and cardiac volume (Muddassir and Pressman 2007). Therefore, dogs with a restricted mitral valve opening, increased peak velocity of early diastolic transmitral flow or MTG with known causes, such as a high heart rate and cardiac volume overload, should be defined as having functional MS (Pendray and Breznock 1994). Dogs with a small MVA for which the cause of increased MTG is not obvious may be defined as having mild MS.

The median heart rate in healthy BT was significantly higher than the control group but lower than BT with mitral valve abnormalities. The transmitral flow rate is strongly affected by heart rate in humans with MS (Baumgartner et al. 2009). A study using a computational tool reported that the transmitral flow rate changes with altering heart rates. Also, a higher heart rate was shown to cause a fusion of passive and active mitral inflow in late diastole, and the active atrial contraction was, therefore, more responsible for maintaining stroke volume and reinforcing the mitral inflow velocity (Meschini et al. 2020). The highest MTG was also found at the fastest heart rates in an experimental study in dogs (Appleton
1991). In the present study, heart rate was the strongest predictor of MTG in healthy dogs. The combination of a smaller MVA and increased HR in BT may explain the higher MTG in healthy BT.

The group of BT with mitral valve abnormalities had increased LA and LV internal dimensions and volume parameters compared with the healthy BT. Mitral regurgitation causes cardiac remodeling due to volume overload with increased compliance in the left atrium and left ventricle as well as increased LA pressure (Nagueh et al. 2016). The severity of MR has been reported to correlate with the peak velocity of early diastolic transmitral flow (Özdemir et al. 2001). This indicates that MR and volume overload increase MTG.

The median EPSS in the BT with mitral valve abnormalities was significantly higher than in the healthy BT. The EPSS depends on mitral valve excursion, transmitral blood flow, and LV function (Lehmann et al. 1983, Massie et al. 1977). Interestingly, the mitral valve apparatus in BT seems to be less flexible compared to Dachshund (EPSS: median 1.8 mm, range 0.0-4.0 mm), (Garncarz et al. 2018) and Beagle and German Shepherd dogs (mean 3.3 ± 1.3 mm) (Kirberger 1991). The complex cardiac phenotype in BT including leaflets thickening and fusion of commissures, smaller mitral valve area and thickened, shortened and fused chordae tendineae reduces the mobility of mitral valve leaflets. Mitral stenosis often gives a high EPSS and causes an abnormally increased distance between the mitral valve and septal wall during diastole (Kirberger 1991). An EPSS is a frequently used indicator of LV function. Systolic dysfunction is associated with an increased LV internal dimension at end-systole or LV end-systolic volume, decreased fractional shortening or ejection fraction and increased EPSS (Wess 2021). In this study, we found that 7 out of 18 BT with mitral valve abnormalities had systolic dysfunction. This indicates that an increased EPSS in those dogs may be the results of a multifactorial mechanism including systolic dysfunction, enlargement of the left ventricle and a non-flexible mitral valve apparatus.
A major limitation of the study was its retrospective design. Additionally, BT with occult heart diseases such as arteriosclerosis and secondary myocardial disease may have been included in this study as only echocardiography was used to characterize the cardiac phenotype. Furthermore, some echocardiographic parameters were not available for all BT due to missing cine loops. The dog owners elected to participate, which may have influenced the high occurrence of heart disease in this study. However, our findings are supported by previous studies (O’Leary and Wilkie 2009, O’Leary et al. 2005). The index MVA to BSA was used for the comparison between healthy BT and derived MVA values (O’Grady et al. 1986) for dogs with a similar BSA; this index was not validated. A longitudinal study is needed to evaluate if BT have early-onset MMVD and develop MS over time. There was no histopathology to define whether thickened leaflets are myxomatous, degenerative or dysplastic. However, studies have been published that support MMVD as the causative pathology in BT (O’Leary and Wilkie 2009). Finally, abnormalities of the papillary muscles and chordae tendineae may be underestimated in this study as not all images were optimized for this assessment.

Conclusions

Our study identified a complex cardiac phenotype including mitral valve abnormalities and aortic stenosis in BT, with two-thirds of dogs affected. The cut-off value of 3.5 mmHg for normal MTG combined with a smaller MVA can be used to diagnose MS in dogs. These echocardiographic findings of small MVA and mitral annulus diameter as well as increased MTG suggest that all BT may have some degree of MS. We therefore suggest that these echocardiographic measurements will be useful for determining the cardiac phenotype of mitral valve abnormalities in BT. Future prospective studies should evaluate the effect of regular screening echocardiograms in young and adult BT with a focus on breeding programs and disease progression. Furthermore, well-defined diagnostic criteria for diagnosis of MS,
such as those suggested in this study, should be established to allow for comparative studies
across different BT populations.

Conflicts of Interest Statement

The authors do not have any conflicts of interest to disclose.
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XXX (2021) Transthoracic two-dimensional and three-dimensional echocardiography for the measurement of mitral valve area planimetry in English Bull Terriers with and without heart disease. *Journal of Veterinary Cardiology* 36, 169-179
Figure legends

FIG 1. (A) A parasternal short-axis view at the level of the mitral valve from a healthy English Bull Terrier (BT). Note a mitral valve area measurement by planimetry using two-dimensional echocardiography (MVA$_{2D}$) of 2.5 cm$^2$, (B) Continuous-wave Doppler recording of the mitral valve inflow from a healthy BT. Transmitral flow was traced to calculate the mean transmitral gradient (MTG). Note a MTG of 2.2 mmHg, (C) A parasternal short-axis view at the level of the mitral valve from a BT with a smaller MVA$_{2D}$ of 1.6 cm$^2$, (D) Continuous-wave Doppler recording of the mitral valve inflow from a BT with mitral stenosis. Note an increased MTG of 9.3 mmHg. A: peak velocity of late transmitral flow, cm$^2$: square centimeter, E: peak velocity of early diastolic transmitral flow, IVS: interventricular septum, LVPW: left ventricular posterior wall, mmHg: millimeter of mercury, MTG: mean transmitral gradient, MVA$_{2D}$: mitral valve area measurement by planimetry using two-dimensional echocardiography.

Figure 2 (A, B) A 3-year-old male BT with severe mitral stenosis. Arrow indicates severe thickened mitral valve. MTG= 8.3 mmHg, MVA$_{2D}$= 1.3 cm$^2$

MTG was relatively low due to a concomitant severe dynamic aortic stenosis (Left ventricular outflow tract velocity > 7 m/s) and concentric hypertrophy. Recently, this dog was euthanized at 8 years of age with a MTG of 26.8 mmHg and a MVA of 0.5 cm$^2$

(C, D) A 4-year-old female BT with myxomatous mitral valve degeneration and left atrial enlargement. arrow indicates hockey-stick appearance of anterior mitral leaflet. MTG= 18.4 mmHg, MVA$_{2D}$= 1.6 cm$^2$

(E, F) 12-year-old male English Bull Terrier with mitral stenosis. Arrow indicates the fusion of the mitral valve leaflets. MTG= 18.9 mmHg, MVA$_{2D}$= 1.3 cm$^2$. 

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AML, anterior mitral leaflet; IVS, interventricular septum; LA, left atrium; LV, left ventricle; MTG, mean transmitral gradient.

(G, H) A 7-year-old male English Bull Terrier with physiological MS due to volume overload. A thickening of the anterior (arrow) and posterior mitral valve, mitral regurgitation and subsequent cardiac enlargement are present. MTG= 13.2 mmHg, MVA$_{2D}$= 2.6 cm$^2$. 
Table 5 Multiple linear model with Gamma as the distribution of response and log as the link function between mean transmitral gradient (MTG) and heart rate, mitral valve area measurement by planimetry using two-dimensional echocardiography (MVA\textsubscript{2D}) and left atrial end-systolic volume indexed to body weight (LAEDV:kg) in the healthy BT group

<table>
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<th>β</th>
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<td>0.066–1.893</td>
<td>0.093</td>
<td>0.036</td>
</tr>
</tbody>
</table>

CI: confidence interval,
Table 2. Echocardiographic findings of mitral valve abnormalities in 47 English Bull Terriers

<table>
<thead>
<tr>
<th>Echocardiographic findings</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitral regurgitation</td>
<td>36</td>
</tr>
<tr>
<td>Mild mitral regurgitation</td>
<td>32</td>
</tr>
<tr>
<td>Severe mitral regurgitation</td>
<td>4</td>
</tr>
<tr>
<td>Thickening of mitral valve</td>
<td>34</td>
</tr>
<tr>
<td>Restricted mitral valve movement</td>
<td>18</td>
</tr>
<tr>
<td>Hockey-stick appearance of anterior mitral leaflet</td>
<td>6</td>
</tr>
<tr>
<td>Thickening of chordae tendineae</td>
<td>5</td>
</tr>
<tr>
<td>Enlargement of papillary muscle</td>
<td>2</td>
</tr>
<tr>
<td>Mitral valve prolapse</td>
<td>1</td>
</tr>
<tr>
<td>Fusion of mitral valve leaflets</td>
<td>7</td>
</tr>
<tr>
<td>Systolic anterior motion</td>
<td>1</td>
</tr>
</tbody>
</table>
Table 3. Reference intervals for peak velocity of early diastolic transmitral flow and mean transmitral gradient for both pulsed-wave Doppler and continuous-wave Doppler from 120 healthy dogs of 19 different breeds

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Median</th>
<th>SD</th>
<th>Min.</th>
<th>Max.</th>
<th>Reference interval</th>
<th>Lower limit 90% CI</th>
<th>Upper limit 90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>E</td>
<td>CW   (m/s)</td>
<td>0.91</td>
<td>0.91</td>
<td>0.16</td>
<td>0.55</td>
<td>1.2</td>
<td>0.57–1.2</td>
<td>0.55–0.65</td>
</tr>
<tr>
<td></td>
<td>PW   (m/s)</td>
<td>0.79</td>
<td>0.78</td>
<td>0.15</td>
<td>0.48</td>
<td>1.2</td>
<td>0.51–1.1</td>
<td>0.48–0.55</td>
</tr>
<tr>
<td>MTG</td>
<td>CW   (mmHg)</td>
<td>1.6</td>
<td>1.5</td>
<td>0.73</td>
<td>0.22</td>
<td>3.7</td>
<td>0.47–3.5</td>
<td>0.22–0.54</td>
</tr>
<tr>
<td></td>
<td>PW   (mmHg)</td>
<td>1.2</td>
<td>1.0</td>
<td>0.59</td>
<td>0.22</td>
<td>3.7</td>
<td>0.40–2.8</td>
<td>0.22–0.48</td>
</tr>
<tr>
<td>HR</td>
<td>CW   (bpm)</td>
<td>109</td>
<td>110</td>
<td>23</td>
<td>55</td>
<td>167</td>
<td>58–156</td>
<td>55–75</td>
</tr>
<tr>
<td></td>
<td>PW   (bpm)</td>
<td>110</td>
<td>111</td>
<td>24</td>
<td>55</td>
<td>171</td>
<td>65–166</td>
<td>55–72</td>
</tr>
</tbody>
</table>

CW: continuous-wave Doppler, CI: confidence interval, E: peak velocity of early diastolic transmitral flow, HR: heart rate, MTG: mean transmitral gradient, PW: pulsed-wave Doppler, SD: standard deviation
Table 1. Distribution of heart diseases in 101 English Bull Terriers

<table>
<thead>
<tr>
<th>Associated heart disease</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy</td>
<td>35</td>
</tr>
<tr>
<td>MMVD</td>
<td></td>
</tr>
<tr>
<td>Isolated MMVD</td>
<td>27</td>
</tr>
<tr>
<td>MMVD and AS</td>
<td>7</td>
</tr>
<tr>
<td>MMVD and pericardial disease</td>
<td>1</td>
</tr>
<tr>
<td>MMVD and DCM-like phenotype</td>
<td>1</td>
</tr>
<tr>
<td>MMVD associated with MS and AS</td>
<td>2</td>
</tr>
<tr>
<td>MMVD associated with MS and AS and PS</td>
<td>1</td>
</tr>
<tr>
<td>MMVD associated with MS</td>
<td>5</td>
</tr>
<tr>
<td>MMVD associated with MS and AS (MTG &lt; 3.5 mmHg)</td>
<td>1</td>
</tr>
<tr>
<td>MS (MTG &lt; 3.5 mmHg)</td>
<td>1</td>
</tr>
<tr>
<td>Mitral valve prolapse</td>
<td>1</td>
</tr>
<tr>
<td>AS</td>
<td>18</td>
</tr>
<tr>
<td>Unclassified</td>
<td>1</td>
</tr>
</tbody>
</table>

AS aortic stenosis, DCM dilated cardiomyopathy, MMVD myxomatous mitral valve degeneration, MS mitral stenosis, MTG mean transmitral gradient, PS pulmonic stenosis.

MMVD was defined as the presence of thickened mitral leaflets and/or thickened and fused chordae tendineae. Mitral stenosis were defined as MVA\textsubscript{3D} measurements < 1.8 cm\textsuperscript{2} or MVA\textsubscript{2D} measurements < 2.1 cm\textsuperscript{2}. Mitral stenosis was considered clinically significant when the MTG was above the upper limit of the reference interval for the MTG from the control group, in addition to thickened mitral leaflets, and mitral valve motion characteristic of valve stenosis on the two-dimensional image including incomplete diastolic leaflet separation and restricted diastolic movements.
Unclassified: a dog was diagnosed as unclassified based on eccentric left ventricular
enlargement with a marked systolic dysfunction associated with a mild aortic regurgitation.
Table 4. Demographic data and selected conventional echocardiographic variables for healthy English Bull Terriers (BT) and BT with mitral valve abnormalities

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unit of measurement</th>
<th>Healthy BT n = 25</th>
<th>BT with mitral valve abnormalities n = 18</th>
<th>Median difference (95% CI)*</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>months</td>
<td>35.0 (16.0–155.0)</td>
<td>32.5 (15.0–152.0)</td>
<td>0 (-12.0, 10.0)</td>
<td>0.98</td>
</tr>
<tr>
<td>Weight</td>
<td>kg</td>
<td>27.0 (21.0–33.0)</td>
<td>27.8 (21.5–40.0)</td>
<td>-1.0 (-4.0, 2.0)</td>
<td>0.55</td>
</tr>
<tr>
<td>LVIDd</td>
<td>mm</td>
<td>37.3 (31.5–44.0)</td>
<td>44.7 (34.1–65.7) **</td>
<td>-7.3 (-10.2, -3.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVIDdN</td>
<td>cm/kg$^{0.294}$</td>
<td>1.4 (1.3–1.6) **</td>
<td>1.7 (1.4–2.3) *</td>
<td>-0.27 (-0.38, -0.15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVIDs</td>
<td>mm</td>
<td>27.5 (20.4–32.0)</td>
<td>35.0 (26.4–50.9) **</td>
<td>-7.4 (-10.7, -4.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVIDsN</td>
<td>cm/kg$^{0.315}$</td>
<td>0.95 (0.75–1.1) **</td>
<td>1.2 (0.89–1.8) **</td>
<td>-0.28 (-0.39, -0.17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FS</td>
<td>%</td>
<td>28.0 (24.0–36.0)</td>
<td>21.5 (16.0–34.0) **</td>
<td>7.0 (4.0, 9.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EPSS</td>
<td>mm</td>
<td>4.3 (0.0–7.1)</td>
<td>7.6 (5.0–15.7) **</td>
<td>-3.8 (-5.1, -2.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ao sax</td>
<td>mm</td>
<td>18.0 (14.4–21.2)</td>
<td>19.0 (15.1–21.5)</td>
<td>-0.56 (-1.5, 0.47)</td>
<td>0.33</td>
</tr>
<tr>
<td>LAD sax</td>
<td>mm</td>
<td>21.6 (16.6–27.0)</td>
<td>25.9 (20.3–45.1) **</td>
<td>-4.2 (-6.6, -1.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LA sax: Ao sax</td>
<td>%</td>
<td>1.2 (0.94–1.5)</td>
<td>1.3 (1.1–2.3) *</td>
<td>-0.19 (-0.41, -0.06)</td>
<td>0.03</td>
</tr>
<tr>
<td>Ao lax</td>
<td>mm</td>
<td>15.3 (13.0–17.4)</td>
<td>15.7 (11.7–19.3)</td>
<td>0 (-1.4, 1.1)</td>
<td>0.94</td>
</tr>
<tr>
<td>MAD</td>
<td>mm</td>
<td>21.7 (18.9–26.0)</td>
<td>22.3 (15.3–28.1)</td>
<td>-1.1 (-3.2, 1.1)</td>
<td>0.28</td>
</tr>
<tr>
<td>MVA$^{2D}$</td>
<td>cm$^{2}$</td>
<td>3.1 (2.1–3.6)</td>
<td>2.9 (1.3–4.1)</td>
<td>0.1 (-0.3, 0.5)</td>
<td>0.57</td>
</tr>
<tr>
<td>LVEDVI</td>
<td>mL/m$^{2}$</td>
<td>43.3 (27.4–61.1)</td>
<td>58.7 (42.1–130.1) **</td>
<td>-18.2 (-30.5, -10.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVESVI</td>
<td>mL/m$^{2}$</td>
<td>16.1 (10.5–30.5)</td>
<td>23.7 (14.8–68.3) **</td>
<td>-9.9 (-16.5, -5.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EF</td>
<td>%</td>
<td>62.0 (50.1–73.0)</td>
<td>58.0 (40.0–69.0)</td>
<td>5.0 (1.0–9.0)</td>
<td>0.09</td>
</tr>
<tr>
<td>LAEDV/kg</td>
<td>mL/kg</td>
<td>0.43 (0.32–0.77)</td>
<td>0.67 (0.39–2.8) **</td>
<td>-0.22 (-0.33, -0.13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LAESV/kg</td>
<td>mL/kg</td>
<td>0.19 (0.09–0.32)</td>
<td>0.26 (0.15–1.5) **</td>
<td>-0.08 (-0.13, -0.03)</td>
<td>0.001</td>
</tr>
<tr>
<td>AV Vmax (CW)</td>
<td>m/s</td>
<td>2.0 (1.4–2.4)</td>
<td>2.1 (1.8–2.4)</td>
<td>-0.1 (-0.27, 0.04)</td>
<td>0.21</td>
</tr>
<tr>
<td>PV Vmax (PW)</td>
<td>m/s</td>
<td>1.2 (0.5–1.5)</td>
<td>1.2 (0.57–1.7)</td>
<td>0 (-0.18, 0.19)</td>
<td>0.95</td>
</tr>
<tr>
<td>HR (CW)</td>
<td>bpm</td>
<td>137 (111–202)</td>
<td>153 (94–185) *</td>
<td>-17 (0.32, -1.0)</td>
<td>0.042</td>
</tr>
<tr>
<td>E (CW)</td>
<td>m/s</td>
<td>1.1 (0.84–1.4)</td>
<td>1.4 (1.1–3.0) *</td>
<td>-0.33 (-0.71, -0.15)</td>
<td>0.002</td>
</tr>
<tr>
<td>MTG (CW)</td>
<td>mmHg</td>
<td>2.8 (1.7–6.3)</td>
<td>6.7 (3.6–20.8) **</td>
<td>-3.4 (-7.3, -1.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PTG (CW)</td>
<td>mmHg</td>
<td>5.3 (2.9–9.7)</td>
<td>9.7 (5.2–34.0) **</td>
<td>-4.9 (-12.1, -2.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HR (PW)</td>
<td>bpm</td>
<td>135 (107–213)</td>
<td>148 (115–177)</td>
<td>-6.0 (-22.0, 12.0)</td>
<td>0.46</td>
</tr>
<tr>
<td>MTG (PW)</td>
<td>mmHg</td>
<td>2.2 (1.2–3.9)</td>
<td>2.7 (1.9–9.3) *</td>
<td>-0.83 (-2.0, -0.1)</td>
<td>0.031</td>
</tr>
<tr>
<td>PTG (PW)</td>
<td>mmHg</td>
<td>3.8 (2.6–6.0)</td>
<td>4.9 (3.6–16.0) *</td>
<td>-1.33 (-4.0, -0.49)</td>
<td>0.005</td>
</tr>
<tr>
<td>E (PW)</td>
<td>m/s</td>
<td>0.92 (0.81–1.1)</td>
<td>1.1 (0.94–2.0) **</td>
<td>-0.23 (-0.55, -0.1)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Data are presented as median (range).

Ao diameter (hinge point of aortic leaflets) aortic root diameter, AV Vmax: aortic peak velocity, bpm: beats per minute, BT: English Bull Terrier, cm: centimeter, cm$^2$: square centimeter, cm/kg$^{0.294}$: centimeter per kilogram raised to the power of 0.294, cm/kg$^{0.315}$: centimeter per kilogram raised to the power of 0.315, CW: continuous-wave Doppler, E: peak velocity of early diastolic transmitral flow, EF: ejection fraction, EPSS: E-point to septal separation, FS: fractional shortening, HR: heart rate, kg: kilogram,
LAD: left atrial diameter, LAEDV:kg: left atrial end-diastolic volume indexed to body weight, LAESV:kg: left atrial end-systolic volume indexed to body weight, lax: long axis, LA:Ao: ratio of the left atrial dimension to the aortic annulus dimension, LVEDVI: left ventricular end-diastolic volume indexed to body surface area, LVESVI: left ventricular end-systolic volume indexed to body surface area, LVIDd: left ventricular internal dimension at end-diastole, LVIDdN: normalized left ventricular internal dimension at end-diastole, LVIDs: left ventricular internal dimension at end-systole, LVIDsN: normalized left ventricular internal dimension at end-systole, m/s: meter per second, MAD: mitral annulus diameter, mL/kg: milliliter per kilogram, mL/m²: milliliter per square meter, mm: millimeter, mmHg: millimeter of mercury, MTG: mean transmitral gradient, MVA₂D: mitral valve area measurement by planimetry using two-dimensional echocardiography, PTG: peak transmitral gradients, PV V max: pulmonic peak velocity, PW: pulsed-wave Doppler, sax: short axis

* Statistically significant difference (P < 0.05) between healthy BT group and BT with mitral valve abnormalities group

** Statistically significant difference (P < 0.001) between healthy BT group and BT with mitral valve abnormalities group

Hodges-Lehmann median difference with 95% confidence interval (CI)