Agreement between echocardiographic techniques in assessment of the left ventricular myocardial performance index in rabbits

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Objective—To report reference values and examine the agreement in the myocardial performance (Tei) index of the left ventricle (LVTI) as measured by tissue Doppler imaging (TDI), pulsed-wave Doppler imaging (PWD), and M-mode echocardiography in clinically normal rabbits.

Animals—26 clinically normal male New Zealand White rabbits.

Procedures—Echocardiographic examinations that included TDI, PWD, and M-mode echocardiography were performed. Rabbits were sedated by SC administration of ketamine and midazolam. Intraclass correlation coefficients (ICCs) were used to measure absolute agreement among the 3 echocardiographic techniques. Intraclass correlation coefficients were computed for values *a* and *b* and for the equation (a – b)/b used to determine LVTI; value *a* equals the sum of isovolumic contraction time, ejection time, and isovolumic relaxation time, and value *b* equals the left ventricular ejection time. Values of ICC > 0.75 indicated good agreement between 2 echocardiographic techniques.

Results—For value *a*, Pearson correlation coefficients between pairs of techniques were all high ($r \geq 0.7$). However, only the septal TDI and the lateral wall TDI had good agreement (ICC, 0.86). For value *b*, correlations were generally low with the exception of the correlation between the septal and the lateral wall TDI. For value *b*, TDI was the only technique with good agreement (ICC, 0.77). For LVTI, only TDI techniques had a significantly positive correlation. All the other correlations were close to zero with a paradoxic moderate negative correlation between PWD-determined LVTI and lateral wall TDI–determined LVTI.

Conclusions and Clinical Relevance—For LVTI, the absolute agreement was poor between all pairs of techniques. (*Am J Vet Res* 2009;70:464–471)

Traditional echocardiographic assessment of left ventricular diastolic function relies on Doppler patterns of mitral inflow. Transmitral velocities are directly related to left atrial pressure (preload) and independently and inversely related to ventricular relaxation. The use of mitral valve inflow patterns to assess diastolic function remains limited because mitral inflow patterns are highly sensitive to preload and can change dramatically with progression of diastolic dysfunction.[1]

Pulsed TDI can be used to quantify the velocity of myocardial wall and valve annulus motion. Variables obtained by TDI are more independent of preload and afterload than classic hemodynamic Doppler measurements.[2–4] In humans, pulsed TDI of the myocardial wall immediately adjacent to mitral annulus reflects systolic and diastolic left ventricular function in clinically normal subjects and in those with a wide number of cardiac diseases.[5–8]

The myocardial performance (Tei) index has become a widely used echocardiographic variable for the assessment of global systolic and diastolic function in humans with congenital and acquired cardiac disease. The major advantage of this index is that it is not age or heart rate dependent and does not depend on any geometric assumption.[9–11] The Tei index is calculated according to the equation (a – b)/b. Several studies[12–18] regarding LVTI data, which rely on more conventional

Abbreviations

ICC	Intraclass correlation coefficient
LVTI	Left ventricular myocardial performance (Tei) index
MME	M-mode echocardiography
PWD	Pulsed-wave Doppler imaging
TDI	Tissue Doppler imaging

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echocardiographic techniques, express values as mean ± SD. However, statistical analyses that establish more accurately relationships and agreement between echocardiographic techniques in clinically normal subjects and in those with several diseases are not well described.

The purpose of the study reported here was to provide reference values and examine the agreement for LVTI values measured by use of TDI, PWD, and MME in clinically normal New Zealand White rabbits. To our knowledge, such comparisons of the various echocardiographic techniques for assessing LVTI have not been reported. From a clinical point of view, it is important to establish whether the Tei index value is similar when evaluated via different echocardiographic techniques, particularly during follow-up of a group of patients. In routine patient evaluation, it is important to define cardiac function or dysfunction by use of accurate but also technically simple techniques. Because these techniques are substantially time-consuming, in daily practice, it is not usual or feasible to perform all of them.

Materials and Methods

Animals—The study was performed according to the Portuguese Law for Animal Welfare. Anesthetic and testing methods conformed to those outlined by the NIH.[19] Examinations were performed in 26 clinically normal male New Zealand White rabbits (*Oryctolagus cuniculus*) that were 16 to 18 weeks old and weighed 1.7 to 3.5 kg. Rabbits were free of signs of cardiovascular or respiratory tract disease and were determined to be clinically normal on the basis of a physical examination that included careful thoracic auscultation. Rabbits were housed in adequate cages in a controlled environment at temperatures of 20° to 25°C with 12 hours of light and 12 hours of dark/d. A commercial pellet diet and water were supplied ad libitum. The weight of each rabbit was recorded prior to anesthesia.

A combination of ketamine hydrochloride[a] (20 mg/kg) and midazolam[b] (2 mg/kg) was administered SC to each rabbit to minimize defensive movements and facilitate complete echocardiographic examination. The anesthetic combination allowed rabbits to breathe spontaneously. Recording was typically completed approximately 30 minutes after administration of ketamine and midazolam.

Echocardiographic studies—Transthoracic standard 2-dimensional MME, PWD, and color Doppler echocardiographic examinations were performed. The apical 4-chamber TDI of the mitral annulus was also included in the echocardiographic evaluation. The PWD of mitral inflow and left ventricular outflow and MME of mitral and aortic valves were also acquired in all rabbits. The examination was performed from right and left parasternal locations by use of an ultrasound unit[c] equipped with a variable-frequency (3.5- to 6.9-MHz) phased-array transducer. All measurements were recorded with simultaneous electrocardiography at a sweep speed of 100 and 200 mm/s for off-line analysis. Three representative cycles were measured, and a mean was calculated for each rabbit. All images were stored in the system for off-line analysis. Care was taken to maintain adequate contact while avoiding excessive pressure on the chest of rabbits. For the right and left parasternal views, rabbits were placed in right and left lateral recumbency over a gap in the tabletop through which the ultrasound probe was brought from below and placed on a shaved area on the cranial aspect of the lower portion of the right and left thoracic wall. Systematically, the echocardiographic approach started by MME acquisition, followed by PWD recording and finally TDI recording. Echocardiographic measurements were obtained from standard views.[20] Calipers were used to measure structures to the nearest millimeter by means of a leading-edge–to–leading-edge technique according to accepted echocardiographic standards for dogs.[20–22]

The right parasternal long-axis view with 2-dimensional guided MME was used for evaluation of several points of the mitral valve motion. In the same view, aortic and left atrial diameters were evaluated at the level of the aortic valve. These measurements were made from the leading edge of the first endocardial surface to the leading edge of the second endocardial surface. Doppler examinations were performed according to protocols established for dogs and cats.[23–25] Heart rate

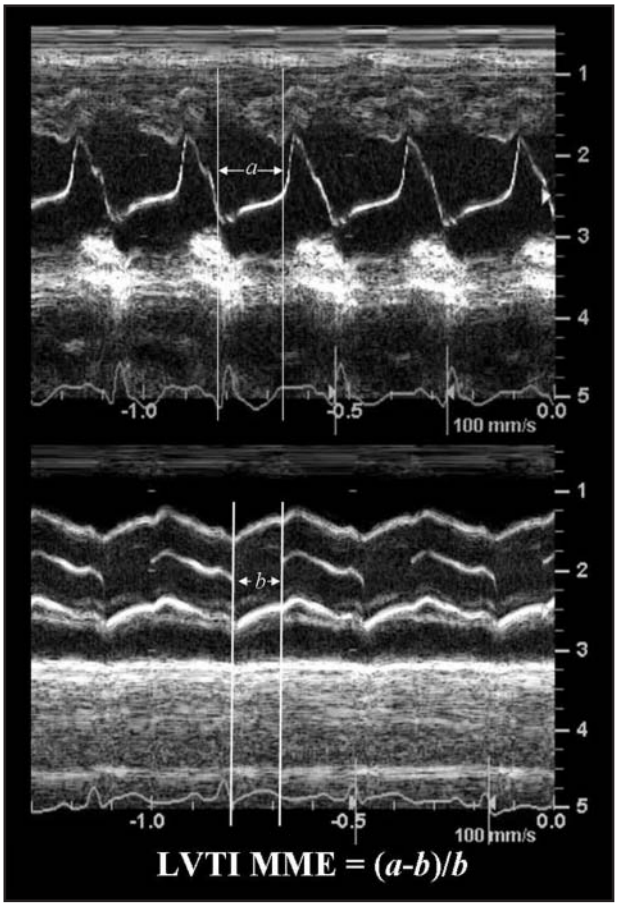

Figure 1—M-mode echocardiographic recording used to determine LVTI in a New Zealand White rabbit. Value *a* is measured from mitral valve closure to the following mitral valve opening. Value *b* corresponds to the interval between aortic valve opening and closure.

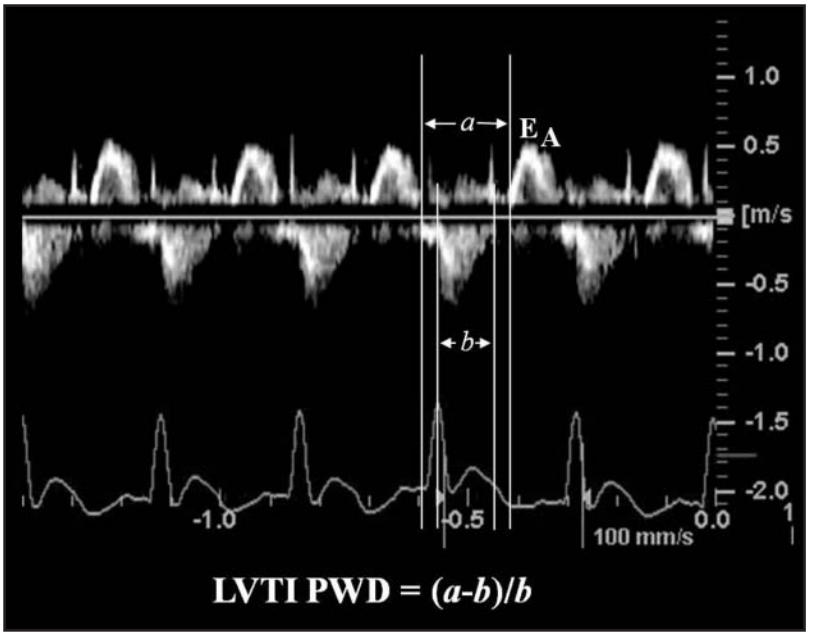

Figure 2—Pulsed-wave Doppler imaging recording used to determine LVTI in a New Zealand White rabbit. Value *a* is measured from the trailing edge of late diastolic transmitral PWD flow A wave to the leading edge of subsequent early diastolic transmitral PWD flow E wave. Value *b* is obtained by measuring the interval between the leading and trailing edges of left ventricular outflow systolic PWD tracing.

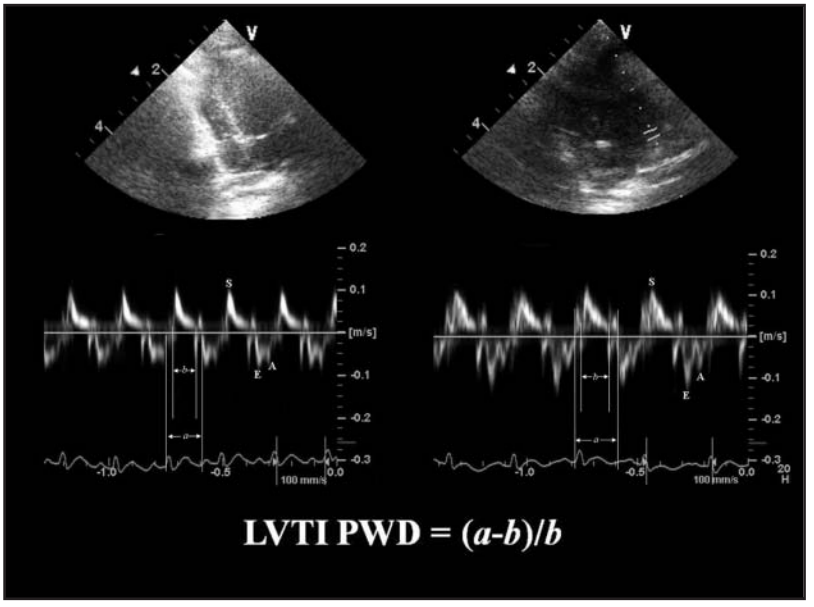

Figure 3—Tissue Doppler imaging recording of the interventricular septum (left panel) and left ventricular lateral wall (right panel) used to determine LVTI in a New Zealand White rabbit. Value *a* is measured from the trailing edge of late diastolic TDI mitral annular A wave to the leading edge of subsequent early diastolic TDI mitral annular E wave. Value *b* corresponds to the interval between the leading and trailing edges of the systolic TDI mitral annular S wave.

was calculated from MME, PWD, and TDI data. Aortic flow and mitral E- and A-wave velocities were recorded via PWD from the left parasternal apical 5-chamber view.[24] The sample volume was positioned between the aortic and mitral valves to allow simultaneous acquisition of the PWD tracings of the left ventricular inflow and outflow tracts. Alignment was maximized in the 2-dimensional view, and no angle of correction was used. Velocities were recorded as the maximal value on the outer edge of the peak velocity spectrum.[24]

Longitudinal velocities within the myocardium were recorded with TDI from the apical window with the pulsed mode. The sample volume (2 mm) was placed within a myocardial segment, and the spectral recording of velocities within the segment obtained. For optimal recording of tissue velocity, both gain and filter settings were set low. As recommended, the sample volume was placed at the junction of the left ventricular wall and the mitral annulus.[26] Recordings were made at the mitral annulus level both in the septum and in the left ventricular lateral wall.

Tei index evaluation—The LVTI was calculated as previously described.[11,14,16–18,26–28] For evaluation of TDI, PWD, and MME for determination of LVTI, a measurement technique previously described for humans was used.[15] For the 3 types of echocardiography, value *a* equals the sum of isovolumic contraction time, ejection time, and isovolumic relaxation time. Value *b* equals the left ventricular ejection time. The LVTI is calculated according to the equation (a – b)/b.

Value *a* for MME-determined LVTI was measured from mitral valve closure to subsequent mitral valve opening on the mitral valve MME tracing. Value *b* for MME-determined LVTI was measured from aortic valve opening to aortic valve closure on the aortic valve MME tracing (**Figure 1**). The MME recording was obtained from the standard parasternal long-axis view.

Value *a* for PWD-determined LVTI was measured from the trailing edge of the PWD late mitral A wave to the leading edge of the subsequent PWD early mitral E wave. Value *b* for PWD-determined LVTI was measured from the leading edge to the trailing edge of the left ventricular outflow tract PWD tracing (**Figure 2**).

Value *a* for TDI-determined LVTI was measured from the trailing edge of the mitral annular A wave to the leading edge of the subsequent TDI mitral annular early diastolic (E) wave. Value *b* for TDI-determined LVTI was measured from the leading edge to the trailing edge of the TDI mitral annular systolic (S) wave (**Figure 3**). Both TDI and PWD recordings were made from the standard apical view, and PWD acquisitions were made in the same cardiac cycle (ie, 5-chamber view).

Statistical analysis—Data were collected by use of a trackball-driven cursor[c] and the ultrasound sys-

tem software.[d] Measured heartbeats were selected on the basis of quality of the echocardiographic recording, quality of the ECG recording, and presence of a regular cardiac rhythm. Data were expressed as mean ± SD values for body weight, fractional shortening and ejection fraction (obtained from left ventricular MME tracing), heart rate (measured from PWD, MME, and TDI tracings), and LVTI acquisitions (obtained from 3 echocardiographic techniques).

Heart rates measured by use of PWD, MME, and TDI were compared by use of an ANOVA for repeated measures. Pairwise comparisons were conducted, and the level of significance was adjusted to 0.017 according to the Bonferroni correction.

Intraclass correlation coefficients were used to measure absolute agreement among the 3 echocardiographic techniques for obtaining LVTI. Intraclass correlation coefficients were computed for values *a* and *b* and for LVTI. Values of ICC > 0.75 indicated good agreement between 2 echocardiographic techniques. Bland-Altman plots were used as a graphic method to measure agreement. In these plots, both systematic and random differences between the techniques were determined.[29] Pearson correlation coefficients were also determined as a means to assess linear associations but not necessarily agreement among echocardiographic techniques. Analyses were performed by use of commercially available software,[e] and the ICC model chosen was the 2-way mixed model.

Results

Body weight was 2.25 ± 0.41 kg. Heart rates as calculated from MME, PWD, and TDI were 258.04 ± 37.34 beats/min, 261.07 ± 37.25 beats/min, and 248.69 ± 32.33 beats/min, respectively. Differences in heart rates among echocardiographic techniques were significant

Table 1—Intraclass correlation coefficients and Pearson correlation coefficients (*r*) for the comparison of each pair of techniques used to obtain value *a*, value *b*, and LVTI in 26 rabbits.

Comparison of techniques	Value *a*		Value *b*		LVTI	
	ICC	*r*	ICC	*r*	ICC	*r*
MME vs PWD	0.70	0.70	0.17	0.52	0.08	0.34
MME vs S TDI	0.54	0.72	0.30	0.46	–0.02	–0.05
MME vs LW TDI	0.56	0.74	0.25	0.43	–0.02	–0.07
PWD vs S TDI	0.59	0.87	0.43	0.54	–0.11	–0.17
PWD vs LW TDI	0.60	0.84	0.52	0.59	–0.40	–0.47
S TDI vs LW TDI	0.86*	0.87	0.77*	0.81	0.60	0.67

*Values of ICC > 0.75 indicated good agreement between 2 echocardiographic techniques.
S = Septal. LW = Lateral wall.

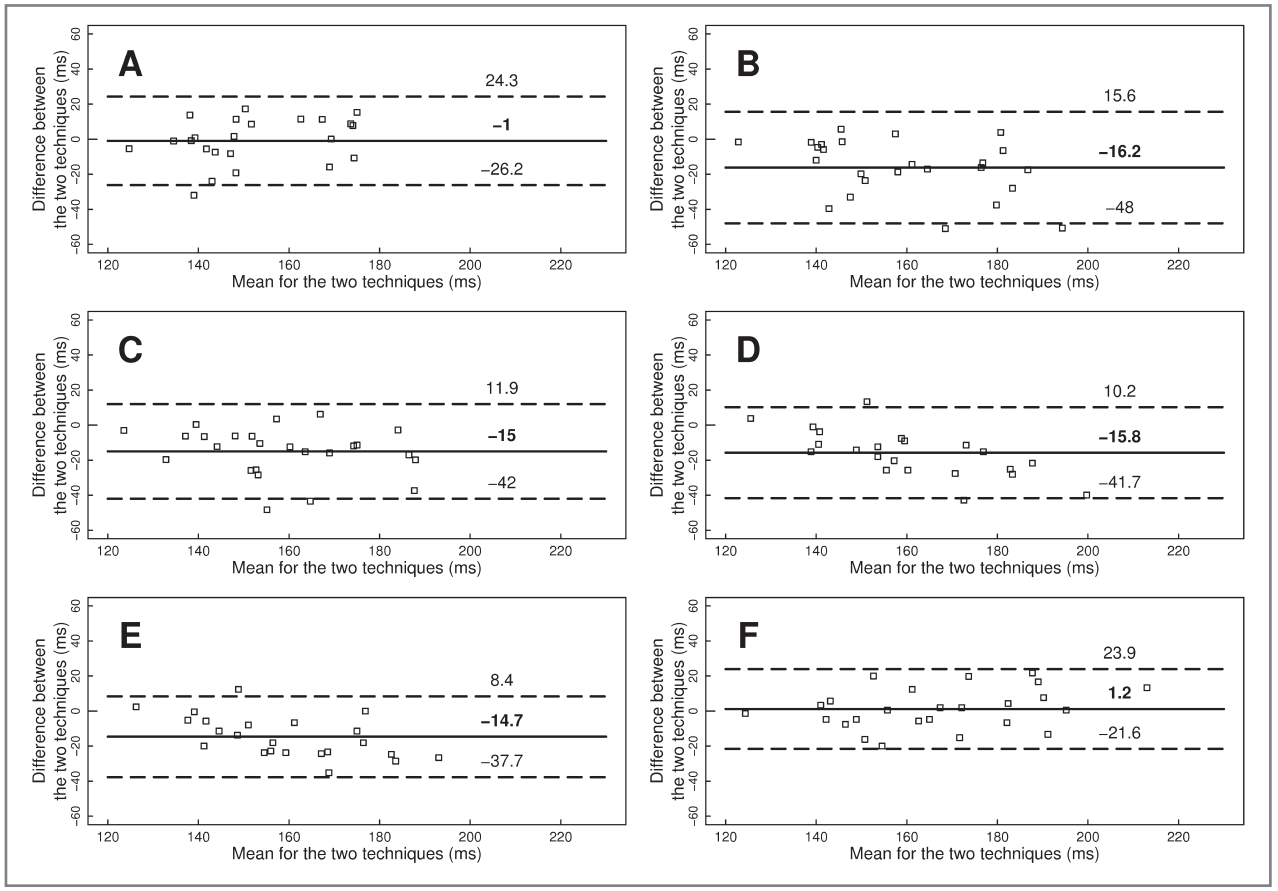

Figure 4—Bland-Altman plots representing agreement in the determination of LVTI value *a* between MME versus PWD (A), MME versus septal TDI (B), MME versus lateral wall TDI (C), PWD versus septal TDI (D), PWD versus lateral wall TDI (E), and septal TDI versus lateral wall TDI (F) in 26 rabbits. X-axes indicate mean value for each pair of techniques; y-axes indicate differences in values between techniques. Solid lines represent the mean bias given by the difference in mean values between each pair of techniques. Dashed lines indicate the 95% upper and lower limits of agreement.

(P = 0.012) for the overall test of equal means. Pairwise comparisons with Bonferroni correction revealed that only the difference between PWD-determined and TDI-determined heart rates was significant (P = 0.012). Fractional shortening and ejection fraction were 36.01 ± 4.31% and 69.58 ± 5.33%, respectively.

The MME-, PWD-, septal TDI–, and lateral wall TDI–determined LVTI reference values were 0.27 ± 0.15, 0.59 ± 0.10, 0.67 ± 0.23, and 0.64 ± 0.14, respectively. Echocardiographic acquisitions were made in sinus rhythm. Value *a* was obtained by MME, PWD, and TDI (left ventricular septal and lateral wall acquisitions). Pearson correlation coefficients between techniques were high ($r \geq 0.7$), indicating significant associations (**Table 1**). Only comparison of septal TDI with lateral wall TDI resulted in an ICC (0.86) for value *a* that was indicative of good agreement. Graphically, it was evident that although intervals of variation of differences among techniques had similar ranges (upper limits minus lower limits of approx 22 milliseconds), systematic differences among techniques were considerable (**Figure 4**). Measurements obtained by TDI (septal and lateral wall acquisitions) were a mean of 14 to 16 milliseconds higher than those obtained by MME and PWD. Bias between MME and PWD was identical to that obtained by septal and lateral wall TDI. Ranges for the limits of agreement were similar for all pairs of techniques.

Value *b* was obtained by MME, PWD, and TDI. Correlations were generally low with the exception of the correlation for value *b* between septal TDI and lateral wall TDI (Table 1). Only comparison of septal TDI with lateral wall TDI resulted in an ICC (0.77) for value *b* indicative of good agreement. Value *b* measured by MME was a mean of 20 to 24 milliseconds higher than that for other techniques (**Figure 5**). A small bias existed between PWD and both TDI techniques. The smaller range for the limits of agreement was obtained for PWD and lateral wall TDI (–29.7 to 19.7 milliseconds).

The LVTI data were obtained by MME, PWD, and TDI. Correlation for LVTI was significantly positive only between TDI techniques (Table 1). Correlations for LVTI between all other techniques were close to zero with a paradoxic moderate negative correlation between PWD-determined LVTI and lateral wall TDI–determined LVTI. For LVTI, absolute agreement was poor for all techniques. The highest ICC (0.60) for LVTI was obtained between the TDI techniques. The MME-determined LVTI was a mean of 0.3 to 0.4 milliseconds lower than LVTI determined by other techniques. Lateral wall TDI–determined and septal TDI–determined LVTI had a mean difference of zero (**Figure 6**). Potentially, a proportional error occurred in which, for lower values of LVTI, the lateral wall TDI measurements were higher than septal TDI measurements, and for higher values of LVTI, the septal TDI measurements were higher than

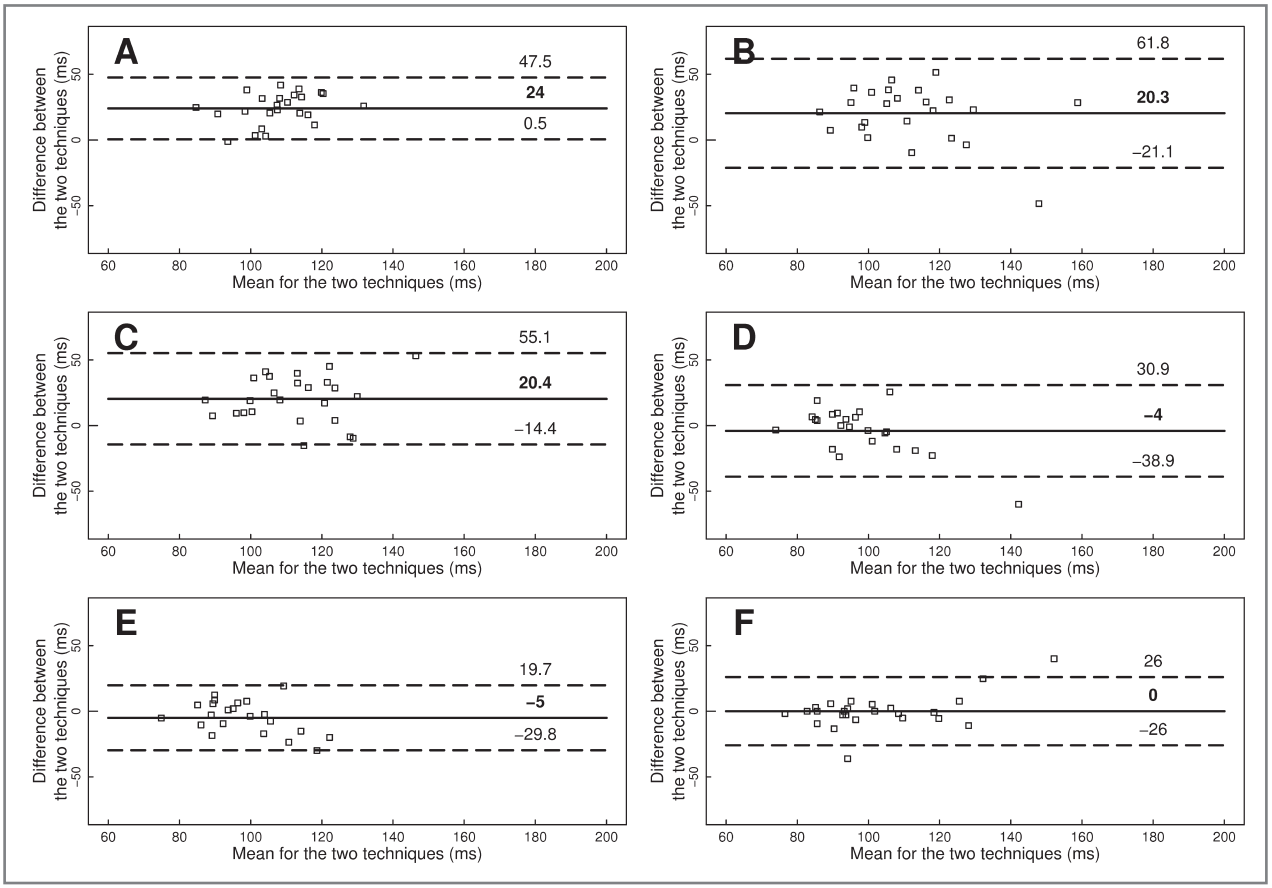

Figure 5—Bland-Altman plots representing agreement in the determination of LVTI value *b* between MME versus PWD (A), MME versus septal TDI (B), MME versus lateral wall TDI (C), PWD versus septal TDI (D), PWD versus lateral wall TDI (E), and septal TDI versus lateral wall TDI (F) in 26 rabbits. *See* Figure 4 for remainder of key.

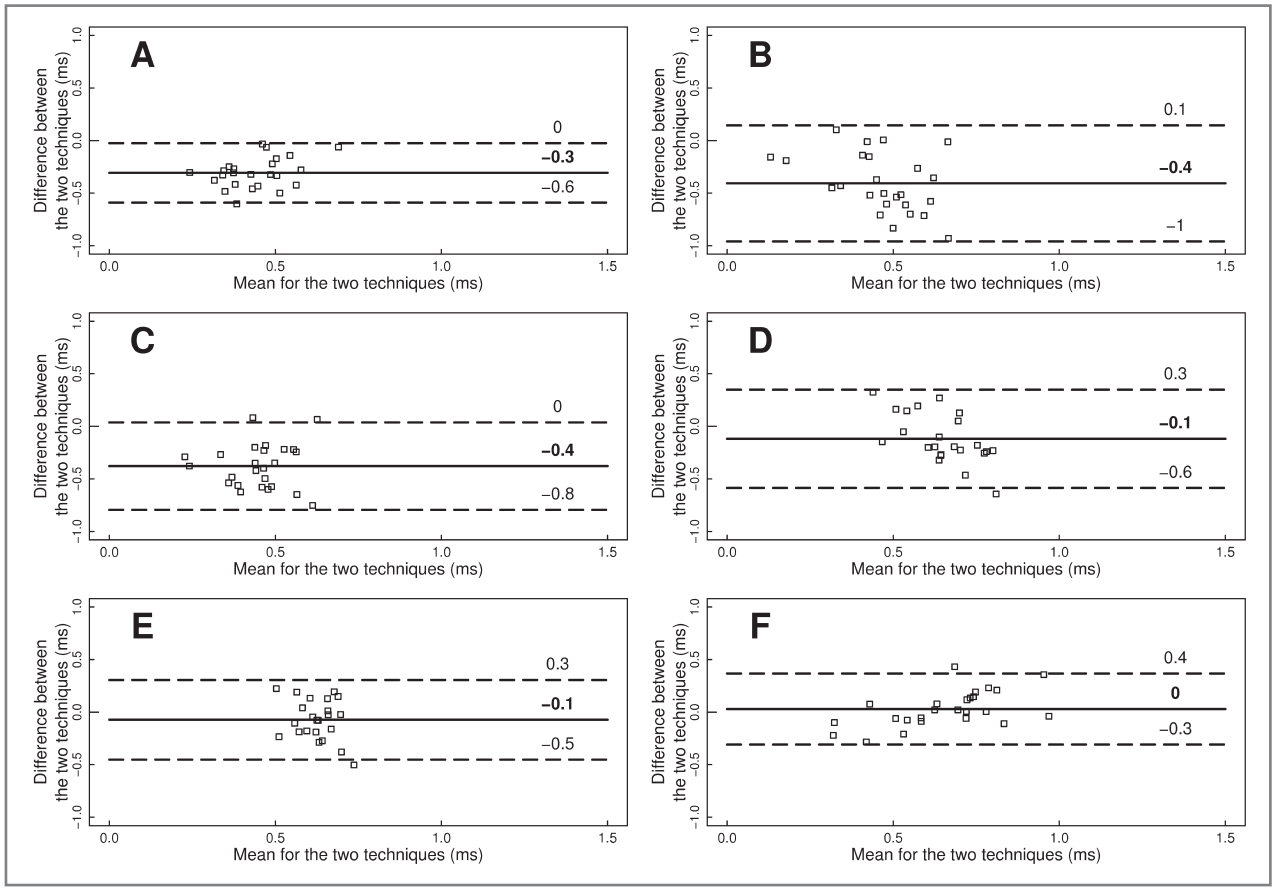

Figure 6—Bland-Altman plots representing agreement in the determination of LVTI between MME versus PWD (A), MME versus septal TDI (B), MME versus lateral wall TDI (C), PWD versus septal TDI (D), PWD versus lateral wall TDI (E), and septal TDI versus lateral wall TDI (F) in 26 rabbits. *See* Figure 4 for remainder of key.

the lateral wall TDI measurements. A linear regression on the means of the 2 measurements with the differences between the 2 as the predictor revealed a significant (r^2 = 0.36) slope.

Discussion

Results of the study presented here provide reference values for LVTI in New Zealand White rabbits and indicate that absolute agreement among LVTI values obtained by TDI, PWD, and MME is poor. The Tei index may be obtained by different echocardiographic techniques, according to the formula (a – b)/b. The Tei index as originally described[30] has 2 important limitations. One is that the interval between the end and the onset of mitral inflow and ejection time is measured sequentially (ie, not in the same cardiac cycle). The other limitation is that without measuring the individual isovolumic intervals, it cannot be determined whether the altered global function is mainly the result of systolic, diastolic, or combined dysfunction.[30] Critical discrepancies exist in LVTI obtained by use of the 3 echocardiographic techniques because they measure different time intervals for values *a* and *b* of the LVTI. Cui et al[15] found that measurement of MME value *a* begins at the same time as TDI value *a* but ends before TDI value *a* or PWD value *a*. Measurement of TDI value *a* begins after PWD value *a* and ends after PWD value *a*. Therefore, measurements of value *a* are similar for both TDI and PWD but smaller for MME. Measurement of TDI value *b* begins slightly before PWD value *b*, and measurement of TDI value *b* ends slightly before PWD value *b*. Measurement of MME value *b* begins at the same time as TDI value *b* but ends after TDI value *b* and PWD value *b*, resulting in a larger MME value *b* versus TDI value *b* and PWD value *b*. These acquisition differences, innate to each echocardiographic technique, cause the MME-determined LVTI to be lower than the PWD-determined LVTI or TDI-determined LVTI.

The PWD-determined LVTI measurements may require the use of different cardiac cycles to measure more accurately values *a* and *b* and define precisely the beginning and ending points. In these instances, even slight changes in heart rate between the time of evaluation of values *a* and *b* may be a source of error.[15] To overcome this problem, in the study presented here, PWD-determined LVTI acquisitions were performed in the same cardiac cycle, as previously reported.[26,31] Measurements of the ejection and isovolumic times can be achieved by PWD through an apical 5-chamber view. Nevertheless, the identification of the mitral and aortic profiles can be disturbed by valvular regurgitation and sample volume location.[32–34] In theory, measuring time intervals by use of myocardial velocities is not equivalent to the measurement of blood flow time intervals. Gaibazzi et al[14] found mild agreement between PWD-

determined and TDI-determined LVTI when used in a clinically normal human, which is not in total accordance with our results. When evaluated by use of only mean ± SD values, results were similar to ours. However, some differences in methods can, at least in part, explain these apparent discrepancies between the study findings. In the present study, values *a* and *b* for PWD-determined LVTI were obtained in the same cardiac cycle (5-chamber view), and ECG monitoring was used systematically to overcome some difficulties in the acquisition of the correct intervals. The use of the LVTI formula raises another problem because small variations in values *a* and *b* acquire much higher magnitude in the final value of LVTI.

Left ventricular dysfunction results in prolongation of isovolumic contraction time and isovolumic relaxation time with ejection time shortening. As a result, the LVTI is increased in patients with left ventricular dysfunction and is well documented for several diseases.[35,36]

In studies[15,17] in humans, mean MME-determined LVTI values were consistently and significantly less than LVTI values determined by TDI and PWD. Spencer et al[28] found some age-dependent changes in LVTI in a population of adult patients. In fact, results of previous studies[37,38] indicate that left ventricular ejection time may change with age. Others have also found significant prolongation of isovolumic relaxation time with age in clinically normal humans.[39–42] Cui et al[15] found no significant association between LVTI, as measured by any of the 3 echocardiographic techniques, and age or heart rate after controlling for the effect of body surface area. Our results indicate that the LVTI is inversely related with the heart rate. This is in agreement with the data reported by Robertson et al.[43]

Our results regarding values *a* and *b* of the LVTI formula are similar to those of other studies.[14,15] Mean ± SD of the LVTI is also in agreement with that in the literature.[14,15,44] Differences among the various techniques for LVTI data observed in the present study are presumably the result of several potential factors already discussed. On the basis of our findings, comparison of LVTI values obtained by different echocardiographic techniques should be interpreted with caution. The application of LVTI should probably be limited to the follow-up of a group of patients with the same echocardiographic technique to monitor the progression of cardiac function or dysfunction. Our results indicate that for LVTI, only the TDI techniques provided measurements that had a significant positive correlation. All the other correlations were close to zero with a paradoxic moderate negative correlation between PWD-determined LVTI and lateral wall TDI–determined LVTI. For LVTI, absolute agreement was poor for all the techniques. Lateral wall TDI–determined and septal TDI–determined LVTI had a mean difference of zero. Despite the potential proportional error for the septal versus lateral wall value of the LVTI, values *a* and *b* had good agreement. Of the various echocardiographic techniques, TDI-determined LVTI is probably the most precise, as values *a* and *b* are necessarily measured in the same cardiac cycle. In our study, values *a* and *b* for PWD-determined LVTI were obtained in the same cardiac cycle.

Intraobserver or interobserver variability was not evaluated in this study, which is a potential limitation. Nevertheless, results of a study[45] in dogs revealed that overall, the intraobserver measurements were highly repeatable. Additionally, it has been demonstrated that between 2 observers, there was an acceptable level of variation (< 20%) in the majority of 2-dimensional and MME measurements.[46] Chetboul et al[45] reported that for dogs, the intraexamination variability was better under anesthetized conditions. In conclusion, despite the discrepancies between the LVTI measurements obtained by use of different echocardiographic techniques, this myocardial performance index remains a potentially useful tool for serial evaluation of systolic and diastolic global ventricular function if its drawbacks and limitations are taken into account.

a. Imalgene 1000, Merial Portuguesa, Rio de Mouro, Portugal.
b. Midazolam APS, Farma—APS, Produtos Farmacêuticos SA, Lisboa, Portugal.
c. GE Vivid 7 system, GE VingMed Ultrasound, GE, Porto, Portugal.
d. GE EchoPAC workstation, version 3.2, GE VingMed Ultrasound, GE, Porto, Portugal.
e. SPSS, version 15, SPSS Inc, Chicago, Ill.

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