

Standard Article

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Echocardiographic Assessment of Left Ventricular Function in Healthy Horses and in Horses with Heart Disease Using Pulsed-Wave Tissue Doppler Imaging

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Background: Assessment of left ventricular (LV) function by tissue Doppler imaging (TDI) is not well established in horses with heart disease.

Objectives: To describe the use of pulsed-wave (PW) TDI for the assessment of LV function, establish reference intervals, investigate effects of mitral regurgitation (MR), aortic regurgitation (AR), and primary myocardial disease (MD), and provide proof of concept for the use of PW TDI in Warmblood horses with heart disease.

Animals: Thirty healthy horses, 38 horses with MR, 25 with AR, 8 with MD.

Methods: Echocardiograms were retrospectively analyzed. Reference intervals were calculated. PW TDI indices of healthy horses and horses with MR, AR, and MD were compared by one-way ANOVA and Dunnett's test.

Results: A complete set of PW TDI variables could be obtained in 94 of 101 horses. Variables corresponding to isovolumic intervals were most difficult to measure. Valvular regurgitation influenced variables describing isovolumic contraction and ejection. Horses with MD had significantly shortened ET_m (-118.5 [-154.1 to -82.9] ms; mean difference [95% CI of difference of means]), increased PEP_m/ET_m (0.11 [0.05 to 0.17]), prolonged IMP_m (0.28 [0.18 to 0.37]), increased S_1 (8.9 [5.2 to 12.6] cm/s), and decreased E_1 (-2.6 [-4.7 to -0.5] cm/s), E_m (-14.2 [-19.9 to -8.5] cm/s), and E_m/A_m ratio (-1.6 [-2.6 to -0.6]).

Conclusions and Clinical Importance: Pulsed-wave TDI might be useful for detection of LV dysfunction in horses with primary MD. The clinical value of TDI in horses with MR and AR remains uncertain.

Key words: Aortic regurgitation; Echocardiography; Mitral regurgitation; Myocardial disease; Ventricular function.

Transthoracic echocardiography is considered a standard diagnostic procedure and is well established for evaluation of cardiac disorders in horses.^{1,2} The modalities routinely employed during a comprehensive echocardiographic workup include two-dimensional echocardiography (2DE), M-mode echocardiography (MME), and Doppler echocardiography (DE). These modalities allow subjective and objective assessment of cardiac structures and chamber dimensions and serve to describe and quantify the systolic functional characteristics of the left ventricle (LV). However, diastolic LV function and regional myocardial function are rarely

Abbreviations:

2DE	two-dimensional echocardiography
A_m	late-diastolic LV wall motion velocity at the time of atrial contraction
ANOVA	analysis of variance
AoD_{ed}	aortic (sinus) diameter at end diastole
AR	aortic regurgitation
BWT	body weight
CI	confidence interval
DE	Doppler echocardiography
E_1	LV wall motion velocity during the phase of isovolumic relaxation
E_m	early-diastolic LV wall motion velocity during the phase of rapid ventricular filling
ET_m	ejection time
HR	heart rate
IMP_m	index of myocardial performance
$IVCT_m$	isovolumic contraction time
$IVRT_m$	isovolumic relaxation time
LAA_{max}	maximum left atrial area measured at end systole
LAD_{max}	maximum left atrial diameter measured at end systole
LVEF	left ventricular ejection fraction
LVFS	left ventricular fractional shortening
$LVID_d$	internal diameter of the LV at end diastole
$LVID_s$	internal diameter of the LV at peak systole
LV	left ventricle or left ventricular
MD	myocardial disease
MME	M-mode echocardiography
MMVD	myxomatous mitral valve disease
MR	mitral regurgitation
MWT_d	mean wall thickness at end diastole
PAD_{ed}	pulmonary artery (sinus) diameter at end diastole
PEP_m	pre-ejection period
PW	pulsed wave
R^2	coefficient of determination
RWT_d	relative LV wall thickness at end diastole
S_1	LV wall motion velocity during the phase of isovolumic contraction
SD	standard deviation

Abbreviations:

2DE	two-dimensional echocardiography
A_m	late-diastolic LV wall motion velocity at the time of atrial contraction
ANOVA	analysis of variance

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considered and cannot be readily evaluated by these modalities.

Tissue Doppler imaging (TDI) is one of the more recent technological advances that allows quantitative characterization of regional wall motion velocities.^{3,4} Both in people and in small animals, the clinical applicability of TDI has been established and the modality has been successfully applied for the assessment of systolic and diastolic LV function and estimation of ventricular filling pressures.⁴⁻⁷ It might have diagnostic and prognostic implications in cats and dogs with cardiomyopathies⁸⁻¹⁰ and aid in the diagnosis of subclinical LV dysfunction in asymptomatic human patients with aortic and mitral regurgitation.¹¹⁻¹³

The feasibility, techniques, and reliability of TDI for characterization of LV radial wall motion in healthy horses have been investigated.^{14,15} The potential clinical use of TDI for the assessment of systolic and diastolic LV function in horses has been demonstrated in a case report describing impaired systolic and diastolic LV function and subsequent recovery in a horse with nutritional myodegeneration¹⁶ and in horses exposed to lasalocid.¹⁷ Furthermore, the use of TDI in horses has also been described for quantitative analysis of stress echocardiograms,¹⁸ for the assessment of left atrial mechanical function,¹⁹⁻²¹ for noninvasive measurement of atrial fibrillation cycle duration,^{22,23} and to investigate the influence of atrioventricular interaction on mitral valve closure and LV isovolumic contraction.²⁴

However, to date, reference intervals for TDI indices of normal LV systolic and diastolic function have not been reported in healthy horses. Furthermore, alterations of TDI variables in association with mitral regurgitation (MR), aortic regurgitation (AR), and primary myocardial diseases (MD) have not been described.

The goal of this study was to describe the use of pulsed-wave (PW) TDI for the assessment of LV function in a clinical setting, to establish normal reference intervals for a variety of PW TDI variables in a population of clinically healthy Warmblood horses, to investigate the effects of MR, AR, and primary MD on the respective variables, and to provide proof of concept for the use of PW TDI variables to assess abnormal systolic and diastolic LV function in horses with heart disease.

Materials and Methods

Study Population

The study population was composed of healthy horses and horses with cardiac disease that had been presented to the Equine Hospital of the Vetsuisse Faculty, University of Zurich, Switzerland, between 2007 and 2012. All horses had been examined by a single observer (CCS) according to a standard cardiovascular examination protocol.

Inclusion criteria were Warmblood breed, age >4 years, and the availability of a complete medical record and of digitally stored echocardiographic recordings that included pulsed-wave tissue Doppler tracings of the radial motion of the LV free wall at the chordal level. Furthermore, horses had to be healthy (based on medical history, physical examination, and complete routine

echocardiographic examination including two-dimensional, M-mode, and Doppler echocardiography) or had to be diagnosed with a primary disorder of MR, AR, or MD. Clinical diagnosis of MD was based on (i) exclusion of primary valvular, pericardial, and vascular disease and congenital malformations and (ii) the presence of two or more of the following findings: persistent sinus tachycardia (HR > 50 bpm) at rest that was not related to stress, excitement, pain, hypovolemia, electrolyte disorders, fever, anemia, or drug effects; ventricular ectopy; concentric LV hypertrophy (relative LV wall thickness at end diastole > 0.6) in the absence of volume depletion; decreased LV systolic function (LV fractional shortening < 30% based on 2DE and MME); and markedly increased plasma cardiac troponin I concentrations (cTnI > 0.25 ng/mL). Horses had to have a predominant sinus rhythm during echocardiographic examination. Horses with atrial fibrillation or with other cardiac comorbidities were excluded from the study. The majority of horses were examined without sedation. Of those that were examined under sedation, only 5 horses with MR were retained in the study population to assess the influence of sedation on TDI variables. In all other groups, the number of horses examined under sedation was too small for statistical comparison; these horses were therefore excluded from the study. The 5 horses included in the analysis had been sedated with detomidine^a only (10–20 mcg/kg IV) or with detomidine (20 mcg/kg IV) and butorphanol^b (10–20 mcg/kg IV) in combination.

Echocardiography

All echocardiographic recordings had been obtained by a single observer (CCS) according to previously described imaging standards^{14,18,19} and had been stored as still images or cine loops in digital raw data format.^c

Routine transthoracic 2DE, MME, and color DE had been performed prospectively by a single observer (CCS) to assess cardiac structures, valvular competence, chamber dimensions, and LV systolic function. Basic echocardiographic measurements of left atrial and left ventricular size and function and dimensions of the great vessels had been performed as described elsewhere.^{14,18,19} Grading of severity of MR and AR, respectively, was achieved by a scoring system taking into account the duration of the regurgitant signal, high-velocity jet area and flow disturbance, regurgitant signal duration, and the number of imaging planes in which the high-velocity jet could be observed in the receiving chamber.²⁵

The LV had been imaged in tissue velocity imaging mode^d by means of a right parasternal short-axis view at the level of the chordae tendineae.¹⁴ For the pulsed-wave TDI (PW TDI) recordings, a sample volume 5.9 mm in width at a frequency of 1.7/3.6 MHz (octave harmonics) had been used. The sample volume had been placed on the LV free wall so that it covered the subendocardial region during diastole and stayed on the myocardium throughout the cardiac cycle. The velocity scale had been set to a range of –30 to +20 cm/s. The simultaneous 2D image was frozen during the PW TDI recordings. Three separate still images and cine loop recordings, respectively, each containing at least 3 consecutive cardiac cycles, had been stored for each echocardiographic view. A single lead base–apex electrocardiogram had been recorded simultaneously.

For the purpose of this study, the PW TDI recordings were reanalyzed retrospectively by a single observer (TRK) blinded to group assignment. All measurements were performed on a dedicated computer workstation^d as previously described (Supporting Information, Figure S1).¹⁴ The outer edge of the strongest echo was measured at standard gain settings, and the sweep speed was set to 66.67 mm/s. Briefly, the following variables were measured: Systolic wall motion was characterized by the isovolumic contraction velocity (S_1), the ejection velocity (S_m), the pre-ejection period (PEP_m),

the isovolumic contraction time (IVCT_m), the ejection time (ET_m), the PEP_m/ET_m ratio, and the IVCT_m/ET_m ratio. Diastolic wall motion was characterized by the isovolumic relaxation velocity (E_1), the early-diastolic velocity during the phase of rapid ventricular filling (E_m), the late-diastolic velocity at the time of atrial contraction (A_m), the isovolumic relaxation time (IVRT_m), and the E_m/A_m ratio. The index of myocardial performance (IMP_m, Tei index) was calculated as $IMP_m = (IVCT_m + IVRT_m)/ET_m$.

Three representative, nonconsecutive cardiac cycles (i.e. one cycle in each of the three separately stored images) were measured, and individual measurements were subsequently averaged for further analyses. Cycles during marked transient tachycardia or immediately following a sinus pause, a 2nd-degree atrioventricular block or a cycle containing an ectopic beat, were excluded from analysis. In a subset of horses, cardiac cycles, or both, some components (i.e. velocity waves) of the PW TDI recordings were not clearly discernible. If this was the case, the respective components were not measured and measurements were termed missing.

Data Analyses and Statistics

Data analyses and statistics were performed by commercially available computer software.^{e,f,g}

Age, body weight, heart rate, and basic echocardiographic variables were summarized groupwise by mean and standard deviation (SD). Summary statistics for PW TDI indices in healthy Warmblood horses were calculated by mean, SD, and median, and the reference intervals were constructed as the interval between the 5th and the 95th percentile. The relationship of PW TDI indices to age and body weight, respectively, was assessed by linear regression analyses.

The basic echocardiographic variables and the PW TDI indices of healthy horses and horses with MR, AR, and MD, respectively, were compared by a one-way analysis of variance (ANOVA). When the *F*-test revealed significant differences between groups, Dunnett's posthoc test was used for pairwise comparison of the MR, AR, and MD group, respectively, with the group of healthy horses. The corresponding mean differences and 95% confidence intervals (CI) of the differences of means between groups were also calculated and reported.

For the assessment of the influence of sedation on PW TDI variables in horses with MR, sedated horses were compared to a subpopulation of 10 unsedated horses that were selected to match severity of MR, age, and BWT. Differences in PW TDI variables were assessed by an unpaired *t*-test, and the difference between means and the 95% CI of the difference of means between groups were reported.

Horses with MR and AR, respectively, were grouped according to regurgitation severity. Horses with trivial and mild regurgitation and horses with moderate and severe regurgitation, respectively, were pooled, and the groups were then compared to the group of healthy horses by a one-way ANOVA followed by Dunnett's posthoc test and corresponding mean differences and 95% CI of the differences of means between groups were calculated.

The level of significance was $P = .05$ for all statistical analyses.

Results

Demographics of the study population, resting heart rate, and basic echocardiographic measurements are summarized in Table 1.

The quality of the PW TDI recordings allowed offline analyses in the majority of horses and cardiac cycles. A complete set of PW TDI variables could be obtained in 94 of 101 horses. However, some components of the PW TDI tracings, including IVCT_m, S_1 , IVRT_m, and

E_1 , could not be consistently measured in all horses (Table 2).

The summary statistics and reference intervals of PW TDI variables obtained in clinically healthy Warmblood horses are shown in Table 3. Regression analyses indicated that none of the PW TDI variables was significantly related to age or body weight.

Table 4 provides an overview on PW TDI variables in healthy horses and in horses with MR, AR, and MD. The results show that PEP_m, PEP_m/ET_m, and S_1 were significantly increased in horses with MR compared to healthy horses, whereas only E_m was significantly decreased in horses with AR. Horses with myocardial disease had significantly shortened ET_m, increased PEP_m/ET_m, prolonged IMP_m, increased S_1 , decreased E_1 and E_m , and decreased E_m/A_m ratio.

The influence of sedation on PW TDI variables in horses with MR is shown in Table 5. The results show that PEP_m, PEP_m/ET_m, and IVCT_m/ET_m were significantly prolonged in the group of sedated horses compared to the unsedated horses matched for MR severity, breed, age, and BWT.

Tables 6 and 7 summarize the findings in horses with MR and AR, respectively, grouped according to severity of regurgitation. With the exception of S_1 , none of the PW TDI variables was significantly altered in horses with trivial and mild MR when compared to healthy horses. On the other hand, horses with moderate or severe MR had significantly prolonged PEP_m and IVCT_m, increased PEP_m/ET_m, IVCT_m/ET_m, and IMP_m, and increased S_1 . Horses with trivial or mild AR had significantly prolonged PEP_m, shortened ET_m, increased PEP_m/ET_m, IVCT_m/ET_m, and IMP_m, and decreased E_m . Horses with moderate or severe AR showed no significant alterations compared to healthy horses.

Discussion

This study provides reference intervals for PW TDI variables of LV radial wall motion in a population of clinically healthy horses and provides proof of concept for the use of PW TDI for clinical assessment of LV systolic and diastolic function, with particular value in horses with myocardial disease.

The population included in this study was limited to Warmblood horses, because this breed predominates the caseload of the University of Zurich's Equine Hospital. In most horses, adequate quality PW TDI data were obtained. However, there was a small number of horses in which measurements were not possible despite the evaluation of several still images with multiple cardiac cycles captured (Table 2). The most difficult measurements to obtain were those of the isovolumic time intervals (IVCT_m, IVRT_m) and the corresponding myocardial velocities (S_1 , E_1). The missing data are related to the short timing and relatively low velocity of isovolumic events and the influence of image quality, motion artifacts, and other individual patient factors, leading to a low signal-to-noise ratio. In previous studies evaluating the use of PW TDI and color-coded TDI measurements in horses, variables characterizing the

Table 1. Demographics of the study population and basic echocardiographic measurements. Continuous data are summarized as mean \pm SD. The differences between the groups with heart disease and the healthy group are reported as mean difference (95% CI of difference of means).

Variable	Unit	Healthy	Mitral regurgitation	Mitral regurgitation (sedated)	Aortic regurgitation	Myocardial disease	ANOVA P value
n		30	33	5	25	8	
Sex		12 f, 0 m, 18 mc	12 f, 1 m, 20 mc	2 f, 3 m, 0 mc	6 f, 1 m, 15 mc	3 f, 1 m, 4 mc	
Age	y	12 \pm 4	12 \pm 5	7 \pm 6	17 \pm 5*	17 \pm 7*	<.0001
BWT	kg	570 \pm 53	572 \pm 60	538 \pm 66	582 \pm 54	554 \pm 22	.114
HR	bpm	39 \pm 6	39 \pm 8	32 \pm 3	39 \pm 5	53 \pm 15*	.0001
PAD _{ed}	cm	6.8 \pm 0.5	-0.1 (-5 to 5)	6.4 \pm 0.5	7.4 \pm 0.7*	14 (7 to 22)	<.0001
AoD _{ed}	cm	7.9 \pm 0.6	-0.02 (-0.4 to 0.3)	-0.4 (-1.1 to 0.3)	0.6 (0.2 to 1.0)	7.3 \pm 0.4	
LAA _{max}	cm ²	101.1 \pm 9.0	8.0 \pm 0.6	7.4 \pm 0.6	8.2 \pm 0.6	0.4 (-0.1 to 1.0)	.0521
LAD _{max}	cm	12.4 \pm 0.8	0.03 (-0.3 to 0.4)	-0.5 (-1.2 to 0.2)	0.3 (-0.1 to 0.7)	7.8 \pm 0.5	
LVID _d	cm	11.5 \pm 0.9	111.1 \pm 19.2*	97.6 \pm 8.3	108.6 \pm 15.8	-0.1 (-0.7 to 0.5)	<.0001
LVID _s	cm	7.0 \pm 0.8	10.0 (0.6 to 19.3)	-3.5 (-21.3 to 14.4)	7.5 (-2.5 to 17.5)	-20.9 (-35.6 to -6.2)	<.0001
LVFS	%	40 \pm 5	13.1 \pm 1.3*	12.0 \pm 1.1	13.3 \pm 1.0*	11.3 \pm 0.9*	<.0001
RWT _d	cm	0.51 \pm 0.05	0.7 (0.04 to 1.3)	-0.4 (-1.6 to 0.8)	0.9 (0.2 to 1.6)	-1.1 (-2.1 to -0.07)	<.0001
MWT _d	cm	2.9 \pm 0.2	12.4 \pm 1.1*	11.1 \pm 0.7	13.3 \pm 1.8*	10.0 \pm 1.5*	<.0001
LAD _{max} /LVID _d		1.1 \pm 0.1	0.9 (0.1 to 1.7)	-0.4 (-1.9 to 1.1)	1.8 (1.0 to 2.6)	-1.5 (-2.7 to -0.2)	<.0001
			7.7 \pm 0.9*	7.6 \pm 1.0	7.9 \pm 1.1*	6.1 \pm 1.6	
			0.8 (0.2 to 1.5)	0.7 (-0.6 to 1.9)	1.0 (0.3 to 1.7)	-0.8 (-1.8 to 0.2)	
			38 \pm 4	33 \pm 7*	41 \pm 4	39 \pm 9	.0085
			-2.4 (-5.6 to 0.7)	-7.5 (-13.5 to -1.4)	0.6 (-2.8 to 4.0)	-1.2 (-6.2 to 3.8)	
			0.45 \pm 0.05*	0.54 \pm 0.11	0.46 \pm 0.08	0.75 \pm 0.20*	<.0001
			-0.06 (-0.1 to -0.008)	0.03 (-0.07 to 0.1)	-0.05 (-0.1 to 0.004)	0.2 (0.2 to 0.3)	
			2.8 \pm 0.2	3.0 \pm 0.7	3.0 \pm 0.3	3.7 \pm 0.5*	<.0001
			-0.2 (-0.3 to 0.03)	0.1 (-0.3 to 0.5)	0.07 (-0.1 to 0.3)	0.8 (0.5 to 1.0)	
			1.1 \pm 0.1	1.1 \pm 0.1	1.0 \pm 0.1*	1.1 \pm 0.1	.0105
			-0.02 (-0.08 to 0.04)	0.003 (-0.1 to 0.1)	-0.07 (-0.1 to -0.01)	0.06 (-0.04 to 0.2)	

BWT, body weight; f, female; m, male; mc, male castrated; HR, heart rate; PAD_{ed}, pulmonary artery (sinus) diameter at end diastole; AoD_{ed}, aortic (sinus) diameter at end diastole; LAA_{max}, maximum left atrial area measured at end systole, prior to opening of the mitral valve; LAD_{max}, maximum left atrial diameter measured at end systole, parallel to the mitral annulus; LVID_d, internal diameter of the left ventricle at end diastole; LVID_s, internal diameter of the left ventricle at peak systole; LVFS, left ventricular fractional shortening; RWT_d, relative wall thickness at end diastole [RWT_d = (IVS_d + LVFW_d)/LVID_d], where IVS_d is the interventricular septal thickness and LVFW_d is the left ventricular free wall thickness at end diastole; MWT_d, mean wall thickness at end diastole [MWT_d = (IVS_d + LVFW_d)/2]; LAD_{max}/LVID_d, LAD_{max}-to-LVID_d ratio. All measurements were obtained from right parasternal long-axis (great vessels, left atrium) or short-axis (left ventricle) imaging planes. Values marked by an asterisk are significantly different to values measured in healthy horses.

Table 2. Summary of missing measurements. The numerator depicts the number of horses and cycles, respectively, in which the respective variable could not be measured because the respective peak velocity, time interval, or both were not clearly discernible. The denominator depicts the total number of horses included in the study and the total number of analyzed cycles, respectively.

Variable	Horses	Cycles
	Number of horses in which variable could not be measured/total number of horses	Number of cycles in which variable could not be measured/total number of analyzed cycles
PEP _m	0/101 (0.0%)	7/303 (2.3%)
ET _m	0/101 (0.0%)	7/303 (2.3%)
IVCT _m	1/101 (1%)	28/303 (9.2%)
IVRT _m	5/101 (5%)	58/303 (19.1%)
S ₁	1/101 (1%)	34/303 (11.2%)
S _m	0/101 (0.0%)	8/303 (2.6%)
E ₁	6/101 (6%)	61/303 (20.1%)
E _m	0/101 (0.0%)	8/303 (2.6%)
A _m	0/101 (0.0%)	10/303 (3.3%)

PEP_m, pre-ejection period; ET_m, ejection time; IVCT_m, isovolumic contraction time; S₁, isovolumic contraction velocity; S_m, ejection velocity; IVRT_m, isovolumic relaxation time; E₁, isovolumic relaxation velocity; E_m, early-diastolic velocity during the phase of rapid ventricular filling; A_m, late-diastolic velocity at the time of atrial contraction.

isovolumic periods showed low-to-moderate variability and, in agreement with this study, they could not be measured in all horses and in all recorded cycles.^{14,18} These findings highlight the importance of optimizing

image quality and of capturing multiple sequential recordings containing several cardiac cycles to maximize the chances of obtaining diagnostic information. Furthermore, they emphasize the fact that isovolumic PW TDI variables should only be measured and interpreted if the corresponding velocity waves are clearly identified.

The reference intervals for PW TDI variables of LV radial wall motion (Table 3) provided in this study can serve as a basis for the assessment of PW TDI variables in Warmblood horses with heart disease. Previously reported measurement and recording variability and the inherent biologic variability of PW TDI variables¹⁴ should be taken into consideration when interpreting PW TDI measurements and drawing conclusions about altered LV systolic function, diastolic function, or both in individual cases.

In people, dogs, and cats, it is well documented that myocardial systolic function and diastolic function decrease with age, leading to a decreased S_m and E_m and increased A_m velocities.^{2,5,26-30} However, the present data did not reveal a significant influence of age on PW TDI variables in horses. While these findings might indicate species-related differences in regard to the aging process of myocardial function, it may simply be related to fact that 23 of the healthy horses included in the study population were aged ≤15 years and only one horse was older than 20 years (i.e., 23 years). Therefore, studies including a population of horses with a wider age range will be required to definitively characterize age-related changes of myocardial function in this species.

The clinical use of PW TDI for the assessment of LV mechanical function in horses with valvular regurgitation has not been previously described. In humans and

Table 3. Summary statistics and reference intervals of PW TDI variables obtained in clinically healthy, unsedated Warmblood horses (n=30).

Variable	Unit	Summary statistics				Linear regression			
		Mean	SD	Median	5th–95th Percentile	Age		Body weight	
						R ²	P value	R ²	P value
PEP _m	ms	121	14.1	119	96–149	0.005	.70	<0.001	.88
ET _m	ms	421	24.7	422	374–475	0.06	.18	0.06	.18
PEP _m /ET _m		0.29	0.033	0.28	0.24–0.36	0.004	.73	0.01	.56
IVCT _m	ms	87	12.3	88	65–107	0.01	.57	0.02	.45
IVRT _m	ms	52	14.5	49	36–90	0.09	.12	0.01	.55
IVCT _m /ET _m		0.21	0.031	0.21	0.15–0.26	<0.001	1.0	0.06	.21
IMP _m		0.33	0.050	0.32	0.25–0.42	0.03	.41	0.08	.16
S ₁	cm/s	9	2.7	9	6–18	0.06	.20	0.12	.071
S _m	cm/s	12	1.4	11	10–15	0.1	.077	<0.001	.87
E ₁	cm/s	8	2.4	7	4–13	0.06	.22	0.003	.80
E _m	cm/s	35	5.6	34	27–45	0.09	.11	0.003	.76
A _m	cm/s	12	3.1	11	8–20	0.05	.25	0.06	.19
E _m /A _m		3.1	0.77	3.0	2.0–4.6	<0.001	.90	0.05	.26

PEP_m, pre-ejection period; ET_m, ejection time; PEP_m/ET_m, PEP_m-to-ET_m ratio; IVCT_m, isovolumic contraction time; IVCT_m/ET_m, IVCT_m-to-ET_m ratio; S₁, isovolumic contraction velocity; S_m, ejection velocity; IVRT_m, isovolumic relaxation time; IMP_m (Tei index), index of myocardial performance, calculated as $IMP_m = (IVCT_m + IVRT_m)/ET_m$; E₁, isovolumic relaxation velocity; E_m, early-diastolic velocity during the phase of rapid ventricular filling; A_m, late-diastolic velocity at the time of atrial contraction; E_m/A_m, E_m-to-A_m ratio.

Table 4. PW TDI indices in healthy horses and horses with cardiac disease. All recordings had been obtained in unsedated horses. Values marked by an asterisk are significantly different to values measured in healthy horses.

Variable	Unit	Healthy n = 30	Mitral regurgitation n = 33	Aortic regurgitation n = 25	Myocardial disease n = 8	ANOVA P value
		Mean ± SD	Mean ± SD Mean difference (95% CI of difference of means)			
PEP _m	ms	120.5 ± 14.1	134.5 ± 20.8*	129.4 ± 22.0	116.4 ± 30.6	.022
ET _m	ms	420.5 ± 24.7	416.2 ± 42.2	417.1 ± 29.9	302.0 ± 68.6*	<.0001
PEP _m /ET _m		0.29 ± 0.033	0.33 ± 0.067*	0.31 ± 0.063	0.40 ± 0.132*	.0004
IVCT _m	ms	86.6 ± 12.3	99.4 ± 22.7	93.2 ± 24.6	95.8 ± 20.9	.11
IVRT _m	ms	52.4 ± 14.5	51.0 ± 15.4	48.8 ± 11.6	59.3 ± 31.1	.47
IVCT _m /ET _m		0.21 ± 0.031	0.24 ± 0.069	0.27 ± 0.22	0.33 ± 0.11	.068
IMP _m		0.33 ± 0.050	0.36 ± 0.086	0.34 ± 0.078	0.61 ± 0.21*	<.0001
S ₁	cm/s	9.1 ± 2.7	11.6 ± 2.7*	8.5 ± 2.3	18.0 ± 10.7*	<.0001
S _m	cm/s	11.6 ± 1.4	12.5 ± 1.9	12.4 ± 1.7	11.5 ± 2.8	.18
E ₁	cm/s	7.6 ± 2.4	7.8 ± 1.7	6.9 ± 2.3	5.0 ± 1.2*	.011
E _m	cm/s	34.6 ± 5.6	34.2 ± 5.2	30.3 ± 6.2*	20.4 ± 9.6*	<.0001
A _m	cm/s	11.9 ± 3.1	12.6 ± 4.3	12.8 ± 4.6	16.4 ± 8.3	.11
E _m /A _m		3.1 ± 0.77	3.0 ± 1.24	2.7 ± 1.13	1.5 ± 0.86*	.002
			-0.04 (-0.7 to 0.6)	-0.4 (-1.1 to 0.3)	-1.6 (-2.6 to -0.6)	

For legend, see Table 3.

Table 5. Influence of sedation on PW TDI variables in Warmblood horses with MR. Continuous data are summarized as mean ± SD. Indices that show significant differences are marked by an asterisk.

Variable	Unit	MR unsedated	MR sedated	P value	Difference between means	95% CI of difference between means
n		10	5			
Severity of MR		5 mild, 5 moderate	4 mild, 1 moderate			
Breed		WB	WB			
Age	y	6.9 ± 4.1	7.4 ± 5.9	.85	0.5	-5.1 to 6.1
BWT	kg	556 ± 47	538 ± 66	.55	-18	-82 to 46
HR	bpm	37 ± 6	33 ± 4	.21	-4	-10 to 2
PEP _m	ms	125.7 ± 20.9	156.4 ± 29.2	.034*	30.7	2.6 to 58.8
ET _m	ms	445.5 ± 29.3	419.8 ± 38.4	.17	-25.7	-64.0 to 12.6
PEP _m /ET _m		0.28 ± 0.045	0.38 ± 0.089	.016*	0.09	0.02 to 0.17
IVCT _m	ms	89.3 ± 23.4	118.6 ± 31.9	.063	29.3	-1.8 to 60.4
IVRT _m	ms	58.4 ± 17.7	53.2 ± 11.0	.56	-5.2	-24.0 to 13.6
IVCT _m /ET _m		0.20 ± 0.052	0.29 ± 0.091	.035*	0.09	0.007 to 0.16
IMP _m		0.33 ± 0.079	0.42 ± 0.111	.11	0.09	-0.02 to 0.19
S ₁	cm/s	10.1 ± 2.2	10.2 ± 2.8	.94	0.1	-2.7 to 2.9
S _m	cm/s	11.7 ± 1.4	10.4 ± 1.1	.099	-1.3	-2.9 to 0.3
E ₁	cm/s	8.7 ± 1.8	7.8 ± 2.0	.39	-0.9	-3.1 to 1.3
E _m	cm/s	33.9 ± 4.3	32.0 ± 6.5	.51	-1.9	-7.9 to 4.1
A _m	cm/s	13.0 ± 4.6	8.6 ± 1.8	.063	-4.4	-9.1 to 0.3
E _m /A _m		3.0 ± 1.2	3.8 ± 1.3	.25	0.8	-0.6 to 2.2

For legend, see Table 3.

Table 6. PW TDI measurements in Warmblood horses with mitral regurgitation of different severity. All horses were unsedated. The values marked by an asterisk are significantly different to the values in healthy horses.

Variable	Unit	Healthy n = 30	Trivial + mild MR n = 16	Moderate + severe MR n = 17	ANOVA P value
		Mean ± SD	Mean ± SD	Mean ± SD	
		Mean difference (95% CI of difference of means)			
PEP _m	ms	120.5 ± 14.1	128.6 ± 18.4	140.0 ± 21.8*	.0023
ET _m	ms	420.5 ± 24.7	416.8 ± 46.4	415.6 ± 39.2	.88
PEP _m /ET _m		0.29 ± 0.033	0.31 ± 0.060	0.34 ± 0.073*	.0043
IVCT _m	ms	86.6 ± 12.3	91.4 ± 24.0	106.8 ± 19.2*	.0018
IVRT _m	ms	52.4 ± 14.5	52.3 ± 14.5	49.8 ± 16.7	.84
IVCT _m /ET _m		0.21 ± 0.031	0.22 ± 0.063	0.27 ± 0.068*	.0018
IMP _m		0.33 ± 0.050	0.34 ± 0.082	0.38 ± 0.088*	.053
S ₁	cm/s	9.1 ± 2.7	11.3 ± 3.0*	11.8 ± 2.4*	.0026
S _m	cm/s	11.6 ± 1.4	12.4 ± 1.5	12.5 ± 2.2	.14
E ₁	cm/s	7.6 ± 2.4	8.2 ± 1.9	7.4 ± 1.4	.48
E _m	cm/s	34.6 ± 5.6	33.3 ± 6.0	35.1 ± 4.3	.60
A _m	cm/s	11.9 ± 3.1	12.6 ± 4.9	12.7 ± 3.1	.12
E _m /A _m		3.1 ± 0.77	3.1 ± 1.44	3.0 ± 1.05	.96
			0 (−0.7 to 0.7)	−0.1 (−0.8 to 0.6)	

For legend, see Table 3.

dogs with valvular regurgitation, it has been suggested that TDI might aid in the detection of subclinical LV dysfunction^{31–33} and the prediction of increased pulmonary capillary wedge pressure³⁴ and congestive heart failure.^{35–38} Detection of early subclinical LV dysfunction in horses may provide useful additional information, for example, when investigating horses with murmurs detected on prepurchase examinations or during the evaluation of horses with poor performance. Additionally, further stratification of myocardial function would be useful in clinical trials looking at treatments reducing or slowing the progression of valvular heart disease in horses.

It needs to be noted that TDI recordings for the assessment of LV function in humans and small animals are most commonly obtained from apical views, with the cursor placed at the mitral valve annulus, and therefore describe LV long-axis motion. In adult horses, true apical views cannot be obtained and adequate alignment of the Doppler beam with longitudinal mitral annular motion cannot be achieved. Therefore, TDI recordings for the assessment of LV function are usually limited to radial wall motion of the LV free wall at the chordal level that can be reliably assessed by standard short-axis views, allowing optimal alignment with wall motion.^{14–16,18} In dogs and cats, both longitudinal motion and radial motion have been studied and both

were considered diagnostically valuable.^{9,39} It is possible however, that long-axis and short-axis motion of the LV wall might be altered differently with various diseases such as AR and MR,⁴⁰ explaining some of the discrepancies found between this study and previous studies in humans and small animals. Importantly, loading conditions, heart rate, and sympathetic tone affect TDI variables, suggesting that TDI is associated with the same limitations as conventional echocardiography in evaluation of LV systolic and diastolic dysfunction.³⁵

In this study, only TDI variables characterizing the isovolumic contraction period (i.e., PEP_m, PEP_m/ET_m, IVCT_m, IVCT_m/ET_m, S₁, and IMP_m) were significantly altered in horses with MR compared to healthy horses. Changes in systolic time intervals were in agreement with those observed in people and small animals.^{2,41} In this respect, it is important to understand how isovolumic periods can be affected by valvular insufficiencies. Horses with early-systolic MR, starting before aortic valve opening, will not have a true isovolumetric period because of regurgitant flow into the low-pressure left atrium. Hence, if the regurgitant volume is sufficiently large, this will—in addition to potentially altered myocardial contractility—influence both the systolic time intervals and the myocardial velocities during this period. The time that is required to reach ejection

Table 7. PW TDI measurements in Warmblood horses with aortic regurgitation of different severity. All horses were unsedated. The values marked by an asterisk are significantly different to the values in healthy horses.

Variable	Unit	Healthy n = 30	Trivial + Mild AR n = 6	Moderate + Severe AR n = 19	ANOVA P value
		Mean ± SD	Mean ± SD	Mean ± SD	
		Mean difference (95% CI of difference of means)			
PEP _m	ms	120.5 ± 14.1	144.3 ± 20.9*	124.6 ± 20.6	.013
ET _m	ms	420.5 ± 24.7	388.2 ± 22.6*	426.3 ± 26.1	.0073
PEP _m /ET _m		0.29 ± 0.033	0.37 ± 0.054*	0.30 ± 0.055	.0003
IVCT _m	ms	86.6 ± 12.3	106.2 ± 27.9	89.1 ± 22.8	.070
IVRT _m	ms	52.4 ± 14.5	52.8 ± 19.8	47.6 ± 8.5	.48
IVCT _m /ET _m		0.21 ± 0.031	0.27 ± 0.072*	0.21 ± 0.064	.018
IMP _m		0.33 ± 0.050	0.41 ± 0.124*	0.32 ± 0.047	.018
S ₁	cm/s	9.1 ± 2.7	9.7 ± 1.5	8.1 ± 2.4	.28
S _m	cm/s	11.6 ± 1.4	12.3 ± 1.4	12.4 ± 1.9	.24
E ₁	cm/s	7.6 ± 2.4	7.6 ± 1.8	6.5 ± 2.5	.27
E _m	cm/s	34.6 ± 5.6	28.2 ± 6.9*	31.0 ± 6.0	.022
A _m	cm/s	11.9 ± 3.1	13.3 ± 4.5	12.7 ± 4.7	.65
E _m /A _m		3.1 ± 0.77	2.3 ± 0.93	2.8 ± 1.18	.19
			−0.8 (−1.7 to 0.2)	−0.3 (−0.9 to 0.4)	

For legend, see Table 3.

pressures will increase, and the early-systolic loss in LV volume will accelerate wall motion kinetics. This, at least partly, explains the prolonged systolic time intervals (i.e., PEP_m, PEP_m/ET_m, IVCT_m, IVCT_m/ET_m) and IMP_m as well as the faster S₁ seen in the horses with moderate-severe mitral regurgitation when compared with the healthy horses (Tables 4 and 6).

The ejection phase indices were not significantly altered in horses with MR, although a trend of faster S_m was observed. This is likely because of a combined effect of MR-related alterations in myocardial contractility and loading conditions, which depending on severity and stage of disease can either facilitate (decreased afterload and increased contractility related to increased preload) or impair LV ejection (loss of preload-reserve and decreased contractility because of myocardial remodeling and failure). The diastolic PW TDI indices did not indicate significant alterations in LV diastolic function in horses with MR.

In horses with AR, E_m was decreased compared to healthy horses. The ET_m was decreased, whereas PEP_m, PEP_m/ET_m, IVCT_m/ET_m, and IMP_m were increased in horses with trivial-to-mild (but not in moderate-to-severe) AR, indicating mild LV systolic dysfunction (Tables 4 and 7). The fact that none of the variables was significantly altered in horses with moderate-to-severe AR suggests that the clinical use of TDI for the

assessment of LV function in horses with AR may be limited. This seems to be in contrast to findings in people, where reduced S_m, E_m, and A_m and prolonged IVCT_m, IVRT_m, and IMP_m provide indices of subclinical LV dysfunction that may serve as prognostic indicators in asymptomatic patients with severe aortic regurgitation.^{11–13,42,43} However, it should be noted that classification of valvular regurgitation based on receiving chamber analysis of the regurgitant jet may not entirely reflect the hemodynamic status in individual horses. The average degree of LV enlargement reported in the study population of horses with AR was considered mild to moderate, and overall LV systolic function based on LVFS was not impaired (Table 1). Hence, the data suggest that the horses with moderate-to-severe AR included in this study still had preserved LV systolic function. In humans, depending on the chronicity and severity of disease, the remodeling process is a continuum, with concentric hypertrophy of the LV seen with patients that have AR with a preserved LV ejection fraction (LVEF) whereas eccentric hypertrophy was found in patients that have reduced LVEF.⁴⁴ When classified on the basis of severity of regurgitation, no difference in LV systolic or diastolic TDI variables is detected between groups of people with moderate or severe AR, whereas classification based on LVEF (preserved or reduced) shows marked differences in TDI

variables between the two groups.⁴⁴ Throughout the remodeling process, the degree of LV systolic and diastolic function may change with respect to relaxation, compliance, and recoil in response to changing wall thickness, LV volume, filling pressures, and other factors. While this is purely hypothetical, it might therefore be possible that the horses with moderate-to-severe AR included in this study were at a stage of LV remodeling that preserved LV function when assessed by TDI variables.

Overall, based on the current data, the clinical value of TDI in horses with MR and AR remains uncertain. It should also be taken into account that none of the horses included in the study was in congestive heart failure.

One of the most useful aspects of TDI in human and small animal echocardiography has been the ability to detect subtle systolic and diastolic myocardial dysfunction in patients with a wide variety of diseases including ischemic heart disease, dilated and hypertrophic cardiomyopathy, restrictive cardiomyopathy, and constrictive pericarditis.^{5-7,9,45-51} While myocardial diseases are considered uncommon and are rarely reported in horses, they might in fact be under-recognized because of the lack of established diagnostic methods.¹ Based on the current results, there is potential for TDI to identify LV dysfunction related to myocardial disease in horses. Previously, data from healthy horses for comparison were lacking, but the reference intervals described in this study can provide a starting point for recognition of LV diastolic dysfunction caused by these less commonly identified diseases. Previous reports indicate that TDI allows detection of systolic and diastolic LV dysfunction in horses with nutritional and toxic myocardial damage in horses.^{16,17} Although there were only a small number of horses diagnosed with primary myocardial disease in this study, the results provide further proof of concept for the use of PW TDI to detect LV systolic and diastolic dysfunction in horses with myocardial disease. Strikingly, the IMP_m , a composite index of systolic and diastolic LV function, was double that of healthy horses. This was the result of a markedly (and significantly) decreased ET_m and the slightly (but not significantly) increased $IVCT_m$ and $IVRT_m$ and indicated marked LV myocardial dysfunction in affected horses. Accordingly, PEP_m/ET_m was significantly increased in horses with myocardial disease compared to healthy horses, indicating impaired LV systolic function. It should be noted that a decrease in preload can also increase pre-ejection period and decrease LV ejection time,² causing alterations in systolic time intervals similar to those seen in this study. Indeed, horses with MD showed decreased LAD_{max} , LAA_{max} , and $LVID_d$ when compared to the healthy horses, indicating a decrease in preload. Similar findings, including increases in RWT_d and MWT_d that were related to the decrease in $LVID_d$, were previously reported in horses with marked hypohydration.⁵² However, increases in RWT_d and MWT_d were more pronounced in the present study, and none of the horses with myocardial disease were clinically volume-depleted at the time of

echocardiography. Therefore, decreased preload and LV pseudohypertrophy as a result of dehydration is unlikely to explain the results of this study. Heart rate must also be considered a confounding factor when assessing preload, with higher heart rates resulting in a shorter filling time for both the LA and LV. In fact, horses with myocardial disease had a higher heart rate during the echocardiography. Increases in IMP_m and PEP_m/ET_m were previously found in healthy horses with increased heart rates immediately after exercise,¹⁸ but the increases found in this study were more pronounced for the respective heart rates. Furthermore, $IVCT_m$ and $IVRT_m$ after exercise were not prolonged but showed a tendency to shorten.¹⁸ This suggests that the findings obtained in this study, while certainly influenced by increased heart rate and sympathetic stimulation, can largely be attributed to primary myocardial disease.

Doppler-derived transmitral flow velocities (E wave, A wave, E/A ratio, E-wave deceleration time, and deceleration slope) are commonly used in combination with TDI-derived wall motion velocities (E_m , A_m , E_m/A_m ratio) in humans and small animals for the assessment of diastolic LV function and filling pressures.^{2,5,6} However, PW Doppler recordings of transmitral flow velocities are difficult to obtain, are relatively unreliable, and may not be suitable to detect subtle changes in diastolic LV function in adult horses.^{16,19,20,53} Therefore, objective information about diastolic myocardial function of horses has historically been unavailable. With the use of TDI, evaluation of diastolic myocardial function is possible through measurement of E_m and A_m velocities and $IVRT_m$.^{14,16} In this study, the horses with myocardial disease showed a marked decrease in E_m with nonsignificant increase in A_m velocity and a resulting significant decrease in E_m/A_m ratio, suggesting impaired ventricular relaxation with a compensatory increase in left atrial booster pump function in an attempt to maintain cardiac output.^{2,5,6,45} This was not demonstrated in horses with MR and AR, respectively. The decrease in E_m cannot be explained by higher heart rate, as E_m has previously been shown to increase with tachycardia.¹⁸ As stated above, none of the horses with myocardial disease were clinically volume-depleted at the time of echocardiography, suggesting that the results can also not be explained by a decrease in venous return and preload. Therefore, the marked decrease in E_m and E_m/A_m ratio may in fact represent a hallmark of LV diastolic dysfunction in horses with myocardial disease. The only caveat might be the advanced age of the group of horses with myocardial disease and the potential influence of age on E_m , A_m , and other TDI variables. As discussed above, the data of this study are inconclusive concerning the influence of advanced age (i.e., age >15 year) on myocardial function in horses. But this should certainly be kept in mind when interpreting TDI recordings in older horses with suspected myocardial disease. Nonetheless, based on the current data, it seems unlikely that the alterations in PW TDI variables seen in horses with myocardial disease were solely age-related.

A few studies have addressed the influence of sedation on echocardiographic indices of cardiac size and

function.^{54–58} Alpha-2 agonists cause a reduction in heart rate, an increased incidence of 2nd-degree AV block, and a reduction in LV systolic performance. In horses with valvular regurgitation, they cause an increase in valvular regurgitant fraction related to drug-induced alterations in ventricular filling (preload) and systemic arterial pressures (afterload).

Only a small number of sedated horses with MR was evaluated in this study (Table 5). Unfortunately, a comparison of the findings in the same group of horses before and after sedation was not possible because of the retrospective nature of the study. Therefore, the PW TDI variables of the sedated horses were compared to a subgroup of normal horses that were selected to match severity of MR, breed, age, and body weight (Table 5). Based on the available data, there were significant differences in PEP_m , PEP_m/ET_m , and $IVCT_m/ET_m$ in sedated horses when compared to unsedated horses with MR. These findings support the current knowledge that sedation with detomidine (with or without butorphanol) suppresses LV systolic function, likely because of a combined effect on myocardial contractility, loading conditions, and heart rate.⁴¹ Generally, the data suggest that sedation should be avoided if possible or at least taken into consideration when PW TDI is used to assess LV systolic function in horses with MR.

In conclusion, this study documents the clinical use of PW TDI for assessing LV systolic and diastolic function in a population of healthy horses and horses with a variety of cardiac diseases. Variables corresponding to isovolumic intervals (i.e., $IVCT_m$, S_1 , $IVRT_m$, E_1) were most difficult to measure and could not always be obtained. Reference intervals for PW TDI variables of radial LV wall motion were established. Based on this healthy horse population, there was no evidence of age-related diastolic myocardial dysfunction as seen in humans and small animals. However, the age range of the available population was limited, and the data are therefore inconclusive concerning changes in LV function in horses with advanced age. When assessing LV systolic function in horses with MR, sedation with detomidine (with or without butorphanol) should be avoided where possible. Although some variables of LV function were altered in horses with valvular regurgitation, the clinical value of PW TDI in horses with MR and AR could not be well documented and remains uncertain at this time. However, the available data provide proof of concept for the use of PW TDI in the assessment of LV function in horses with primary MD, with particular emphasis on evaluation of LV diastolic function.

^c GraphPad Prism v6.03 for Windows, GraphPad Software, La Jolla, CA

^f SigmaStat/SigmaPlot 12.5, Systat Software Inc., Erkrath, Germany

^g Microsoft Office Excel 2013, Microsoft Corporation, Redmond, WA

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Off-Label Antimicrobial Declaration: The authors declare no off-label use of antimicrobials.

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Footnotes

^a Domosedan ad us. vet., Provet AG, Lyssach b. Burgdorf, CH

^b Alvegesic 1% forte ad us. vet., Virbac (Switzerland) AG, Glattbrugg, CH

^c GE Vivid 7 BTO4, GE Healthcare, Glattbrugg, Switzerland

^d EchoPAC Software v3.1.3, GE Healthcare, Glattbrugg, Switzerland

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Figure S1. Pulsed-wave tissue Doppler images of the left ventricular free wall, recorded at the level of the chordae tendineae, showing representative myocardial velocity waves (A) and time intervals (B).