UNIVERSIDADE FEDERAL DO PARANÁ

FRANCIELLI AMBROSINI

AVALIAÇÃO DO SEIO CORONÁRIO COMO MEDIDA AUXILIAR NO DIAGNÓSTICO DA HIPERTENSÃO PULMONAR EM CÃES.

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Dissertação apresentada ao Programa de Pós- Graduação em Ciências Veterinárias, do Setor de Ciências Agrárias, Universidade Federal doParaná, como requisito parcial à obtençãodo título de Mestre em Ciências Veterinárias.

Orientador: Prof. Dr. Marlos Gonçalves Sousa

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Os membros da Banca Examinadora designada pelo Colegiado do Programa de Pós-Graduação CIÊNCIAS VETERINÁRIAS da Universidade Federal do Paraná foram convocados para realizar a arguição da dissertação de Mestrado de **FRANCIELLI AMBROSINI** intitulada: **AVALIAÇÃO DO SEIO CORONARIANO COMO MEDIDA AUXILIAR NO DIAGNÓSTICO DE HIPERTENSÃO PULMONAR EM CÃES**, sob orientação do Prof. Dr. MARLOS GONÇALVES SOUSA, que após terem inquirido a aluna e realizada a avaliação do trabalho, são de parecer pela sua APROVAÇÃO no rito de defesa.

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Aos meus amados filhos Millena e Emmanuel.

Ao meu grande e eterno amor Ivanio.

RESUMO

Introdução/objetivos: a síndrome da hipertensão pulmonar é caracterizada por um aumento sustentado da pressão na vasculatura pulmonar. O diagnóstico padrão-ouro é feito com cateterismo cardíaco, mas a ecocardiografia destina-se a realizar a abordagem probabilística. O seio coronário (SC) é uma estrutura vascular que aumenta com o aumento da pressão no átrio direito, pressão na artéria pulmonar e está relacionado com o prognóstico da hipertensão pulmonar (HP). Este estudo visa validar o uso desta medida em cães, como parâmetro complementar ao diagnóstico desta condição. Animais: foi realizada avaliação ecocardiográfica de 61 cães, subdivididos em grupos de acordo com a probabilidade de HP. Materiais e métodos: estudo observacional analítico e transversal. As medidas ecocardiográficas padrão foram registradas pelo mesmo avaliador na janela paraesternal esquerda e direita. O seio coronariano foi medido no início do QRS e ao final da onda t do eletrocardiograma, em triplicata, e em seguida a respectiva media foi indexada pelo peso, raiz cúbica do peso, diâmetro da aorta e área de superfície corporal. O SC foi comparado com TAPSE, FAC, RPAD, AT/ET, AP/AO. Resultados: As médias indexadas ou não foram maiores em PH_h comparado a PH_i e PH_l ($p<0,01$), mas não diferiram do grupo controle. A medida de SC aumenta progressivamente de acordo com a probabilidade de HP. As curvas ROC para identificação de pacientes com HP apresentaram AUC>0,7 para a média de todas as indexações do SC. CS_{QRSAo},CS_{TB}, CS_{TAO}, CS_{QRSR}, CS_{TW} apresentaram correlação positiva com insuficiência tricúspide (RHO>0,6 e $p<0,001$). Na análise de sobrevida, CS_{TW}, CS_{QRSB}, CS_{TB}, CS_{QRSW}, CS_{TAo}, CS_{QRSR}, $_{a}CS_{T}$, CS_{QRSAo}, $_{a}CS_{QRS}$, CS_{TR} apresentaram valores satisfatórios de sensibilidade e especificidade (AUC>0,7), e até melhores comparado aos outros índices ecocardiográficos. O coeficiente de correlação intraclasse apresentou resultados >0,9 tanto na avaliação intra quanto interobservador. Conclusões: O SC sofre dilatação na HP. Foi adequado para o diagnóstico de pacientes com HP, mas não mostrou diferença nos pacientes do grupo controle. O uso do diâmetro SC é recomendado para a abordagem ecocardiográfica probabilística da HP quando indexado, especialmente pela área de superfície corporal e/ou diâmetro da aorta e é considerado um bom indicador prognóstico para HP.

Palavras-chave: pressão átrio direito, dilatação seio coronário; regurgitação tricúspide; probabilidade de hipertensão pulmonar; artéria pulmonar.

ABSTRACT

Introduction/objectives: Pulmonary hypertension syndrome is augmented by a sustained increase in vasculature. The gold standard diagnosis is made with cardiac catheterization, but echocardiography is intended to perform the probabilistic approach. Coronary sinus (CS) is an enlarged vascular structure with increasing pressure that is not right pulmonary artery pressure and is related to the prognosis of pulmonary hypertension (PH). This study aims to validate the use of this measure in dogs, as a complementary parameter to the diagnosis of this condition. Animals: an echocardiographic evaluation was performed on 61 dogs, subdivided into groups according to the probability of PH. Materials and methods: analytical and cross-sectional observational study. Standard echocardiographic measurements were recorded by the same evaluator in the left and right parasternal window. The coronary sinus was medium and medium at the beginning of the QRS and at the end of the electrocardiogram waveform, respectively, and then the medium cubic was indexed by weight, cube root weight, aortic diameter and body surface area. SCwas compared with TAPSE, FAC, RPAD, AT/ET, AP/AO. Results: Means indexed or not were higher in PHh compared to Phi and PHI (p<0.01), but did not differ fromthe control group. SC measurement increases according to the possibility of PH TheROC curves for identifying patients with PH showed AUC>0.7 for the mean of all SC indexes. CSQRSA, CSTB, CSTAO, CSQRSR, CSTW apparently positive with tricusp function (RHO>0.6 and p<0.001). In the lifetime analysis, CSTw, CSQRSB, CSTB, CSQRSW, CSTAo, over CSQRSR, CSQRSAo, overQRS, CSTR, patterns, sensitivity and specificity values (AUC>0.7), and even better compared to echocardiographic indices. Both intraclass evaluation results presented >0.9 in intra and interobserver. Conclusions: SC undergoes dilation in HP. It was adequate for the diagnosis of patients with PH, but showed no difference in patients in the control group. The use of SC diameter is recommended for the probabilistic echocardiographic approach to PH when indexed, especially by body surface area and/or aortic diameter, and is considered a good prognostic indicator for PH.

Keywords: right vertical pressure; coronary sinus dilatation; tricuspid regurgitation; probability of pulmonary hypertension; pulmonary.

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LIST OF ABBREVIATIONS

AT	Pulmonary Flow Acceleration Time
AT/ET	Pulmonary flow acceleration-to ejection time ratio
BSA	Body surface área
CS	Coronary Sinus
$_{a}CS_{QRS}$	Average of CS measured at the beginning of the QRS complex
CS_{QRSAo}	CS_{QRS} aorta-indexed
CS_{QRSB}	CS_{QRS} body surface area-indexed
CS_{QRSR}	CS_{QRS} root-indexed
CS_{QRSW}	CS_{QRS} weight-indexed
$_{a}CS_{T}$	Average of CS measured at the end of the T wave
CS_{TAo}	CS_{T} aorta-indexed
CS_{TB}	CS_{T} body surface area-indexed
CS_{TR}	CS_{T} root-indexed
CS_{TW}	CS_{T} weight-indexed
E	Specificity
ET	Pulmonary Artery Ejection Time
FAC	Fractional Area Change
PH	Pulmonary Hypertension
PH_{l}	Low PH probability
PH_{h}	High PH probability
PH_{i}	Intermediate PH probability
S	Sensitivity
TAPSE	Tricuspid Annular Plane Systolic Excursion
TR PV	tricuspid regurgitation peak velocity
TR PG	tricuspid regurgitation pressure gradient

SUMMARY

INTRODUCTION

Pulmonary hypertension (PH) is a multifactorial condition resulting from the imbalance of endogenous and exogenous vasodilator and vasoconstrictor factors acting in the pulmonary artery and resulting increase of pressure [17]. In people, pulmonary hypertension is characterized by an increase in either pulmonary systolic pressure above 25 mmHg or diastolic blood pressure above 19 mmHg [6], criteria also used in dogs. Its origin may be related to disturbances in the precapillary (arterial) or postcapillary (venous) vascular resistance of the pulmonary vascular system [11, 12].

In spite of the advanced diagnostic techniques available nowadays, cardiac catheterization remains the gold standard for measurement of systolic, mean and diastolic pulmonary artery pressure [5,19]. However, the echocardiogram is the indirect method most used in dogs for PH diagnostic. With that technique, tricuspid regurgitation peak velocity is used to estimate pulmonary artery systolic pressure, which is interpreted together with other echocardiographic signs of remodeling in the pulmonary artery, ventricles, right atrium and caudal vena cava, to establish the probability of having PH [11, 19].

Nonetheless, the use of tricuspid regurgitation peak gradient as a substitute for invasive pulmonary artery pressure measurement is subject to flaws for both diagnosis and classification [2, 20, 10]. Evaluation by echocardiography can lead to underdiagnosis of PH or incorrect classification of PH severity in many canine patients, especially in acute cases. Therefore, other echocardiographic surrogates for the existence and severity of PH are warranted [18].

The coronary sinus (CS) is a venous structure that lies in the posterior sulcus between the left atrium and left ventricle. Drains the veins of the myocardium and opens in the right atrium. An increase in its diameter can be used as an indication of increased pressure in the right atrium [1]. In human beings, CS diameter was positively correlated with pulmonary artery systolic pressure [8] and is related to prognosis of PH [3]. To the best of our knowledge, the role played by PH in the characteristics of CS anatomy has not been investigated in dogs. Since PH is associated with increased right atrium pressure, we hypothesized that PH would change the diameter of the CS [18; 26). Thus, the aims of this study were three-fold: (1) to evaluate the anatomy of the CS using echocardiography in dogs with PH; (2) to assess whether changes in CS anatomy might predict the probability of a dog having PH; and (3) to assess the prognostic applicability of such measurements in comparison with other surrogates for right ventricular function.

ANIMALS, MATERIALS AND METHODS

This is a cross-sectional analytical observational study, carried out at a Veterinary Teaching facility between January 2021 and September 2021. Client-owned-dogs attending a referral practice with diagnosis of low, intermediate and high probability of PH, regardless of age, breed and weight, were included in the study. Also, healthy dogs were recruited to serve as controls. Data were collected regarding the use of medications, probable identification of the origin of PH (pre- or post-capillary) and history of decompensation of heart failure. Echocardiographic assessments were performed using an ultrasound equipment equipped with 2-12 MHZ multifrequency transducers (Affiniti 50, Philips). No sedation was used. The animals were restrained in right and left lateral decubitus as recommended by the American College of Veterinary Internal Medicine [24]. All measurements were obtained by the same operator (FA). Exclusion criteria included animals with overt signs of congestive heart failure, labored breathing, congenital heart disease, RV outflow tract obstruction, intracardiac tumor or uncooperative animals unable to tolerate the exam. This study was approved by the institutional animal ethics committee under protocol number 027/2020.

Classification by probability of PH

To classify the probability of PH, tricuspid regurgitant flow was measured and the pressure gradient between right ventricle and right atrium was calculated using the modified Bernoulli equation. For the analysis of tricuspid regurgitation, a clearly visible envelope was considered, with dense marking of the envelope and a good quality signal. Also, anatomical sites at which alterations are likely to be documented were evaluated (ventricles, pulmonary artery, right atrium and caudal vena cava). These findings were used to establish the probability of animals having PH as low PH (PH_l), intermediate (PH_i), or high (PH_h), as recommended as recommended by the American College of Veterinary Internal Medicine [19]. Of note, patients which did not present echocardiographic evidence, i.e. those which were unlikely to have PH, were used as controls.

Coronary sinus measurement

The CS is located in the left atrioventricular groove. From the left parasternal window, modified apical four-chamber images were recorded (i.e. with a slight cranial tilt of the transducer). Triplicate measurements of the CS diameter were obtained at the beginning of the QRS complex (CS_{QRS}) and at the end of the T wave (CS_T) (Fig. 1A and 1B, respectively).

Pulmonary artery assessment

From the right parasternal window, short-axis images of the heart base were obtained to show the pulmonary artery bifurcation. Measurements included pulmonary artery diameter, pulmonary artery-to-aorta ratio (PA/Ao), ejection and acceleration time of the pulmonary flow, as well as the ratio of these values (AT/ET). Lastly, we calculated the right pulmonary artery distensibility (maximum systolic inner diameter – minimum diastolic inner diameter/maximum systolic inner diameter * 100).

Left ventricular assessment

Using either apical 4- or 5-chamber images, we recorded the isovolumic relaxation time and ratio between mitral E wave (rapid ventricular filling) and A wave (atrial contraction), E wave deceleration time (EDT). All Doppler assessments were interrogated with the best alignment to avoid underestimation.

Right ventricular assessment

Modified apical 4-chamber images optimized for the RV were used to measure tricuspid annular plane systolic excursion (TAPSE), and the fractional area change (FAC).

STATISTICAL ANALYSIS

Descriptive analyses of the data were performed with an estimate of mean, median, standard deviation, 25% and 75% percentiles of the quantitative variables and simple and relative frequencies of the qualitative variables. Also, CS_T and CS_{QRS} measurements were normalized using four different indices: 1) body weight (BW) (CS_{TW} and CS_{QRSW}) [mm/kg]; 2) the cubic root of the BW (CS_{TR} and CS_{QRSR}) [in mm/$\sqrt[3]{kg}$]; 3) the diameter of the aorta (CS_{TAo} and CS_{QRSAo}); and 4) the body surface area (CS_{TB} and CS_{QRSB}) [mm/m^2], which was obtained through the following formula: $BSA = K \times (\text{BW in grams}^{\frac{2}{3}}) \times 10^{-4}$

K=constant (10.1 for dogs)

All data underwent the Shapiro-Wilk normality test. To investigate the statistical difference of variables between controls and PH groups (PH_l, PH_i, PH_h, an ANOVA test followed by the post-hoc Tukey test was used whenever data was normally distributed. For data that did not attain a gaussian distribution we used the Kruskal Wallis test followed by Dunn’s test to compare groups.

Pearson's or Spearman's correlation coefficient was used to investigate the correlation between echocardiographic variables and CS_T and CS_{QRS}. To interpret the relevance of the correlation, the following classification was adopted: correlation coefficients <0.3 (poor), 0.3 and 0.5 (fair), 0.6 and 0.8 (moderately strong) and> 0.8 (very strong) [4].

To verify which indexes best identified dogs with either PH_i or PH_h, the dogs of the study were divided into two groups: high/intermediate probability and low probability/controls. Then, the best cutoff point for CS measurements to identify dogs with PH_i or PH_h was determined by constructing the ROC curves and calculating the area under the curve (AUC). AUC>0.7 was considered adequate [13].

Kaplan-Meier curves were used to investigate the prognostic applicability of echocardiographic indices and CS measures, with mortality as the final outcome. Also, we analyzed the survival of patients according to the presence/absence of overt clinical signs, as well as the probability of PH.

To calculate intra-observer and inter-observer coefficients of variation, echocardiographic images obtained in 10% of patients enrolled in this investigation were randomly selected for repeat measurements of CS_T and CS_{QRS} by both the same observer (FA) and a second investigator blinded to the results (BCPV). Repeat measures were compared with intraclass correlation coefficient. Values less than 0,5 are indicative of poor reliability, values between 05 and 0,75 indicate moderate reliability, values between 0.75 and 0.9 indicate good reliability, and values greater than 0.90 indicate excellent reliability [13].

All analyzes were performed using Graphpad Prism software version 9.0® and tests were considered significant when $p<0.05$.

RESULTS

This study included 61 dogs (34 males; 27 females; 4-5 years (n=3); 6-11 years (n=30); and 12-17 years (n=28) met the inclusion criteria. Of these, 38 dogs (62,3 %) were diagnosed with PH, with 28 (73,7%), 7 (18,4%) and 3 (7,9%) of them considered to be either pre-capillary, post-capillary or mixed in origin, respectively. Also, the probability of having PH was determined to be low (PH_l) in 15 dogs (24,5%), intermediate (PH_i) in 11 (18,03%), and high (PH_h) in 12 (19,7 %). Of note, 23 dogs were recruited to serve as controls, i.e. were not considered as having PH based criteria described elsewhere [19]. Several breeds were represented in the study, including Airedale Terrier, Beagle, Boxer, French Bulldog, Bull Terrier, Chihuahua, Cocker Spaniel, Great Dane, Fila Brasileiro, Fox Terrier, Pekingese, Miniature Poodle, Spitz (one each), Dachshund, Standard Poodle, Schnauzer (two each), Labrador Retriever, Lhasa Apso (three each), Pinscher (n=6), Shih Tzu (n=9), and mixed breed dogs (n=20). While control dogs had a mean age of 9.2 years, PH dogs had a men age of 12 years (PH_l 10.8 years; PH_i 11.6 years; PH_h 13.5 years).

While none of the animals in the control group were on medications, 19 (50%) PH dogs were treated. Of the dogs with PH_l 13.3% received pimobendan, 6.7% were on furosemide and enalapril and 6,7% combination of salmeterol xinafoate and fluticasone propionate. For dogs with Ph_i, 45,5% were taking medications, including sildenafil (9,1%), combination of salmeterol and fluticasone propionate (9,1%), enalapril (18,2%), and furosemide and pimobendan (18,2%). Lastly, 83.3% of dogs with PH_h were medicated. While pimobendan associated with at least two diuretics was used in 41.7% of that population, sildenafil was used either alone (25%) or associated with diuretics (16,7%).

Table 1 present the echocardiographic variables used to assess the probability of PH in dogs. Post hoc multiple comparison tests identified differences between PH categories. Tricuspid regurgitation velocity and gradient were higher in animals with PH_h as compared to dogs with PH_l and PH_i. Also, PA/Ao ratio was higher in PH_h dogs when compared to PH_i and PH_l. The diameter of ${}_aCS_T$, CS_{TW}, CS_{TR}, CS_{TB}, ${}_aCS_{QRS}$, CS_{QRSW}, CS_{QRSR} and CS_{QRSB}. The measure of CS_{TAo} and CS_{QRSAo} were lower as the probability of PH increased, as they are inversely proportional (Table 2). As the probability of PH increases, the diameter of the CS increases accordingly.

CS_{QRSB}, CS_{TB}, CS_{QRSR}, CS_{TW}, CS_{TR} and AP/Ao showed a moderate to strong positive correlation with tricuspid regurgitation peak velocity (Table 3). CS_{Tao} and CS_{QRSAo} had a moderate to strong negative correlation with tricuspid regurgitation peak velocity. Interestingly, in most cases correlations were better than that obtained between tricuspid regurgitation peak velocity and standard echocardiographic parameters used as criteria to assess the probability of PH in dogs.

ROC curves were constructed to assess cut-offs, sensitivity and specificity of echocardiographic variables to identify dogs with the more advanced forms of PH (i.e., PH_i and PH_h). AUC >0.7 were documented for tricuspid regurgitation peak velocity, tricuspid regurgitation pressure gradient, PA/Ao, as well as all measurements related to CS width (Table 4). ROC curves were also used to assess how several echocardiographic variables perform to predict mortality. The highest AUC (>0.8) were documented for tricuspid regurgitation peak velocity, CS_{QRSW}, CS_{QRSAo}, CS_{TAo}, and PA/Ao (Table 5). In addition, the measurements of CS_{QRSB}, CS_{TB}, CS_{TW}, CS_{TR}, CS_{QRSR}, had AUC>0.7, and were considered adequate.

Figure 2 and Figure 3 present the analysis of survival of patients with PH according to the cut-off points of EC measurements and other echocardiographic variables used as criteria for identifying PH, respectively. Patients with $CS_{TAo}<5$, $CS_{QRSAo}<6$ had a median survival of 180 days. Those with $CS_{QRSW} > 0.034$ or TR

PV > 306 had a median survival of 150 days. It was not possible to calculate survival time.

The intraclass correlation coefficient was >0.9 in all analysis, both intraobserver and interobserver assessment of the $_{a}CS_{T}$ and $_{a}CS_{QRS}$ measurements.

DISCUSSION

As far as these authors know, this is the first study evaluating how the CS diameter changes in dogs with PH, as well as its correlation with echocardiographic markers of PH. The CS measurement proved to be easy to acquire and exhibited excellent repeatability and reproducibility. Nonetheless, since several breeds were enrolled in this study, having CS measurements normalized to body size was necessary to compare different populations. Although several indexes were effective and showed good results, we recommend the use of body surface area and aortic diameter as standard indexes.

Although easily visualized, the CS has been traditionally ignored in the standard echocardiographic evaluation of animals. Interestingly, at least in people dilation of the coronary sinus has been recognized as an index of heart failure severity [27]. A study in people undergoing cardiac catheterization documented a positive correlation between CS diameter and right atrial pressure [15]. This finding might represent an advantage of CS measurements since methods intended to estimate right atrial pressure using the tricuspid regurgitation pressure gradient are neither validated for dogs not recommended [21, 22]. In our study, dogs with the higher probability of PH presented wider CS dimensions, similar to what has been reported in people [3]. Such finding is ascribed to the elevated pulmonary artery systolic pressure [14, 6] which eventually causes the elevation of right atrial pressure [1]. Also, dilation of the CS was demonstrated by computed tomography in humans with increased pulmonary artery pressure [9], whereas another investigation demonstrated a significant correlation between the dilated CS and pulmonary artery systolic pressure, right atrial pressure, right heart chamber volumes, right ventricular ejection fraction and inferior vena cava [8]. Cetin et al (2015) [3] demonstrated that people with LV of normal size and function had an increased CS diameter when they had moderate and severe PH and it was correlated with pulmonary artery systolic pressure and right atrial pressure. This study was able to detect CS dilatation in patients with low, intermediate and high PH. This suggests that it may be an early indicator for PH, even in those cases where severe remodeling has not yet occurred. As there was no difference in the control group compared to the other groups, it can be said that this measure is safe for the diagnosis only of those affected by the disease. It is possible that there is a difference in this dilation when comparing patients with pre and post capillary PH, and this can be further investigated in future studies.

Tricuspid regurgitation peak velocity is an indirect measure of pulmonary artery systolic pressure. In spite of its flaws [23, 7], it is the most indicated method to date [19]. In this study, a positive correlation existed between CS diameter and tricuspid regurgitation peak velocity. In animals with early development of pulmonary hypertension, is frequently the absence of regurgitant jets [25, 22]. That being said, CS width might represent a surrogate for pulmonary artery systolic pressure in dogs at which tricuspid regurgitation is not properly identified and also complementary for diagnostic.

When absent from pathologies, the CS it is a venous structure that is difficult to perceive in the echocardiogram [15]. This study demonstrated that patients with low to higher degrees of PH have dilatation of this structure, which can be easily visualized. This is probably due to the dilation that occurs in the right atrium [5]. Obtaining this measure has sensitivity and specificity, comparable to tricuspid regurgitation and was as good or better than TAPSE, FAC, AT/ET and RPAD and the highest Likelihood ratio values, after tricuspid regurgitation, were from SC. This indicates that this is a significant predictor of PH, corroborating with Gunes et al [5]. Thus, the CS is an index that can be added to the probabilistic assessment of PH in dogs and that it contributes to improving the accuracy of the routine examination, in agreement with the recommendation by Gunes et al (2008) [5]. However, the prevalence of dilated CS in patients with PH is still unknown and may be the subject of future investigations.

Regardless of the etiology of the disease, knowing aspects related to survival and prognosis is essential [16]. The ROC curves demonstrate that CS can be an excellent prognostic indicator, even in the short term. Other variables such as RPAD, TAPSE, AT/ET, FAC and PA/Ao were previously investigated and suggested as good prognostic indicators [18], which was not seen in this study. Recognizing the best echocardiographic variables associated with survival time in dogs is important to assist in clinical follow-up, treatment and certainly a better technical conduct and relationship with the owner. Furthermore, the association of different variables in the assessment of patients with PH leads more effectively to an assertive diagnosis [22]. In this study, CS proved to be efficient as a predictor of death from PH and therefore should be considered during the prognostic analysis of dogs.

LIMITATIONS

This study should be interpreted having in mind its many limitations. Firstly, we lack a gold standard for determining pulmonary artery pressure, and diagnosis of PH was solely based on echocardiographic surrogates.

Although every effort was made to exclude cases which might present a dilated CS in the absence of PH (i.e. congenital right heart disease, pericardial effusion, degenerative tricuspid valve disease) we acknowledge that vascular anomalies such as persistent left cranial vena cava were not completely ruled out by means of a microbubble study or computed tomography.

Although the CS measurements were indexed by weight, the heterogeneity of the group may be a limitation to be considered. In addition, studies with a larger number of dogs, with a specific dog breed group and followed for a larger period offer a good alternative for future investigations, especially for analysis of survival since few animals reached the final outcome.

CONCLUSIONS

CS measurement can be performed at the beginning of the QRS and/or at the end of the T wave. Indexing is recommended, especially by aortic diameter and body surface area. The CS undergoes remodeling with probability of PH. CS measurement can be used to assess intermediate and high probability of PH and is positive correlated with tricuspid regurgitation. This measure has good sensitivity and specificity as a prognostic indicator, even better than other echocardiographic variables. in addition, it is a measure with good repeatability and reproducibility and is easy to obtain during the exam.

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FIGURAS

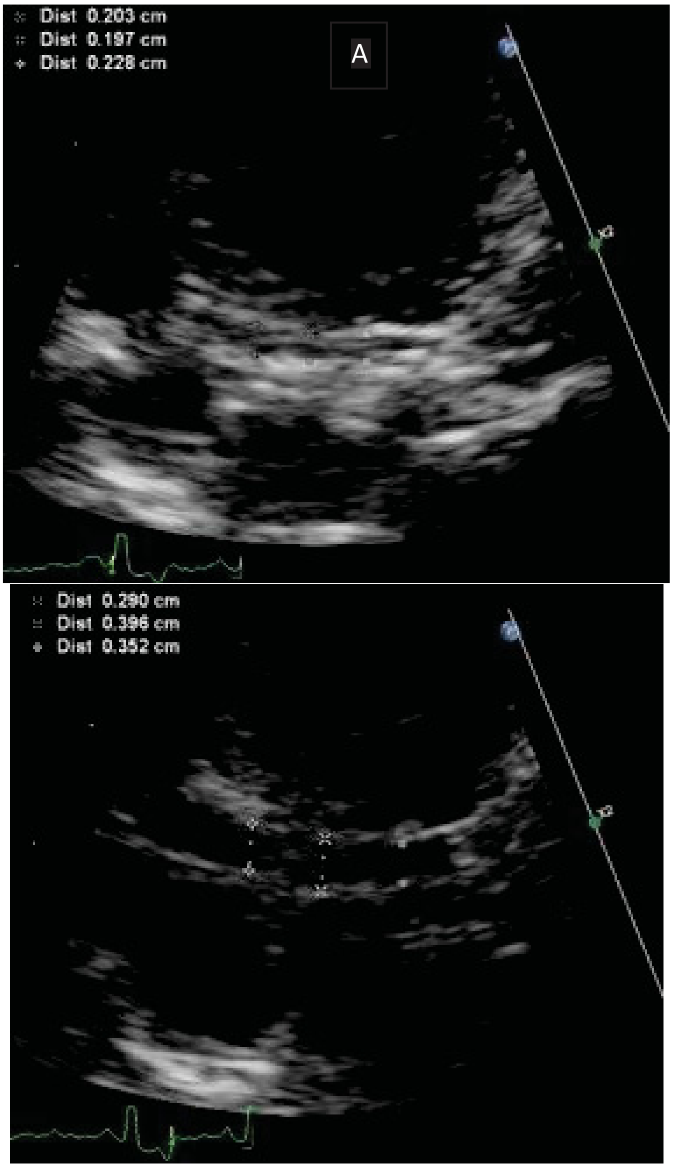

Figure 1 –Modified apical 4-chamber images used to measure the coronary sinus in dogs at the beginning of the QRS complex (A) and at the end of the T wave (B).

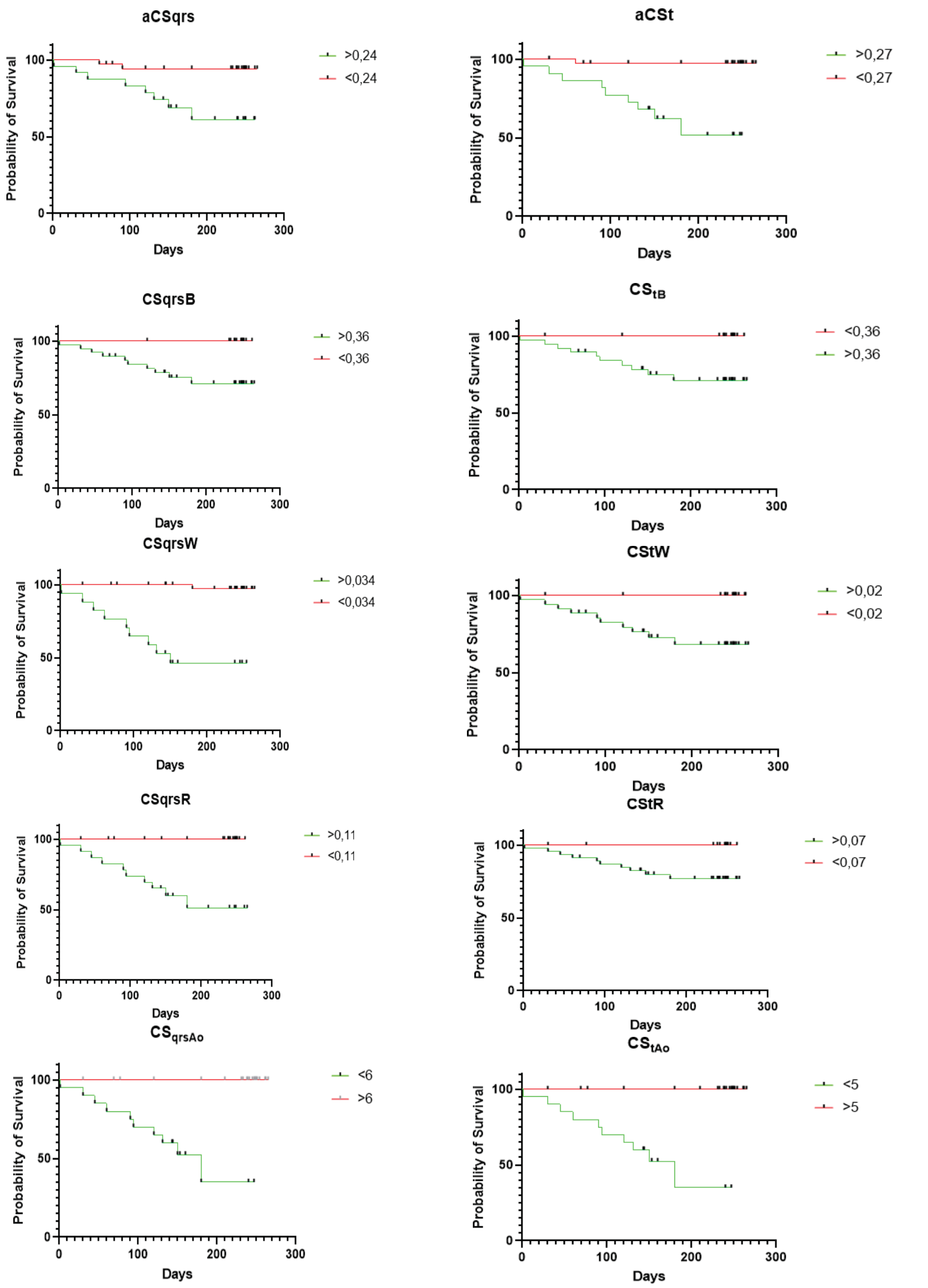

Figure 2. Survival analysis of dogs with varying degrees of PH according to measurement of CS. $_aCS_T$: average coronary sinus diameter measured at the end of the T wave; $_aCS_{QRS}$: average coronary sinus diameter measured at the beginning of the QRS complex; CS_{QRSB}: coronary sinus diameter measured at the beginning of the body surface area-indexed QRS complex; CS_{QRSAo}: coronary sinus diameter measured at the beginning of the aorta-indexed QRS complex; CS_{QRSR}: coronary sinus diameter measured at the beginning of the root of body weight-indexed; CS_{QRSW}:coronary sinus diameter measured at the beginning of the wheight-indexed; CS_{TB}:coronary sinus diameter measured at the end of the T wave, indexed by the body surface area; CS_{TAo}: coronary sinus diameter measured at the end of the T wave, indexed by aorta; CS_{TR}: coronary sinus diameter measuredat the end of the T wave, indexed by root; CS_{TW}:coronary sinus diameter measured at the end of the T wave, indexed by wheight.
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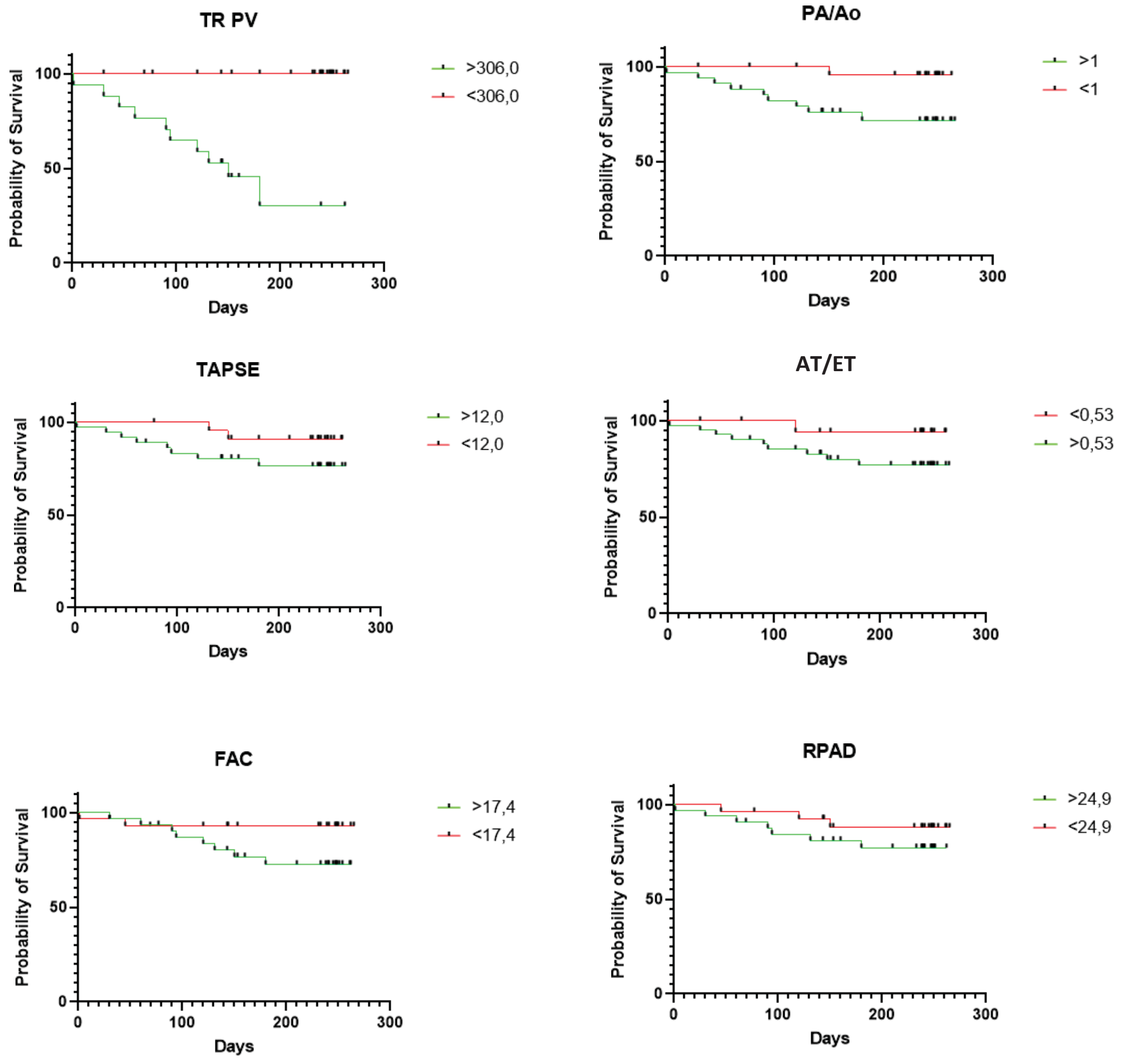

Figure 3. Survival analysis of dogs with varying degrees of PH according to echocardiographics variables. TR PV: tricuspid regurgitation peak velocity; TAPSE: : tricuspid annular plane systolic excursion; FAC: fractional area change; PA/Ao: pulmonary artery -to- aorta ratio; AT/ET: pulmonary flow acceleration-to ejection time ratio;; RPAD: Right pulmonary artery distensibility;.

TABLES

Table 1. Echocardiographic variables used to evaluate the probability of PH in dogs. Data are presented as either mean±SD or median (IQR).

	Controls	**PH_l**	**PH_i**	**PH_h**	p-value
FAC (%)	17±14.6	24.5±18	25.5±12	20,5±15.2	0.361
PA/Ao	0.93(-0.19)a	0.92(0.2)a	1.09(-0.25)c	1.26(-0.5)b	<0.001
ET (ms)	169(28.5)	156(34.5)	124(59.5)	123(45)	0.05
AT (ms)	75.3±30.5	69.9±30.9	68.9±21.4	66.1±25.9	0.051
AT/ET	0.5(0.2)	0.5(0.1)	0.5(0.2)	0.5(0.2)	0.606
RPAD %	28.7±9.6	25.9±11.2	25.1±9.3	27.6±9.5	0.742
TR PV (cm/s)	0(0)	256(39.6)c	284(72.5)a	436.8(77.2)b	<0.001
TR PG (mmHg)	.	26.5(8.25)c	40(19.5)a	74,0(26.75)b	<0.001

FAC: fractional area change; PA/Ao: pulmonary artery -to- aorta ratio; ET: pulmonary flow ejection time; AT: pulmonary flow acceleration time; AT/ET: pulmonary flow acceleration-to ejection time ratio; RPAD: Right pulmonary artery distensibility; TR PV: tricuspid regurgitation peak velocity; TR PG: tricuspid regurgitation pressure gradient.

Table 2. Measurements of the CS obtained at end-systole (end of the T wave) and end-diastole (beginning of the QRS complex) in healthy dogs and dogs with PH. Data are presented as either mean±SD or median (IQR).

	Control	**PH_l**	**PH_i**	**PH_h**	**p-value**
$_aCS_T$	0.22±0.19 a	0.1 (0.13-0.21)a	0.36±0.25 b	0.56±0.26 c	<0.0001
CS_{TW}	0.02±0.01 a	0.02±0.01 a	0.05±0.03 b	0.06(0.04-0.14) c	<0.0001
CS_{TR}	0.09±0.05 a	0.08±0.02 a	0.17±0.09 b	0.28(0.15-0.37) c	<0.0001
CS_{TB}	0.36±0.16 a	0.39±0.11 a	0.87±0.45 b	1.3(0.82-2.45) c	<0.0001
CS_{TAo}	9.04(7.6-16.3) a	9.22±2.6 a	4.19(3.2-9.2) b	3.05±1.9 c	<0.0001
$_aCS_{QRS}$	0.23±0.17 a	0.15±0.06 a	0.25±0.15 b	0.42(0.29-0.7) c	0.0002
CS_{QRSW}	0.02±0.01 a	0.016(0.01-0.02) a	0.03±0.01 b	0.05(0.03-0.1) c	<0.0001
CS_{QRSR}	0.09±0.04 a	0.07±0.02 a	0.12±0.05 b	0.20(0.1-0.2) c	<0.0001
CS_{QRSB}	0.38±0.15 a	0.35±0.1 a	0.6±0.2 b	1.04(0.6-1.4) c	<0.0001
CS_{QRSAo}	8.45(6.5-10.7) a	10.5±1.7 a	6.9±3.6 b	3.6±1.7 c	<0.0001

$_aCS_T$: average coronary sinus diameter measured at the enda of the T wave; CS_{TW}:coronary sinus diameter measured at the end of the T wave, indexed by wheight; CST_R: coronary sinus diameter measured at the end of the T wave, indexed by root; CS_{TB}: coronary sinus diameter measured at the end of the T wave, indexed by the body surface area; CS_{TAo}: coronary sinus diameter measured at the end of the T wave, indexed by aorta $_aCS_{QRS}$: average coronary sinus diameter measured at the beginning of the QRS complex; CS_{QRSW}:coronary sinus diameter measured at the beginning of the wheight-indexed; CS_{QRSR}: coronary sinus diameter measured at the beginning of the root of body weight-indexed; CS_{QRSB}: coronary sinus diameter measured at the beginning of the body surface area-indexed QRS complex; CS_{QRSAo}: coronary sinus diameter measured at the beginning of the aorta-indexed QRS complex; IQR: interquartile range; SD: standard deviation.

Table 3. Correlations between echocardiographic variables and tricuspid regurgitation peak velocity.

	p-value	RHO
CS_{QRSB}	<0.0001	0.7
CS_{TB}	<0.0001	0.7
CS_{QRSR}	<0.0001	0.6
CS_{TW}	<0.0001	0.6
PA/Ao	<0.0001	0.6
CS_{TR}	<0.0001	0.6
CS_{QRSW}	<0.0001	0.5
$_{a}CS_{T}$	<0.0001	0.2
$_{a}CS_{QRS}$	<0.0001	0.2
ET	0.045	0.2
AT	0.055	0.1
TAPSE	0.267	-0.1
FAC	0.364	-0.3
RPAD	0.41	-0.6
AT/ET	0.689	-0.6
CS_{TAo}	<0.0001	-0.7
CS_{QRSAo}	<0.0001	-0.7

CS_{QRSB}: coronary sinus diameter measured at the beginning of the body surface area-indexed QRS complex; CS_{TB}: coronary sinus diameter measured at the end of the T wave, indexed by the body surface area; CS_{QRSR}: coronary sinus diameter measured at the beginning of the root of body weight-indexed; CS_{TW}:coronary sinus diameter measured at the end of the T wave, indexed by wheight; PA/Ao: pulmonary artery-to-aorta ratio; CS_{TR}: coronary sinus diameter measured at the end of the T wave, indexed by root; CS_{QRSW}: coronary sinus diameter measured at the beginning of the wheight-indexed; $_{a}CS_{T}$: average coronary sinus diameter measured at the enda of the T wave; $_{a}CS_{QRS}$: average coronary sinus diameter measured at the beginning of the QRS complex; ET: pulmonary artery ejection time; AT: pulmonary artery acceleration time; TAPSE: tricuspid annular plane systolic excursion; FAC: fractional area variation; RPAD: right pulmonary artery distensibility; AT/ET: ratio pulmonary artery acceleration and ejection time; CS_{TAo}: coronary sinus diameter measured at the end of the T wave, indexed by aorta; CS_{QRSAo}: coronary sinus diameter measured at the beginning of the aorta-indexed QRS complex.

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Table 4. Cut-off points, sensitivity and specificity of several echocardiographic variables used for identifying dogs with intermediate or high probability of PH.

	AUC	Cut-off	Sensitivity	95% CI	Specificity	95% CI	Likelihood ratio
TR PV	0.98	< 271.0	94.4	74.2% to 99.7%	95.6	79.0% to 99.8%	21.7
TR PG	0.97	< 30.0	93.3	70.2% to 99.7%	95.6	79.0% to 99.8%	21.5
CS_{TW}	0.9	< 0.023	83.8	68.9% to 92.4%	87.0	67.9% to 95.5%	6.4
CS_{QRSB}	0.9	< 0.48	83.8	68.9% to 92.4%	87.1	67.9% to 95.5%	6.4
CS_{TB}	0.9	< 0.71	100	90.6% to 100.0%	78.4	58.1% to 90.4%	4.6
CS_{QRSW}	0.9	< 0.02	72.3	57.0% to 84.6%	91.3	73.2% to 98.5%	8.4
PA/Ao	0.9	< 1.04	88.9	74.7% to 95.6%	78.3	58.1% to 90.4%	4.1
CS_{TAo}	0.9	> 5.7	94.6	82.3% to 99.0%	82.6	62.9% to 93.0%	5.4
CS_{QRSR}	0.9	< 0.12	91.9	78.7% to 97.2%	73.9	53.5% to 87.5%	3.5
$_{a}CS_{T}$	0.8	< 0.25	89.2	75.39% to 95.7%	82.6	62.9% to 93.0%	5.1
CS_{QRSAo}	0.8	> 6.1	89.2	75.3% to 95.7%	78.3	58.1% to 90.3%	4.1
$_{a}CS_{QRS}$	0.8	< 0.24	78.4	62.8% to 88.6%	69.6	49.1% to 84.4%	2.6
CS_{TR}	0.7	< 0.15	94.6	82.3% to 99.0%	82.6	62.9% to 93.0%	5.4
TAPSE	0.6	< 12.0	48.7	33.4% to 64.1%	78.3	58.1% to 90.3%	2.2
FAC	0.5	< 16.6	55.6	39.68% to 70.5%	72.7	51.9% to 86.9%	2.0
AT/ET	0.5	< 0.49	60	43.6% to 74.5%	54.6	34.7% to 73.1%	1.3
RPAD	0.5	> 12.80	100	90.1% to 100.0%	14.3	5% to 34.6%	1.2

TR PV: tricuspid regurgitation peak velocity; TR PG: tricuspid regurgitation pressure gradient; PA/Ao: pulmonary artery-to-aorta ratio; CS_{TW}: coronary sinus diameter measured at the end of the T wave, indexed by wheight; CS_{QRSB}: coronary sinus diameter measured at the beginning of the body surface area-indexed QRS complex; CS_{TB}: coronary sinus diameter measured at the end of the T wave, indexed by the body surface area; CS_{QRSW}: coronary sinus diameter measured at the beginning of the wheight-indexed; PA/Ao: pulmonary artery-to-aorta ratio; CS_{TAo}: coronary sinus diameter measured at the end of the T wave, indexed by aorta; CS_{QRSR}: coronary sinus diameter measured at the beginning of the root of body weight-indexed; $_{a}CS_{T}$: average coronary sinus diameter measured at the enda of the T wave; CS_{QRSAo}: coronary sinus diameter measured at the beginning of the aorta-indexed QRS complex; $_{a}CS_{QRS}$: average coronary sinus diameter measured at the beginning of the QRS complex; CS_{TR}: coronary sinus diameter measured at the end of the T wave, indexed by root; TAPSE: tricuspid annular plane systolic excursion; FAC: fractional area variation; AT/ET: ratio pulmonary artery acceleration and ejection time; RPAD: right pulmonary artery distensibility.

Table 5. Cut-off points for echocardiographic variables with better specificity and sensitivity values to predict deaths from PH.

	AUC	Cut-off	Sensitivity	95% CI	Specificity	95% CI	Likelihood ratio
TR PV	0.9	> 306.0	100	72.3% to 100.0%	86	73.8% to 93.1%	7,1
CS_{QRSW}	0.9	> 0.034	90	59.6% to 99.5%	84	71.5% to 91.7%	5,6
CS_{QRSAo}	0.9	< 6.1	100	72.3% to 100.0%	76	62.6% to 85.7%	4,2
CS_{TAo}	0.9	< 5.	100	72.3% to 100.0%	80	67% to 88.8%	5
PA/Ao	0.8	> 1.0	90	59.6% to 99.5%	74	60.5% to 84.1%	3,5
CS_{QRSB}	0.7	> 0.36	90.6	71.1% to 98.3%	47,5	32.9% to 62.5%	1,7
CS_{TB}	0.7	> 0.36	90.5	71.1% to 98.3%	52,5	37.5% to 67.1%	1,9
CS_{TW}	0.7	> 0.02	85.7	65.4% to 95.0%	60	44.6% to 73.7%	2,1
CS_{TR}	0.7	> 0.07	90.5	71.1% to 98.3%	47,5	32.9% to 62.5%	1,7
CS_{QRSR}	0.7	> 0.11	71.4	50.0% to 86.2%	76	62.6% to 85.7%	3,0
FAC	0.6	> 17.4	88.9	56.5% to 99.4%	53,1	39.4% to 66.3%	1,9
RPAD	0.6	> 24.9	87.5	52.9% to 99.4%	45,8	32.6% to 59.7%	1,6
$_{a}CS_{T}$	0.6	> 0.27	52.4	32.4% to 71.7%	77,5	62.5% to 87.7%	2,3
AT/ET	0.6	< 0.53	88.9	56.5% to 99.4%	41,7	28.9% to 55.7%	1,5
$_{a}CS_{QRS}$	0.6	> 0.24	57.1	36.6% to 75.5%	67,5	52.0% to 79.9%	1,6
TAPSE	0.6	> 12.00	80	49.0% to 96.5%	42	29.4% to 55.8%	1,4

TR PV: tricuspid regurgitation peak velocity; CS_{QRSW}: coronary sinus diameter measured at the beginning of the wheight-indexed; ; CS_{QRSAo}: coronary sinus diameter measured at the beginning of the aorta-indexed QRS complex; CS_{TAo}: coronary sinus diameter measured at the end of the T wave, indexed by aorta; PA/Ao: pulmonary artery-to-aorta ratio; CS_{QRSB}: coronary sinus diameter measured at the beginning of the body surface area-indexed QRS complex; CST_{B}: coronary sinus diameter measured at the end of the T wave, indexed by the body surface area; CS_{TW}:coronary sinus diameter measured at the end of the T wave, indexed by wheight; CS_{TR}: coronary sinus diameter measured at the end of the T wave, indexed by root; CS_{QRSR}: coronary sinus diameter measured at the beginning of the root of body weight-indexed; FAC: fractional area variation; RPAD: right pulmonary artery distensibility; ${}_{a}CS_{T}$: average coronary sinus diameter measured at the enda of the T wave; AT/ET: ratio pulmonary artery acceleration and ejection time; ${}_{a}CS_{QRS}$: average coronary sinus diameter measured at the beginning of the QRS complex; TAPSE: tricuspid annular plane systolic excursion.