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Diagnostic performance of P wave duration in the identification of left atrial enlargement in dogs

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Abstract

Objectives: To determine sensitivity and specificity of P wave duration in the identification of left atrial enlargement in dogs.

Methods: Electrocardiograms from normal dogs and dogs with various cardiovascular diseases were evaluated. Inclusion criteria were the availability of an electrocardiogram showing a stable isoelectric line, easily recognizable P waves and good quality two-dimensional echocardiographic estimate of left atrial dimensions using the left atrial to aortic root ratio.

Using a metal caliper system, P wave duration was measured to the nearest 10 milliseconds for six consecutive heart beats; data were then averaged for each dog. The accuracy of P wave duration in predicting left atrial enlargement was determined using a receiver operating characteristic analysis.

Results: One hundred and fifty-six dogs were included in the study. Average P wave durations of 20, 30, 40 and 50 milliseconds yielded sensitivities of 100, 85, 68 and 40% and specificities of 0, 16, 64 and 93%, respectively, for the diagnosis of Left Atrial Enlargement by echocardiography. The estimated area under curve of the receiver operating characteristic curve was 0·70 (95% confidence interval: 0·60 to 0·80).

Clinical Significance: The diagnostic performance of P wave duration for identification of left atrial enlargement in dogs presents considerable limitations.

Introduction

Left atrial enlargement (LAE) is a common finding in patients with cardiac disease, and is strongly correlated to clinical conditions and development of left sided congestive heart failure or death, both in humans (Bouzas-Mosquera and others 2011) and in veterinary medicine (Borgarelli and others 2008). Techniques frequently used to assess left atrial (LA) dimensions in the clinical setting include thoracic radiography and echocardiography (Nakayama and others 2001), while magnetic resonance imaging, computed tomography (Kühl and others 2011) and angiography (Bartunek and others 1994) are also performed, particularly in human medicine to assess LA dimensions.

Electrocardiography (ECG) is a widely available and cost-effective diagnostic tool. The most robust application for electrocardiography is the evaluation of arrhythmias or conduction abnormalities. However, in both veterinary and human medicine, ECG is also used to evaluate the presence of cardiac enlargement (Hazen and others 1991; Nakayama and others 2001, Schober and others 2007; Tsao and others 2008), although its accuracy is widely discussed.

In physiologic conditions, the wave front of cardiac activation starts with the depolarization of the sinus node (SN), spreads preferentially through the internodal and interatrial pathways and the atrial working myocardium, and reaches the atrioventricular node (Sakamoto and others 2005). The mean vector of atrial activation follows a dorsal-to-ventral, cranial-to-caudal and right-to-left direction. This typically results in positive P waves in the caudal leads: II, III and aVF with different amplitude according to the presence of sinus arrhythmias (Moise 1998). It is generally accepted that P wave duration reflects the activation of the atrial muscle, that it depends primarily upon the mass of tissue excited and that, when prolonged, P wave could represents a criterion for LAE, both in humans (Surawicz 1986) and in veterinary medicine (Lombard and Spencer 1985). However, Waldo and others (1971) demonstrated that the presence of specialized conduction pathways (internodal tracts) plays an important role in the sequence of atrial depolarization, and that intra-atrial lesions can affect the duration of the P wave leading to a prolonged P wave duration. Therefore, P wave prolongation may also be regarded as a marker of abnormal intra- and interatrial conduction, which might render P wave duration a less reliable index of LAE. Therefore, it is important to quantify the actual performance of this simple, non-invasive tool in predicting LAE in the general population of dogs presenting for cardiac evaluation. Several studies in the human literature described the agreement between LAE detected by ECG and echocardiography (Zeng and others 2003; Tarastchuk and others 2006; Lee and others 2007) or magnetic resonance imaging (Tsao and others 2008). Recently, Schober and others (2007) published data on the agreement of ECG and thoracic radiography in the assessment of LAE in cats. The aim of this study was to assess the diagnostic performance of P wave duration in identifying the presence of LAE in dogs using the echocardiographic LA/Ao ratio as gold standard.

Materials and methods

Medical records from dogs in which an echocardiographic and electrocardiographic study were acquired during the same visit were evaluated. Data were collected from January 2007 to December 2009. Electrocardiograms were recorded, as previously described (Kraus and others 2002), in unsedated dogs gently restrained in right lateral recumbency using two commercially available electrocardiographs (PageWriter Xli, M1700A and Ates Medica, Easy ECG: machine 1 and 2, respectively). All electrocardiographic studies were printed on thermal paper, at a paper speed of 50 mm/s and sensitivity of 10 mm/1 mV. Filter was on (50 Hz). Echocardiograms were acquired according to published standards (Thomas and others 1993) in unsedated dogs restrained on a fenestrated table and imaged from the dependent side, using commercially available units: GE, Vivid 7, M4s (2·0 to 3·5 MHz) and M7s (4 to 8 MHz) probes; Esaote, My Lab 30, PA 122 (5 to 7·5 MHz) and PA 230 (2·5 to 3·5 MHz) probes. Echocardiographic studies were digitally stored for off-line analysis. All offline echocardiographic and ECG measurements were performed by a single operator, blinded to the clinical diagnosis.

Duration of the P wave was measured in lead II using a metal caliper system directly on thermal paper, starting from the point where the deflection leaves the isoelectric line, and ending at the point where the deflection returns to the isoelectric line, excluding line width (from leading edge to leading edge). No magnification was used. P wave duration was estimated at the nearest 10 milliseconds. Data were acquired from six consecutive heart beats and their average was computed, in order to include a representative sample of both the acceleration and deceleration phases when sinus arrhythmia was present.

Left atrial dimensions were estimated with 2D echocardiography from a right parasternal short-axis view at the heart base, as previously described (Rishniw and Erb 2000). The diameter of the aortic root was measured at the level of the commissure between the non-coronary and right coronary aortic valve leaflet. The diameter of the left atrium was measured along a line "extending from and parallel to the commissure between the non-coronary and left coronary aortic valve cusps to the distant margin of the left atrium" (Rishniw and Erb 2000). Care was taken to avoid inclusion of the terminal portion of pulmonary veins in the measurement of the LA internal diameter. Both measurements were performed on the first frame after aortic valve closure. The ratio between these two measurements (LA/Ao) was then obtained, and considered normal if it was <1·6 (Rishniw and Erb 2000). Mild LAE was arbitrarily considered with LA/Ao ≥ 1·6 and <1·8; moderate LA/Ao ≥1·8 and <2; severe LA/Ao ≥ 2. Dogs were divided into four groups based on the presence of normal LA/Ao ratio, mild, moderate or severe LAE (groups 1, 2, 3 and 4, respectively).

Statistical analysis

In order to evaluate the degree of consistency in P wave measurement for individual dogs, we computed its repeatability. Repeatability of P wave duration can be defined as the ratio of the between-dog variance to the total variance (i.e. between-dog variance plus within-dog variance). Alternatively, one may interpret repeatability as the proportion of the variability expressed amongst (rather than within) individuals. In order to estimate repeatability of P wave duration, we used the variance components estimates obtained from fitting the model described in the previous paragraph such that: $\hat{r} = \hat{\sigma}^2_{btw} / \left(\hat{\sigma}^2_{btw} + \hat{\sigma}^2_{within} \right)$, whereby $\hat{r}$ is the estimated repeatability, $\hat{\sigma}^2_{btw}$ is the estimated between-dog variance and $\hat{\sigma}^2_{within}$ represents the estimated within-dog variance.

A preliminary analysis consisted of an estimation of the Pearson correlation coefficient between continuous values of LA/Ao ratio and P wave duration (as the average of six consecutive measurements). More in-depth analyses included a general linear mixed model, which was fitted to the response variable "P wave duration" measured in milliseconds. The model used for analysis included the fixed effect of LA/Ao classification group, ECG machine (two levels) and the covariates bodyweight and age. Interactions between fixed effects (both factors and covariates) were evaluated but were excluded from the final model based on maximum-likelihood-based model fit criteria and non-significant P-values (in order to prevent model overparameterization). Also included in the model was a random blocking effect of dog nested within LA/Ao classification group in order to recognize dog as the experimental unit for LA/Ao classification group and to accommodate the technical replication due to six P waves measured on each dog. Satterthwaite's method was used to approximate degrees of freedom and Kenward Roger's procedure was used to correct bias of estimated standard errors (se).

The statistical model was fitted using the MIXED procedure of SAS (Version 9.2, SAS Institute Inc). Model assumptions were evaluated using studentized residual plots and assumptions were considered to be appropriately met. Pairwise comparisons were conducted using Tukey-Kramer's adjustment to avoid inflation of type I error rate. Results are reported as least square mean estimates and corresponding se or 95% confidence interval (CI).

The predictor "P wave duration" was then sequentially dichotomized at thresholds of 20, 30, 40 and 50 milliseconds. Sensitivity and specificity of dichotomized "P wave duration" for detecting LAE were estimated and are reported with their exact CI based on binomial proportions. Computations were conducted using the FREQ procedure of SAS Version 9.2 (SAS Institute Inc).

Finally, a logistic regression model was fitted to the binary response "LAE diagnosed with echocardiography". The model included the covariates P wave duration (expressed as the average of measurements taken in six consecutive cycles), bodyweight and age. The model was fitted using the GLIMMIX procedure of SAS Version 9.2 (SAS Institute Inc). Predicted probabilities of LAE as per this model were used to create the corresponding ROC curve.

Results

One hundred and fifty-six dogs (74 females, 44 of which were spayed; 82 males, 35 of which were neutered) were included in the study. There were 37 mixed breed dogs, 10 Dobermann, 9 Labrador retriever, 7 golden retriever, 6 each of boxer and Chihuahua, 5 American cocker spaniel, 4 each of bullmastiff, dachshund and Yorkshire terrier; the remaining 64 dogs belonged to 41 different breeds.

Fifty-eight dogs were considered healthy, whereas 45 dogs were affected by mitral valve disease, 28 had tricuspid valve dysplasia, 13 pulmonic stenosis; 87 other cardiac diseases were also present in the study population.

Bodyweight (BW) was not available for two dogs (one rottweiler and one cavalier King Charles spaniel). The median BW was 23·49 kg (IQR 10·65 to 32·08; n=154) and median age was 6·00 years (IQR 3·00 to 9·00; n=156).

Seven dogs had subaortic stenosis (sAS) and one dog aortic stenosis (AS), conditions that may be associated with an abnormal aortic morphology (Bonagura and Lehmkuhl 1999). In order to avoid the inclusion of patients with an LA/Ao ratio falsely altered by pathological aortic dimensions, the expected aortic dimension normalized to BW was calculated, as suggested by Hall and others (2008), and compared this figure with reference values. Only in one of the eight dogs with sAS or AS, the measured value was outside the suggested interval. However, it was decided not to exclude this dog from the analysis because the deviation from the reference value was trivial (measured indexed value 0·8; reference value 0·93 ±0·12) (Hall and others 2008).

One hundred and six dogs (67·95%) had normal LA dimensions, 50 dogs had LAE, of which: 16 dogs (10·26%) had mild LAE, 11 dogs (7·05%) moderate and 23 dogs (14·74%) had severe LAE.

A preliminary analysis indicated evidence for a positive correlation between LA/Ao ratio and P wave duration (estimated Pearson correlation coefficient R^2=0·47; P<0·0001). Figure 1 presents a scatter plot to illustrate the association between LA/Ao ratio and P wave duration. A more comprehensive analysis indicated that differences in P wave duration were apparent between LA/Ao groups (P<0·0001), namely dogs with normal left atrial dimensions and dogs with mild LAE showed shorter P wave duration than dogs with severe LAE. In fact, there was evidence of a linear effect of LA/Ao categories on P wave duration (P<0·0001), indicating a proportional mean increase in P wave duration across consecutive LA/Ao categories.

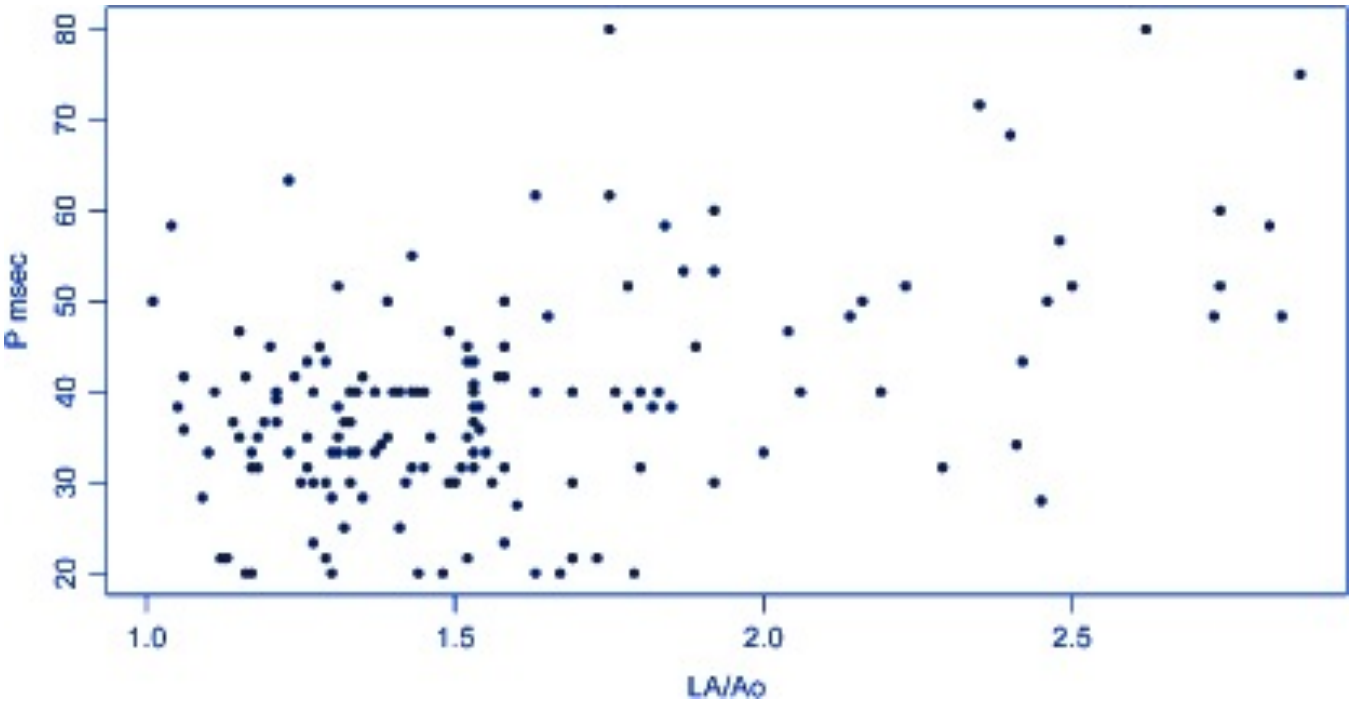

Figure 1.
Scatterplot illustrating the relationships between average P wave duration (y axis) for individual dogs and their LA/Ao ratio (x axis). Estimated Pearson correlation coefficient R̂=0·47; P<0·0001

Least squares mean estimates and corresponding se of P wave duration of dogs with normal LA dimensions, as compared to mild, moderate and severe LAE, were 37·52 (se=1·54), 41·67 (se=2·72), 46·06 (se=3·05) and 51·97 (se=2·28), respectively. The sample median LA/Ao ratio in the population was 1·47 (range 1·01 to 2·87), whereas the sample median value of P wave duration was 38·33 milliseconds (range 20 to 80 milliseconds).

Repeatability of P wave duration was estimated at r̂=0·78. This means that approximately 78% of the variability observed in P wave duration was explained by differences between dogs, whereas an approximate 22% could be explained by variability in repeated measurements on a given dog.

Differences between ECG machines as well as the association of P wave duration with BW and age were evaluated. A marginally significant difference between ECG machines was identified on P wave duration (P=0·089); in particular, measurements taken with machine 2 showed marginally longer P wave durations than those taken with machine 1 (estimated least square means and standard errors were 41·85, se 1·17 milliseconds and 46·75, se 2·75 milliseconds, respectively).

After accounting for the effects of machines, bodyweight and age were both identified to be positively associated with P wave duration (P<0·0001 and P=0·03, respectively); at any given age (six years), every kilogram increase in bodyweight was associated with an estimated mean increase in P wave duration of 0·30 (se 0·05) milliseconds. Similarly, every additional year of age was associated with an estimated mean increase in P wave duration of 0·48 (se 0·22) milliseconds considering that bodyweight is kept constant (23 kg).

Figure 2 illustrates the ROC curve analysis using logistic regression with P wave duration as an explanatory variable to predict LAE. It must be emphasized that measurement of P wave duration in the clinical setting is limited to non-decimal values, and that it is often expressed in multiples of 10 milliseconds. Therefore the ROC, evaluating P wave duration as the only covariate, was further studied, dichotomizing the covariate at thresholds of 20, 30, 40 and 50 milliseconds. Results, including estimated sensitivity and specificity of each threshold, are reported in Table 1 and in Fig 2; estimated AUC was 0·70, with 95% CI [0·60 to 0·80]

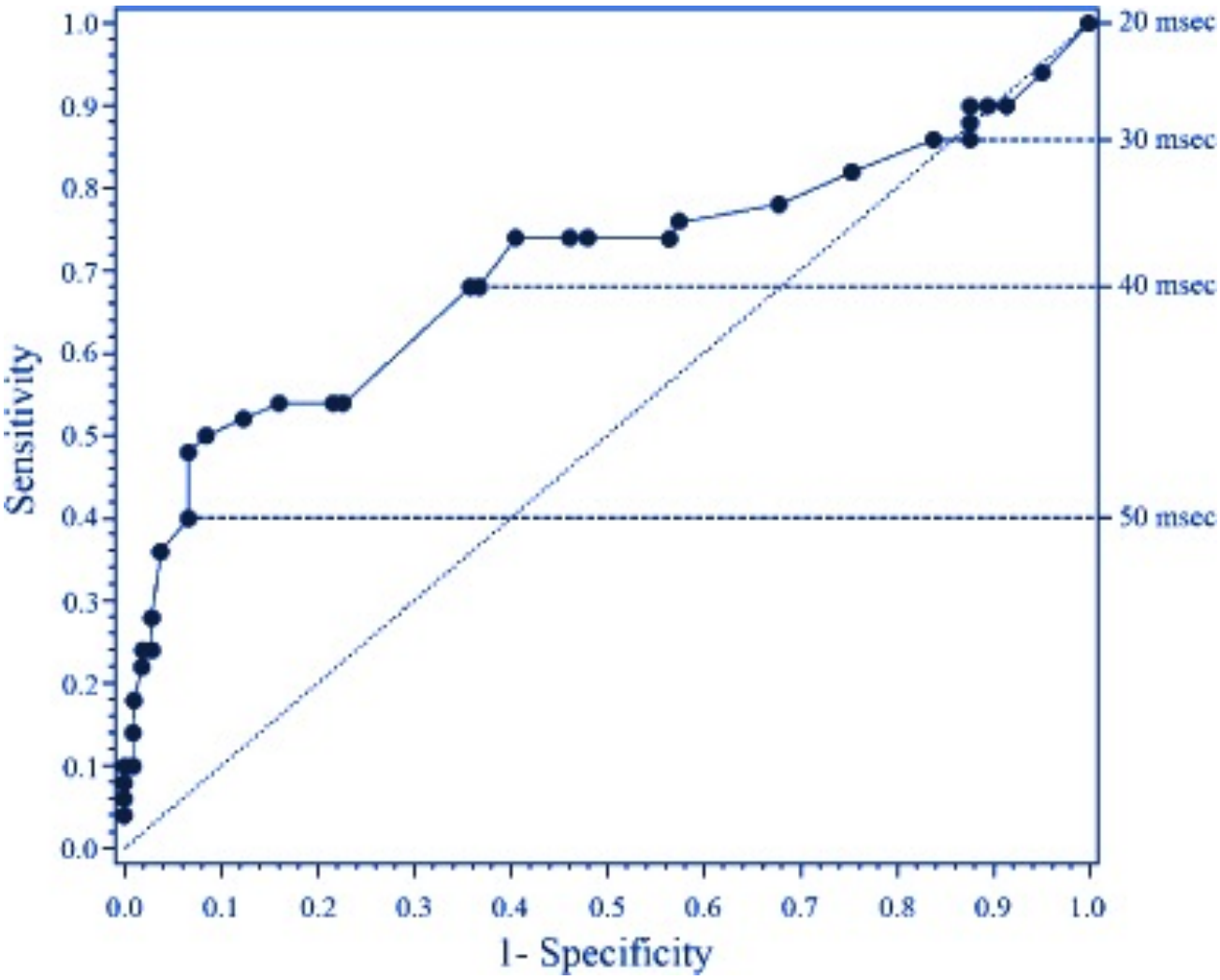

Figure 2.

Estimated sensitivity and specificity of P wave to detect LAE at each threshold P wave (exact threshold points are reported on the right axis); ROC curve including covariate P wave duration. Exact sensitivity and specificity values are reported in Table 1. Estimated AUC 0·70, se=0·05, 95% CI [0·60 to 0·80]

Table 1. Estimated sensitivity and specificity (and 95% CI) of selected thresholds of P wave duration in the diagnosis of LAE based on the model including the covariate P wave duration as a predictor

	P wave duration selected diagnostic thresholds			
	20 milliseconds	**30 milliseconds**	**40 milliseconds**	**50 milliseconds**
Estimated sensitivity % (CI%)	100% (93 to 100)	86% (73 to 94)	68% (53 to 80)	40% (26 to 54)
Estimated specificity % (CI%)	0% (0)	16% (9 to 24)	64% (54 to 73)	93% (87 to 97)

Estimated AUC of 0.70, se=0.05 and 95% CI [0.60 to 0.80]

We expanded our ROC analysis by incorporating into the logistic regression model additional explanatory variables known to be associated with prevalence of LAE, namely BW and age. Figure 3 illustrates the estimated ROC curve with corresponding estimates of sensitivity and specificity of P wave duration, to predict LAE after accounting for the effects of bodyweight and age. The estimated AUC for this ROC analysis was 0·82 with 95% CI [0·75 to 0·89].

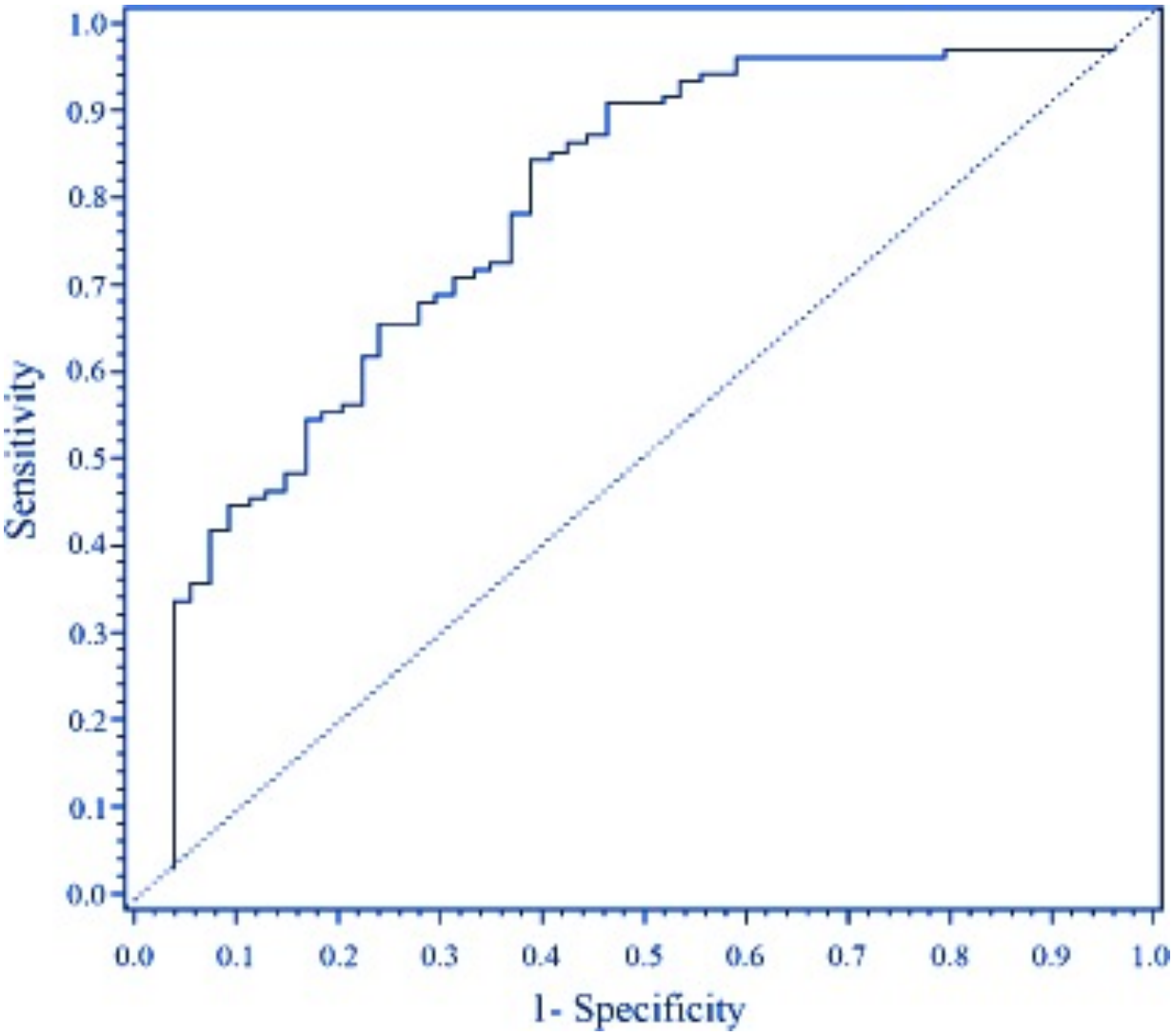

Figure 3.

ROC analysis indicating estimated sensitivity and specificity of P wave duration for diagnosis of LA enlargement after accounting for bodyweight and age. Estimated AUC 0·82, se 0·03, 95% CI [0·75 to 0·89]

Discussion

To the authors' knowledge, this is the first study investigating the diagnostic performance of the ECG P wave duration to detect LAE in dogs with various diseases. Furthermore, this is the first time that sensitivity and specificity of different clinically relevant cut off values of P wave duration measurements has been assessed in the detection of LAE in dogs. By itself, P wave duration showed a limited ability to detect LAE. In fact, although there is an increased specificity of P wave duration from 20 up to 50 milliseconds, the possibility to discriminate the presence of LAE detected by echocardiography was poor. Similarly, in humans, individual ECG P wave changes (P wave duration, axis and morphology) do not reliably detect nor predict the presence of anatomic atrial enlargement, when compared with cardiac magnetic resonance imaging (Tsao and others 2008) or echocardiography (Ikram and others 1977; Lee and others 2007).

When the covariates P wave duration, bodyweight and age were included in the analysis, the estimated AUC for the ROC increased from 0·70 to 0·82. However, specificity and sensitivity were still suboptimal from a clinical standpoint.

It has been reported that LA abnormalities are associated with a prolongation in left atrial depolarization and this corresponds to a prolonged ECG P wave duration (Surawicz 1986). An association between P wave duration and LA/Ao by echocardiography was observed in our study, but the ability of P wave duration to predict LAE as determined by echocardiography was poor.

In this study the repeatability of measurement of P wave duration was estimated at 78% in variability between dogs, whereas an approximate 22% is explained by variability in repeated measurements in a given dog. The presence of wandering pacemaker or possible intermittent inter- or intra-atrial conduction disorders can alter P wave measurement (Moise 1998) obtained from a single beat. In the present study, the decision to assess six consecutive beats was made to reduce the risk of over- or under- estimating the length of the P wave.

According to literature and these results (as discussed below), LA dimensions (potentially affected by BW and definitely affected by the presence of true LAE) and abnormal atrial electrophysiologic properties (associated with LAE or perhaps age related) correspond to changes in P wave duration: in effect, based on the current data, a weak positive correlation between P wave duration, bodyweight and age was found. O'Grady and others (1992) reported that normal P wave duration varies according to BW; in that review article, a difference of 5 milliseconds was reported between small or medium dogs and giant dogs (0·04 and 0·045 seconds, respectively). Blumenthal and others (1996) described the following values of P wave duration based on bodyweight: <20 kg, 41·6 milliseconds, 20 to 25 kg, 44·9 milliseconds, 25 to 35 kg, 46·3 milliseconds. In the present study, every additional year of age was associated with an estimated mean increase in P wave duration of 0·48 milliseconds (keeping constant the BW, 23 kg), while every kg increase in BW was associated with an estimated mean increase in P wave duration of 0·30 milliseconds (keeping constant the age, six years). In human medicine, Pipberger and others (1967) described prolonged P waves in older patients, although the authors considered this increase clinically irrelevant. The present result is conceptually similar to Pipberger's findings.

Simonson (1972) hypothesized that the presence of remodeling and fibrosis in the aged human cardiac muscle could alter many electrocardiographic findings, including QRS axis, QT length, and also P wave morphology.

Since P wave duration and LA/Ao ratio values were correlated, it is not surprising that P wave duration was significantly different between LA/Ao groups. In fact, P wave duration is known to be affected by the size of the left atrium (Lombard and Spencer 1985; Surawicz 1986). However, it must be emphasized that inter- and intra-atrial conduction velocities also contribute to P wave duration: in fact, in human beings, prolonged P wave duration has been recorded in the absence of LAE (Ariyarajah and others 2005).

We documented a difference between the two electrocardiographs, with machine 2 showing a marginal effect toward a greater P wave duration. The difference between the two machines averaged approximately 5 milliseconds. This difference is unlikely to be relevant from the clinical point of view because the difference is below 10 milliseconds, and therefore unlikely to be detectable by the human eye at a paper speed of 50 mm/s.

This study presents several potential limitations. First, it enrolled a relatively small sample size with different degrees of LAE and therefore findings are not necessarily representative of the whole population. Second, inclusion of data acquired with different electrocardiographic and ultrasound units could have added an additional source of variability due to differences in device calibration. However, even though a marginal effect of the ECG machine was observed, this should be considered of minimal clinical significance. Finally, electrophysiological studies to rule out the presence of intra- or interatrial conduction disorders responsible for P wave prolongation were not performed.

In conclusion, the current study confirms the relatively modest diagnostic performance of P wave duration in predicting the presence of LAE, when compared to the echocardiographic gold standard. The presence of LAE is an important prognostic factor in several cardiovascular diseases, and P wave duration should not be considered a reliable indicator.

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