Acta Scientiae Veterinariae, 2024. 52: 1969.

RESEARCH ARTICLE
Pub. 1969

ISSN 1679-9216

Right Ventricular Longitudinal Function in the Assessment of Fluid Responsiveness in Healthy Dogs

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ABSTRACT

***Background*:** An essential component in the treatment of critically ill patients is volume replacement, but excessive intravascular fluid administration is associated with increased morbidity and mortality. Therefore, this intervention is only beneficial in patients who are fluid responsive, that is, when the individual has an increase in at least 15% of the stroke volume after a volume challenge administration. In addition, one of the determinants of fluid responsiveness is the systolic function, associated with the dynamic interactions between intravascular volume (preload) and vascular tone (afterload). Within this context, the aim of this study is to evaluate if conventional and advanced echocardiographic parameters of right ventricular longitudinal systolic function can assess fluid responsiveness in healthy spontaneously breathing dogs. The hypothesis was that some of these parameters would differ between responsive and non-responsive animals and could be used as a complementary measure for assessment of fluid responsiveness.

***Materials, Methods & Results*:** This is a prospective study with 22 healthy dogs over 1 year of age included. The animals were referred to the Veterinary Medical Teaching Hospital of the Federal University of Paraná (UFPR) for elective neutering procedure. All dogs underwent conventional and advanced echocardiographic examination before and after administration of a volume challenge with 10 mL/kg lactate ringer intravenously for 20 min. The parameters evaluated were the fractional area change (FAC), the tricuspid annular plane systolic excursion (TAPSE), free wall longitudinal strain (LSt), and tissue motion annular displacement (TMAD). Based on the aortic velocity integral time variation, 31.82% of dogs were considered responsive and 68.18% were non-responsive to the volume challenge. For conventional echocardiography, TAPSE (mm/kg) > 1.35 ($P = 0.018$) had a good combination of sensitivity (85.71%) and specificity (86.67%), area under the curve value (0.814) and a relative smaller gray zone interval (1.04-1.66) for the identification of responsive dogs before volume challenge. Although, TAPSE (mm/m^2) was also higher in the responsive dogs ($P = 0.023$) before volume challenge. As for advanced echocardiography, the TMAD (mm/kg) > 0.75 ($P = 0.010$) after volume challenge had the best combination of sensitivity (85.71%) and specificity (86.67%), area under the curve value (0.852) and a relative smaller gray zone interval (0.57-0.92) for the identification of responsive dogs. The LSt (%) and TMAD (mm/m^2) were also significantly higher in responsive dogs ($P = 0.031$; $P = 0.011$) after volume challenge.

***Discussion*:** Some of the echocardiographic parameters for assessing right ventricular systolic function differed between responsive and non-responsive dogs proving to been useful in the fluid responsiveness evaluation. To the author's knowledge, this is the 1st study to investigate the right ventricular systolic function in the assessment of fluid responsiveness in healthy, spontaneously breathing dogs. TAPSE and TMAD showed some advantages in terms of execution, although TAPSE (mm/kg) > 1.35 before the volume challenge had the power to predict fluid responsiveness without the need of a fluid administration, which can be seen as a great advantage, especially for patients with volume overload. However, it is also necessary to perform this type of evaluation in individuals with hemodynamic alterations to allow better understand the applicability of these techniques.

Keywords: canine, longitudinal strain, stroke volume, tissue motion annular displacement.

DOI: 10.22456/1679-9216.141446

Received: 25 July 2024 Accepted: 17 October 2024 Published: 4 Novemmber 2024

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INTRODUCTION

An essential component in the treatment of critically ill patients is volume replacement [25]. However, in dogs and cats the excessive intravascular fluid administration is associated with increased morbidity and mortality [7,28]. In this way, it has been suggested that volume replacement is only beneficial in patients deemed to be fluid responsive as defined by an ≥15% increase in stroke volume after a volume challenge [5,10,27].

The concept of fluid responsiveness can be explained by the Frank-Starling principle and curve in which, within a certain limit, the greater the stretching of the cardiomyocytes, the greater the force of contraction and, consequently, the greater the stroke volume and venous return [24]. The individuals in the ascending portion of the curve are called "preload dependent" and the ones in the plateau of the curve are called "non-preload dependent" [11,22].

For a patient to be fluid responsive, both the right and left ventricles must be functioning on the ascending part of the Frank-Starling curve [23]. Thus, the systolic function, associated with the dynamic interactions between intravascular volume (preload) and vascular tone (afterload), is one of the determinants of fluid responsiveness [8,9].

The echocardiographic assessment of right ventricular function has attracted increasing interest in veterinary cardiology. In the context above, its assessment following a volemic challenge could be useful in classifying the individual as responsive or non-responsive. Therefore, the aim of this study was to evaluate whether conventional and advanced echocardiographic parameters of right ventricular systolic function could assess fluid responsiveness in healthy, spontaneously breathing, dogs.

MATERIALS AND METHODS

Study design and animals

This is a prospective study with 22 healthy dogs. The animals were referred to the Veterinary Medical Teaching Hospital of the Federal University of Paraná (UFPR) for elective neutering procedure and the owners gave informed consent for inclusion of their pets in the study. Inclusion criteria for healthy dogs were based on the age (over 1-year-old), history of disease, physical examination, complete blood count and echocardiographic and electrocardiographic examinations. The animals that showed any alteration of the mentioned exams were excluded of the study.

Interventions

Standardized Doppler technique was used for indirect measurement of systolic blood pressure (SBP). The mean of 5 stable values of SBP (with a variation < 10%) was recorded and animals were considered normotensive when the SBP was between 80 and 160 mmHg [3].

The 1st echocardiographic evaluation (T0) was performed prior to the volemic challenge and the 2nd echocardiographic evaluation was performed (T1) within 5 min of completion of fluid administration. The volemic challenge was performed using an infusion pump administering lactated ringer's [10 mL/kg IV for 20 min]. Electrocardiographic evaluation was performed simultaneously with the echocardiographic examination, to identify heart rate and rhythm. Dogs were excluded from the study if they had cardiac rhythms of non-sinus origin, bradycardia or tachycardia. This entire procedure was performed before neutering.

The echocardiographic examination was performed in all dogs without sedation, with dogs breathing spontaneously and positioned in left and right lateral recumbency according to pre-established recommendations [37]. All examinations were performed by the same operator (SL) using standard equipment Philips Affiniti 50 equipped with 2-4, 3-8 MHz and 4-12 phased-array transducers[1].

Fluid responsiveness classification

The measurement of the aortic velocity time integral (VTI Ao) was performed by the apical 5 chamber image obtained through the left parasternal window. The mean of 3 measurements of the VTI Ao with the best alignment possible over a respiratory cycle was used for the calculation of the variation of the VTI Ao (ΔVTI Ao), according to the formula:

$\Delta VTI\ Ao = (VTI\ Ao\ T1 - VTI\ Ao\ T0) / VTI\ Ao\ T0 \times 100$

The value of the ΔVTI Ao has determined the classification of patients as responsive and non-responsive to the fluid challenge. The responsive individuals were considered those with ΔVTI Ao ≥15%

and non-responsive with ΔVTI Ao <15 % [5,27]. For statistical analysis, dogs were subdivided into 2 groups, responsive and non-responsive to the volemic challenge, and evaluations were made at T0 and T1.

Conventional echocardiographic evaluation

Videos of apical 4-chamber (A4C) optimized for the right ventricle were acquired to obtain the fractional area change (FAC) and the tricuspid annular plane systolic excursion (TAPSE). FAC was calculated by the percentage difference between the areas of the right ventricle at the end of diastole and at the end of systole. TAPSE represents the longitudinal displacement in millimeters of the annular plane of the tricuspid valve in images obtained by M-mode with the cursor positioned at the insertion of the lateral leaflet of the tricuspid valve with the right ventricle free wall. In addition, TAPSE (mm) was indexed by body weight (mm/kg) and by body surface area (mm/m^2) according to the formula:

$$BSA = K \text{ x } (\text{body weight in grams}^{2/3}) \text{ x } 10^{-4}$$

$$K = \text{constant (10.1 for dogs)}$$

Advanced echocardiographic evaluation

Videos of apical 4-chamber (A4C) optimized for the right ventricle were obtained over at least 5 cardiac cycles for offline measurement of longitudinal strain (LSt) and tissue motion annular displacement (TMAD). The echocardiographic equipment software automatically detected the right ventricular myocardium for assessment of LSt. Manual adjustments were performed when necessary to ensure accurate identification of the limits of the myocardium. This parameter was defined as the percentage of myocardial deformation of the right ventricle in the longitudinal plane during a cardiac cycle. However, only the 3 myocardial segments of the right ventricle free wall (basal, medium and apical) were taken into account to calculate the LSt, which was obtained through the mean value of deformation of the aforementioned segments (Figure 1).

To obtain the TMAD, 3 regions of interest were manually established: the 1st, at the insertion of the lateral tricuspid leaflet; the 2nd, at the insertion of the septal tricuspid leaflet; and the 3rd, at the epicardial region of the apex of the right ventricle. After selecting the regions of interest, myocardial screening was performed automatically by the equipment's software (Figure 2).

The TMAD was calculated, in millimeters (mm) and percentage (%), from the apex-base displacement of the virtual midpoint between the 2 regions of interest of the tricuspid valve annulus in relation to the total length of the right ventricle. In addition, TMAD (mm) was indexed by body weight (mm/kg) and by body surface area (mm/m^2) according to the formula described above.

Statistical analysis

For the qualitative variables the frequencies (%) were estimated and for the quantitative variables the mean and standard deviation or median and range were calculated, depending on the distribution of the samples. The Shapiro-Wilk test was used to the distribution analysis.

For data with normal distribution the t-test or Student t test were used and for data with non-normal distribution the Wilcoxon or Mann-Whitney were used. Some comparisons of means were carried out as follows: responsive in T0 versus responsive in T1; non-responsive in T0 versus non-responsive in T1; responsive versus non-responsive in T0; and responsive versus non-responsive in T1.

Among the echocardiographic parameters that differed between responsive and non-responsive dogs at T0 or T1, the positive (PPV) and negative (NPV) predictive values were calculated, ROC curves were plotted to obtain the area under the curve (AUC) and 95% confidence interval (CI). The Youden index was determined to identify the best cut-off value and its combination of sensitivity and specificity. Also, the gray zone was calculated with the aim of identifying the inconclusive zone of the studied cutoff values, and this zone was defined by cutoff values with 90% sensitivity and specificity (10% diagnostic tolerance).

Finally, dogs were subdivided into individuals with sinus rhythm versus sinus arrhythmia and compared to verify the influence of rhythm on the echocardiographic variables studied. The correlation coefficient of Pearson (normal distribution) or Spearman (non-normal distribution) were calculated to investigate the influence of age, body weight, heart rate and SBP. All analysis were performed using the same software[2] and the level of statistical significance adopted was $P < 0.05$.

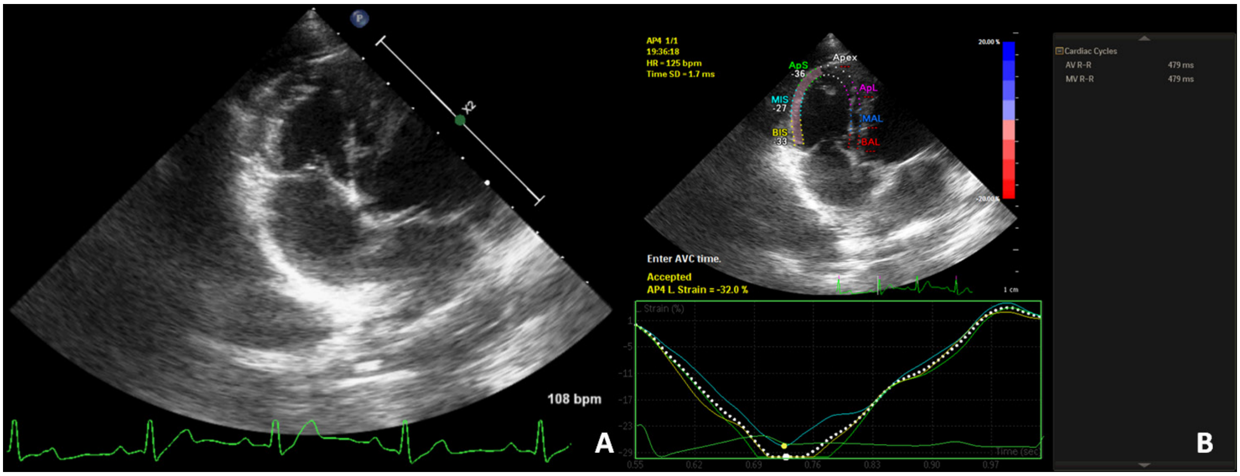

Figure 1. Advanced echocardiography showing the apical 4-chamber image optimized for the right ventricle (A) used to obtain the longitudinal strain (LSt) in percentage (B) of a healthy dog non-responsive to the fluid challenge.

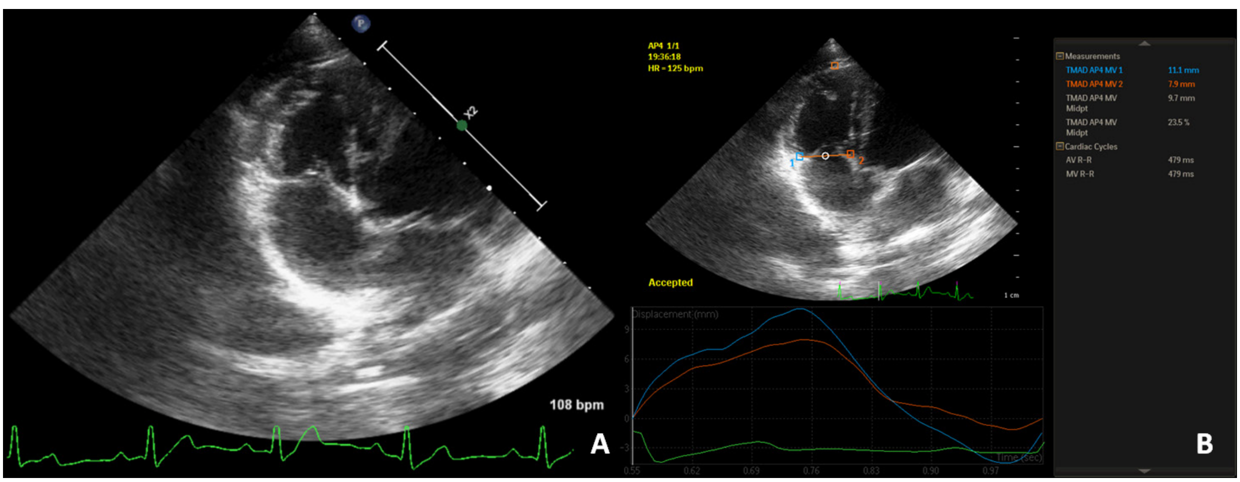

Figure 2. Advanced echocardiography showing the apical 4-chamber image optimized for the right ventricle (A) used to obtain the global tissue motion annular displacement (TMAD), in millimeters (mm) and percentage (B), of a healthy dog non-responsive to the fluid challenge.

RESULTS

A total of 22 dogs were included in the study, being that 12 (54.5%) were females and 10 (45.5%) males. The age of the animals ranged between 1 and 9 years (median: 2 years). The dogs were of different sizes with a mean and standard deviation of body weight of 12.8 (± 6.4) kg. The most commonly represented breeds were: mixed breed dogs (13), followed by Lhasa Apso (5), Australian Cattle (2), Shih-tzu (1) and Yorkshire Terrier (1).

SBP was measured in 77.3% (17) of the dogs, with a mean of 113 (± 15.7) mmHg. Among the heart rhythm, sinus arrhythmia (SA) was observed in 72.7% (32) and sinus rhythm (SR) was observed in 27.3% (12) of the evaluations. At T0, animals with SR showed significantly higher values of FAC compared to animals with SA (P = 0.0266). Heart rhythm did not affect TAPSE and any of the advanced echocardiographic parameters evaluated.

Based on the value of ΔVTI Ao, 31.8% (7) of the dogs were considered responsive and 68.2% (15) non-responsive to the volume challenge. The VTI Ao (cm) of the responsive dogs were significantly lower compared with the non-responsive ones before the volume challenge [P = 0.0005] (Figure 3). The mean and standard deviation or median and range of all echocardiographic parameters evaluated are shown in Table 1.

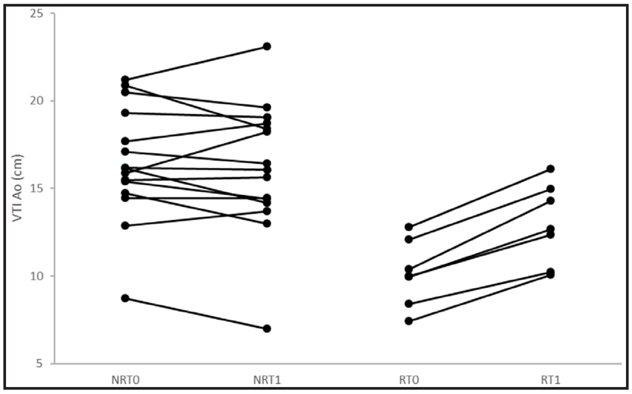

Figure 3. Box-plot graphs showing the minimum, maximum, median and interquartile ranges of the VTI Ao before and after the volume challenge of dogs classified as responsive (n = 7) and non-responsive (n = 15). [Ao: aorta; NRT0: non-responsive time 0; NRT1: non-responsive time 1; RT0: responsive time 0; RT1: responsive time 1; VTI: velocity time integral].

FAC did not differ between responsive and non-responsive dogs at T0 and T1. TAPSE (mm) and (mm/m^2) increased significantly at T1 in the group of non-responsive animals [$P = 0.049$; $P = 0.042$]. TAPSE (mm/kg, mm/m^2) were significantly higher at T0 in responsive patients compared to the non-responsive ones [$P = 0.018$; $P = 0.023$] (Figure 4). The LSt (%) and TMAD (mm/kg, mm/m2) were significantly higher in responsive dogs compared to the non-responsive ones [$P = 0.031$; $P = 0.010$; $P = 0.011$] at T1 (Figure 5). Also, TMAD (mm, %) increased significantly at T1 in the group of non-responsive animals [$P = 0.034$ and $P = 0.029$].

The conventional echocardiographic parameters that differed between responsive and non-responsive dogs were TAPSE (mm/kg, mm/m^2) at T0. For the advanced echocardiographic parameters, LSt (%) and TMAD (mm/kg, mm/m^2), differed between responsive and non-responsive animals at T1. The best cut-off values of the cited parameters, with their respective PPV, NPV, sensitivity, specificity, AUC, 95% CI and gray zone interval are described in Table 2. The ROC curves are presented in Figure 6 and the sensitivity and specificity graphs with the demarcation of the gray zone are shown in Figure 7.

TAPSE (mm/kg, mm/m^2) showed a correlation with age at T0. Also, TAPSE (mm) and all its indexes correlated with body weight at T0 and T1. FAC (%) at T0, TAPSE (mm) at T1 and TAPSE (mm/m2) at T0 correlated with heart rate. No correlations were observed between advanced echocardiographic parameters with age or heart rate. However, the LSt (%) and TMAD (mm, %, mm/kg, mm/m^2) showed correlation with weight at T0 or T1. None of the variables studied showed a correlation with SBP. The results of the correlation analysis are described in Table 3.

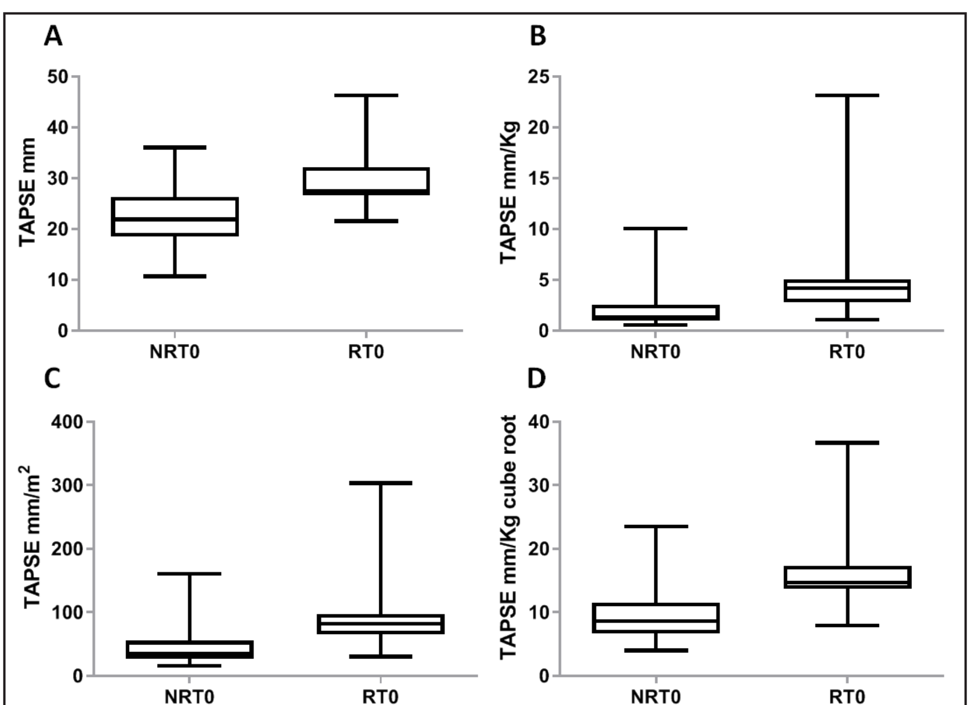

Figure 4. Box-plot graphs showing the minimum, maximum, median and interquartile ranges of conventional echocardiographic parameters that differed between responsive (n = 7) and non-responsive (n = 15) dogs. [NRT0: non-responsive time 0; RT0: responsive time 0; TAPSE: tricuspid annular plane systolic excursion].

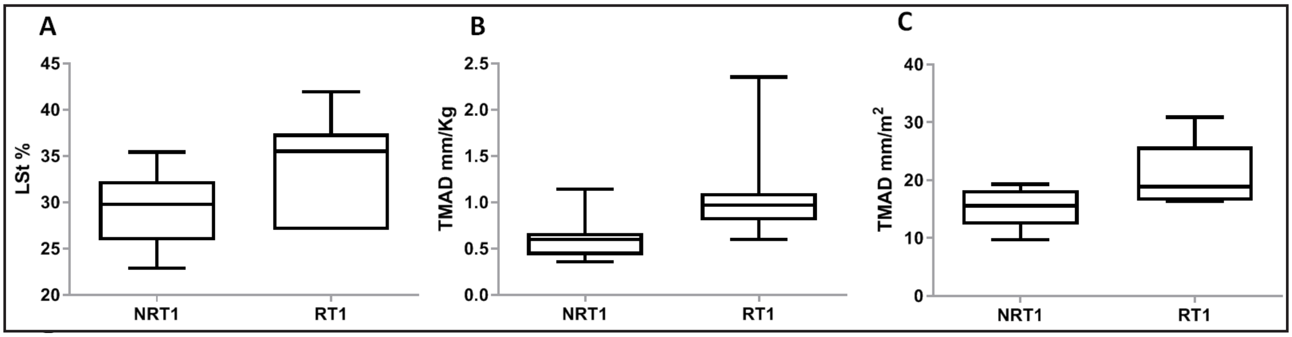

Figure 5. Box-plot graphs showing the minimum, maximum, median and interquartile ranges of advanced echocardiographic parameters that differed between responsive (n = 7) and non-responsive (n = 15) dogs. [LSt: longitudinal strain; NRT1: non-responsive time 1; RT1: responsive time 1; TMAD: tissue motion annular displacement].

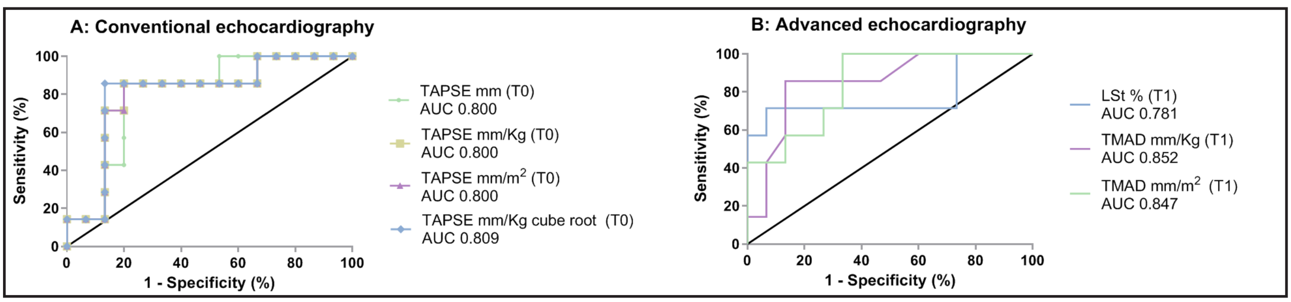

Figure 6. ROC curves and AUC values of conventional (A) and advanced (B) echocardiographic parameters that differed between responsive (n = 7) and non-responsive (n = 15) dogs. [AUC: area under the curve; LSt: longitudinal strain; TAPSE: tricuspid annular plane systolic excursion; TMAD: tissue motion annular displacement; T0: time 0; T1: time 1].

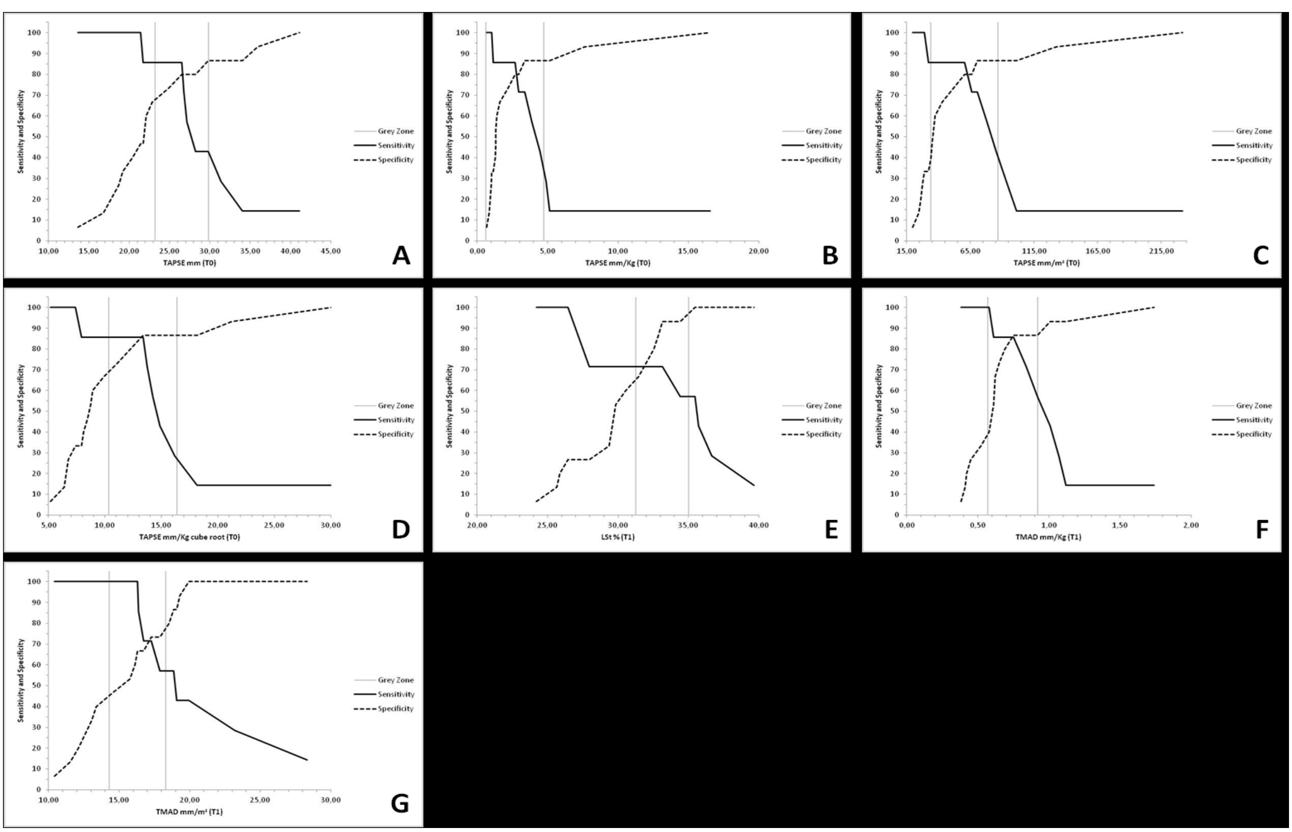

Figure 7. Sensitivity and specificity graphs with the gray zone interval demarcation of conventional (A, B, C & D) and advanced (E, F & G) echocardiographic parameters that differed between the responsive (n = 7) and non-responsive (n = 15) dogs. [LSt: longitudinal strain; TAPSE: tricuspid annular plane systolic excursion; TMAD: tissue motion annular displacement; T0: time 0; T1: time 1].

Table 1. Mean and standard deviation or median and range of all echocardiographic parameters assessed for dogs classified as responsive (n = 7) and non-responsive (n = 15).

Conventional echocardiographic parameters				
	Non-responsive		Responsive	
	T0	T1	T0	T1
FAC (%)	52.83 (± 9.28)	50.86 (± 11.94)	54.19 (± 7.29)	51.80 (± 9.67)
TAPSE (mm)	22.60 (± 6.89)	23.44 (18.72-42.99)	30.23 (± 7.81)	26.34 (17.82-46.22)
TAPSE (mm/Kg)	1.32 (0.57-10.00)	1.44 (0.82-11.94)	4.16 (1.05-23.11)	4,13 (0.90-23.11)
TAPSE (mm/m^2)	35.34 (15.98-160.3)	40.41 (25.25-191.4)	81.95 (30.43-303.3)	85.04 (26.14-303.3)
TAPSE (mm//$\sqrt[3]{}$kg)	8.63 (4.02-23.49)	10.08 (6.97-28.05)	14.64 (7.87-36.68)	14.75 (6.76-36.68)
Advanced echocardiographic parameters				
	Non-responsive		Responsive	
	T0	T1	T0	T1
LSt (%)	27.67 (± 7.07)	29.64 (± 3.38)	30.24 (± 8.55)	34.01 (± 5.45)
TMAD (mm)	6.91 (± 2.26)	8.30 (± 2.61)	5.71 (± 2.24)	7.60 (± 3.27)
TMAD (%)	18.17 (± 5.24)	22.70 (15.30-29.10)	20.13 (± 6.36)	21.30 (18.20-43.40)
TMAD (mm/kg)	0.49 (0.18-1.53)	0.60 (0.36-1.14)	0.88 (0.23-2.50)	0.97 (0.60-2.35)
TMAD (mm/m^2)	13.18 (± 5.35)	15.54 (9.75-19.31)	17.39 (± 8.44)	18.88 (16.30-30.84)
TMAD (mm/$\sqrt[3]{}$kg)	2.89 (± 0.89)	3.40 (± 0.77)	3.01 (± 1.06)	3.79 (± 0.92)

LSt: longitudinal strain; TAPSE: tricuspid annular plane systolic excursion; TMAD: tissue motion annular displacement; T0: time 0; T1: time 1. Data with normal distribution were expressed by the mean and standard deviation and data with abnormal distribution were expressed by the median and interquartile range.

Table 2. Cut - off values for identification of the responsive patient with their respective positive predictive value (PPV), negative predictive value (NPV), sensitivity, specificity, area under the curve (AUC), 95% confidence interval (CI) and gray zone interval of echocardiographic parameters that differed between responsive (n = 7) and non - responsive (n = 15) dogs.

Conventional echocardiographic parameters	Cutoff Value	PPV	NPV	Sensitivity %	Specificity %	AUC (95% CI)	Gray Zone
TAPSE (mm) T0	> 26.53	0.40	0.59	85.71	80.0	0.800 (0.60 - 0.99)	23.23 - 29.82
TAPSE (mm/Kg) T0	> 2.68	0.40	0.59	85.71	80.0	0.800 (0.59 - 1.0)	0.63 - 4.72
TAPSE (mm/m^2) T0	> 60.29	0.40	0.59	85.71	80.0	0.800 (0.59 - 1.0)	33.88 - 86.69
TAPSE (mm/$\sqrt[3]{}$kg) T0	> 13.35	0.36	0.63	85.71	86.67	0.809 (0.60 - 1.0)	10.32 - 16.37
Advanced echocardiographic parameters	**Cutoff Value**	**PPV**	**NPV**	**Sensitivity %**	**Specificity %**	**AUC (95% CI)**	**Gray Zone**
LSt (%) T1	> 33.15	0.27	0.72	71.43	93.33	0.781 (0.52 - 1.0)	31.26 - 35.03
TMAD (mm/kg) T1	> 0.75	0.36	0.63	85.71	86.67	0.852 (0.67 - 1.0)	0.57 - 0.92
TMAD (mm/m^2) T1	> 16.29	0.54	0.45	100.0	66.67	0.847 (0.68 - 1.0)	14.28 - 18.29

AUC: area under the curve; CI: confidence interval; LSt: longitudinal strain; NPV: negative predictive value; PPV: positive predictive value; TAPSE: tricuspid annular plane systolic excursion; TMAD: tissue motion annular displacement; T0: time 0; T1: time 1.

Table 3. Correlation coefficient r and the *P* value of all the echocardiographic parameters evaluated in relation to age, body weight, heart rate and systolic blood pressure of the dogs (n = 22) selected for the study.

Conventional echocardiographic parameters	Age (months)		Body Weight (kg)		HR (bpm)	
	R	*P*	R	*P*	R	*P*
FAC (%) T0	0.318	0.172	-0.053	0.816	0.483	0.023
FAC (%) T1	0.065	0.783	0.067	0.767	0.150	0.506
TAPSE (mm) T0	0.504	0.023	-0.787	< 0.0001	0.418	0.053
TAPSE (mm) T1	0.108	0.649	-0.608	0.003	-0.016	0.944
TAPSE (mm/Kg) T0	0.447	0.048	-0.947	< 0.0001	0.323	0.143
TAPSE (mm/Kg) T1	0.270	0.249	-0.934	< 0.0001	0.231	0.301
TAPSE (mm/m^2) T0	0.452	0.045	-0.941	< 0.0001	0.324	0.141
TAPSE (mm/m^2) T1	0.249	0.290	-0.906	< 0.0001	0.195	0.385
TAPSE ($mm/\sqrt[3]{kg}$) T0	0.476	0.034	-0.910	< 0.0001	0.397	0.067
TAPSE ($mm/\sqrt[3]{kg}$) T1	0.230	0.330	-0.836	< 0.0001	0.148	0.511
Advanced echocardiographic parameters	Age (months)		Body Weight (kg)		HR (bpm)	
	R	*P*	R	*P*	R	*P*
LSt (%) T0	0.311	0.183	-0.444	0.038	-0.044	0.844
LSt (%) T1	0.248	0.291	-0.150	0.505	0.322	0.144
TMAD (mm) T0	-0.438	0.053	0.329	0.1343	-0.198	0.377
TMAD (mm) T1	-0.261	0.265	0.735	< 0.0001	-0.374	0.086
TMAD (%) T0	-0.188	0.426	-0.328	0.136	0.053	0.815
TMAD (%) T1	-0.195	0.409	0.499	0.018	-0.244	0.275
TMAD (mm/kg) T0	0.225	0.339	-0.766	< 0.0001	0.269	0.226
TMAD (mm/kg) T1	0.354	0.126	-0.776	< 0.0001	0.252	0.257
TMAD (mm/m^2) T0	0.116	0.626	-0.677	0.0005	0.213	0.340
TMAD (mm/m^2) T1	0.284	0.225	-0.473	0.026	0.149	0.508
TMAD ($mm/\sqrt[3]{kg}$) T0	-0.162	0.495	-0.269	0.225	0.026	0.909
TMAD ($mm/\sqrt[3]{kg}$) T1	-0.143	0.547	0.290	0.191	-0.209	0.350

FAC: fractional area change; LSt: longitudinal strain; TAPSE: tricuspid annular plane systolic excursion; TMAD: tissue motion annular displacement; T0: time 0; T1: time 1.

DISCUSSION

Some echocardiographic parameters used, particularly TAPSE before fluid challenge and LSt and TMAD after fluid challenge, were higher in responsive dogs. To the author's knowledge, this is the 1st study to investigate the right ventricular systolic function in the assessment of fluid responsiveness in healthy, spontaneously breathing dogs.

All the echocardiographic parameters cited assess predominantly the longitudinal systolic function. This kind of assessment is important, especially for the right side of the heart, because the longitudinal shortening is the dominant deformation of the right ventricle which provides the major contribution to stroke volume during systole [19,29,30]. Therefore, it is important to establish the relationship between volume status and echocardiographic indices.

TAPSE (mm/kg and mm/m^2) were higher in responsive dogs even before the volume challenge (Figure 4). Previous studies have already shown that some echocardiographic indices of right ventricular function are affected by volume change in humans [1,16], research animals [15] and dogs [14,26]. Within this context, this variable can be considered as an option in the prediction of fluid responsiveness without the need for fluid administration since the difference found was before volume challenge.

TAPSE (mm/kg) > 1.35 provided a good AUC value with a good combination of sensitivity and specificity and a relatively small gray zone intervals (Table 2; Figures 6 and 7). However, identifying if an additional fluid bolus will improve the stroke volume or cause volume overload with acceptable accuracy is not always possible, for that reason it is fundamental to take into account the gray zone approach [4]. Values that fall outside the gray zone can be considered reliable, whereas values that fall within this interval should be interpreted with greater caution [27]. In the last case, other available clinical parameters should be assessed to guide fluid strategies [4].

In the group of non-responsive animals, it was also identified that TAPSE (mm and mm/m^2) increased significantly after fluid challenge. It has already been demonstrated that TAPSE is significantly increased by volume overload [26], that is, this parameter can be considered as a preload-dependent index despite the volume status of the patient.

TAPSE is one attractive echocardiographic parameter for routine clinical use because it is less dependent on optimal right ventricular image quality and resolution and is easy to acquire and measure [31,38]. In this case, it could be an option for the use of non-cardiologists. On the other hand, its acquisition is angle dependent [40] and uses a single segment to assess the longitudinal function of the right ventricle [2]. Such factors must be taken into account, especially when training veterinarians of other specialties.

LSt (%) and TMAD (mm/kg, mm/m^2), were higher in responsive dogs after fluid challenge (Figure 5). Also, in the group of non-responsive animals TMAD (mm, %) increased significantly after fluid challenge. In a sense, the findings regarding advanced echocardiography techniques are similar to the findings regarding TAPSE, which represents a conventional echocardiography measure, except for the fact that the difference found between responsive and non-responsive dogs was after volume challenge. In that case, the advanced echocardiographic parameters has no predictive value as the conventional echocardiographic index such as TAPSE.

TMAD (mm/kg) > 0.75 provided the best AUC value with a good combination of sensitivity and specificity and a relative small gray zone intervals (Table 2; Figures 6 and 7). TMAD is a speckle tracking technique that assesses systolic function by measurement of the displacement of the valve annulus in relation to the cardiac apex [35]. A previous study demonstrated that TMAD is correlated with TAPSE and free wall LSt [34]. This technique was shown to be less influenced by endocardial definition, myocardial losses and the insonation angle [18,24]. Besides that, is a fast, reproducible, and promising method for assessing right ventricular systolic function in healthy dogs [33]. Although this evaluation method has its advantages in relation to execution and has presented de best AUC value of the study, even so, the predictive power of TAPSE may be more interesting in practical terms, especially in cases of greater risk of volume overload.

TAPSE (mm) showed a moderate to strong positive correlation with body weight, meanwhile your indexes showed a moderate to strong negative correlation with body weight, and, also, TAPSE (mm/kg, mm/m^2) showed a weak to moderate positive correlation with age. In addition, LSt (%) and TMAD (mm, %, mm/kg, mm/m^2) predominantly showed a weak to moderate negative correlation with body weight. Several echocardiographic indices of cardiac structure and function are known to be affected by body size and age [14,34,39], however, standardization of measurements of the right ventricle is still a problem [21]. A previous study has identified significantly lower values of right ventricular LSt in dogs weighing more than 20 kg. The specific mechanism to this finding is still unknown, but the authors pointed that the time required for the propagation of right ventricular systole may be prolonged because of the large size of the heart in larger dogs [26].

Before fluid challenge, dogs with SR showed significantly higher values of FAC compared to animals with SA. In addition, FAC showed a weak positive correlation with heart rate. Probably the highest FAC values were identified in dogs with RS, as these individuals had higher heart rate. A correlation between FAC and heart rate has already been reported [19]. In this case, the heart rate should be considered when assessing FAC.

Of the 22 dogs selected, most animals were considered non-responsive (68.2%), being that the VTI

Ao (cm) of these individuals before volume challenge were significantly higher compared with the responsive ones (Figure 3). Theoretically, a normovolemic individual without myocardial dysfunction should be responsive. However, in spontaneously breathing patients it is particularly difficult to assess fluid responsiveness [12,17], since the heart-lung interaction causes a cyclic variation in stroke volume [13,17]. It is worth mentioning that this group represents the vast majority of critically ill individuals who require intravenous fluid [17]. Also, fluid responsiveness may be affected by the method of fluid challenge (type of fluid and administration rate) [6] and how the right ventricle will accommodate the abrupt load change [16].

Previous studies are contradictory regarding the response of the right ventricle. In dogs, some of the right ventricular function indices are preload dependent [26]. However, in experimental studies the right ventricular longitudinal function remained preserved [15], as well as the contractility for long period of times in volume overload [36]. Finally, the changes in loading conditions of humans after blood donations had little impact on measures of right ventricular function, highlighting the ability of young healthy individuals to compensate for mild to moderate volume changes [16]. These contradictory findings may be related to the morphological and functional differences of the RV in relation to the LV, also known as biventricular interdependence. In mammals, the RV is more compliant and contains approximately 10 to 15% more volume compare to the LV. Due to these anatomical differences, volume overload is better tolerated by the RV, however, its adaptation mechanisms have not yet been fully elucidated [32]. In this case, it is possible that the volume challenge needs to be performed individually depending on the clinical status of the patient, since it seems that individuals without loading changes on the right heart have a greater capacity to accommodate the extra volume administered in the RV.

Although no deleterious effects of the volume challenge were identified in the dogs of the present study, animals with volume overload may not be fluid tolerant [23,27]. Hypervolemic patients with severe clinical conditions are more likely to develop negative sequelae secondary to excess fluid administration [20,27]. In this case, the management of fluid therapy should also be based on the presence of other signs of hemodynamic instability (or peripheral hypoperfusion) and the absence of risks related to volume overload [25].

There are a number of limitations to this kind of study which must be considered when interpreting the results. The use of the volume challenge to classify the patient with regard to fluid responsiveness requires that the stroke volume be inferred using a precise method, and the accuracy of the VTI Ao measured by transthoracic echocardiography is dependent of a good alignment. Although the echocardiography has a number of advantages regarding its execution, the accurate assessment is challenging because of the complex geometry and contractile properties of the right ventricle. In that case, the authors recognize that this technique may be difficult to implement in clinical practice by veterinarians with limited experience in echocardiography. The software used for LSt and TMAD was developed for assessing the left ventricle. SBP was not measured in all the dogs of the study. Finally, only healthy individuals were included in this study and it is likely that animals with hemodynamic instability caused by different clinical conditions, including cardiac diseases, will react differently in terms of fluid responsiveness.

CONCLUSIONS

In conclusion, some of the echocardiographic parameters for assessing right ventricular systolic function differed between responsive and non-responsive dogs to the volume challenge proving to been useful in the fluid responsiveness evaluation. TAPSE (mm/kg) > 1.35 before the volume challenge had the power to predict fluid responsiveness without the need of a fluid administration. The assessment of right ventricular function has attracted increasing interest in veterinary cardiology and it is possible that this procedure may complement the evaluation of fluid responsiveness in healthy spontaneously breathing dogs. However, it is also necessary to perform this type of evaluation in individuals with hemodynamic alterations in order to better understand the applicability of these techniques.

MANUFACTURERS

[1]Philips Affiniti 50 ultrasound system. Andover, MA, USA.

[2]Software GraphPad Prism for Windows. La Jolla, CA, USA.

***Ethical approval*.** The study was approved by the Animal Use Ethics Committee of the Federal University of Paraná (UFPR), Curitiba, PR, Brazil with the protocol number 058/2019.

***Declaration of interest*.** The authors report no conflicts of interests. The authors alone are responsible for the content and writing of paper.

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