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# Quantification of myocardial stiffness using magnetic resonance elastography in right ventricular hypertrophy: initial feasibility in dogs

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ABSTRACT

*Introduction:* Myocardial stiffness is an important determinant of cardiac function and is currently invasively and indirectly assessed by catheter angiography. This study aims to demonstrate the feasibility of quantifying right ventricular (RV) stiffness noninvasively using cardiac magnetic resonance elastography (CMRE) in dogs with severe congenital pulmonary valve stenosis (PVS) causing RV hypertrophy, and compare it to remote myocardium in the left ventricle (LV). Additionally, correlations between stiffness and selected pathophysiologic indicators from transthoracic echocardiography (TTE) and cardiac magnetic resonance imaging were explored.

*Methods:* In-vivo CMRE was performed on nine dogs presenting severe congenital PVS using a 1.5 T MRI scanner. T1-MOLLI, T2-prepared-bSSFP, gated-cine GRE-MRE and LGE (PSIR) sequences were used to acquire a basal short-axis slice. RV and LV-free-wall (FW) stiffness measurements were compared against each other and also correlated to ventricular mass, RV and LV FW thickness, T1 and T2 relaxation times, and extracellular volume fraction (ECV). Peak transpulmonary pressure gradient and myocardial strain were also acquired on eight dogs by TTE and correlated to RV-FW systolic stiffness. Potential correlations were evaluated by Spearman's rho ($r_s$).

*Results:* RV-FW stiffness was found to be significantly higher than the LV-FW stiffness both during end-systole (ES) ($p = 0.002$) and end-diastole (ED) ($p = 0.029$). Significant correlations were observed between RV-FW ES and LV-FW ED stiffness versus ECV ($r_s$=0.75; p-value = 0.05). Non-significant moderate correlations were found between LV-FW ES ($r_s = 0.54$) and RV-FW ED ($r_s = 0.61$) stiffness versus ECV. Furthermore, non-significant correlations were found between RV or LV-FW stiffness and the remaining variables ($r_s < 0.54$; p-value > 0.05).

*Conclusion:* This study demonstrates the feasibility of determining RV stiffness. The positive correlations between stiffness and ECV might indicate some interdependence between stiffness and myocardial extracellular matrix alterations. However, further studies are warranted to validate our initial observations.

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## 1. Introduction

Myocardial stiffness is an important marker of myocardial performance in a variety of cardiac diseases [1–3]. To date, myocardial stiffness has been clinically assessed by catheter angiography using pressure–volume (P-V) measurements [2,4]. However, cardiac catheterization is an expensive and invasive procedure, with risk of complications, which limits its regular use in daily clinical practice [5]. For this reason, the development of noninvasive methods to accurately estimate intrinsic stiffness of the myocardium would be of great clinical interest.

Two-dimensional and Doppler echocardiography is the primary noninvasive imaging modality used for evaluation of cardiac function and anatomy [6]. Several echocardiographic parameters are clinically accepted as surrogates of intrinsic myocardial properties, for example, estimation of pressure gradients between cardiac chambers or through stenotic valvular lesions, and myocardial deformation analysis using tissue Doppler or speckle tracking imaging [7].

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Magnetic resonance elastography (MRE) is a novel noninvasive imaging technique that has been used to map the shear stiffness of soft tissues in different organs [8–11]. In MRE [12], cyclic mechanical waves are introduced in the region of interest, which are then tracked using a phase-contrast MR sequence. Subsequently, these wave images are mathematically processed to obtain spatial stiffness maps using an inversion algorithm [13]. Previous studies applying this technique to the heart have demonstrated changes in left ventricular (LV) stiffness over the cardiac cycle, showing good correlation with invasive pressure measurements [14,15]. The application of cardiac MRE (CMRE) to measure myocardial elastic properties has the potential to facilitate noninvasive assessment of myocardial dysfunction and relaxation abnormalities related to increased myocardial stiffness [16].

Other cardiac magnetic resonance (CMR) methods have recently been developed to allow quantitative analysis of myocardial T1 and T2 relaxation times [17,18]. An imaging-based measurement of extracellular volume fraction (ECV) using T1 relaxation times has also been proposed [19]. These intrinsic relaxation times and ECV measurements are altered in the presence of myocardial extracellular space modifications [18,20], with changes developing in proportion to connective tissue variation in the setting of myocardial infarction, hypertrophic cardiomyopathy, non-ischemic cardiomyopathy, aortic stenosis, and other pathologies causing focal and diffuse fibrosis [20–22]. T2 relaxation times are prolonged in conditions culminating with myocardial edema, such as from acute myocarditis or acute myocardial ischemic injury [23,24]. While previous studies have demonstrated that excess myocardial interstitial fluid or fibrosis cause increased myocardial stiffness [25,26], T1 and T2 relaxation times have not yet been correlated with either invasive or noninvasive measures of myocardial stiffness.

To the best of our knowledge, there have been no studies applying CMRE to quantitation of right ventricular (RV) stiffness. This is because the normal RV walls, in contrast to the LV, have just a few millimeters of thickness, precluding CMRE derived stiffness quantification using current techniques. To overcome this restriction, we enrolled a specific cohort of client-owned dogs diagnosed with congenital pulmonary valve stenosis (PVS), leading to prominent concentric RV hypertrophy (RVH) [27,28]. Since pathophysiological consequences related to PVS have been described in both humans and dogs, a naturally occurring animal model such as this might provide insight into the human disorder [27,29].

The aim of our study was to demonstrate the feasibility of quantifying RV free-wall (FW) stiffness using CMRE and correlate it against selected pathophysiologic indicators from echochardiography and CMR, in dogs with severe congenital pulmonary stenosis causing concentric RVH. In addition, we determine any significant difference in stiffness measurements between RV and LV-FW, where LV-FW is used as a remote myocardium for comparison.

## 2. Materials and methods

### 2.1. Animal preparation

In-vivo imaging was performed on nine client-owned dogs of different breeds presenting with severe congenital pulmonary stenosis (6 males and 3 females, age: 4 to 59 months, weight: 4 to 34 kg), in compliance with the Institutional Animal Care and Use Committee. All dogs were premedicated with acepromazine (0.04 to 0.10 mg/kg) and butorphanol (0.20 to 0.40 mg/kg) subcutaneously. A peripheral intravenous catheter was inserted into a cephalic vein and anesthesia was induced with an intravenous injection of ketamine (2.0 to 2.5 mg/kg) and propofol (2.0 to 2.5 mg/kg). The animals were orotracheally intubated and maintained under anesthesia using inhaled isoflurane (1.0% to 2.0%) in 100% oxygen with mechanical ventilation until the recovery phase. Transthoracic 2-dimensional and Doppler echocardiography (TTE) was performed under an identical anesthesia protocol in eight of these dogs within 24 hours of the CMR study. Breath-holds were performed during image acquisition by suspending mechanical ventilation.

### 2.2. TTE acquisition & analysis

TTE was performed using a digital cardiac ultrasound system (Vivid 7 Dimension with EchoPac software package, version BT09, GE Medical Systems, Waukesha, WI, USA) with transducer selection (4, 7, or 10 MHz nominal frequency) matched to the size of the dog and preset for optimal canine imaging. The dogs were positioned in right and left lateral decubitus and two-dimensional cine loops and Doppler echocardiography tracings were acquired with a simultaneous ECG by a single observer (BAS); all raw data were captured digitally for off-line analysis at a digital workstation. A TTE study was not performed in one dog due to concerns of anesthetic duration.

For evaluation of congenital pulmonary stenosis, continuous-wave Doppler tracings were recorded across the pulmonary valve from a right parasternal short-axis imaging plane and an average of 3 to 5 velocity profiles were measured for peak transpulmonary pressure gradient (PTPG) estimations using the modified Bernoulli equation ($\Delta P = 4\ V^2$) [30]. Particular attention was paid to correctly align the ultrasound beam parallel to flow direction to avoid underestimation of the PTPG.

Speckle tracking myocardial deformation analysis of the RV-FW was performed with proprietary speckle-tracking software (EchoPAC 2D Strain software, Q-Analysis (strain module), version 6.1, GE Medical Systems, Waukesha, WI, USA) using the left ventricular 2-chamber algorithm as recently reported in normal dogs [31]. Event timing for pulmonary valve opening and closure relative to the ECG was determined individually for each study by measuring a continuous wave Doppler recording of RV outflow ejection velocity. The region of interest for strain and strain rate measurement was defined by manually tracing the RV-FW endocardial border from the level of the tricuspid valve annulus to the RV apex with manual adjustments to incorporate the entire RV-FW myocardial thickness. Individual RV-FW segments (basilar, mid, apical) were then visually analyzed to assure adequate myocardial tracking by the software and manually adjusted if necessary. Global peak longitudinal strain and strain rate from the entire RV-FW (considered as a single segment and not a mean of the 3 segments) were then recorded as the maximal (most negative) systolic point on the respective global strain or strain rate curve prior to pulmonary valve closure. Each measurement for each dog was repeated in triplicate from 3 separate stored images and the average recorded (Fig. 1).

### 2.3. CMR acquisition & analysis

#### 2.3.1. CMR acquisition

CMR was performed using a 1.5-Tesla MRI scanner (Avanto, Siemens Healthcare; Erlangen, Germany), and a 12-channel phased-array coil (6 anterior elements plus 6 spine coil elements). Animals were placed into the scanner in the supine feet-first position. The following protocol was executed, with the imaging parameters for the sequences outlined in Table 1:

1. Breath-hold segmented balanced steady-state free precession (b-SSFP) cine imaging was performed in 8 to 12 contiguous short-axis planes to cover the RV.
2. ECG-gated gradient-recalled echo cine MRE sequence [32] was performed in a single basal short-axis slice. Mechanical waves were introduced into the heart using a pneumatic driver

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