TITLE: Prognostic value of mitral annular systolic plane excursion and tricuspid annular plane systolic excursion in cats with hypertrophic cardiomyopathy

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Abstract

Introduction: Hypertrophic cardiomyopathy (HCM) has a variable prognosis; left atrial size, presence of clinical signs and left ventricular (LV) systolic function have been shown to predict outcome. Mitral annular plane systolic excursion (MAPSE) and tricuspid annular plane systolic excursion (TAPSE) assess longitudinal ventricular systolic function and are decreased in cats with HCM. The aim of the study was to ascertain whether MAPSE and TAPSE have prognostic value in HCM and if cats with pleural effusion have lower MAPSE and TAPSE than cats with pulmonary oedema.

Animals: 184 client owned cats diagnosed with HCM.

Methods: Retrospective study. Echocardiography was used to diagnose HCM (end-diastolic LV wall thickness ≥ 6mm) and to measure MAPSE and TAPSE. Survival information was obtained.

Results: No multivariable model including MAPSE or TAPSE could be generated in this population. Cats with pleural effusion ± pulmonary oedema had lower MAPSE IVS and TAPSE, compared to cats with pulmonary oedema only. MAPSE IVS was the only factor predicting pleural effusion on multivariable regression model.

Conclusions: Lower MAPSE and TAPSE were not independently associated with outcome on multivariable analysis. Cats with pleural effusion± pulmonary oedema had lower TAPSE and MAPSE IVS than cats with pulmonary oedema and MAPSE IVS was the only predictive factor associated with the development of pleural effusion in this population.

Key words: survival, pleural effusion, pulmonary oedema, feline, echocardiography

PROGNOSTIC VALUE OF MITRAL ANNULAR SYSTOLIC PLANE EXCURSION (MAPSE) AND TRICUSPID ANNULAR PLANE SYSTOLIC EXCURSION (TAPSE) IN CATS WITH HYPERTROPHIC CARDIOMYOPATHY.

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Short title: Prognostic value of MAPSE and TAPSE in HCM

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Abbreviation Table

ATE	arterial thromboembolism
CHF	congestive heart failure
HCM	hypertrophic cardiomyopathy
LVFS	left ventricular fractional shortening
MAPSE	mitral annular plane systolic excursion
MAPSE FW	MAPSE measured at the free wall
MAPSE IVS	MAPSE measured at the interventricular septum
TAPSE	tricuspid annular plane systolic excursion

Introduction

Hypertrophic cardiomyopathy (HCM) is defined as a symmetrical or asymmetrical increase in left ventricular wall thickness in the absence of other cardiovascular or systemic causes that would result in similar changes. [1] Hypertrophic cardiomyopathy is the most common cardiac disease in cats [2,3], it has a variable clinical progression and several echocardiographic parameters have been shown to be of prognostic value. [4-8] Furthermore, recent investigations have identified involvement of the right ventricle in HCM with 29-50% of cats in different studies having an increased thickness of the right ventricular wall [9, 10]. Mitral annular plane systolic excursion (MAPSE) and the right-sided counterpart tricuspid annular plane systolic excursion (TAPSE) are indices of systolic longitudinal displacement of the

atrioventricular annular plane [11, 12]. Mitral and tricuspid annular plane systolic excursion can be obtained by M-mode from echocardiography [11-14], by magnetic resonance imaging (MRI) [15] and TAPSE has also been measured from 2-D cineloops [10]. Mitral and tricuspid annular plane systolic excursion were decreased in cats with HCM compared to healthy control cats [13], and cats with congestive heart failure (CHF) showed the lowest values. One study showed that MAPSE and TAPSE may be of prognostic importance at the univariable level, but the end-point included all-cause mortality due to low number of events and sample size; no multivariable analysis was performed for similar reasons [13]. To the authors' knowledge, the potential prognostic utility of MAPSE and TAPSE in cats with HCM has not been fully evaluated.

Cats in CHF due to HCM can present with either pulmonary oedema and/or pleural effusion [16]. The underlying mechanism(s) responsible for the development of pleural effusion in cats with left-sided congestive heart failure is not fully understood. One study showed that cats with pleural effusion secondary to cardiac disease had poorer left atrial active emptying and increased right ventricular diameters measured by M-mode echocardiography [17], compared to cats that presented with pulmonary oedema. A more recent paper has also identified lower TAPSE values in a subpopulation of cats with pleural effusion compared to cats with pulmonary oedema [10]. Whether the presence of pleural effusion in cats with HCM is associated with a lower value of both MAPSE and TAPSE indicating worse left and/or right heart function has not yet been fully determined.

The aim of the study was to evaluate the prognostic value of MAPSE and TAPSE in a larger population of cats with HCM, for which a longer follow up is available

compared to our previously published study [13] and to determine whether cats presenting with pleural effusion have a lower value of MAPSE and TAPSE compared to cats with pulmonary oedema. Our first hypothesis was that MAPSE and TAPSE would have prognostic value in a population of cats with HCM. Our second hypothesis was that in a subset of cats with HCM and CHF, those presenting with pleural effusion would have lower MAPSE and TAPSE compared to those that presented with only pulmonary oedema.

Animals, materials and methods:

Retrospective study. The study population comprised cats previously included in studies investigating survival in cats with HCM. [7, 8] Inclusion criteria were cats diagnosed with HCM by a board-certified cardiologist or a cardiology resident supervised by a board-certified cardiologist at the Royal Veterinary College, Queen Mother Hospital for Animals based on two-dimensional (2D) echocardiography [18] between June 2004 and August 2009. In addition, cats were required to have a left apical four-chamber cineloop of sufficient quality to enable accurate measurement of MAPSE and TAPSE. Cats were excluded from the study if they had a concurrent diagnosis of hyperthyroidism or hypertension or if no cineloop deemed to be of good quality was available for MAPSE and TAPSE measurement.

Cats were diagnosed with HCM when end-diastolic left ventricular wall thickness measured in B-mode was equal or greater than 6 mm. In addition, left atrial size was assessed on right parasternal short axis view by measuring left atrium to aorta ratio at the onset of QRS [7,19, 20], whilst left atrial diameter in long axis [7,19] was measured from a right parasternal long-axis view, by drawing a line parallel with the mitral annulus bisecting the left atrium in the last frame before mitral valve opening.

Left atrial function was evaluated by measuring left atrial fractional shortening [7] and left atrial ejection fraction [7]. Left ventricular systolic function was assessed using left ventricular fractional shortening (LVFS) on M-mode. [7] Where available, the S' wave of the interventricular septum and left ventricular free wall were measured from mitral annular septal and free wall Tissue Doppler Imaging respectively [19, 21].

Off-line measurement of MAPSE and TAPSE were performed by anatomical M-mode from the left apical four-chamber view as described [13]. Briefly, the anatomical M-mode cursor was aligned parallel to the interventricular septum (IVS) in order to obtain an M-mode tracing for the measurement of MAPSE IVS. Subsequently, the anatomical M-mode cursor was aligned parallel to the free wall (FW) in order to obtain an M-mode tracing for MAPSE FW and finally the cursor was aligned parallel to the right ventricular free wall in order to obtain an M-mode tracing for TAPSE. MAPSE and TAPSE were measured in mm between the most basilar position of the annulus in end-diastole and its most apical displacement at end-systole using the leading edge method. Three consecutive measurements were performed by a single observer (IS) and the results were averaged. MAPSE and TAPSE measurements were performed by a single observer blinded to the clinical status of the patient. All other 2D and Doppler values formed part of the previous study and were measured by a board-certified cardiologist or cardiology resident as described in the original studies [7, 8]. Clinical status classification was no clinical signs, CHF, arterial thromboembolism (ATE), syncope and open mouth breathing during activity based on that described in the previous studies [7,8]. Cats with HCM were classified as not showing clinical signs if they were not receiving diuretic therapy and had no signs or history of increased respiratory rate, dyspnoea, syncope or ATE. To be included in

the CHF group cats had to have documented increased respiratory rate responsive to furosemide and evidence of pulmonary oedema or pleural effusion by imaging (either thoracic ultrasound or thoracic radiography) at the time of presentation or immediately prior to referral. Cats were classified in the pulmonary oedema group if the thoracic radiographs showed an alveolar or interstitial infiltrate and no pleural effusion, whereas cats with pleural effusion had to have at least thoracic ultrasound performed, which confirmed the presence of pleural effusion. Due to the retrospective nature of the study, it was not possible to exclude concurrent pulmonary oedema in cats with pleural effusion and therefore it is possible that a proportion of cats with pleural effusion had concurrent pulmonary oedema. The two groups were therefore classified as pulmonary oedema and pleural effusion ± pulmonary oedema. Aortic thromboembolism was defined based on the location of the thrombus. A limb ATE was defined as a sudden onset painful lower motor neuron deficits in one or more limbs with concurrent pallor and pulselessness. A cerebral ATE was defined based on MRI findings of a well-demarcated lesion that was hyperintense on T2-weighted images. Syncope was defined as a transient episode of loss of consciousness characterised by absence of pre- or postictal signs and rapid recovery. Open mouth breathing during activity was defined as the presence of open mouth breathing noticed by the owners at home only during physical activity (playing or running). [7]

Survival information was obtained by reviewing the electronic clinical archive of the institution and by contacting referring veterinarians or owners. For cats that died, date of death and cause of death (non cardiac, cardiac) were recorded. Cardiac death was defined as euthanasia or natural death following CHF refractory to medical treatment, euthanasia or natural death following ATE or sudden death.

Statistical analysis:

Statistical analysis was performed by a commercially available statistical software [a]. The Shapiro Wilk test was used to verify normal distribution of variables. Normally distributed data are reported as mean (standard deviation, SD) and non-normally distributed data are reported as median (interquartile range, IQR1-3, 25th percentile to 75th percentile).

ANOVA with Tukey post-hoc comparisons, Kruskal Wallis with Dunn post-hoc comparisons or chi-squared tests as appropriate were performed to assess differences based on clinical status at presentation. For analysis of clinical status, cats with open mouth breathing during activity were grouped with cats with syncope due to small group sizes.

Cardiac mortality was the end-point in the survival analysis. Cardiac survival was calculated as the days between diagnosis and death or last visit/contact. Cats still alive at the last point of follow up were right-censored as were cats that died of non-cardiac disease. The Kaplan Meier method was used to estimate survival function and plot time to event curves in the different groups. Continuous variables were explored by division into groups based on quartiles. A log-rank test was used to determine whether a significant difference existed between groups at univariable level. If one or more groups had a disproportionately different hazard (i.e., the quartile curve diverging markedly from the others), a threshold effect was identified and the variable was included in the Cox model as a categorical variable using the cut-off established by the exceptional quartile. Multivariable survival analysis was explored by Cox's proportional hazard analysis.

Student's t test, Mann-Whitney U test or Fisher's exact were performed as appropriate to assess differences within CHF groups (pulmonary oedema and pleural effusion). Multivariable binary logistic regression models were generated to explore factors independently associated with the development of pleural effusion in cats with CHF. Variables significant at $p < 0.2$ were taken forward in a manual forwards stepwise construction. Odds ratios (OR) and 95% confidence intervals (CIs) were calculated and overall model assessment was performed looking at the Hosmer-Lemeshow goodness-of-fit test statistic and the percentage of cases the model correctly classified.

Statistical significance was set at $p < 0.05$. The statistical significance for post-hoc tests with multiple comparisons was set using a Bonferroni correction for 6 comparisons ($p < 0.0083$).

Results:

The study population comprised 184 cats. Median age at presentation was 6.5 years (IQ 1-3 2.8-10.0 years), with a mean body weight of 4.7 kg (SD 1.1kg). Male cats were overrepresented (n=140) compared to female cats (n=44). The majority of cats were Domestic Shorthairs (n=137), followed by British Shorthairs (n=13), Persians (n=10), Domestic Longhair (n=9), Ragdoll (n=5), Sphynx (n=2), and one each of Bengal, Devon Rex, European Shorthair, Exotic Shorthair, Maine Coon, Manx, Oriental Shorthair and Selkirk Rex. One hundred sixty nine cats presented at least one auscultatory abnormality (heart murmur, gallop rhythm or arrhythmia) and the remaining 15 cats had no auscultatory abnormalities. Overall, a heart murmur was auscultated in the majority of cats (n=139), and only a minority presented with a

gallop sound (n=44) or an arrhythmia (n=33). A heart murmur was the only auscultatory abnormality in 102 cats, a gallop was the only auscultatory abnormality in 13 cats and an arrhythmia was the only abnormality in 13 cats. ECGs were performed in 174 cats and an arrhythmia was documented in 54 of them, 26 of which had not been reported on auscultation. A total of 76 cats had clinical signs, including 52 cats with CHF alone, 12 with ATE (including 3 with concurrent CHF), 9 with syncopal episodes and 3 with open mouth breathing during activity at home. Of the 9 cats with syncopal events, 5 were suspected to be secondary to dynamic left ventricular outflow tract obstruction and 4 were suspected to be related to arrhythmic events (two intermittent supraventricular tachycardia, one intermittent ventricular tachycardia and one intermittent third degree AV Block). The three cats that had open mouth breathing during activity at home all had dynamic outflow tract obstruction. The remaining 108 cats did not show clinical signs.

One hundred twenty eight cats (69%) received at least 1 medication. Furosemide (n=61), angiotensin converting enzyme inhibitor (n=65), beta blockers (n=53) and antithrombotic treatments (aspirin n= 33, heparin n= 3, clopidogrel n= 2) were the most common medications. Other medications included spironolactone (n= 14), pimobendan (n=14), positive inotropes during the hospitalisation (one each on dopamine, dobutamine), diltiazem (n=1). Potassium was supplemented in 5 cats, rutin was administered in 2 cats and taurine was administered in 1 cat. All cats with congestive heart failure were receiving furosemide. In addition, cats with pleural effusion± pulmonary oedema were receiving angiotensin converting enzyme inhibitors (n=22), pimobendan (n=12), spironolactone (n= 6), antithrombotic agents (aspirin n=9, heparin n=1, clopidogrel n=1) and potassium supplementation (n=4).

Positive inotropes were administered during hospitalisation (dobutamine n=1, dopamine n=1) and taurine was supplemented in one cat. Cats with pulmonary oedema were receiving angiotensin converting enzyme inhibitors (n=18), pimobendan (n=1), spironolactone (n= 2), antithrombotic agents (aspirin n=9, clopidogrel n=1), beta blockers (n=1) and potassium supplementation (n=1).

Compared to cats not showing clinical signs, cats with congestive heart failure were more likely to have a gallop sound ($p<0.001$), arrhythmia on auscultation ($p=0.002$) or on ECG ($p<0.001$) and were less likely to have a heart murmur ($p< 0.001$) (Table 1). Cats with congestive heart failure also had more severe maximal left ventricular wall thickness ($p<0.001$), enlarged left atrium on both short- ($p<0.001$) and long-axis ($p<0.001$), lower left ventricular fractional shortening ($p<0.001$), poorer left atrial function as assessed by left atrial fractional shortening ($p<0.001$) and ejection fraction ($p<0.001$). A higher prevalence of spontaneous echo-contrast was observed in cats with CHF and ATE ($p<0.001$) (Table 2).

In the overall population MAPSE FW was 4.28 ± 1.15 mm, MAPSE IVS was 3.86 ±1.02 mm and TAPSE 7.65±1.99 mm. Cats with CHF had significantly lower MAPSE FW, MAPSE IVS and TAPSE compared to cats not showing clinical signs (Table 2).

At last follow up, 74 cats were alive, a cardiac cause of death was identified in 71 cats (35 due to CHF, 24 due to ATE and 12 due to sudden death) and 38 cats died of non-cardiac disease. One cat was lost to follow up. When exploring the association between survival and MAPSE FW, MAPSE IVS and TAPSE in the overall HCM population by univariable analysis, Kaplan Meier curves showed that cats in the lowest quartile (MAPSE FW < 3.58 mm, MAPSE IVS < 3.20 mm, TAPSE < 6.33 mm) were more likely to reach the final endpoint (cardiac death) earlier than cats in the

remaining quartiles. Kaplan Meier curves and survival data were therefore presented using these cut-off values (supplement data, figures 1-3). It was not possible to generate a multivariable Cox proportional hazards model that included MAPSE at the left ventricular free wall, MAPSE at the interventricular septum or TAPSE because these parameters were not statistically significant in the final multivariable model, which was similar to a previously published multivariable model [7]. Neither MAPSE FW, MAPSE IVS or TAPSE had prognostic value at the univariable level in the subgroup of cats without clinical signs or in the subgroup of cats with CHF.

Of the 55 cats that presented with CHF (including 3 cats with both CHF and ATE), 32 cats were included in the pleural effusion ± pulmonary oedema group (16 of which had confirmed concurrent pulmonary oedema) and 21 in the pulmonary oedema only group. The remaining 2 cats presented with mild pericardial effusion not causing tamponade. In the CHF group, cats with pleural effusion ± pulmonary oedema had significantly lower MAPSE IVS and TAPSE than cats with pulmonary oedema ($p=0.041$ and $p= 0.020$ respectively). Cats with pleural effusion ± pulmonary oedema had lower LAEF ($p=0.010$) than cats with pulmonary oedema. No statistically significant difference was observed between the groups for MAPSE FW ($p= 0.609$), left atrium to aorta ratio ($p=0.237$), left atrial diameter in long axis ($p= 0.082$), left atrial fractional shortening ($p=0.091$), LVFS ($p=0.071$), peak velocity of systolic mitral annular motion as determined by puled wave Doppler measured at the free wall ($p=0.841$) orat the interventricular septum ($p=0.441$) (Table 2). For the remaining groups of cats with clinical signs (aortic thromboembolism, syncope, exertional dyspnoea), no sub-analyses were performed due to small sample sizes. In the multivariable binary logistic regression model, only MAPSE IVS was independently

associated with development of pleural effusion. The model correctly predicted 62.3% of cases and the Hosmer-Lemeshow test statistic suggested good model fit (p=0.924).

Discussion:

This study has demonstrated that neither MAPSE at the free wall, interventricular septum or TAPSE are independently associated with outcome in cats with HCM. On univariable analysis, MAPSE IVS and TAPSE, but not MAPSE FW, were lower in cats with pleural effusion ± pulmonary oedema than pulmonary oedema only. Multivariable analysis of the above parameters in cats with CHF demonstrated that cats with higher MAPSE IVS were less likely to have pleural effusion.

Mitral and tricuspid annular plane systolic excursions are M-mode derived parameters that assess the longitudinal displacement of the atrio-ventricular annulus during systole, as the heart base moves toward the apex. These parameters can therefore be considered as markers of systolic longitudinal function. Subclinical longitudinal dysfunction is recognised in people with HCM when assessed by deformation imaging [22] and also in cats with HCM when assessed by MAPSE [13]. TAPSE is considered a robust parameter of right ventricular systolic function in people and dogs [12, 23-25]. There is increasing interest in assessing right ventricular size and function in people and cats with HCM [9, 10, 13, 26-29], given that one third of people and cats with HCM have concomitant left and right ventricular wall thickening [9, 27]. In a previous study involving a smaller population of cats, MAPSE and TAPSE were both found to be decreased in cats with HCM compared to healthy cats [13], with cats in CHF having the lowest MAPSE and TAPSE values. Another study found similar results for TAPSE [10].

The present study has confirmed the decrease in MAPSE and TAPSE in cats with CHF compared to cats not showing clinical signs of congestion in a greater number of cats than previously published. Univariable survival analysis of all cats showed that those in the lowest quartile for MAPSE FW, MAPSE IVS and TAPSE had a poorer outcome than cats in the other quartiles. However, neither MAPSE FW, MAPSE IVS or TAPSE were independently associated with outcome at the multivariable level. Furthermore, MAPSE FW, MAPSE IVS and TAPSE did not show prognostic value at univariable level when cats without clinical signs or cats with CHF were assessed separately.

These findings confirm that longitudinal function is impaired in cats with HCM, as also shown in people [15, 22]. This may be compensated by alterations in other cardiac mechanics such as increased torsion [30,31], or circumferential function [22] so that longitudinal function is not itself a major prognostic factor for survival as long as other compensating mechanism are in place. This may explain why a decrease in LVFS had a prognostic impact in cats with HCM in a previous study [7]. LVFS can be considered a marker of short axis function, indicating that as long as circumferential function is maintained, longitudinal function may not impact survival. Once overall systolic function is decreased, as could be the case when both longitudinal and circumferential function decrease, survival may be impaired. Circumferential function assessed by advanced imaging are variable in people affected by HCM [22], but some authors have suggested that it may play a role in preserving overall systolic function.

Cats with pleural effusion ± pulmonary oedema had lower MAPSE IVS and TAPSE, but no difference in MAPSE FW, compared to cats with pulmonary oedema.

Multivariable analysis in this subgroup identified that lower MAPSE IVS was significantly associated with an increased risk of development of pleural effusion. Pleural effusion is a major clinical presentation in cats with CHF and HCM, and the influence of both right ventricular and left atrial function on the development of pleural effusion has been previously studied [10,17]. Our data complements previously published findings, which show that cats with pleural effusion have decreased right and interventricular longitudinal function compared to cats with pulmonary oedema as well as decreased left atrial ejection fraction. These findings would be expected since longitudinal deformation is the dominant component of myocardial deformation of the right ventricle [32] and right ventricular wall thickness and right atrial size are shown to be increased in cats with pleural effusion [10]. Furthermore, the decrease in left atrial ejection fraction in cats with pleural effusion ± pulmonary oedema in this study complements previous data showing a decrease in active atrial emptying in cats with pleural effusion [17]. Mitral annular plane systolic excursion at the interventricular septum was the only factor associated with the development of pleural effusion on multivariable regression analysis, which may indicate a role of the interventricular septum. Based on the available literature and the results of the present study, it is likely that worsening atrial function, decreased right ventricular longitudinal function and possibly more pronounced ventricular interdependence in hypertrophic cardiomyopathy [36] are potentially responsible for the development of pleural effusion. Systolic S' waves measured at the mitral annulus by pulsed wave Doppler results did not correlate with the MAPSE results in cats with CHF in this study. This is likely to reflect the reduced number of cases where the S' wave was available rather than being a true discrepancy between the two techniques,

particularly since these two parameters align closely in human patients [29]. When comparing outcome in cats with pulmonary oedema and pleural effusion ± pulmonary oedema, no difference in survival was found. These findings may suggest that once congestive heart failure develops, the prognosis is poor regardless of the clinical presentation (pleural effusion vs pulmonary oedema).

The authors are aware that the study has limitations. First of all, being a retrospective study, it may contain limitations related with data collection, survival information and classification. This study included clinical patients, which received tailored treatment based on clinician's judgement and personal preference. The timing from stabilisation to echocardiographic assessment was also variable, as well as the treatment protocol, thus we cannot exclude that the effect of treatment may have influenced the results. Fourteen cats received oral pimobendan, which in the vast majority of the cases would have been administered on the basis of, and therefore following, the echocardiographic examination, but we cannot rule out the possibility that some cats received pimobendan prior to echocardiographic assessment. It is not known how much influence this may have had on the reported MAPSE and TAPSE values. Survival information was based on the information provided by the referring vets and only if insufficient information was provided, a questionnaire was sent to the owners. It is possible that some of the cases may have been incorrectly classified into cardiac or non-cardiac cause of death due to a bias in the information provided. Due to the retrospective nature of the study, it was not possible to dichotomise the CHF population into pulmonary oedema versus pleural effusion only. The authors elected not to exclude cats with concurrent pulmonary oedema from the pleural effusion group as the focus was on right ventricular function and the development of pleural

effusion. Mitral and tricuspid annular plane systolic excursion were derived from an M-mode technique, and this can be associated with angle-dependency, however the ability to position the M-mode cursor over the 2D image in the anatomical M-mode limits the weakness of the technique. In addition, in a previous study the coefficient of variation and the interobserver bias was deemed to be acceptable for this technique [13]. Mital and tricuspid annular plane systolic excursions were not normalised to body length, however most cats have body weights that only cover a small range and therefore the lack of normalisation is unlikely to be an important source of error. The presence of pulmonary hypertension was not assessed with echocardiography or invasively. It was beyond the scope of the study to assess correlations with other echocardiographic parameters of right or left ventricular size or function.

Conclusion:

The present study showed that MAPSE and TAPSE were not independently associated with outcome in cats with HCM. Cats with pleural effusion± pulmonary oedema had lower TAPSE and MAPSE IVS at the univariable level and lower MAPSE IVS in the multivariable model than cats with pulmonary oedema, suggesting a potential role of right ventricular function and of the interventricular septum in the development of pleural effusion.

Footnotes:

a. IBM® SPSS® Statistics version 22, IBM (UK) Ltd, Portsmouth, UK

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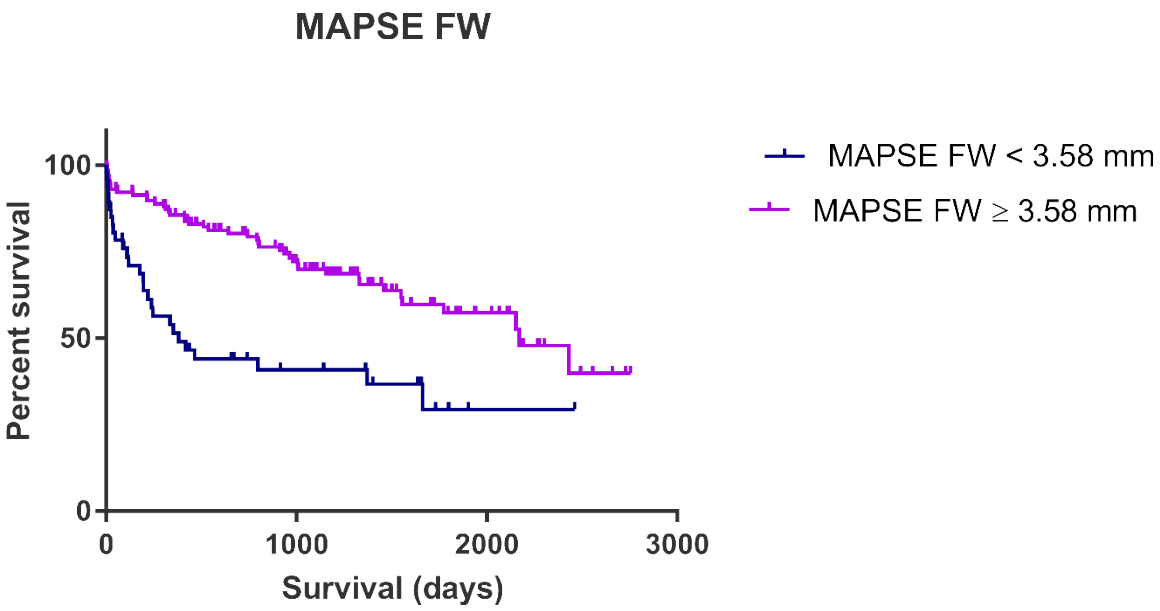
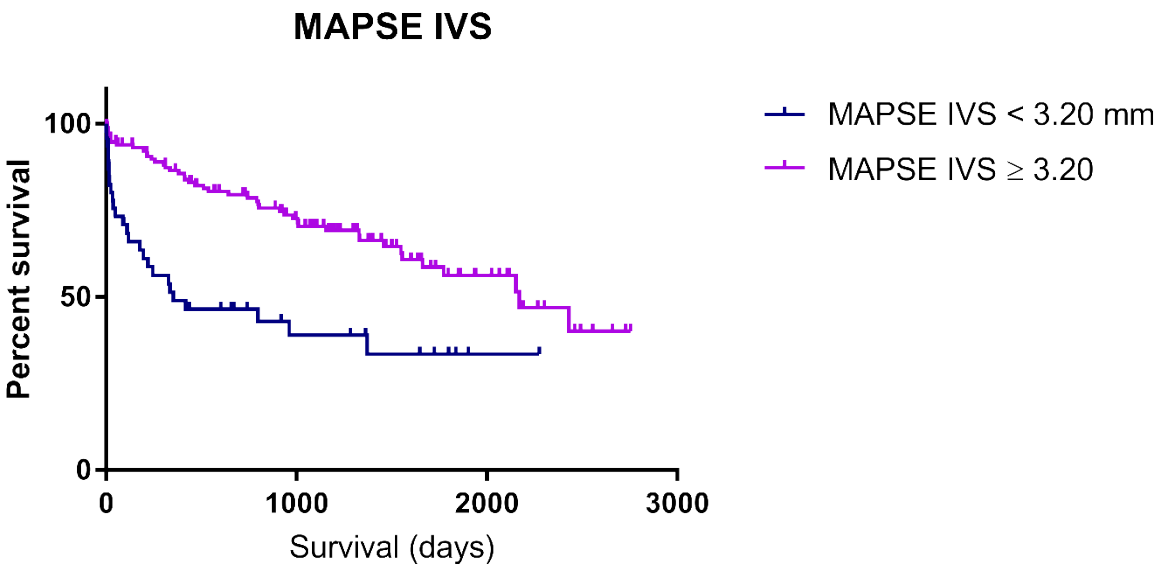


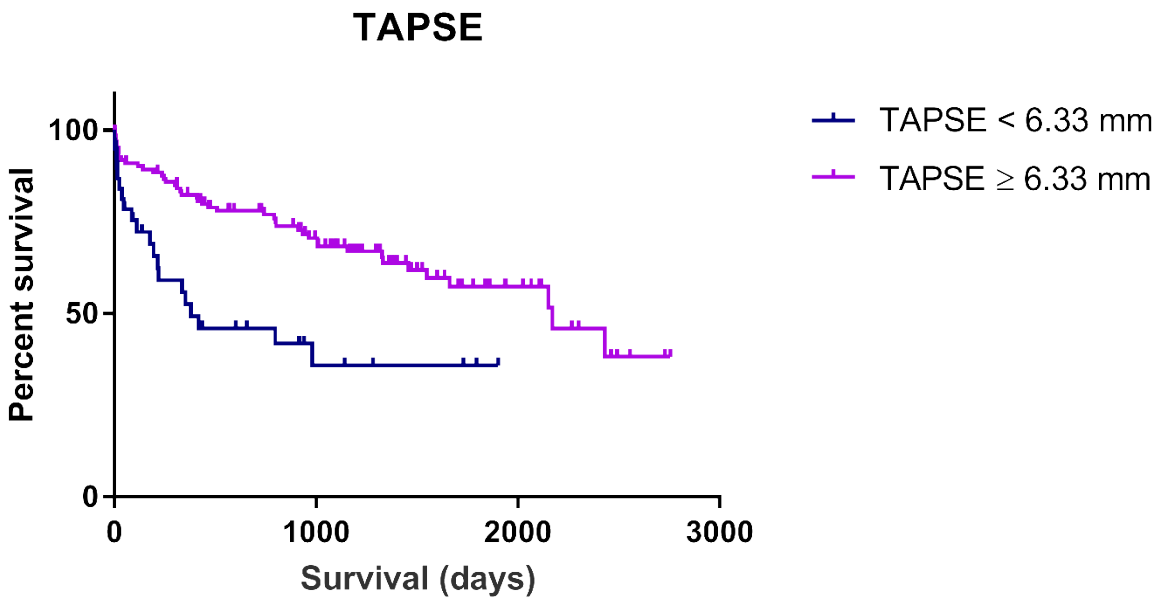
Supplemental material

Fig 1: Univariate Kaplan Meyer survival curve for mitral annular plane systolic excursion measured at the left ventricular free wall (MAPSE FW). Log rank test, p <0.001. Median survival time for MAPSE FW < 3.58 mm is 352 (1-1902) days, for MAPSE FW ≥ 3.58 mm median survival time is 2171 (0-2755) days. MAPSE FW – mitral annular plane systolic excursion measured at the free wall,



Supplemental material

Fig 2: Univariate Kaplan Meyer survival curve for mitral annular plane systolic excursion measured at the interventricular septum (MAPSE IVS). Log rank test, $p < 0.001$. Median survival time for MAPSE IVS < 3.20 mm is 352 (0-2276) days, for MAPSE IVS ≥ 3.20 mm median survival time is 2171 (2-2755) days. MAPSE IVS – mitral annular plane systolic excursion measured at the interventricular septum



Supplemental material
Fig 3: Univariate Kaplan Meyer survival curve for tricuspid annular plane systolic excursion (TAPSE). Log rank test, $p < 0.001$
Median survival time for TAPSE < 6.33 mm is 380 (0-1902) days, for TAPSE ≥ 6.33 mm median survival time is 2171 (2-2755) days. TAPSE – tricuspid annular plane systolic excursion

Table 1: Clinical data in 184 cats with HCM

	No clinical signs n=108	Congestive heart failure n=52	Aortic thromboembolism n=12	Syncope/ open mouth breathing n=12	P value
Age (years)	6.52 (2.72-10.02) n=108	6.95 (2.98-10.21) n=52	6.29 (3.52-10.59) n=12	6.38 (2.80-10.61) n=12	0.963
Sex (% male)	78.7% (85/108)	75.0% (39/52)	75.0% (9/12)	58.3% (7/12)	0.470
Breed (% non-pedigree)	77.8% (84/108)	76.9% (40/52)	100.0% (12/12)	83.3% (10/12)	0.309
Weight (kg)	4.81 ± 1.08 n=96	4.64 ± 1.18 n=50	4.44 ± 0.61 n=12	4.69 ± 1.01 n=11	0.623
Murmur (%)	87.0%[a, b] (94/108)	55.8%[b] (29/52)	50.0%[a] (6/12)	83.3% (10/12)	<0.001
Gallop (%)	13.0%[a] (14/108)	42.3%[a] (32/52)	33.3% (4/12)	33.3% (4/12)	<0.001
Arrhythmia (%)	10.2%[a] (11/108)	34.6%[a] (18/52)	8.3% (1/12)	25.0% (3/12)	0.002
Arrhythmia on ECG (%)	20.0%[a,b] (21/105)	47.8%[a] (22/46)	18.2% (2/11)	75.0%[b] (9/12)	<0.001
Heart rate (bpm)	180 (160-200) n=103	190 (164-200) n=49	180 (148-206) n=12	178 (138-200) n=12	0.755
Respiratory rate (breaths/min)	40 (32-60) n=97	51 (41-60) n=48	48 (40-56) n=11	48 (36-52) n=11	0.063

Table 1: Clinical data in the study population grouped by the absence/ presence and type of clinical signs. Within a line, different superscript letters indicate statistical differences ($p < 0.0083$) between groups. CHF – congestive heart failure, ATE – arterial thromboembolism. Normally distributed data are presented as mean ± standard deviation, non-normally distributed data are presented as median (IQR1-3) and proportions are presented as percentage (nr of cats with clinical sign/total number of cats).

Table 2 Echocardiographic data in 184 cats with HCM

	No clinical signs n=108	Congestive heart failure n=52	Aortic thromboembolism n=12	Syncope/ open mouth breathing n=12	P value
Max 2D LVWd thickness	7.6 (6.8-8.1)[a] n=108	8.5 (7.7-9.7)[a] n=52	8.6 (6.6-9.9) n=12	8.2 (7.3-8.8) n=12	<0.001
LVFS (%)	53.8 ± 11.2[a] n=105	43.1 ± 18.0[a] n=48	45.3 ± 4.0 n=12	51.5 ± 10.8 n=12	<0.001
Infarct (%)	1.9% (2/108)	11.5% (6/52)	0.0% (0/12)	0.0% (0/12)	0.027
LVOTO (%)	74.1%[a] (80/108)	52.4% (22/42)	27.3%[a] (3/11)	72.7% (8/11)	0.003
RVOTO (%)	35.9% (37/103)	32.5% (13/40)	10.0% (1/10)	41.7% (5/12)	0.377
Restrictive filling (%)	8.5%[a,b] (4/47)	70.8%[a] (17/24)	55.6%[b] (5/9)	0.0% (0/4)	<0.001
LAD (mm)	15.5 (14.2-16.8)[a] n=100	22.3 (17.5-5.7)[a,b] n=44	20.1 (14.8-23.9) n=11	15.9 (15.2 -17.3)[b] n=12	<0.001
LA:Ao	1.27 (1.16-1.44)[a,b] n=102	2.17 (1.75-.61)[a, c] n=46	2.15 (1.29-2.60)[b] n=11	1.35 (1.24-1.69)[c] n=12	<0.001
LAFS (%)	22.7 ± 6.7 n=97	9.6 ± 4.9 n=43	14.1 ± 9.1 n=11	19.8 ± 6.3 n=10	<0.001
LAEF (%)	60.1 (50.8-66.0)[a, b] n=97	22.3 (12.3-9.8)[a, c] n=43	27.5 (22.6-46.5)[b] n=11	57.3 (33.6-63.0)[c] n=10	<0.001
SEC/Thrombus (%)	0.0%[a,b] (0/108)	49.0%[a] (25/51)	50.0%[b] (6/12)	8.3% (1/12)	<0.001
MAPSE FW (mm)	4.75 ± 0.88 [a] n=105	3.35 ± 1.06 [a, b] n=51	3.94 ± 1.31 n=12	4.43 ± 1.12[b] n=12	<0.001
MAPSE IVS (mm)	4.16 ± 0.78 [a] n=108	3.08 ± 0.97 [a, b] n=52	3.61 ± 1.34 n=12	4.14 ± 1.15 [b] n=12	<0.001
TAPSE (mm)	8.41 ± 1.65 [a] n=99	6.10 ± 1.89 [a] n=48	7.50 ± 1.61 n=12	7.77 ± 1.90 n=10	<0.001
S' FW (cm/s)	7.0 (6.0-9.0) [a] n=73	5.0 (3.2-7.0)[a] n=19	6.4 (3.7-10.1) n=6	9.0 (6.5-10.5) n=6	0.001
S' IVS (cm/s)	9.0 (8.0-11.0)[a] n=99	6.0 (5.0-7.0)[a, b] n=41	7.3 (6.3-9.1) n=10	9.3 (7.5-14.9)[b] n=9	<0.001

Table 2: Echocardiographic data in the study population grouped by the absence/ presence and type of clinical signs. Within a line, different superscript letters indicate statistical differences ($p < 0.0083$) between groups. Normally distributed data are presented as mean ± standard deviation, non-normally distributed data are presented as median (IQR1-3) and proportions are presented as percentage (nr of cats with echocardiographic finding/total number of cats). CHF – congestive heart failure, ATE – arterial thromboembolism, 2D LVWd – two dimensional end-diastolic left ventricular wall thickness, LVFS – left ventricular fractional shortening, LVOTO – left ventricular outflow tract obstruction, RVOTO – right ventricular outflow tract obstruction, LAD – left atrial diameter in long axis, LA:Ao – left atrium to aorta ratio, LAFS – left atrial fractional shortening, LAEF – left atrial ejection fraction, SEC – spontaneous echo contrast, MAPSE FW – mitral annular plane systolic excursion measured at the free wall, MAPSE IVS – mitral annular plane systolic excursion measured at the interventricular septum, TAPSE – tricuspid annular plane systolic excursion, S' FW – peak velocity of systolic mitral annular motion as determined by pulsed wave Doppler measured at the level of the left ventricular free wall, S' IVS – peak velocity of systolic mitral annular motion as determined by pulsed wave Doppler measured at the level of the interventricular septum

Table 3: Clinical data in 53 cats with hypertrophic cardiomyopathy and congestive heart failure

	Pleural effusion n=32	Pulmonary oedema n=21	P value
Age (years)	9.02 (3.08-11.78) n=32	4.76 (2.58 – 8.38) n=21	0.079
Sex (% male)	71.9% (23/32)	76.2% (16/21)	>0.999
Breed (% non-pedigree)	71.9% (23/32)	90.5% (19/21)	0.167
Weight (kg)	4.52 ± 1.16 n=31	4.72 ± 1.20 n=20	0.561
Murmur (%)	40.6% (13/32)	71.4% (15/21)	0.048
Gallop (%)	53.1% (17/32)	28.6% (6/21)	0.096
Arrhythmia (%)	34.4% (11/32)	23.8% (5/21)	0.544
Arrhythmia on ECG (%)	51.9% (14/27)	30.0% (6/20)	0.152
Heart rate (bpm)	200 (168-200) n=31	180 (160-200) n=19	0.559
Resp rate (breaths/min)	50 (36-60) n=31	60 (48-83) n=18	0.033

Table 3: Clinical data in cats with hypertrophic cardiomyopathy and congestive heart failure . Cats were grouped in the pulmonary oedema group if thoracic radiographs showed alveolar/ interstitial pattern, whereas to be include in the pleural effusion group at radiographic or thoracic ultrasound had to confirm the presence of pleural effusion. A t-test or Mann-Whitney U test (for normally and non- normally distributed data, respectively) to test for significant difference between cats with pleural effusion vs pulmonary oedema.

Table 4: Echocardiographic data in 53 cats with hypertrophic cardiomyopathy and congestive heart failure

	Pleural effusion n=32	Pulmonary oedema n=21	P value
Max 2D LVWd thickness	8.3 (7.6-9.3) n=32	8.5 (7.7-9.8) n=21	0.682
LVFS (%)	39.6 ± 19.0 n=29	48.7 ± 13.4 n=20	0.071
Infarct	19.4% (6/32)	0.0% (0/21)	0.070
LVOTO	34.8% (8/23)	65.0% (13/20)	0.069
RVOTO	14.3% (3/21)	52.6% (10/19)	0.017
Restrictive filling (%)	78.6% (11/14)	66.7% (8/12)	0.665
LAD (mm)	23.3 (19.0-26.8) n=27	20.3 (17.4-22.6) n=18	0.082
LA:Ao	2.44 (1.85-2.61) n=27	2.06 (1.70-2.48) n=20	0.237
LAFS (%)	8.6 ± 4.7 n=24	11.1 ± 4.9 n=20	0.091
LAEF (%)	17.4 (8.6-32.5) n=24	29.1 (20.2-44.1) n=20	0.010
SEC/Thrombus (%)	54.8% (17/31)	42.9% (9/21)	0.572
MAPSE FW (mm)	3.29 ± 1.17 n=32	3.43 ± 0.91 n=21	0.609
MAPSE IVS (mm)	2.87 ± 1.01 n=32	3.42 ± 0.80 n=21	0.041
TAPSE (mm)	5.68 ± 1.95 n=30	6.86 ± 1.47 n=19	0.020
S' FW (cm/s)	4.5 (3.0-7.0) n=14	4.9 (4.0-5.5) n=6	0.841
S' IVS (cm/s)	6.0 (4.1-7.0) n=24	6.5 (5.0-7.1) n=17	0.441

Table 4. Echocardiographic data in cats with hypertrophic cardiomyopathy and congestive heart failure. Cats were grouped in the pulmonary oedema group if thoracic radiographs showed alveolar/ interstitial pattern, whereas to be include in the pleural effusion group at radiographic or thoracic ultrasound had to confirm the presence of pleural effusion. A t-test or Mann-Whitney U test (for normally and non- normally distributed data, respectively) to test for significant difference between cats with pleural effusion vs pulmonary oedema.2D LVWd – two dimensional end-diastolic left ventricular wall thickness, LVFS – left ventricular fractional shortening, LVOTO – left ventricular outflow tract obstruction, RVOTO

– right ventricular outflow tract obstruction, LAD – left atrial diameter in long axis, LA:Ao – left atrium to aorta ratio, LAFS – left atrial fractional shortening, LAEF – left atrial ejection fraction, SEC – spontaneous echo contrast, MAPSE FW – mitral annular plane systolic excursion measured at the free wall, MAPSE IVS – mitral annular plane systolic excursion measured at the interventricular septum, TAPSE – tricuspid annular plane systolic excursion, S' FW – peak velocity of systolic mitral annular motion as determined by pulsed wave Doppler measured at the level of the left ventricular free wall, S' IVS – peak velocity of systolic mitral annular motion as determined by pulsed wave Doppler measured at the level of the interventricular septum

Table 5: multivariable regression model in cats with pleural effusion ± pulmonary oedema vs pulmonary oedema only

	Odds ratio (95% CI)	p value
MAPSE IVS	0.528 (0.281-0.992)	0.047
Constant	11.390	0.023

Table 5. Multivariable binary logistic regression model of factors associated with development of pleural effusion± pulmonary oedema rather than pulmonary oedema alone. MAPSE IVS – mitral annular plane systolic excursion measured at the interventricular septum