UNIVERSIDADE FEDERAL DO PARANÁ

STEPHANY BUBA LUCINA PERIN

USO DE TÉCNICAS DE IMAGEM NA AVALIAÇÃO DE RESPONSIVIDADE A FLUIDOTERAPIA EM CÃES SAUDÁVEIS RESPIRANDO ESPONTANEAMENTE

CURITIBA

2022

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Orientadora: Prof[a]. Dra. Tilde Rodrigues Froes

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Avaliador Interno (UNIVERSIDADE FEDERAL DO PARANÁ)

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“*The future belongs to those who believe in the beauty of their dreams*”

(Eleanor Roosevelt)

RESUMO

A reposição volêmica é considerada como um componente essencial no tratamento de pacientes gravemente acometidos, o excesso de fluido administrado pode ser tão maléfico quanto a falta de fluido. Portanto, a reposição volêmica só é benéfica em pacientes considerados responsivos, ou seja, quando o indivíduo apresenta um aumento em pelo menos 15% do volume ejetado após a administração de uma prova de carga. Um dos determinantes da fluido responsividade é a função sistólica, associada à interação dinâmica entre o volume intravascular (pré-carga) e o tônus vascular (pós-carga). Além disso, a veia cava caudal (VCC) é uma estrutura altamente complacente e mudanças na pressão intravascular ou intratorácica devido ao ciclo respiratório produzem variação no seu diâmetro. Dentro desse contexto, índices dinâmicos de avaliação da fluido responsividade tem surgido levando em consideração a interação entre coração e pulmão. O conceito de fluido responsividade foi inicialmente descrito em pacientes sob ventilação mecânica. No entanto, a maioria dos cães hospitalizados que necessitam de reposição volêmica estão respirando espontaneamente. A presente tese tem por objetivo avaliar se parâmetros de avaliação da função sistólica ventricular esquerda e direita obtidos por ecocardiografia, assim como, parâmetros de ultrassonografia relacionados a mensuração da VCC, são capazes de predizer fluido responsividade em cães saudáveis respirando espontaneamente. Esse projeto foi subdividido em três capítulos, baseados em um estudo prospectivo, realizado com 22 cães saudáveis com mais de um ano de idade, que se apresentaram ao hospital veterinário escola para realização de procedimento eletivo de castração. Todos os cães foram submetidos ao exame ecocardiográfico convencional e avançado e ao exame ultrassonográfico da VCC, antes e depois da administração de uma prova de carga com 10mL/Kg de Ringer Lactato por via intravenosa durante 20 minutos. A classificação de fluido resposividade foi baseada na variação do tempo integral da velocidade aórtica (ΔVTI Ao). No primeiro capítulo, foi estudado a função sistólica ventricular esquerda. Dentre esses parâmetros, o tissue motion annular displacement (TMAD) antes e depois da prova de carga, e o diâmetro interno ventricular esquerdo em diástole normalizado (DIVEDn) antes da prova de carga foram úteis na avaliação de fluido responsividade. No segundo capítulo, foi estudado a função sistólica ventricular direita. Nesse caso, o tricuspid annular plane systolic excursion (TAPSE) antes da prova de carga e o TMAD depois da prova de carga se mostraram úteis do contexto da fluido responsividade. Finalmente, no terceiro capítulo, foram estudados o índice de colapsabilidade da veia cava caudal (ICVCC) e a relação veia cava caudal e aorta (VCC/Ao). As evidências foram fracas de que o ICVCC e a relação VCC/Ao são capazes de diferenciar cães acordados responsivos de não-responsivos. A presente tese trás informações relevantes sobre o uso de índices ecocardiográficos e ultrassonográficos dinâmicos de avaliação da fluido responsividade em cães saudáveis respirando espontaneamente. É possível que futuramente algumas dessas variáveis possam fazer parte da avaliação de fluido responsividade. No entanto, mais estudos são necessários para um melhor entendimento da aplicabilidade dessas técnicas, especialmente em cães com alterações hemodinâmicas.

Palavras-chave: strain longitudinal, tissue motion annular displacement, veia cava caudal, volume ejetado

ABSTRACT

Volume replacement is considered an essential component in the treatment of critically ill patients, but excess fluid administration can be as harmful as the lack of fluid therapy. Therefore, the volume replacement is only beneficial in patients deemed to be fluid responsive, that is, when the individual has an increase in at least 15% of the stroke volume after a volume challenge administration. One of the determinants of fluid responsiveness is the systolic function, associated with the dynamic interactions between intravascular volume (preload) and vascular tone (afterload). In addition, the caudal vena cava (CVC) is a highly compliant structure and changes in intravascular or intrathoracic pressure due to the respiratory cycle produce variation in its diameter. Within this context, dynamic indices to assess fluid responsiveness have emerged taking into account the heart-lung interaction. The concept of fluid responsiveness was initially described in patients under mechanical ventilation. However, most of the hospitalized dogs that need volume replacement are breathing spontaneously. This thesis aim to assess whether echocardiographic parameters for assessing left and right ventricular systolic function, as well as, ultrasound parameters related to CVC measurement, are able to predict fluid responsiveness in healthy spontaneously breathing dogs. The present project was subdivided into three chapters based on a prospective study carried out in 22 client-owned healthy dogs over one year of age that presented to the University teaching hospital for elective neutering procedure. All dogs underwent conventional and advanced echocardiography and ultrasound examination of the CVC, before and after administration of a volume challenge with 10mL/kg lactate ringer intravenously for 20 minutes. The classification of fluid responsiveness were based on the aortic velocity integral time variation (ΔVTI Ao). In the first chapter, the left ventricular systolic function was studied. Among these parameters, the tissue motion annular displacement (TMAD) before and after volume challenge and the left ventricle internal diameter in diastole normalized (LVIDDn) before volume challenge were useful in the assessment of fluid responsiveness. In the second chapter, the right ventricular systolic function was studied. In that case, the tricuspid annular plane systolic excursion (TAPSE) before volume challenge and TMAD after volume challenge proved to be useful in the context of fluid responsiveness. Finally, in the third chapter, the caudal vena cava collapsibility index (CVCCI) and the caudal vena cava and aorta ratio (CVC/Ao) were studied. There was weak evidence that the CVCCI and the CVC/Ao ratio are able to differentiate responsive from non-responsive dogs under spontaneous breathing. The present thesis provided relevant information regarding the use of dynamic echocardiographic and ultrasound indices to assess fluid responsiveness in healthy, spontaneously breathing dogs. It is possible that in the future some of these variables may form a useful part of the evaluation of fluid responsiveness. However, more studies are needed to better understand the applicability of these techniques, especially in dogs with hemodynamic changes.

Keywords: caudal vena cava, longitudinal strain, stroke volume, tissue motion annular displacement

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Ao	- Aorta
VTI Ao	- Aortic velocity time integral
A2C	- Apical 2-chamber
A4C	- Apical 4-chamber
AUC	- Area under the curve
BSA	- Body surface area
CVC	- Caudal vena cava
CVC/Ao	- Caudal vena cava/aorta
CVCCI	- Caudal vena cava collapsibility index
CVP	- Central venous pressure
CI	- Confidence interval
DIVEn	- Diâmetro interno ventricular esquerdo em diástole normalizado
EF	- Ejection fraction
ECG	- Electrocardiography
FAC	- Fractional area change
GLS	- Global longitudinal strain
HR	- Heart rate
ICVCC	- Indice de colapsabilidade da veia cava caudal
LVIDDn	- Left ventricular internal diameter in diastole normalized
LVIDSn	- Left ventricular internal diameter in systole normalized
LSt	- Longitudinal strain
NPV	- Negative predictive value
NRT0	- Non-responsive time 0
NRT1	- Non-responsive time 1
OH	- Ovary-hysterectomy
PV	- Portal vein
PPV	- Positive predictive value
ROC	- Receiving operating curve
RT0	- Responsive time 0
RT1	- Responsive time 1
SF	- Shortening fraction
SA	- Sinus arrhythmia

SR	- Sinus rhythm
SBP	- Systolic blood pressure
T0	- Time 0
T1	- Time 1
TMAD	- Tissue motion annular displacement
TAPSE	- Tricuspid annular plane systolic excursion
VCC	- Veia cava caudal
VCC/Ao	- Veia cava caudal/aorta
VTI	- Velocity time integral

SUMÁRIO

1 INTRODUÇÃO

A reposição volêmica é considerada como um componente crítico no tratamento de pacientes gravemente acometidos, já que tanto a falta quanto o excesso de fluido podem agravar a disfunção orgânica (MARIK et al., 2011). Um adequado plano de reposição volêmica inicia-se com uma avaliação hemodinâmica acurada referente ao estado de hidratação e volume sanguíneo do paciente (JOHNSON, 2016).

Foi constatado, em um estudo médico, que aproximadamente 50% das pessoas em estado crítico não são responsivas a fluido (MONNET et al., 2016; MICHARD et al., 2002). Nesse caso, a administração de volume pode levar à hemodiluição, ao aumento das pressões de enchimento cardíacas e a sobrecarga de volume. Portanto, a fluidoterapia deve ser considerada como qualquer outra terapia medicamentosa, em que tanto a subdosagem quanto a superdosagem são indesejáveis (MONNET et al., 2016).

O conceito de fluido responsividade pode ser explicado pelo princípio e curva de Frank-Starling. Quando os cardiomiócitos são estirados a resposta imediata é a contração, que irá ocorrer de forma proporcional. No entanto, quando os cardiomiócitos são estirados de maneira a ultrapassar o limite físico aceitável eles se tornam incapazes de contrair na mesma intensidade. O princípio de Frank-Starling não apresenta um comportamento linear, portanto, em alguns casos quanto maior o estiramento dos cardiomiócitos, maior será a contração e consequentemente maior será o volume sistólico e o retorno venoso. Já nos casos de estiramento extremo a contração não irá ocorrer na mesma proporção, portanto, o volume sistólico e o retorno venoso não aumentarão (MILLER et al., 2016).

Dentro desse contexto, a função sistólica influencia diretamente no volume de sangue que é ejetado pelo coração a cada batimento cardíaco, denominado volume sistólico. O volume sistólico, por sua vez, depende de três fatores: pré-carga, tensão exercida sobre a parede ventricular ao final da diástole (volume); pós-carga, tensão exercida sobre a parede ventricular ao final da sístole (pressão); e contratilidade (MILLER et al., 2016).

O paciente que recebe uma prova de carga com aumento de pré-carga pode ou não sofrer aumento do volume sistólico a depender da função sistólica (MONNET et al., 2016). Quando o volume sistólico aumenta após a expansão volêmica, significa que este indivíduo apresenta ambos os ventrículos na porção ascendente da curva de Frank-Starling, sendo denominados de "dependente de pré-carga" ou "responsivo". Já quando o volume sistólico não sofre alterações após o tratamento com fluido, significa que este indivíduo atingiu o platô da curva de Frank-Starling, sendo denominados de "não dependente de pré-carga" ou "não responsivo" (CHAVES et al., 2018; MONNET et al., 2013; MICHARD et al., 2002).

Apesar de existirem inúmeras técnicas avançadas para mensuração ou estimativa do volume sistólico, a maioria delas são invasivas e requerem equipamentos específicos, o que torna inviável sua utilização na prática clínica (MARSHALL et al., 2006). Os estudos médicos sugerem que, tanto a ecocardiografia quanto a ultrassonografia abdominal realizada à beira do leito, podem trazer informações referentes a fluido responsividade em tempo real, de forma acurada e com boa reprodutibilidade (CHARRON et al., 2014; KELLY et al., 2015).

Em geral, o parâmetro de fluido responsividade avaliado pode ser classificado como estático ou dinâmico, a depender de como é feita sua mensuração. Os parâmetros estáticos são medidas de pressão e/ou volume que estimam a quantidade de fluido no sistema cardiovascular em um determinado momento, a exemplo da pressão venosa central (PVC), pressão arterial média (PAM), diâmetro da veia cava caudal (VCC) e área diastólica ventricular esquerda (MARIK, 2011). Já os parâmetros dinâmicos tentam determinar a localização do paciente dentro da curva de Frank-Starling através da indução de uma mudança na pré-carga. Tais parâmetros são mensurados em pelo menos dois momentos distintos para avaliar a fluido responsividade, sendo que as principais avaliações levam em consideração as mudanças no débito cardíaco ou volume sistólico (BOYSEN & GOMMEREN, 2021).

Os indivíduos são considerados responsivos a fluido quando o volume sistólico aumenta pelo menos 10 ou 15% após a administração de uma prova de carga (MILLER et al., 2016). Um estudo médico demonstrou que a prova de carga (100 mL em 1 minuto) pode predizer de forma acurada a fluido responsividade por meio da mensuração do velocity time integral (VTI) aórtico pela ecocardiografia transtorácica (MULLER et al., 2011). O cálculo da variação que o VTI aórtico (∆VTI Ao) sofre antes e após uma prova de carga tem sido utilizado para classificar pessoas e cães em responsivos ou não responsivos (MILLER et al., 2016; ORICCO, 2019; BUCCI, 2017).

Além dos parâmetros ecocardiográficos, também já foram descritos alguns parâmetros ultrassonográficos capazes de acessar a fluido responsividade. A exemplo, do índice de colapsabilidade da veia cava caudal (ICVCC), obtido pela mensuração da variação que o diâmetro da veia cava caudal (VCC) sofre com os movimentos respiratórios através de imagens abdominais (LABOVITZ et al., 2010). Em indivíduos hipovolêmicos o diâmetro da VCC varia mais com a inspiração e expiração comparado a indivíduos hipervolêmicos (LABOVITZ et al., 2010). Em pessoas, o ICVCC, obtido pela janela subxifóide, entre 20 e 50% é considerado normal (TUPLIN et al., 2017) e quando maior do que 50% sugere responsividade a fluido (AIRAPETIAN et al., 2015; ABAHUJE et al., 2017).

Em crianças é preferível realizar a avaliação de fluido responsividade por meio da relação do diâmetro da VCC e da aorta (VCC/Ao), pois se trata de uma medida independente do tamanho e peso corporal (WHITSON & MAYO, 2016). Os cães, assim como os pacientes pediátricos, apresentam uma grande variação de tamanho, e por essa razão, sugere-se que o uso da relação VCC/Ao seja mais efetivo (MENEGHINI et al., 2015). O que justifica a utilidade desse parâmetro é que o diâmetro da aorta permanece o mesmo durante a hipovolemia severa, já o diâmetro da VCC reduz. Esse achado já foi descrito em cães com hipovolemia (CAMBOURNAC et al., 2017; KWAK et al., 2017).

Na medicina veterinária os estudos de responsividade a fluido em cães respirando espontaneamente são escassos e controversos. Desse modo, a obtenção de parâmetros ecocardiográficos convencionais e avançados para avaliação da função ventricular, assim como de parâmetros ultrassonográficos relacionados a mensuração da VCC trariam informações relevantes a respeito da fisiologia e do comportamento desses índices que futuramente poderiam ser utilizados nas práticas clínicas como parte da avaliação de fluido responsividade em cães com hipovolemia.

1.1 OBJETIVO GERAL

Estudar o uso de técnicas ecocardiográficas convencionais e avançadas e ultrassonográficas na avaliação de fluido responsividade em cães saudáveis respirando espontaneamente.

1.2 OBJETIVOS ESPECÍFICOS

Verificar se existe diferença entre os índices ecocardiográficos convencionais (fração de ejeção e encurtamento, diâmetro sistólico e diastólico ventricular esquerdo, mudança da área fracional do ventrículo direito e excursão sistólica do plano anular da valva tricúspide) e avançados (deformação miocárdica do ventrículo esquerdo e da parede livre do ventrículo direito e deslocamento do ânulo valvar mitral e tricúspide) de avaliação da função sistólica ventricular esquerda e direita e os índices ultrassonográficos de mensuração da VCC e aorta abdominal pela janela hepática (ICVCC e relação VCC/Ao) em cães classificados como responsivos ou não responsivos a fluido, com base no valor do ∆VTI Ao, antes e após a prova de carga com Ringer Lactado na dose de 10mL/Kg durante 20 minutos. A partir disso, avaliar a capacidade de tais índices em avaliar e predizer a fluido responsividade.

Sobre os índices ultrassonográficos, calcular a repetibilidade intra e interobservador, bem como o tempo médio de aquisição das imagens e das mensurações da VCC e aorta dos animais selecionados.

2 CONVENTIONAL VS. ADVANCED ECHOCARDIOGRAPHIC PARAMETERS FOR PREDICTING FLUID RESPONSIVENESS IN HEALTHY DOGS[1]

ABSTRACT

Background: Volume replacement is considered an essential component in the treatment of critically ill patients, but excess fluid administration can be as harmful as the lack of fluid therapy. Therefore, the volume replacement is only beneficial in patients deemed to be fluid responsive, that is, when the individual has an increase in their stroke volume after administration of a volume challenge. This study aims to assess whether conventional and advanced echocardiographic parameters for assessing left ventricular systolic function are able to predict 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: A prospective study was carried out in which 22 client-owned healthy dogs over 1 year of age that presented to the Veterinary Medical Teaching Hospital for elective neutering procedure were included. All dogs underwent conventional and advanced echocardiographic examination to obtain the left ventricular internal diameter in diastole normalized (LVIDDn), left ventricular internal diameter in systole normalized (LVIDSn), ejection fraction (EF) and shortening fraction (SF) according to the Teichholz methodology, global longitudinal strain (GLS) and tissue motion annular displacement (TMAD). These parameters were evaluated before and after administration of a volume challenge with 10 mL/kg lactate ringer intravenously for 20 min. Based on the variation in aortic velocity integral time (VTI Ao), 31.82% of dogs were considered responsive and 68.18% were non-responsive to the volume challenge. For advanced echocardiography, TMAD indexed by body weight (mm/kg) > 0.89 (P = 0.004) and body surface area (mm/m2) > 18.9 (P = 0.004) after volume challenge had the best area under the curve values (both 0.895) and smaller gray zone intervals (0.52 - 0.81 and 14.89 - 17.88) for the identification of responsive dogs. Although, TMAD (mm/kg and mm/m2) before volume challenge was also higher in the responsive dogs (P = 0.041 and P = 0.029). As for conventional echocardiography, the LVIDDn < 1.39 (P = 0.003) before volume challenge had the best area under the curve value (0.866) and the smallest gray zone interval (1.4 - 1.57) for the identification of responsive dogs. The GLS and the TMAD in millimeters (mm), percentage (%) and indexed by cubic root of weight (mm/$\sqrt[3]{kg}$) did not differ between the responsive and non-responsive dogs before and after volume challenge.
Discussion: TMAD indexed by body weight (mm/kg) and body surface area (mm/m2) before and after volume challenge and the LVIDDn before volume challenge may be useful measures to complement the assessment of fluid responsiveness in spontaneously breathing dogs. This is the first study to use TMAD as a predictive parameter for fluid responsiveness in healthy, spontaneously breathing, dogs. Even it is an advanced echocardiographic technique, TMAD has advantages in terms of execution time and the fact that it is less dependence on image quality or operator experience. It is possible that in the future such variables

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may form a useful part of the evaluation of fluid responsiveness in dogs. However, more studies are needed to better understand the applicability of these techniques, especially in dogs with hemodynamic changes.

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

2.1 INTRODUCTION

Volume replacement is considered an essential component in the treatment of critically ill patients, but excess fluid administration can be harmful [24]. In spontaneously breathing patients it is particularly difficult to assess fluid responsiveness [12,18], since the heart-lung interaction causes a cyclic variation in stroke volume [15]. However, this group represents the vast majority of critically ill individuals who require intravenous fluid [18].

The concept of fluid responsiveness can be explained by the Frank-Starling curve [23]. When individuals are in the ascending portion of the curve, they are deemed “preload dependent” or “responsive”, and the individuals on the plateau of the curve are called “non-preload dependent” or “non-responsive” [9,22]. Volume replacement is only beneficial in patients deemed to be fluid responsive as defined by an ≥ 15% increase in stroke volume [4,8,25]. Stroke volume is dependent on systolic function which is influenced by factors such as preload and afterload [3,7]. Therefore, fluid responsiveness is not a binary or static condition, but varies according to dynamic interactions between intravascular volume, vascular tone and systolic function [7].

Left ventricular systolic function can be assessed by measurement of several parameters in conventional and advanced echocardiography. Within this context, the aim of this study was to assess whether conventional and advanced echocardiographic assessment of left ventricular systolic function could predict fluid responsiveness in healthy spontaneously breathing dogs.

2.2 MATERIALS AND METHODS

Study design and animals

A prospective study that included healthy dogs from 1 year of age presented to a Veterinary Medical Teaching Hospital for elective neutering procedure. Owners gave informed consent for inclusion of their pets in the study. The animals were considered healthy if there were no history of disease, no alteration on the physical examination, complete blood count and echocardiographic and electrocardiographic examinations.

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 [1]. Electrocardiographic evaluation was performed simultaneously with the echocardiographic examination, to identify heart rate and rhythm. Hypotensive or hypertensive dogs and those with cardiac rhythms of non-sinus origin, bradycardia or tachycardia were excluded from the study.

The first echocardiographic evaluation (T0) was performed prior to the volemic challenge, which was performed using an infusion pump administering lactated ringer's at a dose of 10 mL/kg intravenously for 20 min. The second echocardiographic evaluation was performed (T1) within 5 min of completion of fluid administration. 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 [27]. 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

Apical 5 chamber images obtained through the left parasternal window were used to measure the aortic velocity time integral (VTI Ao). Three measurements of the VTI Ao over a respiratory cycle were performed and the mean of these was used for the calculation of the variation of the VTI Ao (∆VTI Ao), according to the formula:

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

The classification of patients as responsive and non-responsive to the fluid challenge was determined by the value of ∆VTI Ao, in which responsivess were considered those with ∆VTI Ao ≥ 15% and non-respondesives with ∆VTI Ao < 15 % [4,25]. 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

Transverse images of the heart in the chordal plane were obtained for M-mode measurements of the left ventricle. The left ventricular internal diameter in diastole (LVIDD), at the beginning of the QRS complex, and the left ventricular internal diameter in systole (LVIDS), after the T wave on the surface electrocardiogram, were evaluated. From these data, ejection fraction (EF) and shortening fraction (SF) were calculated according to the Teichholz methodology. In addition, LVIDD and LVIDS were normalized by body weight (LVIDDn and LVIDSn) [11].

Advanced echocardiographic evaluation

Videos of apical 4-chamber (A4C) and apical 2-chamber (A2C) images were obtained over at least 5 cardiac cycles for offline measurement of global longitudinal strain (GLS) and tissue motion annular displacement (TMAD). The echocardiographic equipment software automatically detected the left ventricular myocardium for assessment of longitudinal strain. 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 left ventricle in the longitudinal plane during a cardiac cycle. From these analyzes, the

GLS in percentage (%) was calculated, using the mean longitudinal strain value obtained in the A4C and A2C images (Figure 1).

To obtain the TMAD, three regions of interest were manually established: the first, at the insertion of the anterior mitral leaflet on the A4C image and at the anterior portion of the mitral annulus on the A2C image; the second, at the insertion of the posterior mitral leaflet on the A4C image and at the inferior portion of the mitral annulus on the A2C image; and the third, at the epicardial region of the apex of the left ventricle on the A4C and A2C images. After selecting the regions of interest, myocardial screening was performed automatically by the equipment's software (Figure 2).

The TMAD obtained from the A4C and A2C images was calculated from the apex-base displacement of the virtual midpoint between the 2 regions of interest of the mitral valve annulus in relation to the total length of the left ventricle. To obtain the global TMAD, the mean values, in millimeters (mm) and percentage (%), of the A4C and A2C images were calculated. In addition, global TMAD (mm) was indexed by body weight (mm/kg), by the cubic root of body weight ($mm/\sqrt[3]{kg}$) and by body surface area (mm/m2) according to the formula:

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

K = constant (10.1 for dogs)

Statistical analysis

The descriptive statistical analysis was performed with the estimate of the frequencies (%) of the qualitative variables, calculation of the mean and standard deviation or median and range of the quantitative variables depending on the distribution of the samples. For the distribution analysis, the Shapiro-Wilk test was used.

Comparisons of means were performed between the group responsive in T0 versus T1, nonresponsive in T0 versus T1, responsive versus nonresponsive in T0 and responsive versus non-responsive in T1. The paired t test or Student t test was used for data with normal distribution (parametric) and Wilcoxon or Mann-Whitney test for data with non-normal distribution (non-parametric).

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 calculated to identify the cut-off value with the best combination of sensitivity and specificity and the gray zone of the echocardiographic parameters that differed between the responsive and non-responsive dogs at T0 or T1. 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).

In addition, dogs were subdivided into 2 groups according to heart rhythm, sinus rhythm when the heart rate varied by less than 10%, or sinus arrhythmia when the heart rate varied by more than 10%. Dogs were compared according to heart rhythm to verify the influence of rhythm on the echocardiographic variables studied. Finally, Pearson correlation (parametric data) or Spearman correlation (non-parametric data) were calculated to verify the influence of age, body weight, average heart rate and SBP in all the studied echocardiographic parameters. All analysis were performed using the same software[2] and the level of statistical significance adopted was $P < 0.05$.

2.3 RESULTS

A total of 22 dogs were included in the study, 54.5% (12) were females and 45.5% (10) 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. The most prevalent heart rhythm was sinus arrhythmia (SA), observed in 72.7% (32) of the evaluations, followed by sinus rhythm (SR), observed in 27.3% (12) of the evaluations. At T1, animals with SA showed significantly higher values of LVIDSn and LVIDDn compared to animals with SR [$P = 0.021$ and $P = 0.036$]. Heart rhythm did not affect any of the advanced echocardiographic parameters evaluated.

Of the 22 dogs selected, 31.8% (7) were considered responsive and 68.2% (15) non-responsive to the volume challenge based on the value of ΔVTI Ao (Figure 3). The mean and standard deviation or median and range of all echocardiographic parameters evaluated are shown in Table 1.

EF and SF increased in responsive dogs at T1 [P = 0.019 and P = 0.017]. LVIDSn was higher in non-responsive animals at T1 [P = 0.018], while LVIDDn was lower in responsive individuals at T0 [P = 0.003] (Figure 4). The GLS and the TMAD (mm, % and mm/$\sqrt[3]{kg}$) did not differ between the responsive and non-responsive dogs at T0 and T1. However, TMAD (mm/kg and mm/m^2) was higher in the responsive dogs at T0 [P = 0.041 and P = 0.029] and T1 [P = 0.004 and P = 0.004] (Figure 5).

The conventional echocardiographic parameters that differed between responsive and nonresponsive dogs were LVIDSn at T1 and LVIDDn at T0. For the advanced echocardiographic parameters only TMAD (mm/kg and mm/m^2) at T0 and T1 varied between groups. 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.

There were no correlations between EF and SF with heart rate and SBP. However, these parameters correlated with body weight and age. The LVIDSn correlated with all variables studied with the exception of SBP, while the LVIDDn correlated with body weight and heart rate. No correlations were observed between advanced echocardiographic parameters with age, heart rate and SBP. However, TMAD (mm, mm/kg and mm/m^2) showed a correlation with body weight. The results of the correlation analysis are described in Table 3.

2.4 DISCUSSION

This is the first study to use TMAD as a predictive parameter for fluid responsiveness in healthy, spontaneously breathing, dogs. Some echocardiographic parameters used for assessment of left ventricular systolic function, in particular TMAD (mm/kg and mm/m^2), were higher in responsive dogs before and after fluid challenge (Figure 5). TMAD is part of an advanced echocardiographic examination but is widely studied in individuals with heart disease to assess longitudinal myocardial fibers [6,10,17,29,30]. This group of muscle fibers seems to be the first to be affected in systolic dysfunction [16].

Since the classification of fluid responsiveness depends on the increase in stroke volume after a fluid challenge, it can be said that ventricular systolic function directly influences fluid responsiveness [24]. Studies have shown that the parameters that measure left ventricular longitudinal myocardial fibers are sufficiently sensitive to detect changes in myocardial performance or subclinical systolic dysfunction [13,14,26,28]. TMAD was higher in responsive dogs, and since the dogs in this study were healthy with no subclinical changes in ventricular systolic function, it can be assumed that responsive individuals had a better myocardial performance.

TMAD was higher in responsive dogs even before the fluid challenge, therefore, this parameter could be used as a predictor of fluid responsiveness without the need for fluid administration. Even it is an advanced echocardiographic technique, TMAD has advantages in terms of execution time and the fact that it is less dependence on image quality or operator experience [30].

TMAD (mm/kg) > 0.89 and TMAD (mm/m²) > 18.9 after volume challenge can be considered the best advanced echocardiographic parameters, as they provided good predictive values, higher AUC values and smaller gray zone intervals (Table 2, Figures 6 and 7). In many cases, the fluid responsiveness indices fall within a range called the gray zone, in which false positive or negative results can occur. This is because such indices represent the simplification of a complex system that does not have a binary nature after fluid administration [5]. In this context, it is suggested that the gray zone interval be taken into account when interpreting any parameter that is predictive of fluid responsiveness. Values that fall outside the gray zone can be considered reliable, whereas values that fall within this interval should be interpreted with greater caution [25].

Although no deleterious effects of the volume challenge were identified in the dogs of the present study, it is known that this intervention is potentially harmful in patients who do not need fluid [25]. In cases where the fluid challenge may harm the individual, the measurement of TMAD (mm/kg and mm/m2) before fluid challenge may provide an alternative measure of myocardial performance that is directly related to fluid responsiveness (Table 2, Figures 6 and 7).

Advanced echocardiographic parameters were less influenced by age, body weight, heart rate, SBP and heart rhythm. There was a positive correlation of TMAD (mm) with body weight (Table 3), because the larger the size of the patient, the greater the absolute displacement in millimeters of the mitral annulus towards the cardiac apex. However, the indexed TMAD (mm/kg and mm/m²) was negatively correlated to body weight (Table 3). The physiological behavior of systolic function in dogs predicts that systolic indices tend to decrease in larger animals, that is, these individuals have a smaller proportional displacement of the mitral annulus towards the cardiac apex [20,30].

GLS did not differ between responsive and non-responsive individuals in the same way as TMAD. A previous study carried out in healthy dogs identified a positive correlation of these parameters [30]. Although GLS and TMAD are correlated, GLS assesses the change in the length of the myocardial segments between systole and diastole providing accurate measurements of myocardial deformation [2]. TMAD assesses the degree of displacement of the valve annulus in relation to the cardiac apex [30]. In this case, the GLS is probably less influenced by the increment in the preload, as it directly assesses myocardial deformation.

LVIDDn < 1.39 before the fluid challenge provided good predictive values, sensitivity and specificity, the best AUC value and the smallest gray zone interval (Table 2, Figures 6 and 7), proving to be the most effective conventional echocardiographic parameter for identifying the responsive patient. A previous study that evaluated dogs with a variety of clinical conditions found a similar result, with LVIDDn ≤ 1.34 having 76.9% sensitivity, 100% specificity and 0.85 AUC in identifying the responsive patient [25]. In addition, LVIDDn has the advantage that potentially responsive individuals can be identified before the volume challenge.

In the present study, the LVIDDn gray zone interval was 1.40 to 1.57, so a dog with LVIDDn > 1.57 can be considered non-responsive with a greater degree of reliability. In the study mentioned above, dogs with LVIDDn >1.67 were considered to be in a hypervolemic state [25]. Animals in these conditions may not be fluid tolerant, which means that after fluid challenge, stroke volume may remain the same or decrease substantially [23,25]. Hypervolemic patients with severe clinical conditions are more likely to develop negative sequelae secondary to excess fluid administration [21,25].

The increase in LVIDSn seen after the fluid challenge in non-responsive dogs (Figure 4) may be linked to the concept of fluid responsiveness. Nonresponsive individuals are those who, after administering a volume challenge do not produce an increase in stroke volume with an increase in preload (plateau of the Frank-Starling curve) [9,22]. Consequently, the extra volume administered affects the internal diameter of the left ventricle. After the volume challenge, responsive dogs had an increase in EF and SF (Figure 4), showing an increase in stroke volume in response to increased preload (ascending portion of the Frank Starling curve) [9,22].

The indices for assessment of systolic function in dogs tend to decrease as with increasing size [20,30] which explains the correlations between EF and SF and body weight (Table 3). LVIDSn and LVIDDn also correlated with weight (Table 3), despite the fact that these parameters are indexed. However, non-responsive dogs had higher mean values of LVIDSn and LVIDDn, which may have influenced the correlation analyzes.

LVIDSn, EF and SF were influenced by age. Although the majority of dogs were young adults (median age 2 years), 3 animals were more than 6-years-old and these individuals were all small breed dogs (Lhasa Apso and Shih-tzu) and, therefore, had greater indices of systolic function. Finally, LVIDSn and LVIDDn were influenced by heart rate and heart rhythm, that is, when dogs had SA with lower heart rates, the ventricular filling time increased and, consequently, the diastolic and systolic ventricular diameters also increased [3].

Only 31.8% of the dogs in this study were considered responsive (Figure 3). Theoretically, a normovolemic individual without myocardial dysfunction should be responsive. However, it has been shown that only half of people with hemodynamic instability, and less than 40% of human patients with sepsis and hypotension, are able to respond adequately to a fluid challenge [22]. In addition to underlying disease, fluid responsiveness is also affected by the method of fluid challenge (type of fluid and administration rate). It is possible that different clinical conditions require different techniques for fluid challenge [19]. 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 [24].

There are a number of limitations to this 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 transthoracic echocardiography is not the gold standard technique for this assessment. Although TMAD has a number of advantages regarding its execution, the authors recognize that this technique is difficult to implement in clinical practice by anesthesiologists or intensivists with limited experience in echocardiography. Also, this echocardiographic technique requires an expensive software. Since spontaneously breathing dogs were studied, the echocardiographic parameters evaluated were static in nature (based on a single observation over time), and it is known that fluid responsiveness depends on the dynamic interaction between preload, afterload, systolic and diastolic function, heart rate and rhythm, vascular physiology and autonomic tone. Finally, only healthy dogs were included in this study and it is likely that animals with hemodynamic instability caused by different clinical conditions will react differently in terms of fluid responsiveness.

2.5 CONCLUSIONS

In conclusion, some of the echocardiographic parameters for assessing left ventricular systolic function differed between dogs responsive and nonresponsive to the fluid challenge. TMAD (mm/kg) > 0.89 and TMAD (mm/m²) > 18.9 after the volume challenge were considered the best advanced echocardiography parameters, while LVIDDn < 1.39 before the volume challenge was considered the best conventional echocardiographic parameter for the identification of the responsive individuals. It is possible that in the future such variables may form a useful part of the evaluation of fluid responsiveness in dogs. However, more studies are needed to better understand the applicability of these techniques, especially in dogs with hemodynamic changes.

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 interest. The authors alone are responsible for the content and writing of paper.

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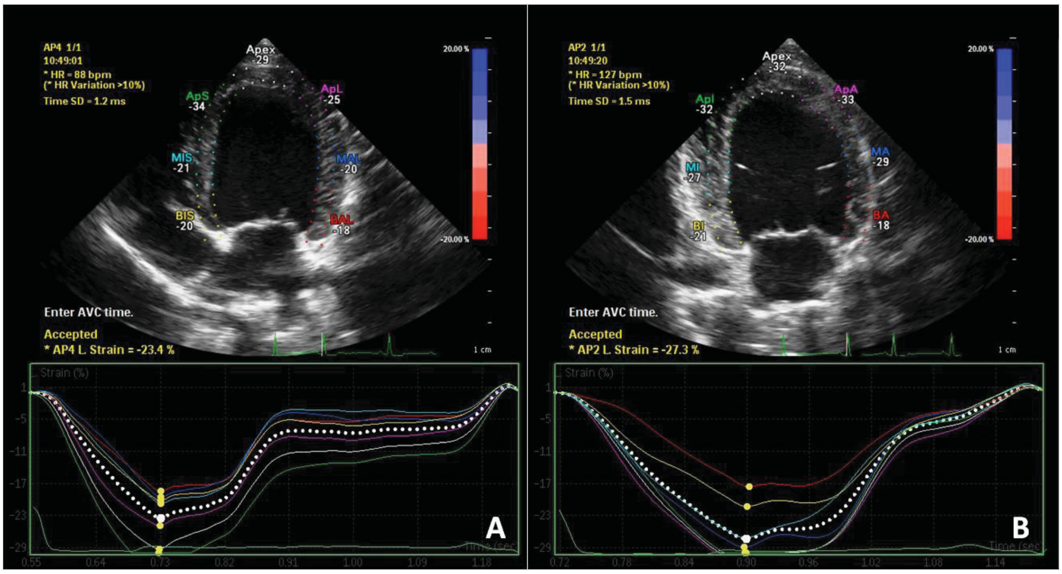

Figure 1. Advanced echocardiography showing the apical 4-chamber (A) and apical 2-chamber (B) images used to obtain the global longitudinal strain (GLS) in percentage (%) of a healthy dog non-responsive to the fluid challenge**.**

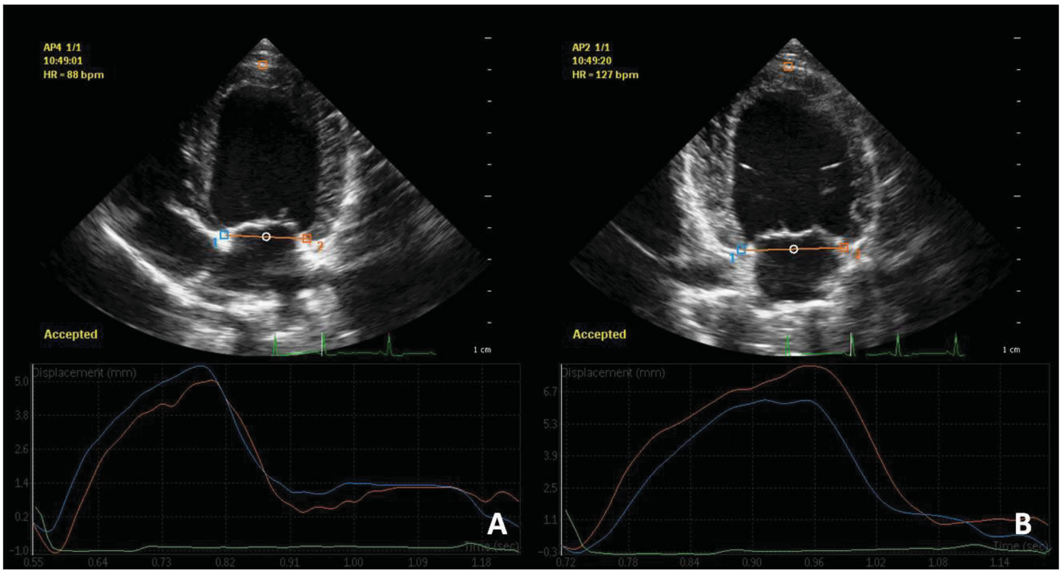

Figure 2. Advanced echocardiography showing the apical 4-chamber (A) and apical 2-chamber (B) images used to obtain the global tissue motion annular displacement (TMAD), in millimeters (mm) and percentage (%), of a healthy dog non-responsive to the fluid challenge.

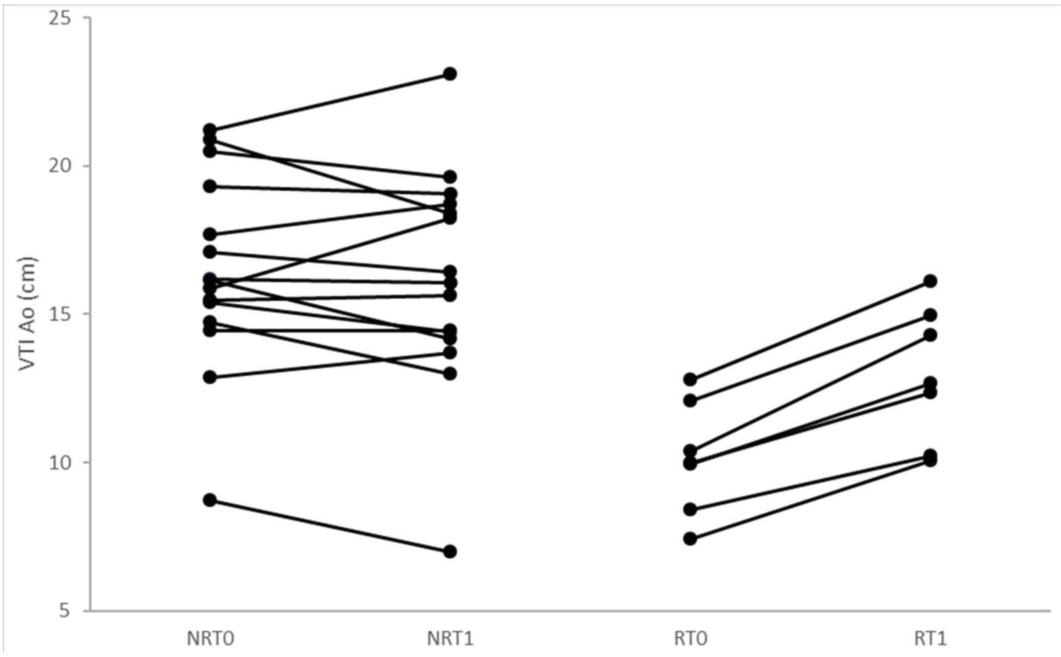

Figure 3. Point-graphs showing the values of the aortic velocity time integral (VTI Ao) before (T0) and after (T1) the administration of the fluid challenge of dogs classified as responsive (n = 7) and non-responsive (n = 15). Ao: aortic; NRT0: non-responsive time 0; NRT1: non-responsive time 1; RT0: responsive time 0; RT1: responsive time 1.

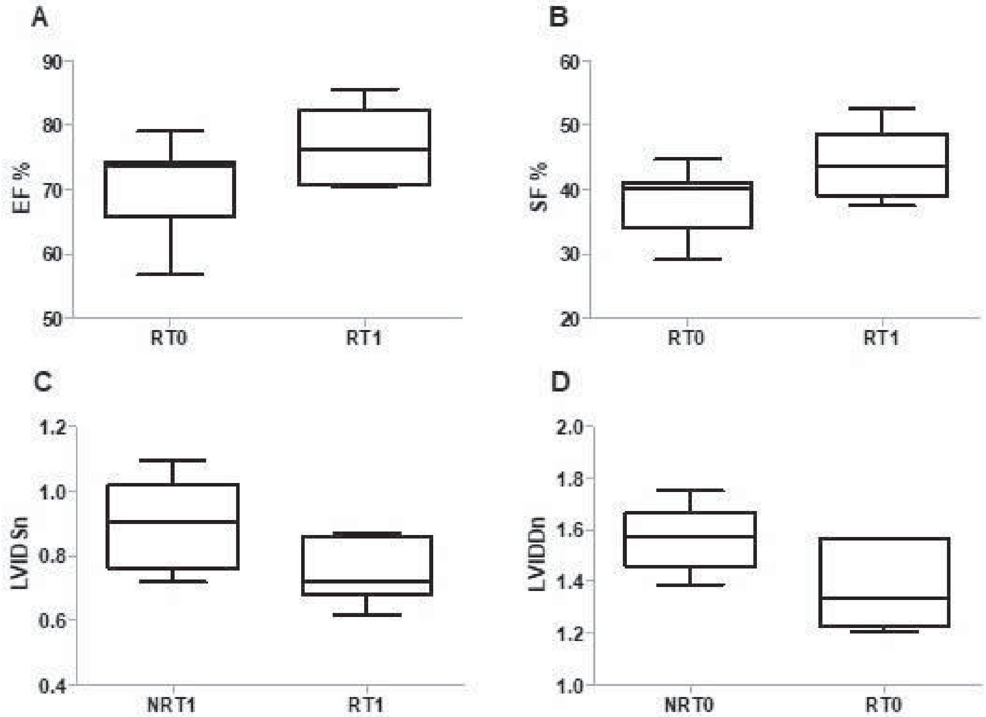

Figure 4. Box-plot graphs showing the minimum, maximum, mean and interquartile ranges of conventional echocardiographic parameters that differed between responsive (n = 7) and non-responsive (n = 15) dogs. EF: ejection fraction. LVIDDn: left ventricle internal diameter in diastole normalized. LVIDSn: left ventricle internal diameter in systole normalized. NRT0: non-responsive time 0; NRT1: non-responsive time 1; RT0: responsive time 0; RT1: responsive time 1; SF: shortening fraction.

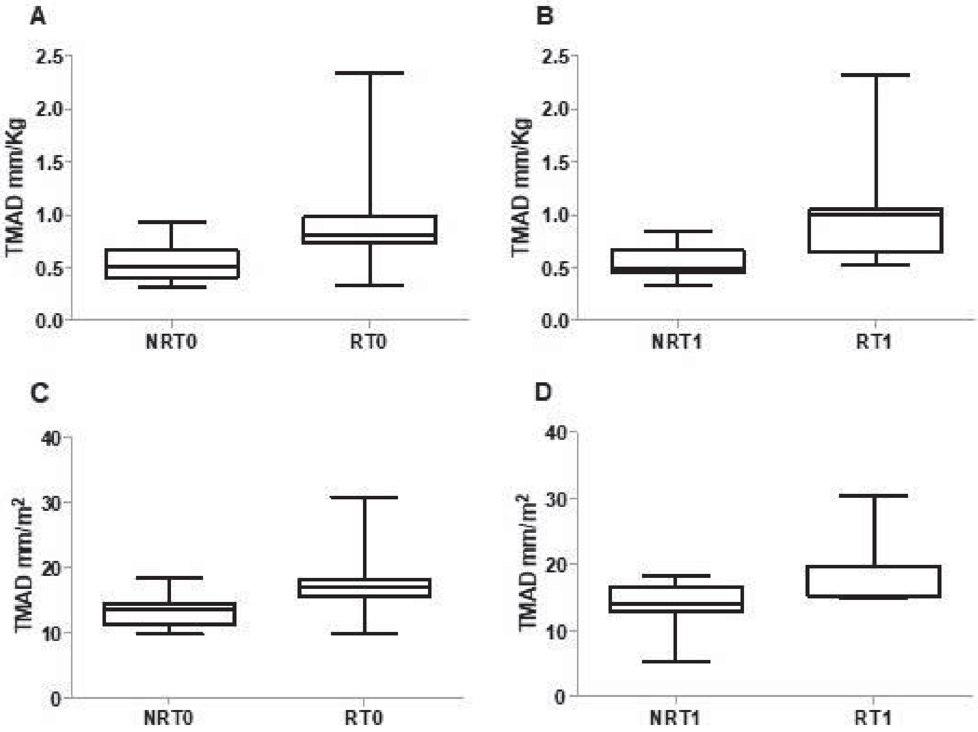

Figure 5. Box-plot graphs showing the minimum, maximum, mean and interquartile ranges of advanced echocardiographic parameters that differed between responsive (n = 7) and non-responsive (n = 15) dogs. NRT0: non-responsive time 0; NRT1: non-responsive time 1 RT0: responsive time 0; RT1: responsive time 1; TMAD: tissue motion annular displacement.

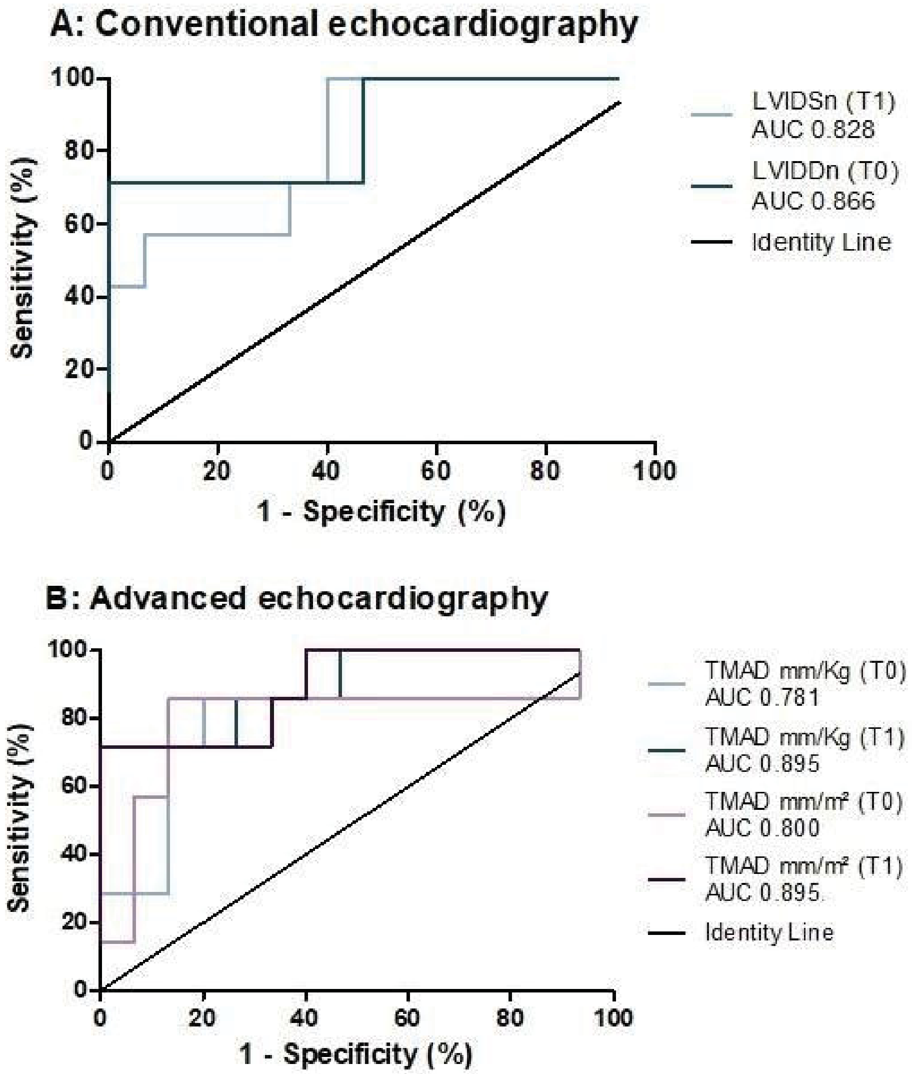

Figure 6. ROC curves and AUC values of conventional (A) and advanced (B) echocardiographic parameters that differed between responsive (N = 7) and non-responsive (N = 15) dogs. AUC: area under the curve; LVIDDn: left ventricle internal diameter in diastole normalized; LVIDSn: left ventricle internal diameter in systole normalized; TMAD: tissue motion annular displacement; T0: time 0; T1: time 1.

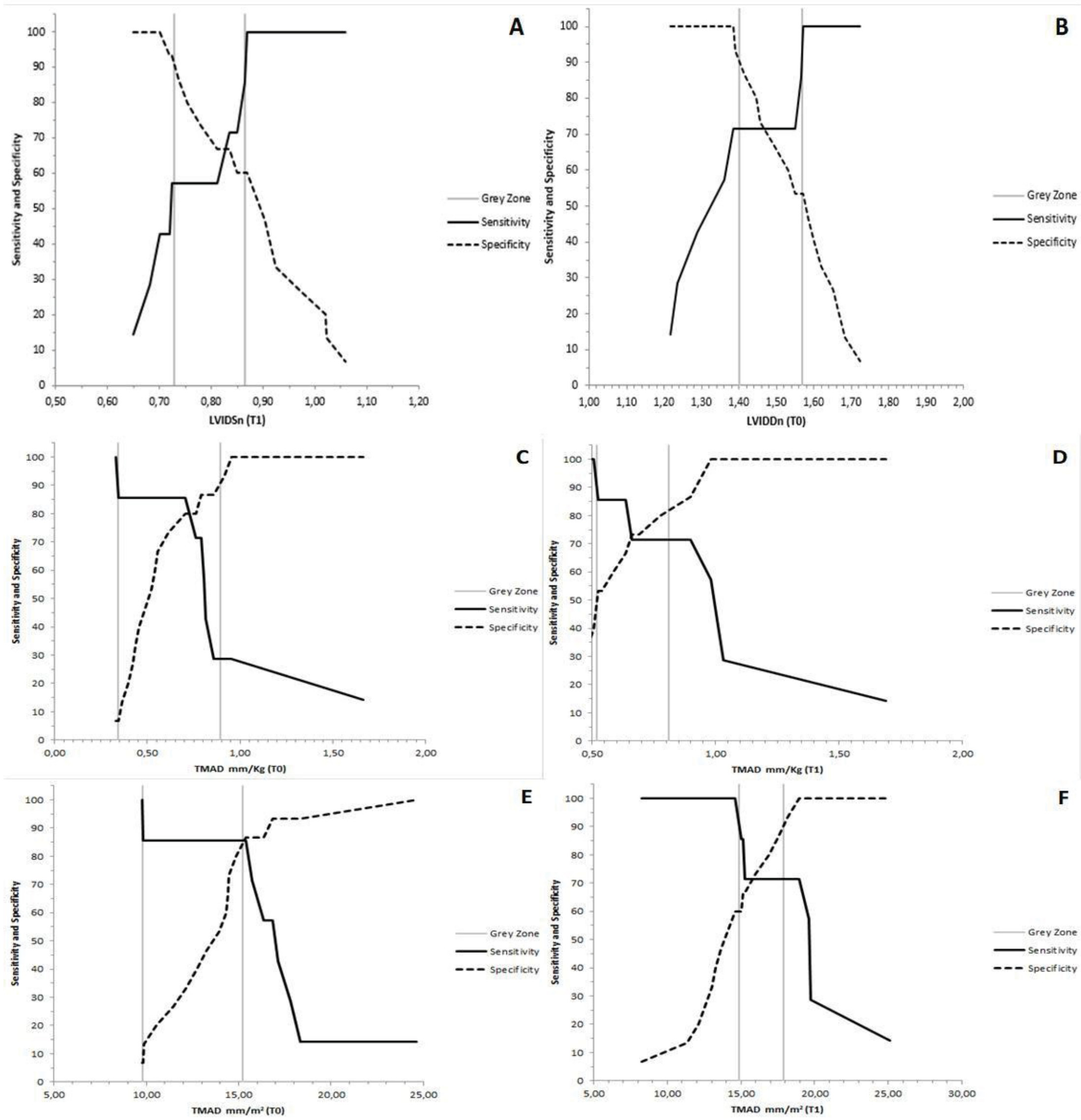

Figure 7. Sensitivity and specificity graphs with the gray zone interval demarcation of conventional (A and B) and advanced (C, D, E and F) echocardiographic parameters that differed between the responsive (n = 7) and non-responsive (n = 15) dogs. LVIDSn: left ventricle internal diameter in systole normalized. LVIDDn: left ventricle internal diameter in diastole normalized; 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) dogs.

Conventional echocardiographic parameters				
	Non-responsive		**Responsive**	
	T0	**T1**	**T0**	**T1**
EF (%)	70.86 (± 8.29)	70.11 (± 8.07)	70.91 (± 7.36)	77.04 (± 5.89)
SF (%)	39.68 (±6.58)	38.98 (±6.36)	38.57 (± 5.25)	44.04 (± 5.59)
LVIDSn	0.89 (± 0.11)	0.89 (± 0.12)	0.80 (± 0.12)	0.75 (± 0.10)
LVIDDn	1.56 (± 0.11)	1.53 (± 0.11)	1.36 (± 0.15)	1.41 (± 0.21)
Advanced echocardiographic parameters				
	Non-responsive		**Responsive**	
	T0	**T1**	**T0**	**T1**
GLS (%)	24.34 (± 3.33)	24.78 (± 2.90)	25.43 (± 4.26)	26.35 (± 2.25)
TMAD (mm)	7.24 (± 1.65)	7.94 (± 2.64)	5.99 (± 1.21)	6.94 (± 1.83)
TMAD (%)	13.54 (± 2.02)	14.70 (3.15-18.65)	15.31 (± 1.57)	16.35 (14.20-19.60)
TMAD (mm/kg)	0.51 (0.32-0.93)	0.49 (0.33-084)	0.81 (0.34-2.35)	1 (0.52-2.33)
TMAD (mm/m^2)	13.64 (9.76-18.43)	114 (5.34-18.33)	16.87 (9.82-30.84)	19.64 (14-30.51)
TMAD (mm/$\sqrt[3]{Kg}$)	2.99 (± 0.47)	3.27 (0.78-4.50)	3.11 (± 0.45)	3.52 (3.21-3.87)

EF: ejection fraction; GLS: global longitudinal strain; LVIDDn: left ventricle internal diameter in diastole normalized; LVIDSn: left ventricle internal diameter in systole normalized; SF: shortening fraction; 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**
LVIDSn T1	<0.87	0.85	0.60	100	60	0.828 (0.648-1.008)	0.73-0.87
LVIDDn T0	<1.39	0.71	0.93	71.43	100	0.866 (0.689-1.044)	1.40-1.57
Advanced echocardiographic parameters	**Cutoff Value**	**PPV**	**NPV**	**Sensitivity %**	**Specificity %**	**AUC (95% CI)**	**Gray Zone**
TMAD (mm/kg) T0	>0.7	0.85	0.80	85.71	80	0.781 (0.533-1.028)	0.34-0.90
TMAD (mm/kg) T1	>0.89	0.71	1.0	71.43	100	0.895 (0.746-1.044)	0.52-0.81
TMAD (mm/m^2) T0	>15.4	0.85	0.86	85.71	86.67	0.800 (0.553-1.047)	9.82-15.22
TMAD (mm/m^2) T1	>18.9	0.71	1.0	71.43	100	0.895 (0.748-1.042)	14.89-17.88

AUC: area under the curve; CI: confidence interval; LVIDDn: left ventricle internal diameter in diastole normalized; LVIDSn: left ventricle internal diameter in systole normalized; NPV: negative predictive value; PPV: positive predictive value; TMAD: tissue motion annular displacement

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

Conventional echocardiographic parameters	**Age (months)**		**Body Weight (kg)**		**HR (bpm)**		**SBP (mmHg)**	
	R	*P*	R	*P*	R	*P*	R	*P*
EF (%) T0	0.076	0.749	-0.468	0.028	0.259	0.243	0.076	0.772
EF (%) T1	0.563	0.010	-0.511	0.015	0.349	0.111	0.001	0.998
SF (%) T0	0.050	0.833	-0.368	0.092	0.242	0.277	0.107	0.683
SF (%) T1	0.552	0.012	-0.451	0.035	0.298	0.178	0.255	0.323
LVIDSn T0	-0.262	0.264	0.652	0.001	-0.349	0.112	0.087	0.739
LVIDSn T1	-0.526	0.017	0.459	0.032	-0.510	0.015	0.054	0.836
LVIDDn T0	-0.290	0.215	0.625	0.002	-0.239	0.283	0.208	0.423
LVIDDn T1	-0.310	0.184	0.296	0.181	-0.465	0.029	0.098	0.708
Advanced echocardiographic parameters	**Age (months)**		**Body Weight (kg)**		**HR (bpm)**		**SBP (mmHg)**	
	R	*P*	R	*P*	R	*P*	R	*P*
GLS (%) T0	0.091	0.702	-0.312	0.157	0.123	0.584	0.407	0.104
GLS (%) T1	0.081	0.733	-0.332	0.131	-0.049	0.829	0.285	0.267
TMAD (mm) T0	-0.403	0.078	0.746	<0.001	-0.223	0.318	0.089	0.734
TMAD (mm) T1	-0.271	0.248	0.836	<0.001	-0.338	0.124	0.166	0.524
TMAD (%) T0	-0.074	0.757	-0.225	0.315	0.319	0.148	0.055	0.833
TMAD (%) T1	0.008	0.972	0.204	0.362	0.285	0.198	0.381	0.131
TMAD (mm/kg) T0	0.348	0.132	-0.906	<0.001	0.255	0.251	-0.044	0.866
TMAD (mm/kg) T1	0.159	0.502	-0.581	0.005	0.233	0.297	0.011	0.966
TMAD (mm/m^2) T0	0.352	0.128	-0.768	<0.001	0.271	0.223	-0.063	0.807
TMAD (mm/m^2) T1	0.225	0.340	-0.451	0.035	0.185	0.410	-0.009	0.970
TMAD (mm/$\sqrt[3]{kg}$) T0	-0.116	0.626	-0.095	0.673	0.056	0.806	0.076	0.771
TMAD (mm/$\sqrt[3]{kg}$) T1	0.144	0.544	0.311	0.159	0.050	0.825	0.373	0.139

EF: ejection fraction; GLS: global longitudinal strain; HR: heart rate; LVIDDn: left ventricle internal diameter in diastole normalized; LVIDSn: left ventricle internal diameter in systole normalized; SF: shortening fraction; SBP: systolic blood pressure; TMAD: tissue motion annular displacement; T0: time 0; T1: time 1

3 RIGHT VENTRICULAR LONGITUDINAL FUNCTION IN THE ASSESSMENT OF FLUID RESPONSIVENESS IN HEALTHY DOGS[2]

ABSTRACT

Background: An essential component in the treatment of critically ill patients is volume replacement, but excessive intravascular fluid administration are 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.
Materials, Methods and Results: This is a prospective study. Twenty-two healthy dogs over one year of age were included, these dogs presented to the University teaching hospital for elective neutering procedure. All dogs underwent conventional and advanced echocardiographic examination before and after administration of a volume challenge with 10mL/kg lactate ringer intravenously for 20 minutes. 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/m2) 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/m2) 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. 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 better understand the applicability of these techniques.

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

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[2] Elaborado de acordo com as normas da revista *Acta Scientiae Veterinariae*

3.1 INTRODUCTION

An essential component in the treatment of critically ill patients is volume replacement [26]. However, in dogs and cats the excessive intravascular fluid administration are associated with increased morbidity and mortality [7,29]. 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 [5,10,28].

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 [25]. 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" [11,23].

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 [24]. 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.

3.2 MATERIALS AND METHODS

Study design and animals

This is a prospective study. Twenty-two healthy dogs that presented to the University teaching hospital for elective neutering procedure were included 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 one 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 first echocardiographic evaluation (T0) was performed prior to the volemic challenge and the second echocardiographic evaluation was performed (T1) within 5 minutes of completion of fluid administration. The volemic challenge was performed using an infusion pump administering lactated ringer’s at a dose of 10mL/kg intravenously for 20 minutes. 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 [38]. 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 five chamber image obtained through the left parasternal window. The mean of three 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 ∆VTI Ao has determined the classification of patients as responsive and non-responsive to the fluid challenge. The responsive individuals were considered those with ∆VTI Ao ≥15% and non-responsive with ∆VTI Ao <15 % [5,28]. For statistical analysis, dogs were subdivided into two groups, responsive and non-responsive to the volemic challenge, and evaluations were made at T0 and T1.

Conventional echocardiographic evaluation

Videos of apical four-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:

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

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

Advanced echocardiographic evaluation

Videos of apical four-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 three 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, three regions of interest were manually established: the first, at the insertion of the lateral tricuspid leaflet; the second, at the insertion of the septal tricuspid leaflet; and the third, 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 two 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 analyzes were performed using the same software[2] and the level of statistical significance adopted was *P* <0.05.

3.3 RESULTS

Twenty-two dogs were included in the study, being that 54.5% (12) were females and 45.5% (10) 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 ∆VTI 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.

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/m^2) 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/m^2) 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.

3.4 DISCUSSION

Some echocardiographic parameters used, particularly TAPSE before fluid challenge and LSt and TMAD after fluid challenge, were higher in responsive dogs. To author's knowledge, this is the first 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 [20,30,31]. 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 [1,17], research animals [16] and dogs [14,27]. 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 relative small gray zone intervals (Table 2, Figure 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 [28]. 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 [27], 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 [32,39]. In this case, it could be an option for the use of non-cardiologists. On the other hand, its acquisition is angle dependent [41] 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, Figure 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 [36]. 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 [19,25]. Besides that, is a fast, reproducible, and promising method for assessing right ventricular systolic function in healthy dogs [34]. 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 [14,35,40], however, standardization of measurements of the right ventricle is still a problem [22]. 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 [27].

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 [20]. 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 [12,18], since the heart-lung interaction causes a cyclic variation in stroke volume [13,18]. It is worth mentioning that this group represents the vast majority of critically ill individuals who require intravenous fluid [18]. 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 [17].

Previous studies are contradictory regarding the response of the right ventricle. In dogs, some of the right ventricular function indices are preload dependent [27]. However, in experimental studies the right ventricular longitudinal function remained preserved [16], as well as the contractility for long period of times in volume overload [37]. 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 [17]. 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 [33]. 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 [24,28]. Hypervolemic patients with severe clinical conditions are more likely to develop negative sequelae secondary to excess fluid administration [21,28]. 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 [26].

There are a number of limitations to this 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.

3.5 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 these assessment 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 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 interest. The authors alone are responsible for the content and writing of paper.

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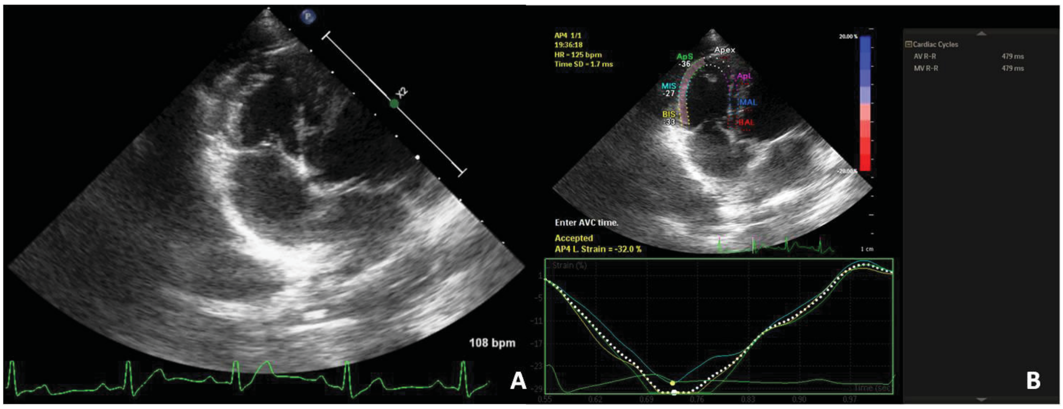

Figure 1. Advanced echocardiography showing the apical 4-chamber image optimized for the right ventricle (A) used to obtain the longitudinal strain (LSt) in percentage (%) (B) of a healthy dog non-responsive to the fluid challenge.

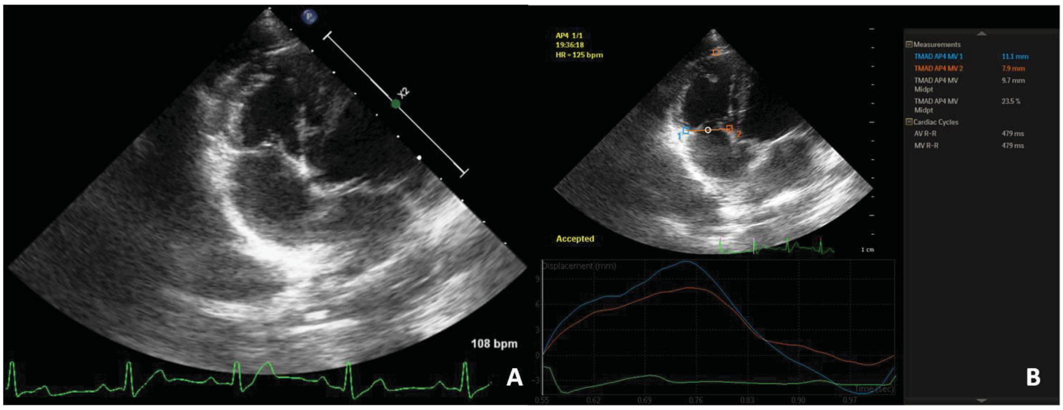

Figure 2. Advanced echocardiography showing the apical 4-chamber image optimized for the right ventricle (A) used to obtain the global tissue motion annular displacement (TMAD), in millimeters (mm) and percentage (%) (B), of a healthy dog non-responsive to the fluid challenge.

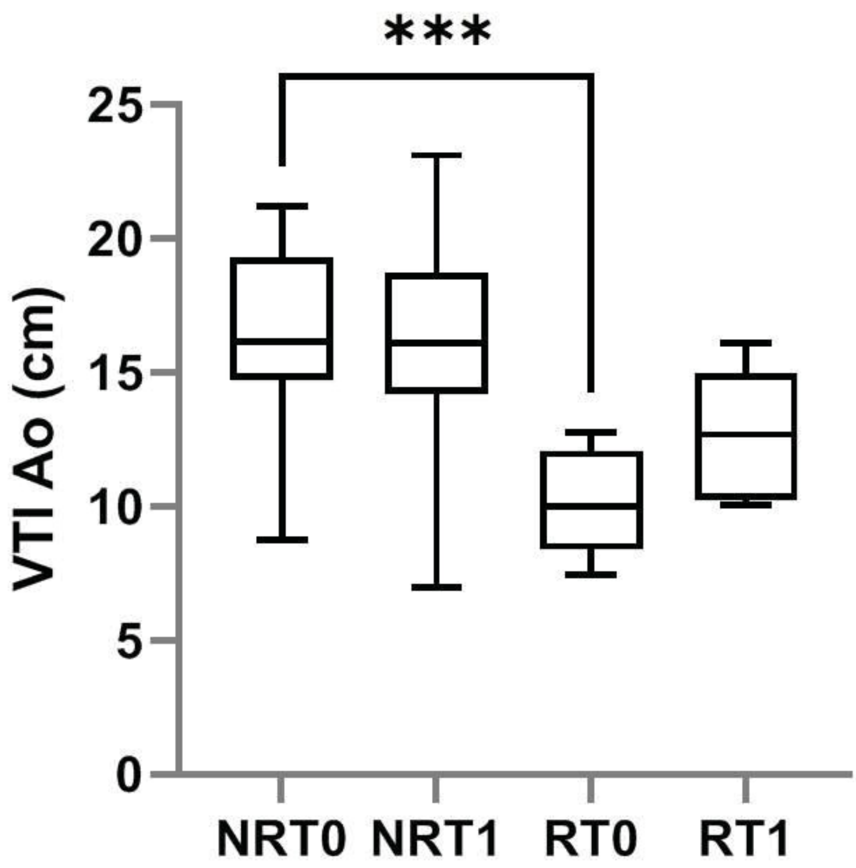

Figure 3. Box-plot graphs showing the minimum, maximum, median and interquartile ranges of the VTI Ao before and after the volume challenge of dogs classified as responsive (n = 7) and non-responsive (n = 15). Ao: aorta; NRT0: non-responsive time 0; NRT1: non-responsive time 1; RT0: responsive time 0;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

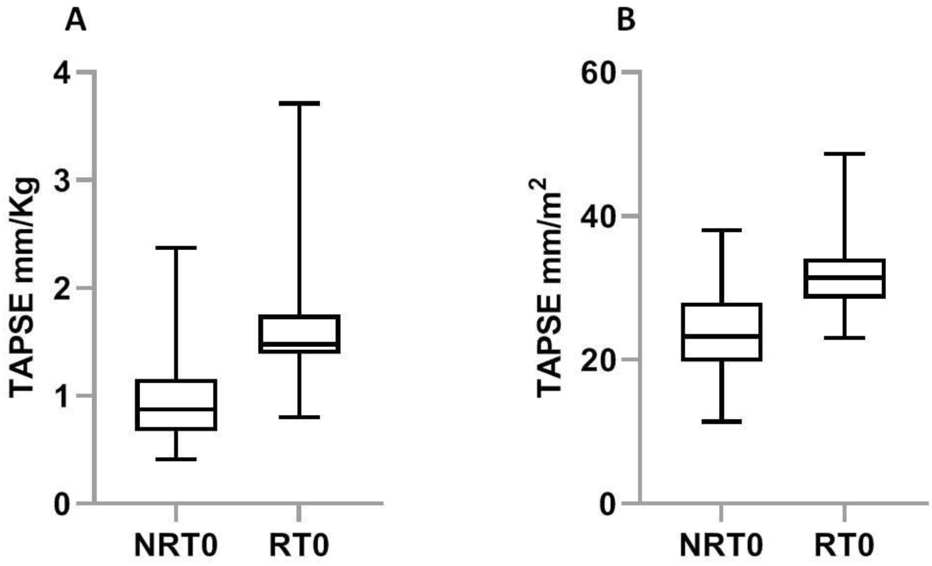

Figure 4. Box-plot graphs showing the minimum, maximum, median and interquartile ranges of conventional echocardiographic parameters that differed between responsive (n = 7) and non-responsive (n = 15) dogs. NRT0: non-responsive time 0; RT0: responsive time 0; TAPSE: tricuspid annular plane systolic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

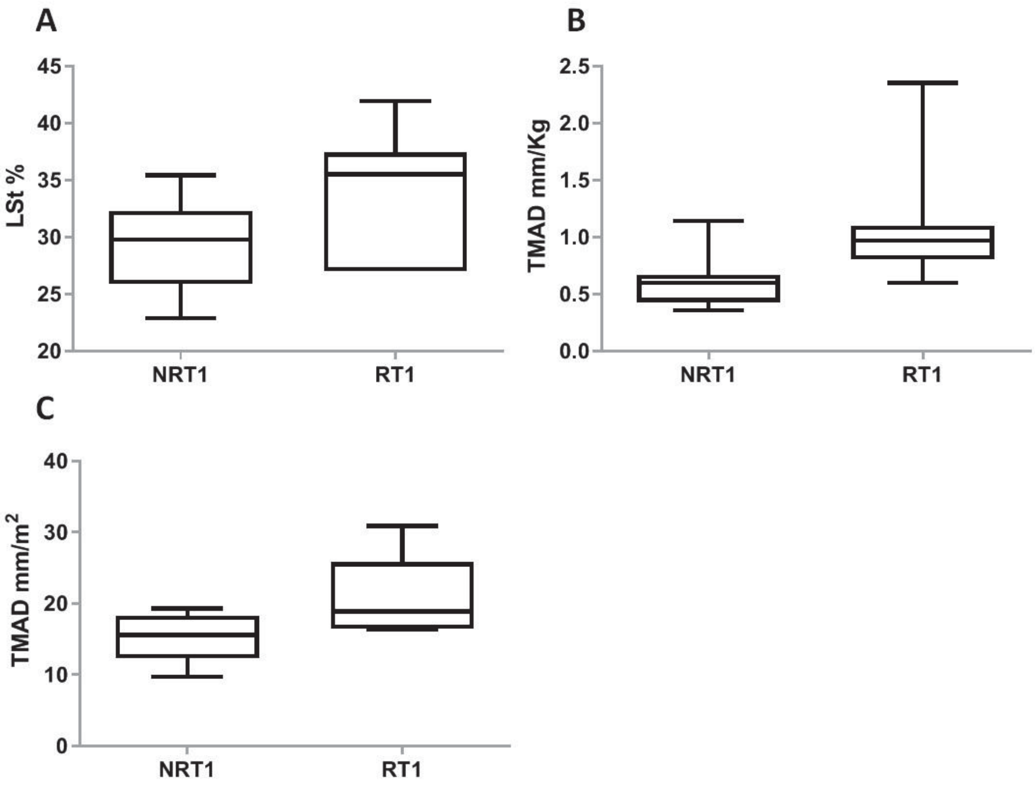

Figure 5. Box-plot graphs showing the minimum, maximum, median and interquartile ranges of advanced echocardiographic parameters that differed between responsive (n = 7) and non-responsive (n = 15) dogs. LSt: longitudinal strain; NRT1: non-responsive time 1; RT1: responsive time 1; TMAD: tissue motion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

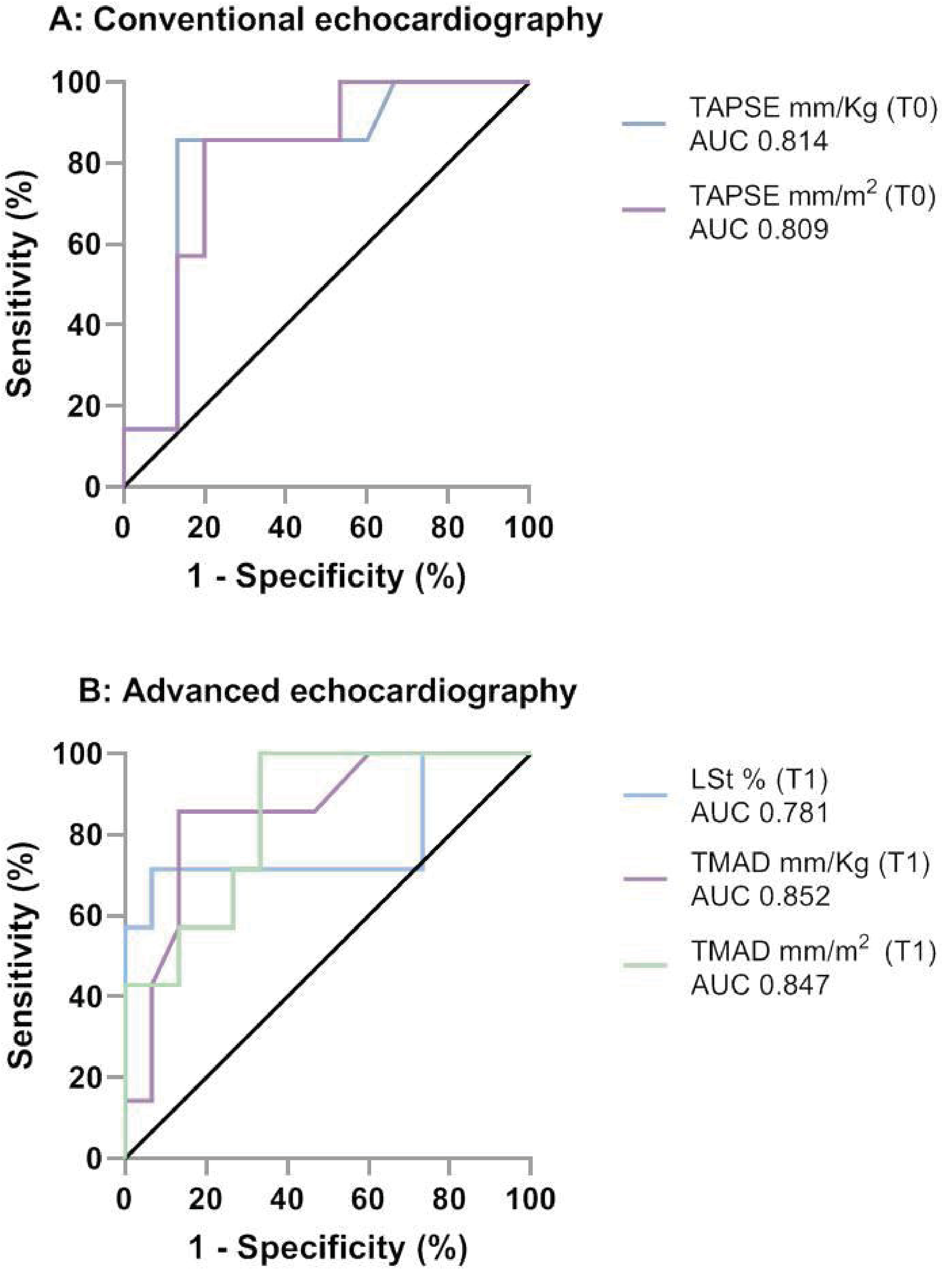

Figure 6. ROC curves and AUC values of conventional (A) and advanced (B) echocardiographic parameters that differed between responsive (N = 7) and non-responsive (N = 15) dogs. AUC: area under the curve; LSt: longitudinal strain; TAPSE: tricuspid annular plane systolic excursion; TMAD: tissue motion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

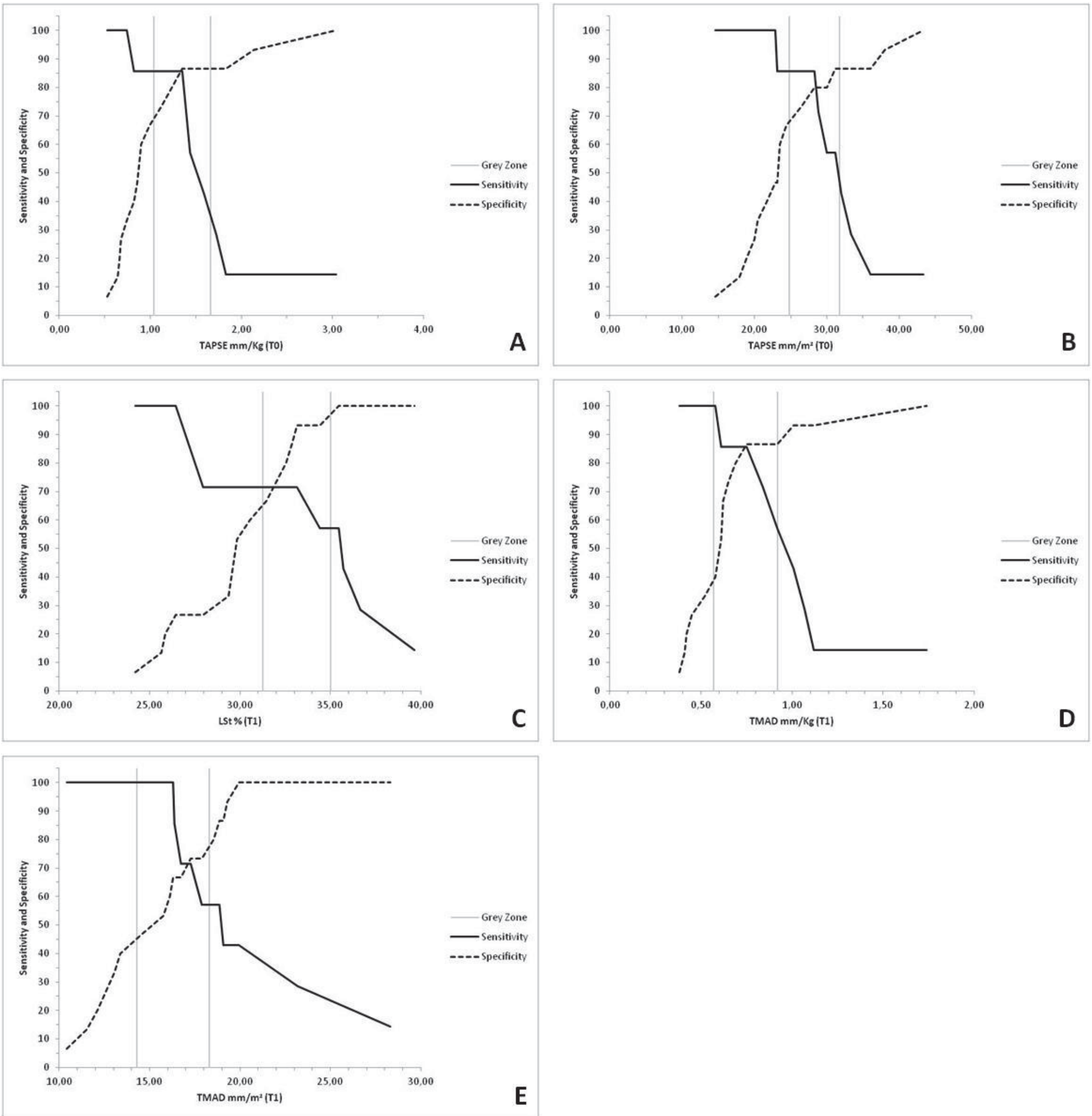

Figure 7. Sensitivity and specificity graphs with the gray zone interval demarcation of conventional (A, B, C and D) and advanced (E, F and G) echocardiographic parameters that differed between the responsive (n = 7) and non-responsive (n = 15) dogs. LSt: longitudinal strain; TAPSE: tricuspid annular 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)	12.74 (± 3.03)[a]	14.67 (± 3.51)[a]	11.40 (± 3.23)	10.06 (± 2.28)
TAPSE (mm/Kg)	0.87 (0.41 - 2.37)[a]	1.02 (0.70 - 2.83)	1.48 (0.80 - 3.71)[a]	1.49 (0.68 - 3.71)
TAPSE (mm/m^2)	24.06 (± 7.25)[ab]	25.02 (19.98 - 45.41)[a]	32.49 (± 7.96)[b]	27.93 (18.96 - 48.62)
Advanced echocardiographic parameters				
	Non-responsive		**Responsive**	
	T0	**T1**	**T0**	**T1**
LSt (%)	27.67 (± 7.07)	29.64 (± 3.38)[a]	30.24 (± 8.55)	34.01 (± 5.45)[a]
TMAD (mm)	6.91 (± 2.26)[a]	8.30 (± 2.61)[a]	5.71 (± 2.24)	7.60 (± 3.27)
TMAD (%)	18.17 (± 5.24)[a]	22.70 (15.30-29.10)[a]	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)[a]	0.88 (0.23-2.50)	0.97 (0.60-2.35)[a]
TMAD (mm/m^2)	13.18 (± 5.35)	15.54 (9.75-19.31)[a]	17.39 (± 8.44)	18.88 (16.30-30.84)[a]

The overwritten letters indicate the parameters that differed significantly from each other. 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/Kg) T0	> 1.35	0.75	0.93	85.71	86.67	0.814 (0.61 - 1.0)	1.04 - 1.66
TAPSE (mm/m^2) T0	> 28.26	0.67	0.92	85.71	80.0	0.809 (0.62 - 0.99)	24.78 - 31.74
Advanced echocardiographic parameters	**Cutoff Value**	**PPV**	**NPV**	**Sensitivity %**	**Specificity %**	**AUC (95% CI)**	**Gray Zone**
LSt (%) T1	> 33.15	0.83	0.87	71.43	93.33	0.781 (0.52-1.0)	31.26-35.03
TMAD (mm/kg) T1	> 0.75	0.66	0.81	85.71	86.67	0.852 (0.67-1.0)	0.57-0.92
TMAD (mm/m^2) T1	> 16.29	0.71	0.81	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)**		**SBP (mmHg)**	
	R	*P*	R	*P*	R	*P*	R	*P*
FAC (%) T0	0.318	0.172	-0.053	0.816	0.483	0.023	0.399	0.112
FAC (%) T1	0.065	0.783	0.067	0.767	0.150	0.506	0.351	0.167
TAPSE (mm) T0	-0.061	0.798	0.631	0.001	0.106	0.636	0.308	0.229
TAPSE (mm) T1	-0.421	0.064	0.804	<0.0001	-0.456	0.032	0.066	0.799
TAPSE (mm/Kg) T0	0.485	0.030	-0.906	<0.0001	0.393	0.070	0.321	0.207
TAPSE (mm/Kg) T1	0.229	0.332	-0.834	<0.0001	0.035	0.875	0.157	0.543
TAPSE (mm/m^2) T0	0.514	0.020	-0.799	<0.0001	0.444	0.038	0.113	0.665
TAPSE (mm/m^2) T1	0.108	0.649	-0.600	0.003	-0.141	0.528	0.122	0.638
Advanced echocardiographic parameters	**Age (months)**		**Body Weight (kg)**		**HR (bpm)**		**SBP (mmHg)**	
	R	*P*	R	*P*	R	*P*	R	*P*
LSt (%) T0	0.311	0.183	-0.444	0.038	-0.044	0.844	0.059	0.820
LSt (%) T1	0.248	0.291	-0.150	0.505	0.322	0.144	-0.283	0.271
TMAD (mm) T0	-0.438	0.053	0.329	0.1343	-0.198	0.377	0.022	0.932
TMAD (mm) T1	-0.261	0.265	0.735	<0.0001	-0.374	0.086	0.248	0.337
TMAD (%) T0	-0.188	0.426	-0.328	0.136	0.053	0.815	0.093	0.721
TMAD (%) T1	-0.195	0.409	0.499	0.018	-0.244	0.275	0.230	0.372
TMAD (mm/kg) T0	0.225	0.339	-0.766	<0.0001	0.269	0.226	0.038	0.885
TMAD (mm/kg) T1	0.354	0.126	-0.776	<0.0001	0.252	0.257	0.188	0.466
TMAD (mm/m^2) T0	0.116	0.626	-0.677	0.0005	0.213	0.340	-0.110	0.675
TMAD (mm/m^2) T1	0.284	0.225	-0.473	0.026	0.149	0.508	0.283	0.271

FAC: fractional area change; HR: heart rate; LSt: longitudinal strain; SBP: systolic blood pressure; TAPSE: tricuspid annular plane systolic excursion; TMAD: tissue motion annular displacement; T0: time 0; T1: time 1

4 ULTRASONOGRAPHIC PARAMETERS IN THE ASSESSMENT OF FLUID RESPONSIVENESS IN HEALTHY SPONTANEOUSLY BREATHING DOGS[3]

ABSTRACT

Background: The concept of fluid responsiveness was initially described in hospitalized patients under mechanical ventilation. However, most of the hospitalized dogs that need volume replacement are spontaneously breathing. The caudal vena cava (CVC) is a highly compliant structure and changes in intravascular or intrathoracic pressure due to the respiratory cycle produce variation in its diameter. Within this context, dynamic indices based on measuring the diameter of the CVC to assess fluid responsiveness have emerged considering the heart-lung interaction. Therefore, the aim of the present study is to evaluate whether ultrasound parameters, such as the caudal vena cava collapsibility index (CVCCI) and the caudal vena cava and aorta ratio (CVC/Ao), are able to assess fluid responsiveness in healthy, spontaneously breathing dogs. As well as evaluating the time required to acquire the images and measurements and their respective interobserver and intraobserver coefficients of variation.
Materials, Methods and Results: A prospective study was carried out in which 22 healthy dogs over one year of age that presented to the veterinary hospital for the elective castration procedure were selected. All animals underwent the measurement of the aortic flow by echocardiography to obtain the value of ∆VTI Ao and subsequent classification of fluid responsiveness. In addition, an ultrasound examination was performed to obtain the CVCCI and the CVC/Ao. These parameters were evaluated before (T0) and after (T1) the administration of a volume challenge with lactate ringer at a dose of 10mL/Kg for 20 minutes. Based on the value of ∆VTI Ao, 31.82% of the dogs were considered responsive and 68.18% non-responsive to the volume challenge. A reduction in the means of CVCCI and an increase in the means of the CVC/Ao ratio were observed after the volume challenge, both in responsive and non-responsive individuals. None of the studied variables differed between dogs classified as responsive and unresponsive, either at T0 or T1. The CVC/Ao ratio at T1 <0.67 was the parameter that demonstrated the best AUC value (0.68) and the best combination of sensitivity (73.33%) and specificity (71.43%) in the identification of non-responsive dogs. The median of the image acquisition and measurement acquisition times were, respectively, 78 (9 - 269) and 136 (86 - 308) seconds. The image acquisition time was significantly shorter compared to the measurement acquisition time (P = 0.0002).
Discussion: Research on fluid responsiveness in spontaneously breathing dogs is contradictory regarding the effectiveness of the indices in identifying responsiveness. In the present study, there was weak evidence that the CVCCI and the CVC/Ao ratio can differentiate responsive from non-responsive dogs, despite the CVC/Ao ratio having been shown to be superior in relation to the CVCCI. Possibly, this superiority is related to the fact that this index can be used in individuals of different sizes. In addition, the diameter of the CVC is measured based on the surface electrocardiography (ECG), allowing for greater standardization of this measurement

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[3] Elaborado de acordo com as normas da Revista *Acta Scientiae Veterinariae*

compared to the CVCCI. The biggest limiting factor of both variables studied is the spontaneous breathing itself, as respiratory movements directly influence the degree of dilation or collapse of the CVC. Therefore, the use of the CVCCI and the CVC/Ao ratio alone in awake dogs may not be safe. In the future, these techniques performed by the same operator in a longitudinal way, possibly, will bring relevant information about the volume status of hospitalized patients, but more research is needed before the institution of this type of practice.

Keywords: abdomen, canine, caudal vena cava, volume challenge

4.1 INTRODUCTION

The concept of fluid responsiveness was initially described in sedated patients under mechanical ventilation. However, most hospitalized individuals who need volume replacement are not in this situation [5,9]. In spontaneously breathing patients, during inspiration the intrathoracic pressure becomes negative, promoting greater venous return and an increase in the stroke volume. On the other hand, during expiration, intrathoracic pressure becomes positive, while venous return and stroke volume decrease [5,24].

The caudal vena cava (CVC) is a highly compliant structure and changes in intravascular or intrathoracic pressure due to the respiratory cycle produce variation in its diameter. During the inspiratory peak the CVC undergoes greater collapse and during the expiratory peak greater dilation [25]. Within this context, dynamic indices for assessing fluid responsiveness have emerged based on the heart-lung interaction. Such indices have demonstrated superiority compared to pre-existing static indices such as central venous pressure (CVP) [2,4,17,22,25].

The assessment of the caudal vena cava collapsibility index (CVCCI) and the caudal vena cava and aorta ratio (CVC/Ao) have been used to assess the volume status in human patients. In responsive patients, the CVCCI tends to be higher and the CVC/Ao ratio is lower, while in non-responsive patients the CVCCI tends to be lower and the CVC/Ao ratio is higher [9,25]. Therefore, the objectives of the present study are to evaluate whether ultrasound parameters, such as the CVCCI and the CVC/Ao ratio, can assess fluid responsiveness in healthy, spontaneously breathing dogs. As well as evaluating the time required to acquire the images and measurements and their respective interobserver and intraobserver coefficients of variation.

4.2 MATERIALS AND METHODS

Study design and animals

A prospective study was carried out in which healthy dogs referred to the Veterinary Teaching Hospital of the Federal University of Paraná for elective ovary-hysterectomy (OH) or orchiectomy surgeries were selected. Animals with concomitant diseases history, significant changes in the physical or echocardiographic examination and younger than one year of age were not included in the study.

Fluid responsiveness classification

Before the surgical procedure, a complete physical examination and the first ultrasound evaluation (T0) were performed, then the patient was submitted to a volume challenge with lactate ringer at a dose of 10 ml/kg for 20 minutes with the aid of an infusion pump, and within 5 minutes after this administration, the second ultrasound evaluation (T1) was performed.

Apical five chamber image in the left parasternal window were acquired to obtain the aortic velocity time integral (VTI Ao). Three consecutive VTI Ao measurements with the best alignment possible were performed and the average between them was considered to calculate the ∆VTI Ao, according to the formula:

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

The classification of patients as responsive and non-responsive was based on the value of ∆VTI Ao, in which responders were considered those with ∆VTI Ao greater than or equal to 15% and non-responders with ∆VTI Ao less than 15% [3,23].

Ultrasonographic evaluation

The ultrasound examination was performed without sedation with all animals breathing spontaneously. The patients were positioned in the left lateral recumbency and the images were acquired through the hepatic window by a technique already described [7]. All examinations were performed by the same operator (SL) using a

Philips Affiniti 50 equipment equipped with 2-12 MHz linear and sectoral transducers[1].

The transducer was positioned parallel to the ribs, between the 10th and 12th right intercostal space, between 5 and 10 cm ventral to the vertebral column, until the transversal view of the porta hepatis was seen. Images were considered adequate when artifacts from air in the lung or gas in the gastrointestinal tract were absent and the aorta, CVC and portal vein (PV) were visualized in a single frame. When it was not possible to produce this image due to the presence of air or gas, a modified view was performed by moving the transducer caudally until the appearance of the right kidney adjacent to the liver with the visualization of the aorta and CVC in a single frame. Care was taken not to apply too much pressure to the transducer on the animal, which could cause the CVC to collapse.

The maximum and minimum diameters of the CVC were measured along its shortest axis in millimeters (mm), from the dorsal inner wall to the ventral inner wall, from two-dimensional images. These measurements were performed using a video recording of at least three consecutive respiratory cycles. To calculate the CVCCI, the average of three CVCmax and CVCmin values were considered, according to the formula [3,7,20]:

$$CVCCI = (CVC_{max} - CVC_{min})/CVC_{max} \times 100$$

The diameters of the CVC in its shortest axis and the aorta were also measured in mm from two-dimensional images during atrial systole (after the P wave on the surface electrocardiogram), according to the technique already described [15]. These measurements were performed in three cardiac cycles and the mean of the CVC_{ecg} and the Ao_{ecg} was considered to calculate the CVC/Ao ratio.

The acquisition times of the images through the conventional or modified hepatic window of all patients were recorded, as well as the acquisition times of the measurements of the studied variables. After 90 days, the variables used to calculate the CVCCI and the CVC/Ao ratio were measured again from the archived videos of ten randomly selected patients. These measurements were repeated by the same observer and by another observer with the same level of training.

Statistical analysis

Descriptive statistics were performed by estimating the frequencies (%) of qualitative variables and calculating the mean and standard deviation or median and range of quantitative variables, depending on the distribution of the samples. To identify the sample distribution, the Shapiro-Wilk test was used.

Comparisons between groups were performed as follows: responsive dogs at T0 versus T1; non-responsive dogs at T0 versus T1; responsive versus non-responsive dogs at T0; and responsive versus non-responsive dogs at T1. In addition, the acquisition times of images and measurements of all the animals were also compared. Paired t test or Student t test were used in samples with normal distribution and the Wilcoxon or Mann-Whitney test were used in samples with abnormal distribution.

Positive (PPV) and negative predictive values (NPV) were calculated, ROC curves were plotted to obtain the area under the curve (AUC) values and the 95% confidence interval (CI). The Youden index was also calculated to identify the cut-off value with the best combination of sensitivity and specificity and the gray zone of the ultrasound parameters obtained. The gray zone was calculated with the objective of identifying the inconclusive region of the proposed cut-off values, this zone was defined by the values with 90% of sensitivity and specificity (10% of diagnostic tolerance).

Pearson's (normal distribution) and Spearman's (abnormal distribution) correlation coefficients were used to verify the influence of weight, age and VTI Ao on the ultrasonographic parameters studied. Finally, the interobserver and intraobserver coefficient of variation of the variables used to calculate the CVCCI and the CVC/Ao ratio were calculated. All analyzes were performed using the same software[2] and the level of statistical significance adopted was $P < 0.05$.

4.3 RESULTS

Twenty-two dogs were included in the present study, 31.8% (7) were classified as responsive and 68.2% (15) non-responsive to the volume challenge based on the value of ΔVTI Ao. The VTI Ao (cm) of the responsive dogs were significantly lower compared with the non-responsive ones before the volume challenge (*P* = 0.0005). Among these animals, 54.5% (12) were female and 45.5% (10) were male, and the age ranged between 9-113 months (median: 28.5 months). The dogs were of different sizes with a mean and standard deviation of weight of 12.8 (± 6.4) kg. The most common breeds were SRD (13), Lhasa Apso (5), Australian Cattle Dog (2), Shih-tzu (1) and Yorkshire Terrier (1).

The mean and standard deviation of the ultrasound variables evaluated, as well as the P values of the comparisons analyzes are described in Table 1 and represented in Figure 1. The only variable that differed in the comparison analyzes was the CVCCI of the responsive dogs between T0 and T1, there was a reduction in this index after the volume challenge. None of the studied variables differed between dogs classified as responsive and non-responsive, either at T0 or T1.

The best cut-off value of the CVCCI and the CVC/Ao ratio for the identification of responsive dogs, with their respective PPV, NPV, sensitivity, specificity, AUC, 95% CI and gray zone are described in Table 2. The ROC curves are represented in Figure 2 and the sensitivity and specificity graphs with the demarcation of the gray zone are shown in Figure 3.

The CVC/Ao ratio after the volume challenge (T1) showed a positive moderate correlation with the ∆VTI Ao. No correlations were observed between the other variables with ∆VTI Ao, age or body weight. The results of the correlation analyzes are described in Table 3.

The median time of acquisition images and measurements were, respectively, 78 (9 - 269) and 136 (86 - 308) seconds. The image acquisition time was significantly shorter compared to the measurement acquisition time (*P* = 0.0002) as shown in Figure 4. The values of the interobserver and intraobserver coefficient of variation of the variables used to calculate the CVCCI and the CVC/Ao ratio are expressed in Table 4.

4.4 DISCUSSION

Published studies on fluid responsiveness in spontaneously breathing dogs are contradictory regarding the effectiveness of the indexes that involve the measurement of the CVC in identifying the responsive individuals. The use of ultrasound techniques to measure the diameter of the CVC are considered as an option for estimating CVP [2,22]. It has already been described that there is a correlation between these variables, making it possible for the hemodynamic assessment to be performed by a rapid, non-invasive method that can be used at the bedside [1,6,12].

In the present study, a reduction in the CVCCI and an increase in the CVC/Ao ratio means were observed after the volume challenge, both in responsive and non-responsive animals (Table 1 and Figure 1). The CVCCI expresses the percentage change in the diameter of the CVC during the respiratory cycle. In humans, it has been shown that CVCCI less than 50%, due to greater dilation of the CVC, is associated with increased CVP secondary to hypervolemia, congestive heart disease or cardiac tamponade. On the other hand, the CVCCI greater than 50%, due to the greater collapse of the CVC, is associated with a reduction in CVP, serving as an indication of hypovolemia [2]. The CVC/Ao ratio is a variable that can be used in individuals of different sizes, because when comparing the diameter of the CVC with that of the aorta, the differences that may exist regarding the varied sizes, weights and ages are corrected [7,10]. The reduction in CVCCI and the increase in the CVC/Ao ratio after the volume challenge observed in the present study indicate that, regardless of the group evaluated, the subjects became less responsive after fluid administration.

There was no statistical difference in the CVCCI and the CVC/Ao ratio between the dogs classified as responsive and non-responsive, before or after the volume challenge (Table 1). Some justifications have already been proposed to explain the reasons why the indices that assess the diameter of the CVC may not be able to discriminate responsive from non-responsive individuals, with the main limiting factor in this case being the spontaneous breathing itself. In awake dogs, respiratory movements can generate different diaphragmatic and thoracic movements at each respiratory cycle, depending on the respiratory effort imposed at that particular moment, which ends up directly influencing the measurement of CVC obtained [14,25].

In this study, dogs with different thoracic conformations, of different sizes and breeds were included. Therefore, it is possible that these variations have interfered in the respiratory pattern of these animals and may have contributed to greater variability in the interaction between thorax and abdomen, leading to reduced predictability of the CVCCI and the CVC/Ao ratio [25]. In addition, many animals were panting during the ultrasound examination, short and shallow breathing can generate minimal changes in the diameter of the CVC, consequently leading to a smaller variation in the CVCCI and the CVC/Ao ratio [18].

Still on the measurement of the CVC diameter, some authors argue that it is not possible to accurately obtain these values at the exact moment of the inspiratory and expiratory peaks in awake individuals. Possibly, the CVCCI and the CVC/Ao ratio would be more accurate in the assessment of fluid responsiveness if they were measured at this exact moment of the respiratory cycle [18]. Since these are spontaneously breathing animals, what was measured in the present study was the observed maximum and minimum diameter of the CVC in a video containing three consecutive respiratory cycles. On the other hand, in awake people, it is more possible to control respiratory factors since the patient may be asked to control breathing at the time of the examination, which could improve the accuracy of the analysis in this species. In addition to respiratory factors, CVC can also be influenced by cardiac function, intra-abdominal pressure, patient recumbency, and artifact related to the application of pressure on the transducer in the animal, causing the vessel to collapse [2,6].

The CVC/Ao ratio at T1 <0.67 was the parameter that showed the best AUC value (0.68) and combination of sensitivity (73.33%) and specificity (71.43%) in the identification of responsive dogs. However, the CVC/Ao ratio at T0 <0.52 was the parameter that best predict fluid responsiveness with an AUC value of 0.66 (Table 2, Figure 2 and 3). Although these values are not so expressive, to the point that the use of the CVC/Ao ratio can be considered safe as a variable that infers on fluid responsiveness in the clinical practice, this index proved to be superior to the CVCCI. In a previous study with spontaneously breathing dogs, the superiority of the CVC/Ao ratio over the CVCCI was also verified in the discrimination of responsive and non-responsive individuals. However, the cited study obtained an AUC value for CVC/Ao ratio of 0.88 [25].

The superiority of the CVC/Ao ratio over the CVCCI may be related to its use in individuals of different sizes, which is an advantage in canine patients of varied breeds [18]. In addition, the diameter of the CVC was measured based on the surface ECG during atrial systole in all patients, allowing for greater standardization of this measurement compared to the visual measurement of the CVCCI. Finally, the CVC/Ao ratio is a static variable, while the CVCCI is a dynamic variable. Static parameters estimate the amount of fluid in the cardiovascular system at a given time

[17]. On the other hand, dynamic parameters infer on fluid responsiveness by inducing changes in pre-load, which can be done with a volume challenge or taking into account the changes that the systolic volume undergoes during respiratory movements [2]. The present study evaluated dogs under spontaneous breathing, it is possible that static variables are better in these circumstances, since in these individuals it is not possible to control respiratory movements.

Studies in veterinary medicine that assess fluid responsiveness in spontaneously breathing individuals are limited and contradictory. It has already been identified that blood donation does not seem to influence the CVCCI and the CVC/Ao ratio [18], but dogs in more advanced stages of mitral valve disease tend to have a reduction in the CVCCI [13]. A survey of 27 hemodynamically compromised dogs suggested that CVCCI accurately predicts fluid responsiveness. However, the authors themselves conclude that further studies are needed before this finding can be extrapolated to a larger population of dogs [9]. On the other hand, another article did not find satisfactory results in the use of the CVCCI, but supports the use of the CVC/Ao ratio [25]. One group of authors observed that in awake patients only a very large variation in the CVC diameter can identify the presence or absence of fluid responsiveness [21]. Finally, the studies that bring the most consistent and promising results from such indices are still those carried out in mechanically ventilated animals [2,3,19].

There are several ways to measure the CVC using different ultrasonographic windows, but there is still no standardization in the use of these techniques in veterinary medicine. In awake dogs, techniques that measure CVC by subxiphoid, paralombar and hepatic view have already been described [7], being that the latter was the method chosen in the present study. Possibly the CVC diameter is affected by the chosen ultrasound window. In a previous study it was observed that the hepatic view seems to be more influenced by respiratory movements compared to the paralombar view [8]. In addition, although the subxiphoid view is easily obtained, its interobserver variation appears to be greater. The authors justify this finding due to the influence of respiratory movements on the liver and diaphragm, in addition to the uncontrolled breathing [7]. Further studies are still needed so that is possible to identify the limitations and indications of each ultrassonographic window in the different groups of patients.

The intraobserver variation was smaller compared to the interobserver variation (Figure 4). The intraobserver and interobserver coefficient of variation of the variables studied were below 13 and 25, respectively (Table 4). In humans, it was observed a greater variation of CVCCI in healthy populations [11], compared to patients with CVCCI values outside established reference intervals [26]. Thus, it is possible that the variables involving the measurement of the CVC present different intra and interobserver variation in populations of dogs with hemodynamic instability.

The acquisition time of images and measurements was relatively fast. Research suggests that this technique can be easily used in the canine species [7], however, non-imaging veterinarians need to do specific training to measure CVC and abdominal aorta [2]. Although this technique has limitations when used in awake patients, it is possible that its longitudinal use in the same individual, performed always by the same operator, may be useful in the assessment of the volume status of hospitalized dogs. For more punctual evaluations, some echocardiographic indices have already been shown to be able to differentiate responsive and non-responsive dogs with good values of sensitivity, specificity, AUC and gray zone intervals [16,23].

There are several limitations of this study that must be considered when interpreting the results obtained. In addition to the factors already discussed regarding spontaneous breathing itself, fluid responsiveness can also be affected by the way the volume challenge is administered, such as the type of fluid and the dose chosen. Although abdominal ultrasound has several advantages in relation to its performance, veterinarians who do not have experience in this area need to receive specific training for the evaluation of CVC and abdominal aorta. In addition, this technique can be even more challenging in animals that are panting or have abdominal discomfort. A relatively small number of dogs were included in this study, so extrapolation of these findings to a larger population of individuals should be done with caution. Finally, only healthy dogs were selected, it is possible that animals with hemodynamic instability caused by different diseases will react differently in terms of fluid responsiveness.

4.5 CONCLUSIONS

In conclusion, the evidence that the CVCCI and the CVC/Ao ratio can differentiate responsive from non-responsive awake dogs was weak. Therefore, its use in the clinical practice alone may not be safe, especially when it comes to spontaneously breathing animals. It is possible that, in the future, the use of these techniques longitudinally and performed by the same operator may provide relevant information on the volume status of hospitalized patients, but more research is needed before the institution of this type of practice.

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 interest. The authors alone are responsible for the content and writing of paper.

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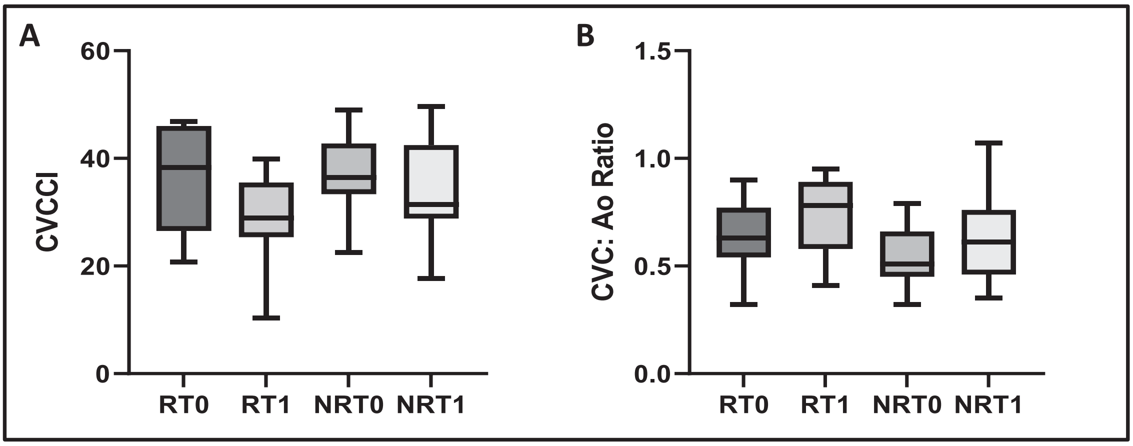

Figure 1. Box-plot graphs showing the minimum, maximum, median and interquartile range of the CVCCI (A) and the CVC/Ao ratio (B) in dogs classified as responsive (n = 7) and non-responsive (n = 15), before (T0) and after (T1) the volume challenge. Ao: aorta; CVC: caudal vena cava; CVCCI: caudal vena cava collapsibility index; NRT0: non-responsive time 0; NRT1: non-responsive time 1; RT0: responsive time 0; RT1: responsive time 1.

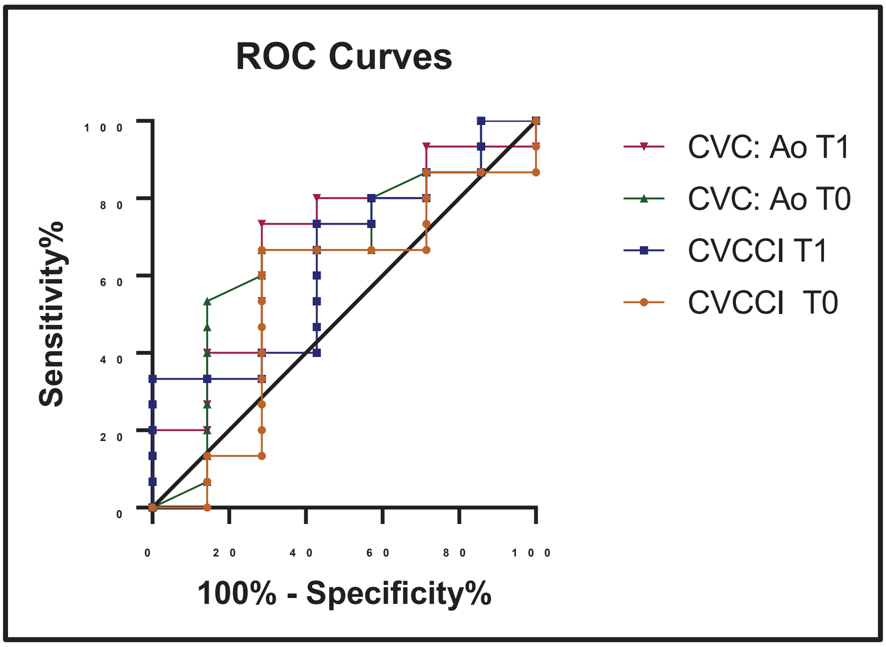

Figure 2. ROC curves and area under the curve (AUC) values of the caudal vena cava collapsibility index (CVCCI) and the caudal vena cava and aorta ratio (CVC/Ao), before (T0) and after (T1) the volume challenge, of dogs classified as responsive (N = 7) and non-responsive (N = 15).

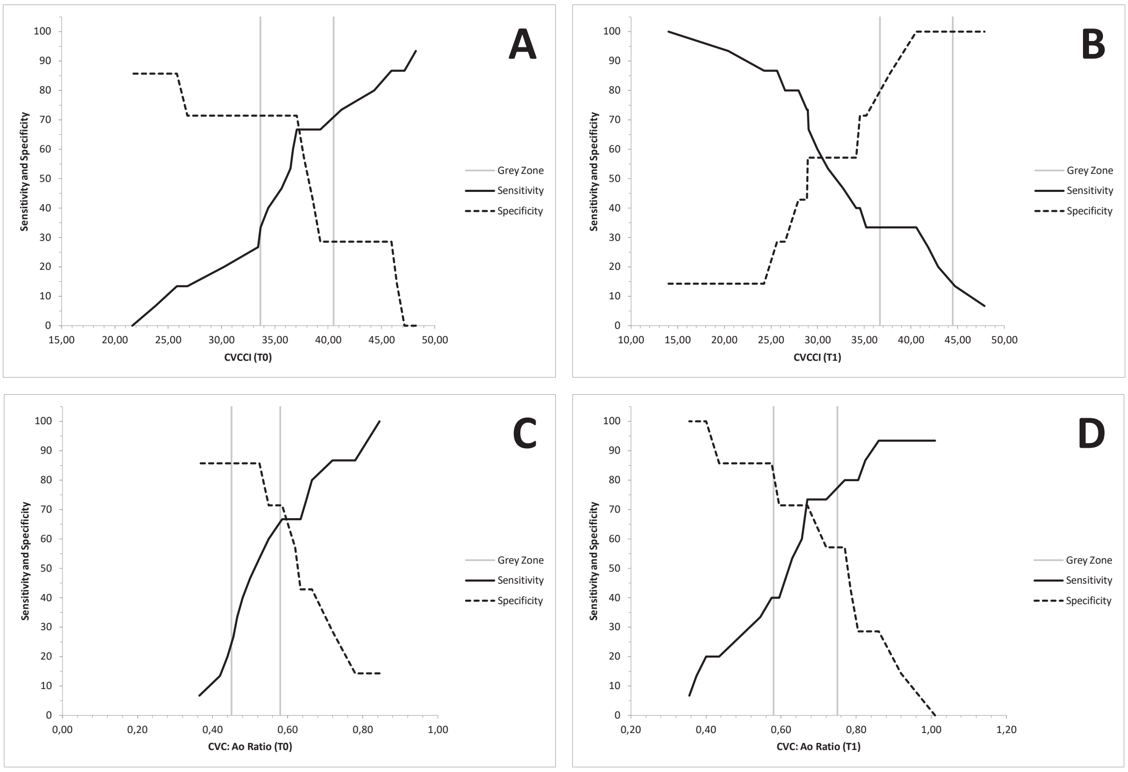

Figure 3. Sensitivity and specificity graphs with the gray zone interval demarcation of the caudal vena cava collapsibility index (CVCCI) (A and B) and the caudal vena cava and aorta ratio (CVC/Ao) (C and D), before (T0) and after (T1) the volume challenge, of the classified dogs as responsive (N = 7) and non-responsive (N = 15).

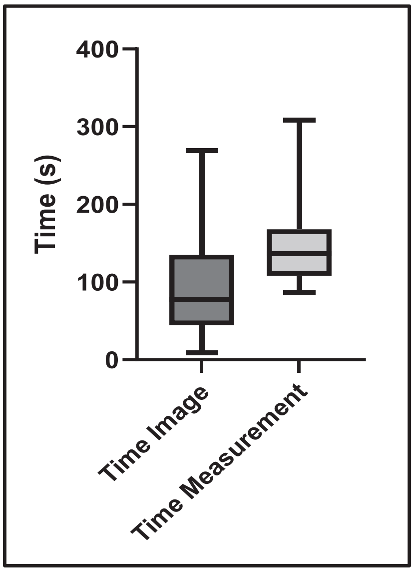

Figure 4. Box-plot graphs showing the minimum, maximum, median and interquartile range of the images and measurements acquisition time in seconds (s) for all dogs included in the study.

Table 1. Mean and standard deviation of the ultrasonographic variables studied in dogs classified as responsive (n = 7) and non-responsive (n = 15), before (T0) and after (T1) the volume challenge, as well as the P values of the comparisons analyzes between the groups studied.

Variables	Responsive		Non-Responsive	
	T0	T1	T0	T1
CVCCI	36.37 (± 9.62)[a]	28.77 (± 9.61)[a]	36.33 (± 7.81)	33.84 (± 9.05)
CVC/Ao	0.63 (± 0.18)	0.72 (± 0.18)	0.54 (± 0.13)	0.62 (± 0.19)

Comparisons	T0 vs. T1		Responsive vs. Non Responsive	
	Responsive	Non Responsive	T0	T1
CVCCI	0.0243	0.3120	0.9927	0.2436
CVC/Ao	0.0604	0.1876	0.2204	0.2526

The overwritten letters indicate the parameters that differed significantly from each other. CVC/Ao: caudal vena cava/aorta; CVCCI: caudal vena cava collapsibility index; T0: time 0; T1: time 1

Table 2. Cutoff values for identification of responsive dogs with their respective positive predictive value (PPV), negative predictive value (NPV), sensitivity, specificity, area under the curve (AUC), confidence interval (CI) of 95% and gray zone of the ultrasonographic variables studied.

Variables	Cutoff values	PPV	NPV	Sensitivity (%)	Specificity (%)	AUC IC 95%	Gray Zone
CVCCI T0	>37.08	0.50	0.83	66.67	71.43	0.55 (0.27 - 0.83)	33.55 - 40.50
CVCCI T1	>40.60	0.41	1.0	33.33	100	0.63 (0.38 - 0.88)	36.70 - 44.49
CVC/Ao T0	<0.52	0.46	0.90	53.33	85.71	0.66 (0.40 - 0.92)	0.45 - 0.58
CVC/Ao T1	<0.67	0.84	0.55	73.33	71.43	0.68 (0.44 - 092)	0.58 - 0.75

Table 3. Correlation coefficient r and P value of the ultrasonographic variables studied, before (T0) and after (T1) the volume challenge, regarding the age (months), body weight (Kg) and ∆VTI Ao of all dogs (N = 22) included in the study.

Variables	**Age (months)**		**Weight (Kg)**		**∆VTI Ao**	
	R	***P***	**R**	***P***	**R**	***P***
CVCCI T0	0.2072	0.3807	-0.0646	0.7751	-0.1158	0.6079
CVCCI T1	0.1409	0.5534	-0.1032	0.6477	-0.3387	0.1232
CVC/Ao T0	0.0184	0.9383	0.2595	0.2435	0.2439	0.2740
CVC/Ao T1	-0.3842	0.0944	0.3960	0.0681	0.4395	0.0407

Table 4. Coefficient of variation of the measurements used to calculate the CVCCI and the CVC/Ao ratio of the animals randomly selected for the interobserver and intraobserver analyzes (N = 10), before (T0) and after (T1) the volume challenge.

Variables	**Interobserver**		**Intraobserver**	
	T0	**T1**	**T0**	**T1**
CVC_{Max} (mm)	10.81	3.68	3.25	5.19
CVC_{Min} (mm)	17.11	8.41	7.39	5.43
CVCCI	24.33	16.58	12.45	12.36
CVC_{ECG} (mm)	14.9	7.78	5.12	6.43
Ao_{ECG} (mm)	5.21	4.46	4.23	3.46
CVC/Ao	18.55	12.04	7.53	7.79

5 CONSIDERAÇÕES FINAIS

Pesquisas de fluido responsividade em indivíduos sob respiração espontânea são escassas e contraditórias. No presente estudo, algumas variáveis ecocardiográficas convencionais e avançadas de avaliação da função sistólica ventricular esquerda e direita, se mostraram eficazes na identificação de fluido responsividade. Sendo que, algumas dessas variáveis foram eficientes mesmo antes da administração da prova de carga. Esse é o primeiro estudo a avaliar o coração direito, assim como índices de ecocardiografia avançada na predição de fluido responsividade em cães saudáveis respirando espontaneamente.

Por outro lado, as variáveis ultrassonográficas que envolvem a mensuração da VCC não se mostraram eficazes na diferenciação de cães classificados como responsivos e não responsivos. Algumas justificativas já foram propostas a esse achado, sendo que a própria respiração espontânea parece ser o maior limitador dessas técnicas. Cães com diferentes conformações torácicas e padrões respiratórios podem apresentar maior ou menor influência no colabamento da VCC. Além disso, em animais acordados é muito difícil realizar medida no momento exato do pico inspiratório ou expiratório. Tais fatores interferem diretamente na mensuração da VCC e nos índices obtidos através dessa mensuração. Por essa razão, os estudos que trazem resultados mais consistentes e promissores a respeito da VCC são aqueles realizados em animais sedados sob ventilação mecânica, onde é possível controlar os vieses da respiração.

Apenas 31.8% dos cães do presente estudo foram considerados responsivos após uma prova de carga. Teoricamente, indivíduos normovolêmicos e sem disfunção miocárdica deveriam ser responsivos em sua maioria. No entanto, são vários os fatores que afetam a fluido responsividade, desde o método utilizado para prova de carga até a própria respiração do paciente. Desse modo, ressalta-se a importância em se avaliar o estado volêmico de forma mais adequada e de se considerar a reposição volêmica como um tratamento medicamentoso, o qual possui suas indicações e benefícios, mas também é capaz de produzir efeitos deletérios quando não bem implementada.

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7 VITA

Médica veterinária graduada pela Pontifícia Universidade Católica do Paraná (PUCPR), campus São José dos Pinhais no ano de 2014.

Concluiu o Programa de Residência em Clínica Médica de Animais de Companhia, modalidade de pós-graduação "Lato sensu", nível I e II na Unidade Hospitalar de Animais de Companhia da PUCPR, no período de Fevereiro de 2014 a Fevereiro de 2016, totalizando 3520 horas.

Cursou a Especialização em Cardiologia Veterinária da Faculdade ANCLIVEPA (SP), no período de Agosto de 2016 a Dezembro de 2018.

Cursou o Programa de Pós-graduação em Ciências Veterinárias da Universidade Federal do Paraná (UFPR), nível Mestrado, no período de Março de 2016 a Março de 2018.

Cursou o Programa de Pós-graduação em Ciências Veterinárias da Universidade Federal do Paraná (UFPR), nível Doutorado, no período de Março de 2018 a Março de 2022.

8 ANEXOS

8.1 ANEXO I - CERTIFICADO DA COMISSÃO DE ÉTICA NO USO DE ANIMAIS (CEUA)

UNIVERSIDADE FEDERAL DO PARANÁ
SETOR DE CIÊNCIAS AGRÁRIAS
COMISSÃO DE ÉTICA NO USO DE ANIMAIS

CERTIFICADO

Certificamos que o protocolo número 058/2019, referente à pesquisa **"Uso de técnicas de imagem na avaliação de responsividade a fluidoterapia em cães saudáveis respirando espontaneamente"**, sob a responsabilidade de **Tilde Rodrigues Froes** – que envolve a produção, manutenção e/ou utilização de animais pertencentes ao filo Chordata, subfilo Vertebrata (exceto o homem), para fins de pesquisa científica ou ensino – encontra-se de acordo com os preceitos da Lei nº 11.794, de 8 de Outubro, de 2008, do Decreto nº 6.899, de 15 de julho de 2009, e com as normas editadas pelo Conselho Nacional de Controle da Experimentação Animal (CONCEA), e foi aprovado pela COMISSÃO DE ÉTICA NO USO DE ANIMAIS (CEUA) DO SETOR DE CIÊNCIAS AGRÁRIAS DA UNIVERSIDADE FEDERAL DO PARANÁ - BRASIL, com grau 2 de invasividade, em 02/10/2019.

Finalidade	Pesquisa científica
Vigência da autorização	Janeiro/2020 até Janeiro/2022
Espécie/Linhagem	*Canis lupus familiaris* (canino)
Número de animais	50
Peso/Idade	Variável/> 1 ano
Sexo	Macho e fêmea
Origem	Hospital Veterinário da Universidade Federal do Paraná, Curitiba/PR, Brasil.

CERTIFICATE

We certify that the protocol number 058/2019, regarding the research **"Use of image techniques in the assessment of fluid responsiveness in healthy spontaneously breathing dogs"** under **Tilde Rodrigues Froes** supervision – which includes the production, maintenance and/or utilization of animals from Chordata phylum, Vertebrata subphylum (except Humans), for scientific or teaching purposes – is in accordance with the precepts of Law nº 11.794, of 8 October, 2008, of Decree nº 6.899, of 15 July, 2009, and with the edited rules from Conselho Nacional de Controle da Experimentação Animal (CONCEA), and it was approved by the ANIMAL USE ETHICS COMMITTEE OF THE AGRICULTURAL SCIENCES CAMPUS OF THE UNIVERSIDADE FEDERAL DO PARANÁ (Federal University of the State of Paraná, Brazil), with degree 2 of invasiveness, in session of 02/10/2019.

Purpose	Cientific research
Validity	January/2020 until January/2022
Specie/Line	*Canis lupus familiaris* (canine)
Number of animals	50
Wheight/Age	Variable/> 1 year
Sex	Male and female
Origin	Veterinary Hospital of the Federal University of Paraná, Curitiba/PR, Brazil.

Curitiba, 02 de outubro de 2019

Chayane da Rocha

Coordenadora CEUA-SCA

Comissão de Ética no Uso de Animais do Setor de Ciências Agrárias - UFPR

8.2 ANEXO II - ARTIGO "CONVENTIONAL VS. ADVANCED ECHOCARDIOGRAPHIC PARAMETERS FOR PREDICTING FLUID RESPONSIVENESS IN HEALTHY DOGS" PUBLICADO NA REVISTA ACTA SCIENTIAE VETERINARIAE

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Conventional vs. Advanced Echocardiographic Parameters for Predicting Fluid Responsiveness in Healthy Dogs

Stephany Buba Lucina, Eloisa Muehlbauer, Vinícius Bentivóglio Costa Silva, Matheus Folgearini Silveira, Marcela Wolf, Julio Pereira dos Santos, Juan Carlos Duque Moreno, Marlos Gonçalves Sousa & Tilde Rodrigues Froes

ABSTRACT

***Background*:** Volume replacement is considered an essential component in the treatment of critically ill patients, but excess fluid administration can be as harmful as the lack of fluid therapy. Therefore, the volume replacement is only beneficial in patients deemed to be fluid responsive, that is, when the individual has an increase in their stroke volume after administration of a volume challenge. This study aim to assess whether conventional and advanced echocardiographic parameters for assessing left ventricular systolic function are able to predict 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*:** A prospective study was carried out in which 22 client-owned healthy dogs over 1 year of age that presented to the Veterinary Medical Teaching Hospital for elective neutering procedure were included. All dogs underwent conventional and advanced echocardiographic examination to obtain the left ventricular internal diameter in diastole normalized (LVIDDn), left ventricular internal diameter in systole normalized (LVIDSn), ejection fraction (EF) and shortening fraction (SF) according to the Teischholz methodology, global longitudinal strain (GLS) and tissue motion annular displacement (TMAD). There parameters were evaluated before and after administration of a volume challenge with 10 mL/kg lactate ringer intravenously for 20 min. Based on the variation in aortic velocity integral time, 31.82% of dogs were considered responsive and 68.18% were non-responsive to the volume challenge. For advanced echocardiography, TMAD indexed by body weight (mm/kg) > 0.89 ($P = 0.004$) and body surface area (mm/m^2) >18.9 ($P = 0.004$) after volume challenge had the best area under the curve values (both 0.895) and smaller gray zone intervals (0.52 - 0.81 and 14.89 - 17.88) for the identification of responsive dogs. Although, TMAD (mm/kg and mm/m^2) before volume challenge was also higher in the responsive dogs ($P = 0.041$ and $P = 0.029$). As for conventional echocardiography, the LVIDDn < 1.39 ($P = 0.003$) before volume challenge had the best area under the curve value (0.866) and the smallest gray zone interval (1.4 - 1.57) for the identification of responsive dogs. The GLS and the TMAD in milimeters (mm), percentage (%) and indexed by cubic root of weight (mm/$\sqrt[3]{kg}$) did not differ between the responsive and non-responsive dogs before and after volume challenge.

***Discussion*:** TMAD indexed by body weight (mm/kg) and body surface area (mm/m^2) before and after volume challenge and the LVIDDn before volume challenge may be useful measures to complement the assessment of fluid responsiveness in spontaneously breathing dogs. This is the first study to use TMAD as a predictive parameter for fluid responsiveness in healthy, spontaneously breathing, dogs. Even it is an advanced echocardiographic technique, TMAD has advantages in terms of execution time and the fact that it is less dependence on image quality or operator experience. It is possible that in the future such variables may form a useful part of the evaluation of fluid responsiveness in dogs. However, more studies are needed to better understand the applicability of these techniques, especially in dogs with hemodynamic changes.

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

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Department of Veterinary Medicine & Postgraduate Program in Veterinary Science (PRPPG), Federal University of Paraná (UFPR), Curitiba, PR, Brazil. CORRESPONDENCE: S.B. Lucina [teh.lucina@hotmail.com]. Agricultural Science Sector - UFPR. Rua dos Funcionários n. 1540. CEP 80035-050 Curitiba, PR, Brazil.