**Usefulness of pulsed-wave Tissue Doppler imaging at the mitral annulus for prediction of new-onset atrial fibrillation**

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**ABSTRACT**

**Introduction:** The time from the onset of the P-wave on electrocardiogram to the peak of late diastolic wave signal (PA-TDI interval) recorded by left atrial Tissue Doppler imaging is a surrogate of the total atrial conduction time and it can predict the development of new-onset AF in people. This study investigated whether PA-TDI interval measured with PW-TDI at level of lateral aspect of the mitral valve could identify dogs which developed AF within 6 months following echocardiography (echo).

**Animals:** 42 dogs were included in the study: 21 dogs that developed AF within 6 months following echo (AF Group) and 21 dogs that did not. Groups were matched for body weight and left atrium to aortic root ratio (LA:Ao).

**Methods:** This was a retrospective study. A review of signalment, underlying disease and echo was done. PA-TDI interval was measured offline with PW-TDI. PA-TDI interval and echocardiographic variables of 2D, M-Mode and PW-TDI were compared between groups. Receiving operator characteristic curves were used to identify the best AF predictor. Univariate and multivariate regression was used to evaluate predictors of PA-TDI interval.

**Results:** The AF group had significantly greater 2D left atrial maximal diameter, left-ventricular (LV) end-diastolic and end-systolic volumes, M-Mode LV internal diameter and LV end-systolic volume indexed for body weight. PA-TDI was significantly longer in the AF group and it was superior to other echocardiographic variables at predicting AF development within 6 months (AUC=0.896).

**Conclusions:** PA-TDI interval measured with PW-TDI at the lateral mitral valve annulus can identify dogs at risk of new-onset AF.

**ABBREVIATIONS:**

|  |  |
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| Abbreviation | Definition |
| 2D LAmax | 2D left atrial maximal diameter |
| A | peak velocity of late diastolic transmitral flow |
| A’ | late diastolic wave signal as measured by Tissue Doppler imaging |
| AF | atrial fibrillation |
| BW | body weight |
| E | peak velocity of early diastolic transmitral flow |
| EDV | end-diastolic volume |
| ESVI | end-systolic volume index |
| IVRT | isovolumic relaxation time |
| LA:Ao | ratio of the left atrial dimension to  the aortic annulus dimension |
| LAmax:Ao | 2D left atrial maximal diameter indexed to aortic root diameter |
| LVIDd | left ventricular internal dimension at end-diastole |
| LVIDs | left ventricular internal dimension at end-systole |
| PA-TDI | time interval from the onset of the P-wave on electrocardiogram to the peak of A’ |
| PW-TDI | pulsed-wave Tissue Doppler imaging |
| TACT | total atrial conduction time |

**Introduction**

Atrial fibrillation (AF) is the most common supraventricular tachyarrhythmia in dogs [1, 2]. It can occur in healthy dogs (lone AF) but is most commonly associated with dilated cardiomyopathy in large and giant breeds and acquired mitral valve disease in the small breeds [3]. Its clinically importance as a negative prognostic factor was shown in one study with Dobermans Pinchers [4] and, more recently, in medium and large breeds [1].

AF is characterized electrocardiographically by a disorganised and fast atrial activity that ultimately leads to detrimental effects. The loss of the atrial function to the ventricular filling combined with the shortened diastolic times due to the typical fast and irregular ventricular rates contributes to an important reduction in the cardiac output and worsening of the left sided filling pressures [1]. Additionally, the chronic tachycardia can also exacerbate the left ventricular systolic and diastolic dysfunction [5, 6].

In humans, the underlying mechanisms for AF have been historically discussed but the main 3 theories suggest that AF is caused by a rapidly discharging, spontaneously active, atrial ectopic foci, by a single re-entry circuit, or by multiple functional reentrant circuits [7]. Currently, there is supporting evidence suggesting that all these mechanisms can be a cause of AF in dogs [8].

It is recognised that atrial enlargement has been a predisposing factor for AF as it can sustain re-entry by allowing wavelets to move about without colliding and terminating each other [2, 8, 9]. Despite this, not all dogs with atrial enlargement develop AF [10]. Other conditions that shorten the refractory period or slows atrial conduction velocity can also favour the development of AF [8, 9].

In contrary to human medicine, there is lack of predictors of this arrhythmia in veterinary cardiology. To the author’s knowledge, only body weight (BW) and left atrial size were shown to be predictive factors of development of AF [10]. In human cardiology, the total atrial conduction time (TACT), which reflects the total time required for atrial electrical activation, can be determined by measuring the maximal P-wave duration in signal-averaged electrocardiogram, and is reported to one of the most powerful predictors of AF [11-13]. The TACT has the advantage of being determined by both atrial dilation and depressed intra-atrial conduction [14, 15].

Due to practical limitations of signal-averaged electrocardiogram, various Doppler echocardiography-derived parameters have been proposed to estimate TACT, including the time from the onset of the P-wave on electrocardiogram to the peak of late diastolic wave signal (A’), termed the PA-TDI interval, recorded at the level of the lateral left atrial wall on colour Tissue Doppler imaging [16] or on pulsed-wave tissue Doppler imaging TDI (PW-TDI) [11, 15].

In human cardiology, a PA-TDI, measured with left atrial PW-TDI, may predict the development of new-onset AF in the general human population [15]. As the A’ is secondary to atrial contraction, it was the objective of this study to test the hypothesis that the measurement of PA-TDI by PW-TDI at the level of lateral mitral valve annulus could also predict the development of new-onset AF in dogs with heart disease.

**Animal, Materials and Methods**

The study protocol was reviewed and approved by the Veterinary Research Ethics Committee of University of Liverpool.

*Inclusion criteria*

For this retrospective study, the echocardiographic database (Echopac, General Electric) of the Small Animal Teaching Hospital, University of Liverpool, was searched for dogs coded with any form of heart disease two and AF between March 2005 and July 2017. The dogs were not eligible to be included in the study if the PW-TDI study had not been performed or if it was of inadequate quality. For the purpose of this study, the PW-TDI study was considered to have an inadequate quality if: (1) onset of the P wave in the continuous electrocardiogram was not clear and well defined; (2) there was complete summation of the early and late diastolic wave signal, (3) the peak of the A’ spectral profile was not obvious and if (4) there were no sinus beats during the recorded PW-TDI studies.

Two groups of dogs were composed with different inclusion criteria. Dogs with cardiac disease that developed a new-onset AF (paroxysmal or sustained) within a 6-month period after a transthoracic Doppler echocardiography were included for data analysis as *AF cases*. When more than one transthoracic echocardiography was available within the 6-month period, only the most recent study prior to the diagnosis of AF was used for analysis. These dogs composed the *AF group*.

For each AF case, the most recently scanned dog in our echocardiographic database that (1) did not develop AF during a 6-month period after a transthoracic echocardiography, (2) had heart disease and (3) had a value of left atrium-to-aortic root ratio (LA:Ao) and BW no more than 25 % different than the LA:Ao and BW of a matched AF case was selected as a *Non-AF case* [e.g. : - 25 ≤ 100 x (BWAF case-BW Non-AF case)/BWAF case ≤ 25]. These dogs composed the *Non-AF group.*

*Clinical data*

Medical records of the dogs included in the study were reviewed and data used for analysis included sex, breed, BW, underlying heart disease, age at the time of the echocardiography, and time from echocardiography until AF (if an AF case).

*Standard echocardiographic data*

Doppler echocardiography had been carried out by board-certified cardiologists or supervised residents with a GE Vivid 7 (General Electric) ultrasound machine with simultaneous single-lead electrocardiogram. Standard echocardiographic views were acquired as previously described [17] and measurement protocols followed. Recordings were stored as still frames or cine loops for offline analysis (Echopac, General Electric). None of the dogs were sedated.

The left atrial size was assessed by the left atrial maximal diameter (2D LAmax), left atrial maximal diameter to aortic annulus diameter ratio (2D LAmax:Ao) and LA:Ao. As previously described [18], the 2D LAmax dimension was performed from the right parasternal long-axis four chamber view at the last frame prior to mitral valve opening by drawing a line that bisects the left atrium into two equal halves and is parallel to the line defining connecting the mitral annulus. The 2D LAmax:Ao (LA enlargement if > 2.6; Bonagura JD, unpublished data) was obtained by dividing the 2D LAmax by the distance between the maximally opened aortic valve leaflets during systole (2D LAmax:Ao >2.6:1 exceed the upper 95% confidence limits for the reference data [19]). The LA:Ao was assessed by 2D from right parasternal short-axis view measured at first frame after closure of the aortic valve at the level of the aortic root as previously reported [20].

Left ventricular end-diastolic and end-systolic internal dimensions (LVIDd, LVIDs) were measured from the right parasternal short-axis view using M-mode at the level of the chordae tendineae [17]. Left ventricular internal dimensions were normalized to BW [21] and fractional shortening was calculated [22].

The left ventricular end-systolic and end-diastolic volume (EDV) were obtained from the right parasternal long-axis four chamber view by the Simpson’s method as previously described [23]. Left ventricular systolic volume were indexed to body surface area (ESVI) and ejection fraction was calculated.

From spectral Doppler of the mitral inflow, the peak velocity of early (E) and late (A) diastolic transmitral flow were measured and E to A ratio was calculated. Mitral inflow data from cases with complete wave summation were excluded from statistical analysis. If partial E and A fusion was present, data were included provided that the A wave commenced during the E wave deceleration at less than 0·2 m/second [24]. Isovolumic relaxation time (IVRT) was measured as previously described in dogs and the E to IVRT ratio was calculated [24, 25].

Recordings of longitudinal PW-TDI of the basal interventricular septum and lateral aspect of mitral valve annulus were used for measurements of the major Tissue Doppler imaging velocities during ventricular diastole (peak velocity of early diastolic mitral annular motion and peak velocity of diastolic mitral annular motion). PW-TDI velocities were excluded from analysis if they had summation of early and late diastolic wave signals.

*Estimation of TACT by PW-TDI*

The TACT was estimated by using PW-TDI at the level of the lateral mitral valve annulus as previously described in human studies that used lateral left atrial PW-TDI [11, 15]. From the left parasternal 4-chamber apical view, the PW-TDI sample was placed on the lateral aspect of the mitral valve annulus. The PA-TDI interval, defined as the time-interval from initiation of the electrocardiographic P wave recorded by the echo machine (lead II) to the peak of the A′ wave of the PW-TDI trace, was measured in three cardiac cycles and averaged (Figure 1).

*Statistical analysis*

A chi-square test for association was conducted between the development of AF (AF group and Non-AF group) and gender, breed and underlying disease. As breed and underlying disease included 3 or more categories, those with expected cell frequencies less than five were collapsed in a new category before analysis using the chi-square test.

An Independent t-test was used to test the hypothesis of no differences in PA-TDI interval, and the other continuous variables, between the AF group and Non-AF group and between males and females. In order to meet the assumptions of the independent T-test, outliers in the data were assessed by inspection of a boxplot and normal distribution each subgroup was assessed by Shapiro-Wilk's test (*p* > .05). Homogeneity of variances was assessed by Levene's test for equality of variances.

For variables with non-normal distribution, Mann Whitney U test was used to evaluate differences between the 2 groups.

To assess linearity between PA-TDI interval and the continuous variables (BW, age, time from echocardiography to diagnosis of AF, R-R interval and echocardiographic parameters), scatterplots of PA-TDI interval against the continuous variables were created. A Pearson's product-moment correlation was run to assess the strength and direction of the linear relationships between PA-TDI interval and the variables that showed linearity in the scatterplots. Preliminary analyses to confirm normality (Shapiro-Wilk’s test; p > 0.05) and absence of outliers were performed. Additionally, from the variables with a linear relationship with PA-TDI, simple linear regression was undertaken to the relationship between these variables and PA-TDI and determine how much of the variation in the PA-TDI interval is explained by the studied continuous variables.

Subsequently, multivariable linear regression was undertaken using variables identified as potentiall associated with PA-TDI in univariable (based on p<0.25). The assumption of linearity as assessed using partial regression plots and a plot of studentized residuals against the predicted values. The independence of residuals was assessed by a Durbin-Watson statistic and it was considered accepted if between 1.5-2.5. The presence homoscedasticity was assessed by visual inspection of a plot of studentized residuals versus unstandardized predicted values. The evidence of multicollinearity was assessed by tolerance values greater than 0.1. Thresholds for identification of unusual points (outliers, high leverage points and highly influential points) was set as studentized deleted residuals greater than ±2.5 standard deviations, leverage values greater than 0.5, and values for Cook's distance above 1. The assumption of normality was assessed by a Q-Q Plot.

As left atrial size was *a priori* considered one of the substrates for AF, ANCOVA was used to determine the direct effect of sex in the PA-TDI interval after controlling for 2D LAmax. As BW has been suggested a predictor of AF[10], a hierarchical multivariable regression was performed to evaluate the predictive value of BW after controlling for 2D LAmax.

Receiving Operator Characteristic (ROC) curves were used to evaluate which continuous variable better discriminated between AF cases and Non-AF cases in our studied sample. Additionally, an analysis of the coordinate points of the ROC curves was performed in order to suggest the cut-off with the best balance for sensitivity and specificity for the variables with Area Under the Curve (AUC) higher than 0.75.

The statistical analysis was performed with SPSS softwarea.

**Results**

42 dogs met the inclusion criteria (AF: 21; Non-AF: 21). The breed distribution in each group is shown in Table 1. There was no statistically significant association between development of AF and breed (P= 0.43). Sex distribution was not significantly different between groups (p=0.06). The AF group included 15 males and 6 females, and the Non-AF group included 9 males and 12 females.

The most common underlying diseases in the AF group and Non-AF group were dilated cardiomyopathy, mitral dysplasia and myxomatous mitral valve disease. The distribution of underlying heart diseases or cardiac abnormalities in each group is summarized in the Table 2. There was no statistically significant association between the underlying cardiac disease and development of AF in the following 6 months (p=0.388).

The BW (p=0.97) and age at the time (p=0.25) of the echocardiography were not significantly different between groups. The mean age of the AF and Non-AF group was respectively 6.1±0.83 years and 7.45±0.78 years. The median BW of the AF group and Non-AF group was respectively 28.6 Kg (IQR: 19.7) and 24.8 Kg (IQR: 19.1). Within the AF group, the time to diagnosis of AF from the echocardiographic exam ranged from 1 to 183 days (median: 41; IQR: 72).

The difference between groups in LA:Ao ranged from -0.5 % to 23 % of the value of LA:Ao of the AF case (Mean: -2.81 %; 95 % CI: -9.20 - 3.58%). The difference between groups in BW ranged from -17.2 % to 24.3 % of the BW of the AF case (Mean: 0.422; 95 % CI: -5.33- 6.18). The difference between the Non-AF cases and AF cases in LA:Ao and BW is illustrated as a percentage of the LA:Ao and BW of AF cases in Figure 2.

In terms of echocardiographic 2D and M-mode-derived parameters (Table 2), the 2D LAmax (p=0.009), the M-Mode LVIDd (p=0.018), EDV (p=0.02) and the ESVI (p=0.006) were significantly greater in the AF group. The remaining standard echocardiographic parameters were not significantly different between groups (Table 2).

The PA-TDI interval was significantly longer (p< 0.001) in the AF group (89.4±12.5 ms) than the Non-AF group (66.8±14 ms). The Pearson's product-moment correlation showed that the PA-TDI interval showed a strong correlation linear correlation with 2D LAmax (r=0.565; p=0.000) and a moderate correlation with age (r= - 0.4; p< 0.008), M-Mode LVIDd (r=0.375; p=0.014), EDV (r=0.479; p=0.001) and ESVi (r=0.327; p=0.035). The other continuous variables, including the remaining echocardiographic parameters, BW (p=0.138), R-R interval (p=0.984) and time from echocardiography to diagnosis of AF (p=0.095) did not have a linear correlation with PA-TDI interval.

Univariable linear regression identfied that 2D LAmax (adjusted R2=0.417; p < 0.001), M-Mode LVIDd (adjusted R2=0.357; p< 0.001), EDV (adjusted R2=0.21; p=0.001), ESVI (adjusted R2=0.167; p < 0.004) and age (adjusted R2=0.14; p= 0.008) were statistically associated with PA-TDI interval (Table 3). In this model, only age, 2D LAmax and ESVI were included in a multivariate regression analysis (Table 4). LVIDd and EDV were not included due to high collinearity with 2D LAmax (Pearson product-moment correlation >0.7). Only 2D LAmax was statistically significantly associated with PA-TDI (p=0.01; B=5.255).

Hierarchical multivariable regression showed that the addition of weight to 2D LAmax did not led to a statistically significant increase (p=0.376) in the coefficient of determination (R2) of the multivariate model.

Males (77.37±3.63 ms) and Females (79.15±4.11 ms) did not show a significantly different PA-TDI interval (p=0.748) and gender did not significantly predict PA-TDI interval in a bivariate analysis (p=0.748). The one-way ANCOVA showed that there was no significantly different in PA-TDI interval between male and females after adjustment for 2D LA max, F(1,38)= 0.003 (p=0.837). The PA-TDI interval difference between groups could not be assessed with one-way ANOVA due to the small sample size of each breed.

The ROC curves showed that PA-TDI interval had the higher AUC (AUC=0.896; p<0.001) which was followed by the 2D LAmax (AUC: 0.765; p=0.003), M-Mode LVIDd indexed to BW (AUC=0.743; p=0.008), M-Mode LVIDd (AUC=0.715; p=0.017) and ESVI (AUC=0.71; p=0.02). The cut-off for PA-TDI interval of 81.16 ms had specificity 90.5 % of and a sensitivity of 81 %. A cut-off for 2D LAmax of 5.34 cm had a specificity of 71.4 % and a sensitivity of 71.4 %. The Figure 3 shows the ROC for PA-TDI and 2D LAmax.

**Discussion**

This study demonstrates that the PA-TDI interval measured with PW-TDI at the level of the lateral aspect of the mitral annulus may help to identify dogs with a substrate vulnerable for AF. When compared to the other continuous echocardiographic parameters, PA-TDI was also the variable that better discriminated between AF and Non-AF cases according to the analysis of different ROC curves. The usefulness of the PA-TDI interval as measured by PW-TDI in predicting of new-onset AF is supported by a human study [15] that used PW-TDI at the level of the lateral wall of the atrial wall. The latter proposed a cut-off of 190ms as a tool in identifying human patients at risk of AF. As left atrial PW-TDI is not protocolarily performed at our centre, the authors of this study elected to use the recorded loops of PW-TDI at the level of mitral valve annulus considering that late diastolic mitral annular motion velocity has been recognized as a good of the contractile left atrial function [26] .

The cut-off for PA-TDI interval of 81.16 ms had a sensitivity (81%) and specificity (90.5%) in our studied sample. Although this cut-off may be clinically helpful in identifying the dogs that will develop AF within 6 months after an echocardiographic exam, its accuracy in the general population should be confirmed in a prospective longitudinal study.

To the authors knowledge, this is the first study showing a potential useful echocardiographic predictor of development of AF after a previous study have suggested left atrial maximal diameter in 4 chamber long axis view [10]. The usefulness of Tissue Doppler imaging measurements of TACT has been shown already in people. PA-TDI interval derived from left atrial PW-TDI was shown to predict development of new-onset AF [15], the presence of paroxysmal AF [27] and the recurrence of AF after AF ablation [28-30]. PA-TDI interval measured by left atrial Colour Tissue Doppler imaging has also been shown to be an independent predictor of AF recurrence following external electrical cardioversion [31] and radiofrequency cathether ablation [16]. Prediction of AF is very important in humans given the elevated risk of thromboembolic events and it has been suggested that prophylactic oral anticoagulation could be used in patients with long PA-TDI [15]. The incidence of thromboembolic complications in dogs with AF is low [32] but this arrhythmia is often associated with shorter survival time and clinical deterioration [2]. Additionally, a long-standing underdiagnosed AF will likely lead to further left atrial enlargement, which can further increase the substrate for perpetuation and exacerbation of this arrhythmia. Therefore, prediction of AF would allow an earlier detection of AF and, potentially, improve the success of rate control or an eventual attempt of electrical cardioversion. Moreover, identifying dogs at elevated risk of developing AF is necessary prior to development of studies focused on its prevention. Whereas there are no veterinary studies evaluating the preventive effect of cardiac drugs, human clinical trials showed that angiotensin receptor blockers and angiotensin-converting enzyme inhibitors decrease the risk of AF in human patients with structural heart and functional heart disease [33-38].

A recent study with human patients with normal or mildly enlarged left atrium and undergoing the first AF ablation showed that the predictive value of the different Tissue Doppler imaging measurements of TACT for recurrence of AF may be reduced in early stages of atrial remodelling [14]. Considering that our study did include a heterogeneous population in terms of left atrial size and enlargement, it is possible that the accuracy of the PA-TDI in predicting development of new-onset AF could be higher if we had included only dogs with large left atria.

The role of atrial conduction time in prediction of atrial fibrillation can be explicated by the multiple wavelet re-entry theory, which suggests that multiple spatially discrete activation fronts (wavelets) resulting in re-entry at changing locations are the basis for AF [39, 40]. Whereas a slower atrial conduction velocity leads to a shorter wavelength of the re-entrant wave fronts, an increased atrial size can sustain more wave fronts of a certain size simultaneously. The prolongation of TACT, which is the time from the initiation of atrial depolarisation and the last depolarisation of the same activation front [41], combines both conduction slowing and atrial dilatation. Therefore, an increased PA-TDI interval, a surrogate of TACT, may reflect the existence of a substrate vulnerable for AF.

Despite both groups being matched for BW and degree of atrial stretch, there was statistically significant difference in 2D LAmax between AF and Non-AF group. This unexpected finding most likely reflects the lack of linear correlation between the linear measurements LA and LA:Ao. In humans, LA dilation is not symmetrical in each of left atrial dimensions and, therefore, changes in one diameter may not be proportionate to and often underestimate changes in other dimensions [42]. In addition to this, according to previous studies, LA:Ao underestimates the left atrial size at higher values of left atrial volume as measured by 3D real-time methods [43] and 2D biplane methods [44]. Moreover, whereas LA:Ao was measured at end-diastole, 2D LAmax is measured and end-systole and can be eventually affected by severity of mitral regurgitation.

2D LAmax was the echocardiographic parameter with the second highest AUC. This was not unexpected considering that this parameter is a surrogate of the left atrial absolute size which has been suggested to play a more important role in AF than atrial relative augmentation/stretch[10]. 2D LAmax was also the only continuous variable that significantly predicted the PA-TDI interval in the univariate and multivariate regression analysis. Where the simple linear regression showed that 2D LAmax accounted for 43.2 % of variation of PA-TDI interval in the sample studied, the multivariate regression showed that an increase in one cm of 2D LAmax is associated with an increase of 5.25 ms in the PA-TDI interval. The influence of left atrial absolute size in the PA-TDI interval was expected as TACT is known to be affected in humans by atrial size [11]. TACT is also affected by atrial conduction velocity [11] and this may explain why echocardiographic surrogates of left atrial absolute size alone did not predict AF as well as PA-TDI interval and why left atrial size did not fully explain the variation in PA-TDI in our study.

BW has been previously suggested as a predictive variable for development of AF in dogs [10]. This was not seen in our study as BW was a variable used in the matching process. Additionally, in the simple linear regression analysis, BW was not statistically significant predictive variable of PA-TDI interval. We hypothesise that the reason for this finding was the large heterogeneity of atrial stretch in dogs with same or similar BW. Left atrial size, which is a major determinant of the TACT, depends on BW and degree of atrial stretch. Therefore, dogs with same BW but markedly different degrees of atrial stretch will have different left atrial sizes and, most likely, different PA-TDI intervals. A hierarchical multivariate regression to assess the effect of BW itself as a predictive factor of the PA-TDI interval after controlling for 2D LAmax. The result suggested that BW does not predict PA-TDI interval even after controlling for left atrial size.

Increased age has been associated with decreased intra-atrial conduction in humans and, consequently, with prolongation of TACT [45, 46]. A study with rats showed that that heterogeneous atrial interstitial fibrosis and atrial cell hypertrophy might contribute to decreased atrial conduction due to aging mechanism [47]. Interestingly, in our study, there was an unexpected inverse linear relationship between PA-TDI interval. Despite not statistically significant, the AF group had a lower age mean than the Non-AF group and we hypothesise that this may have contributed for this inverse linear relationship between age and PA-TDI. Age was also a statistical significant predictor of PA-TDI interval in a simple linear regression model (one year of age would lead to a decrease in 1.8 ms) but the statistical significance was lost in the multivariate analysis. Further studies with dogs of the same breed are required to confirm a prolongation in the PA-TDI interval with age.

AF has been reported to affect more male than female dogs [3, 48]. Therefore, we hypothesized sex would also indirectly affect the PA-TDI by influencing the BW and, consequently, left atrial size. Males, who are usually larger and heavier than females, would have probably a larger LA and longer PA- TDI. However, to confirm this indirect effect, a study comparing healthy male and female of the same breed would be required. Nonetheless, in our study, we attempted to evaluate the direct effect of BW in PA-TDI interval by controlling the covariate 2D LAmax (surrogate of left atrial size). Our results showed that there was no significantly different in PA-TDI interval between male and females after adjustment for 2D LA max. This is supported by a human study that showed that TDI measurements of TACT were not significantly different among men and women in the 20–30 years and those in the 30–40 years [45].

Interestingly, apart from the 2D LAmax, Mode LVIDd, EDV and ESVi were significantly greater in the AF group and these parameters also showed a statistical significant linear correlation with PA-TDI. These findings likely reflect that dogs with more severe cardiac remodelling are more likely to develop AF – dogs with more dilated left ventricles are more likely to have larger left atria and, therefore, longer PA-TDI. These echocardiographic parameters of the left ventricle could also predict the PA-TDI interval in the univariate analysis, but they lost their statistical significance in a multivariate analysis whereas 2D LAmax was the only echocardiographic parameter that remain a statistical significant predictor. This supports that increased left atrial size is the causative factor for prolongation of the PA-TDI interval rather than the confounding covariates M-Mode LVIDd, LVEDV and ESVI.

The retrospective design of this study has its inherent limitations. Most of our AF patients present to our referral centre when they already developed AF and only a small number of cases developed AF following first admission. This led to a small population of AF cases which was heterogeneous in terms of breeds, underlying disease, atrial remodelling and BW. Ideally, the studied AF population as well as controls should be homogeneous for these variables. However, despite the large dispersion of breeds and underlying diseases, we elected to not include only the most representative breeds or diseases as this would considerably decrease our sample population and hamper the selection of controls (Non-AF cases). In order to match the AF cases for BW and atrial structural remodelling, we elected to select Non-AF cases with similar degree of LA:Ao and BW. In order to improve our randomization, the control for each AF case (Non-AF case) was the most recent patient in our echocardiographic database that met the inclusion criteria. For the group matching, the Non-AF cases could not differ more than 25 % from the respective AF cases regarding LA:Ao and BW. This difference cut-off ideally should have been smaller, but this would have decreased our studied population, particularly because it would be difficult to find a control to match giant breeds with AF as they are uncommonly seen at our referral institution. Other limitation of our study are the measurements of left atrial size and stretch. 2D LAmax and LA:Ao are measurements of different one-dimension planes of the left atrium and, therefore, they may not reflect an accurate measurement of atrial absolute size or stretch. Additionally, our study did not include a signal-averaged electrocardiogram or other left atrial PW-TDI measurements to compare with the PA-TDI interval measured at the level of lateral aspect of mitral valve annulus. Additionally, the PA-TDI interval was measured by only one operator (JN) and, therefore, further studies assessing intra and inter-operator variability are necessary. However, whereas myocardial velocities measured with PW-TDI are angle-dependent, PA-TDI is a time measurement and, therefore, seemed to be less affected by poor alignment (unpublished data) according to the operator of this study (JN).

**Conclusions**

This study suggests that PA-TDI interval measured by PW-TDI at level of lateral wall of mitral valve annulus may identify patient with a substrate vulnerable for AF and is potentially superior to 2D LA max. In this study, a cut-off of 81.16 ms had a sensitivity of 81% and specificity of 90.5% in predicting development of AF within 6 months period after an echo. However, considering the inherent limitations of a retrospective study, a prospective study would be necessary to confirm the clinical applicability of this cut-off as well as evaluate the intra and inter-operator variability. Predicting the development of AF in dogs might be important for evaluate future preventive therapies.

**Conflicts of Interests Statement**

The authors do not have any conflicts of interest to disclose.

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**TABLES**

**Table 1: Breeds of the AF and Non-AF group**

|  |  |  |
| --- | --- | --- |
|  | **Breed** | **N** |
| **AF Group (N=21)** | English Springer Spaniel | 4 |
| Great Dane | 2 |
| Cavalier King Charles Spaniel | 2 |
| Cross Breed | 2 |
| Giant Schnauzer | 1 |
| English Bulldog | 1 |
| German Shepherd | 1 |
| Boxer | 1 |
| Labrador Retriever | 1 |
| Doberman Pinscher | 1 |
| Lancashire Heeler | 1 |
| Flat Coated Retriever | 1 |
| English Cocker Spaniel | 1 |
| Golden Retriever | 1 |
| Newfoundland | 1 |
|  | | | |
| **Non-AF Group (N=21)** | Doberman Pinscher | 5 |
| English Springer Spaniel | 3 |
| Cavalier King Charles | 3 |
| Boxer | 3 |
| English Bull terrier | 2 |
| English Cocker Spaniel | 1 |
| Hungarian Vizla | 1 |
| Great Dane | 1 |
| Newfoundland | 1 |
| Rhodesian Ridgeback | 1 |

**Table 2: Underlying diseases or cardiac abnormalities of the AF and Non-AF group.**

|  |  |  |
| --- | --- | --- |
|  | **Cardiac abnormality** | **N** |
| **AF Group** | Dilated cardiomyopathy | 5 |
| Mitral dysplasia | 5 |
| Myxomatous mitral valve disease | 4 |
| Patent ductus arteriosus | 2 |
| Patent ductus arteriosus + Aortic stenosis | 1 |
| Patent ductus arteriosus + Mitral dysplasia | 1 |
| Pulmonic stenosis + Tricuspid dysplasia | 1 |
| Systolic dysfunction secondary to doxorubicin | 1 |
| Bi-atrial enlargement | 1 |
|  | | |
| **Non-AF Group** | Dilated cardiomyopathy | 8 |
| Myxomatous mitral valve disease | 7 |
| Mitral dysplasia | 4 |
| Aortic stenosis | 1 |
| Dilated cardiomyopathy + Myxomatous mitral valve disease | 1 |

**Table 2: Echocardiographic variables of dogs belonging to the AF group and Non-AF groups.**

|  |  |  |  |
| --- | --- | --- | --- |
| ***Echocardiographic variable*** | ***AF group*** | ***Non-AF group*** | ***P value*** |
| 2D LAmax (cm) | 6.13±1.61 | 5.06±0.68 | **0.009** |
| 2D LAmax: Ao | 3.16 (2.3-4.04) | 2.50 (2.28-3.11) | 0.308 |
| A (m/s) | 0.74±0.29 | 0.75±0.28 | 0.997 |
| Aortic annulus diameter (cm) | 2±0.52 | 1.89±0.40 | 0.412 |
| E (m/s) | 1.29±0.62 | 1±0.47 | 0.114 |
| E: IVRT | 1.71 (0.8-3.27) | 1.32 (0.84-2.5) | 0.761 |
| E:A | 1.82±0.73 | 1.42±0.44 | 0.051 |
| EDV (mL) | 147.1±92.5 | 94±32.6 | **0.020** |
| Ejection fraction (%) | 44.3±18.6 | 47.04±17.35 | 0.618 |
| ESV (mL) | 87.9 (32-109.5) | 51 (30.5- 59) | 0.092 |
| ESVI (mL/m2) | 88.15±51.3 | 51.4±25.5 | **0.006** |
| Fractional shortening (%) | 22±12.5 | 22.3±10.8 | 0.916 |
| IVRT (ms) | 75 (53.25-93.25) | 73.5 (59-88) | 0.966 |
| LA:Ao | 2.04±0.54 | 2.07±0.51 | 0.886 |
| M-Mode LVIDd indexed to BW | 2.31±0.6 | 1.93±0.33 | **0.018** |
| M-Mode LVIDs indexed to BW | 1.62±0.42 | 1.3±0.28 | 0.059 |
| M- Mode LVIDd (mm) | 59.54±16.7 | 49.67±6.08 | **0.018** |
| M- Mode LVIDs (mm) | 46.47±15.77 | 38.7±8.42 | 0.054 |
| PA-TDI (ms) | 89.4±12.5 | 66.8±14 | **0.000** |
| PW-TDI A' lat velocity (m/s) | 8.25 (5.8-12.6) | 9.25 (6.6-11.9) | 0.648 |
| PW-TDI A’ sept velocity (m/s) | 7.65±2.42 | 8.2±2.81 | 0.510 |
| PW-TDI E’ lat velocity (m/s) | 13.7±4.71 | 11.48±3.04 | 0.086 |
| PW-TDI A’ sept velocity (m/s) | 12.3 (9.5-15.3) | 8.9 (7.2-13.4) | 0.244 |

Data with a non-parametric distribution (Mann Whitney U test) are listed as median (25th to 75th percentile). Data with a normal distribution (Independent T-test) are listed as mean ±standard deviation. P values with statistical significance (P< 0.05) are shown in bold. 2D LAmax, 2D left atrial maximal diameter; 2D LAmax:Ao, 2D left atrial maximal diameter indexed to aortic root diameter; A, peak velocity of late diastolic transmitral flow; A’ lat, late diastolic motion wave measured at the lateral aspect of the mitral annulus by pulsed-wave Tissue Doppler imaging; A’ sept; late diastolic motion wave measured at the septum by pulsed-wave Tissue Doppler imaging; E, peak velocity of early diastolic transmitral flow; E:A, peak velocity of early diastolic transmitral flow to peak velocity of late diastolic transmitral flow; E:IVRT, peak velocity of early diastolic transmitral flow to isovolumic relaxation time ratio; E’ lat, early diastolic motion wave recorded at the lateral aspect of the mitral annulus by pulsed-wave Tissue Doppler imaging; E’ sept , early diastolic motion wave recorded at the septum by pulsed-wave Tissue Doppler imaging; EDV, left ventricular internal dimension at end-diastole; ESV, left ventricular internal dimension at end-systole; ESVI, end-systolic volume index; IVRT, isovolumic relaxation time; LA:Ao, ratio of the left atrial dimension to the aortic annulus dimension; LVIDd, left ventricular internal dimension at end-diastole; LVIDs, left ventricular internal dimension at end-diastole, PA-TDI interval, time interval from the onset of the P-wave on electrocardiogram to the peak of late diastolic wave signal as measured by pulsed-wave Tissue Doppler imaging; PW-TDI, pulsed-wave Tissue Doppler imaging.

**Table 3: Univariate linear regression analysis of age and echocardiographic variables for prediction of PA-TDI interval.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | ***Model summary*** | | | ***Coefficients*** | |  |
| ***Variable*** | ***R*** | ***R2*** | ***Adjusted R2*** | ***B*** | ***95% confidence interval of B*** | ***P value*** |
| 2D LAmax | 0.657 | 0.432 | 0.417 | 7.872 | 4.867 – 10.878 | 0.000 |
| Age | 0.402 | 0.161 | 0.14 | -0.005 | -0.009 – -0.001 | 0.008 |
| EDV | 0.479 | 0.230 | 0.21 | 0.114 | 0.047 – 0.180 | 0.001 |
| ESVI | 0.432 | 0.187 | 0.167 | 0.170 | 0.057 – 0.284 | 0.004 |
| M-Mode LVIDd | 0.611 | 0.374 | 0.357 | 0.736 | 0.419 – 1.054 | 0.000 |

Only variables with a linear relationship in scatterplots were included in the univariate linear regression analysis. Statistical significance was considered if p< 0.05.

B, slope coefficient; R, correlation coefficient; R2, proportion of variation explained by the variable in the sample; Adjusted R2, percentage of variation explained by the model in the population.

2D LAmax, 2D left atrial maximal diameter; EDV, left ventricular internal dimension at end-diastole; ESVI, end-systolic volume index; LVIDd, left ventricular internal dimension at end-diastole.

**Table 4: Multivariate regression analysis for prediction of PA-TDI interval**

|  |  |  |  |
| --- | --- | --- | --- |
| ***Variable*** | ***B*** | ***95 % Confidence interval of B*** | ***P value*** |
| 2D LAmax | 5.255 | 1.354 – 9.155 | **0.01** |
| Age | -0.002 | -0.006 – 0.001 | 0.147 |
| ESVI | 0.085 | -0.028 – 0.199 | 0.137 |

Multiple regression was run only with the variables that could predict the PA-TDI interval in a simple linear regression. M-mode LVIDd and EDV were not included due to failure of one of the multivariate linear regression analysis’ assumptions (high collinearity with 2D LAmax). Statistical significance was considered if p< 0.05.

B, slope coefficient; R, correlation coefficient; R2, proportion of variation explained by the variable in the sample; Adjusted R2, percentage of variation explained by the model in the population.

2D LAmax, 2D left atrial maximal diameter; ESVI, end-systolic volume index

**FIGURE CAPTIONS**

**Figure 1:** Example measurement of the PA-TDI interval with PW-TDI recorded at the lateral aspect of mitral valve annulus. A’, late diastolic wave signal as measured by Tissue Doppler imaging; E’, early diastolic wave signal as measured by Tissue Doppler imaging; PA-TDI, time interval from the onset of the P-wave on electrocardiogram to the peak of A’.



**Figure 2:** Plot showing the difference in LA:Ao and BW between each one of the 21 pairs of Non-AF cases and AF cases. The difference is expressed as percentage of the LA:Ao and BW of AF cases. BW, body weight; LA/Ao, ratio of the left atrial dimension to the aortic annulus dimension.



**Figure 4:** ROC curves of ESVI (A), 2D LAmax (B), LVIDd indexed to body weight (C), M-Mode LVIDd (D) and PA-TDI (E). The value of Area under the Curve (AUC) for each variable is showed at the center of each plot. 2D LAmax, 2D left atrial maximal diameter; ESVI, end-systolic volume index; IVRT, isovolumic relaxation time; LVIDd, left ventricular internal dimension at end-diastole; PA-TDI interval, time interval from the onset of the P-wave on electrocardiogram to the peak of late diastolic wave signal as measured by pulsed-wave Tissue Doppler imaging.



**FOOTNOTES**

a. SPSS for Windows, Version 18.0, SPSS Inc, Chicago, IL