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Cardiac Tissue Doppler and Tissue Velocity Imaging in Anesthetized New Zealand White Rabbits

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New Zealand white rabbits are commonly used in cardiovascular research. Complete echocardiographic examination of the heart includes the evaluation of tissue Doppler (TDI) parameters, yet normal data are unavailable for rabbits. In addition, tissue velocity imaging (TV) is a potentially useful measure of myocardial function that has not yet been applied to rabbits. Anesthetized New Zealand white rabbits (n = 31) underwent echocardiography to establish the feasibility of performing TDI and TV and establishing corresponding reference values. Standard 2D, M-mode, and Doppler measurements were obtained in all rabbits and showed values comparable to previously published data. Interpretable TDI images were obtained in all 31 rabbits and TV in 24 of 31 rabbits. The values obtained were similar to those seen in healthy cats and are comparable to the values found in adult humans. TDI and TV can easily be added to standard echocardiographic evaluation in rabbits. The values from the current study, obtained in normal rabbits, can be used as reference values to improve characterization of cardiac disease in this species.

Abbreviations: A wave, transmitral peak flow velocity during atrial contraction; A′, peak late diastolic velocity of the wall at the mitral annulus; E wave, transmitral peak flow velocity in early diastole; E′, peak early diastolic velocity of the wall at the mitral annulus; E/A, ratio of transmitral flow; E′/A′, ratio between early and late diastolic velocity of the wall; E/E′, transmitral to early diastolic velocity ratio; S′, peak systolic velocity of the wall at the mitral annulus; TDI, tissue Doppler imaging; TV, tissue velocity imaging.

The New Zealand white rabbit is commonly used in cardiovascular research because several types of cardiac pathology, including atherosclerosis, can be elicited.[29] Starting from the original New Zealand strain of rabbits, several genetic variants have been identified, most notably Watanabe rabbits, which can develop atherosclerotic plaques even if fed low-fat diets, due to genetic abnormalities in lipid metabolism.[25,26] Due to the similarity to the lesions seen in humans, rabbits are often used in toxicology testing and for evaluation of drug effectiveness.[1,19,23] Therefore, the availability of reference values for cardiovascular diagnostic tests would be useful.

Echocardiography is frequently used as a primary diagnostic research tool in the assessment of cardiac performance. Reference values in rabbits for standard M-mode and Doppler images have been published.[9] However, studies using tissue Doppler imaging (TDI) and tissue velocity imaging (TV) have not yet been reported for rabbits. TDI is a reproducible echocardiographic tool that enables quantitative assessment of both global and regional function and timing of myocardial events.[18] TDI can evaluate myocardial function in systole by measuring peak systolic velocity at the mitral annulus (S′) in both the lateral and septal walls. In diastole, valuable parameters include peak myocardial early diastolic velocity measured at the mitral annulus (E′) and the ratio of transmitral flow to E′ (E/E′). Furthermore, the measurement of atrial contraction at the mitral annulus (A′) can be used with relation to the E′ to better ascertain diastolic myocardial function (E′/A′). These measurements with TDI have been shown to be useful in various diseases,[24] including heart failure, hypertension, and acute myocardial infarction.

TV provides similar information to that from TDI, but TV data are obtained from tracking individual speckles in the myocardium and measuring their displacement and the speed of motion. TV provides color-maps of cardiac movement by obtaining mean velocities of multiple left ventricular segments from the same set of beats[30] and therefore allows simultaneous estimation of systolic and diastolic performance. Several clinical uses for this technology and its derivatives (strain and strain rate) include cardiac synchronization imaging, primary myocardial disease progression and diagnosis in humans[7,11-13,15,20] and systolic and diastolic function measurements in animals.[4-6,8,16,21,22]

Because TDI and TV have not been evaluated in rabbits, the purpose of this study was to establish the feasibility of obtaining these measurements in anesthetized rabbits and to report reference values.

Materials and Methods

Approval for this study was obtained from the Institutional Animal Care and Use Committee at Michigan State University. Young healthy male adult SPF New Zealand white rabbits (n = 31) were obtained from a commercial vendor (Harlan Laboratories, Indianapolis, IN). These animals were tested periodically in the facility of origin by using ELISA, culture, PCR,

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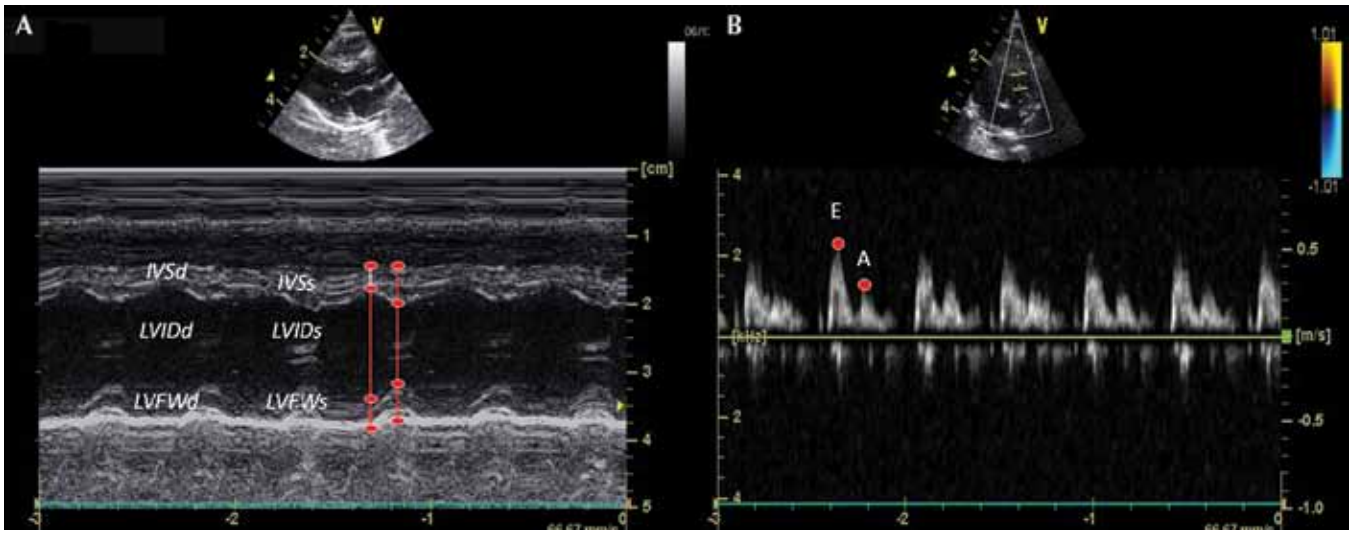

Figure 1. Conventional echocardiographic measurements obtained during the study. (A) Top: B-mode image obtained from parasternal long-axis view. Bottom: M-mode across RV and LV, with measurements of interventricular and free wall thickness in diastole (IVSd and LVFWd, respectively) and systole (IVSs and LVFWs, respectively), left ventricular internal diameter at end-diastole (LVIDd) and end-systole (LVIDs). B) Top: B-mode image obtained from an apical 4-chamber view. Bottom: Pulse wave Doppler imaging of flow across the mitral valve provides mitral inflow velocity patterns from which peak E and peak A waves and E/A ratio are derived.

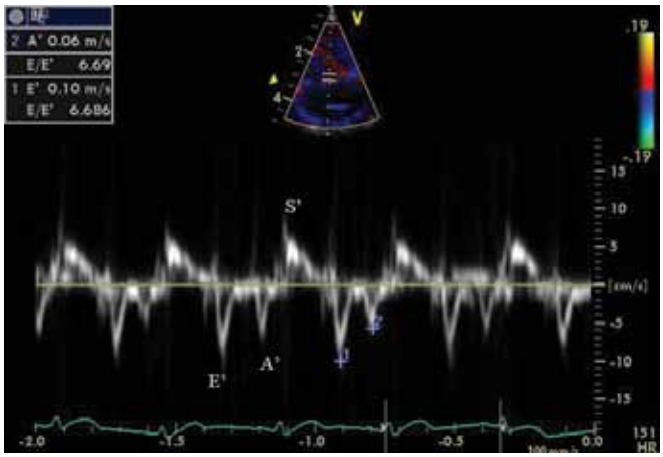

Figure 2. Apical 4-chamber view (top) with TDI obtained at the septal wall (bottom). Peak systolic (S′), peak early diastolic (E′), and peak late diastolic (A′) velocities are noted.

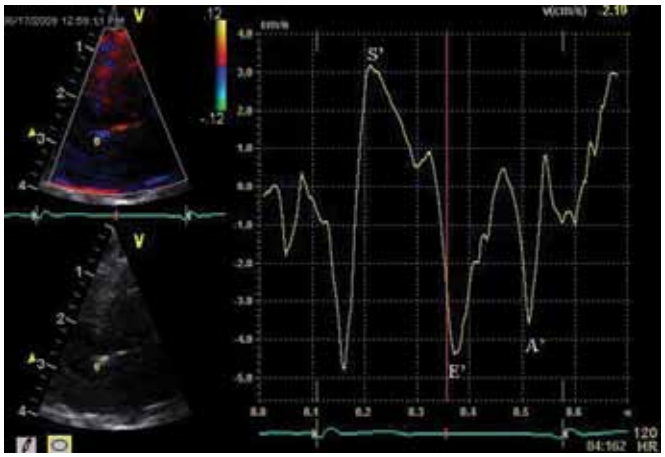

Figure 3. Apical 4-chamber view TV (upper left) with Q-wave analysis (right) obtained from a 1-mm sample area at the septal wall (yellow dot). Peak systolic (S′), peak early diastolic (E′), and peak late diastolic (A′) velocities are noted.

immunofluorescent assay, multiplex fluorescent immunoassay, pathology, and microscopy to confirm their status as pathogen free. Rabbits were tested for rabbit hemorrhagic disease virus, myxomatosis virus, rotavirus, fungi, *Mycoplasma* spp., *Bordetella bronchiseptica*, cilia-associated respiratory bacillus, *Clostridium piliforme*, *Corynebacterium kutscheri*, dermatophytes, *Helicobacter bilis*, *Helicobacter hepaticus*, *Helicobacter* spp., *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Pasterurella multocida*, *Proteus mirabilis*, *Proteus* overgrowth, *Pseudomonas aeruginosa*, *Salmonella* spp., *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Streptococcus* spp., *Toxoplasma* spp., *Treponema cuniculi*, ecto- and endoparasites, enteric protozoans, and *Encephalitozoon cuniculi*. Rabbits were housed in University Laboratory Animal Resources, an AAALAC-accredited animal care facility, in standard 62 × 42 × 76 cm (length × height × depth) stainless steel rabbit caging. The rabbits received husbandry, a standard high-fiber pelleted laboratory rabbit diet (High Fiber Rabbit Diet no. 2031, Harlan Teklad), tap water, and access to veterinary care. The room was maintained at 68 ± 4 °F (20 ± 2 °C) with 10 to 15 air changes hourly, 30% to 70% humidity, and a 12:12-h light:dark cycle.

On the day of the study, food was withheld for approximately 2 to 4 h to reduce abdominal distention and to facilitate obtaining the images. Ketamine (15 to 25 mg/kg IM; Ketaset, Fort Dodge Animal Health, Overland Park, KS) and xylazine (3 to 5 mg/kg IM AnaSed, Lloyd Laboratories, Shenandoah, IA) were used to anesthetized rabbits lightly during echocardiography.

All images were obtained with a Vivid 7 ultrasound system and a 7-MHz probe (General Electric, Milwaukee, WI). Three electrocardiographic leads were placed on a shaved area of the chest wall: one on the right and one on the left upper back midline to right axillary (equivalent); the third 2 in. below the lead on the right. Echocardiographic views were obtained from the right parasternal and left apical windows. Parasternal views were obtained with rabbits placed in dorsal recumbency and the probe positioned with cranial angulation over a shaved area on the lower portion of the thoracic wall. The exact positioning of the transducer was adjusted as necessary to acquire the standard views. For apical views, the transducer was moved slightly caudally and angled cranially. The mean of 3 measurements was obtained for each parameter.

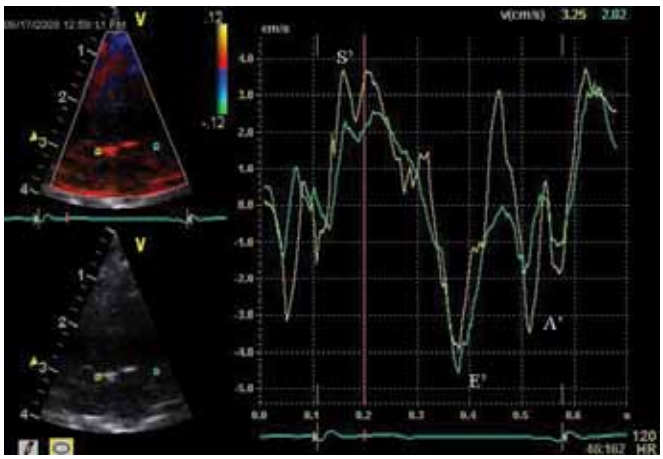

Figure 4. Apical 4-chamber view TV (upper left) obtained from a 1-mm sample area at the lateral wall (green dot) and septal wall (yellow dot) with overlapping Q-wave analysis of each wall (right). Peak systolic (S'), peak early diastolic (E'), and peak late diastolic (A') velocities are noted.

Conventional echocardiography. Echocardiographic measurements by both 2D and M-mode were obtained in the parasternal right axis views (Figure 1 A). These included interventricular and left ventricular free-wall thickness in diastole and systole and left ventricular internal diameter at end-diastole (LVIDd) and end-systole (LVIDs). The aortic root and left atrial diameter measurements were obtained by the 2D images at the heart base, from the short axis, right parasternal view. The left atrial to aortic root ratio then was calculated. Fractional shortening was computed by using the equation [(LVIDd – LVIDs) / LVIDd] × 100% and ejection fraction was calculated by using the Teichholz formula.[27]

Doppler imaging of the mitral valve and aortic valve were obtained from the apical 4-chamber view and the apical 5-chamber view, respectively. From the mitral inflow velocity image, the following measurements were obtained: peak E and peak A waves, E to A ratio, E-wave acceleration and deceleration times (Figure 1 B).

TDI. Electrocardiography was recorded continuously as images were obtained. Images were obtained and stored for analysis by using the offline Echo-PAC system (General Electric). TDI was performed from an apical 4-chamber view with very low 2D gain to maximize visualization of the endocardial and epicardial borders and color Doppler superimposed on grayscale. A 5-mm tissue sampling volume was obtained at the mitral annulus from both septal and lateral walls. To minimize the angle of insonation and improve the accuracy of TDI and TV, the ventricular walls were aligned with the beam during data collection.

From the acquired images, the following diastolic function parameters were measured: E', A', E' to A' ratio, and E to E' wave ratio; the systolic parameter measured was S' (Figure 2).

TV. TV was analyzed from the apical 4-chamber view at the GE Echopac7 (General Electric) workstation after the images had been acquired. On the apical 4-chamber view, by using the Q-Analysis program (General Electric), a 1-mm circular sample area was placed at the mitral annulus of the lateral wall, and minimal adjustments were made to obtain the clearest possible waveform (Figure 3). The same process was repeated for the septal wall (Figure 4). The resulting waves were analyzed for velocity, timing, and peak-to-peak gradients for E', A', and S'.

Statistics. For all parameters, the mean of 3 separate measurements was calculated. Mean, 1 SD, and coefficient of variation (expressed as a percentage) as descriptive statistics were used to summarize the echocardiographic values. Therefore, all descriptive values were given as mean ± 1 SD. The coefficient of variation was used in this study to assess the variation across rabbits (within day). Analysis of the data prior to calculation of reference range showed normal distribution. Reference ranges were calculated by using 2-sided 95% confidence interval. For the gradients (E' lateral to E' septal, A' lateral to A' septal, S' lateral to S' septal), the absolute numbers were used for the calculations. Statistical analysis was performed by using statistical software (Statistica, StatSoft, Tulsa, OK) and Excel (Microsoft, Redmond, WA). Parametric analysis was performed with GraphPad Prism (GraphPad Software, San Diego, CA).

Results

No rabbit was excluded from the study based on the presence of preexisting cardiac conditions identified on echocardiogram. The approximate average age was 2 y. Weights ranged from 2.5 to 4.1 kg. The basic echocardiographic examination was completed during a 30- to 45-min anesthesia window. Table 1 reports data from standard echocardiographic evaluation (M-mode, 2D, and Doppler measurements) and compares these data with previously reported data for this species. The interventricular and posterior left ventricular walls in our study were thicker than the left ventricular walls in lighter (weight, 2.2 to 3.2 kg) New Zealand white rabbits.[9]

Obtaining TDI images required only 4 to 6 min more than obtaining the standard echocardiographic images. Interpretable TDI were obtained in all rabbits (100%); interpretable TV studies were achieved in 24 of 31 rabbits (77%). Interpretable TV images could not be obtained from 5 rabbits due to difficulty in finding the tissue waveform on either the septal or lateral wall. TDI- and TV-derived values are summarized in Table 2. The data obtained showed a larger range of variability than did those obtained by using standard echocardiographic parameters (M-mode, 2D, and Doppler).

Discussion

Our study shows the feasibility of performing complete echocardiographic evaluation in New Zealand white rabbits and provides reference ranges for TDI and TV in this species (Table 2). Anesthesia was used to improve the quality of images and allow safe handling. The anesthesia protocol provided sufficient mechanical and physiologic stability for optimal imaging. In addition, the recovery was uneventful in all rabbits examined. Although ketamine–xylazine alters cardiac function in mice, these effects have not been reported in rabbits.[3,28] The dosage used in this study induced minimal cardiovascular effect, yielded sufficient immobilization, and can be implemented in research and in clinical settings during an echocardiographic exam. Inhalation anesthesia has not been used frequently for cardiac imaging studies in this species because it requires an effective scavenging system, which is not always available, and leads to bradycardia, hypercapnia, and hypoxemia associated with inhalation anesthesia in rabbits.[14]

The average body weight for rabbits is between 2 and 5 kg.[29] This study used New Zealand white rabbits with an average weight greater than previously published[9] but within the range for the species. Although a previous publication[9] speculated that the echocardiographic parameters are not affected by body weight, our results (Table 1) suggest that the M-mode measurements could be dependent on body size. Variation in body size among different breeds of rabbits could cause proportional

Table 1. Values for M-mode, 2D and Doppler echocardiographic variables in New Zealand white rabbits as compared with previously published data (reference 9)

		Current study (n = 31)				
	Previously published[a] (mean ± 1 SD)	Mean ± 1 SD	Minimum	Maximum	Reference range	Coefficient of variation (%)
Weight (kg)	2.59 ± 0.25	3.27 ± 0.3	2.72	4.09	2.60 to 3.93	10
Heart rate (bpm)	155 ± 29	135 ± 18	105	170	99.0 to 172.1	13
Mitral E wave velocity (m/s)	0.59 ± 0.10	0.62 ± 0.12	0.45	0.97	0.37 to 0.87	20
Mitral A velocity (m/s)	0.28 ± 0.07	0.36 ± 0.08	0.23	0.57	0.54 to 0.19	24
E/A	2.19 ± 0.46	1.80 ± 0.54	1.14	3.39	0.72 to 2.89	30
IVSd (mm)	2.03 ± 0.37	2.96 ± 0.42	2.00	4.00	2.11 to 2.82	14
IVSs (mm)	3.05 ± 0.45	4.44 ± 0.73	3.00	6.00	2.98 to 5.92	17
LVIDd (mm)	14.37 ± 1.49	15.72 ± 1.06	14.00	18.00	13.59 to 17.89	7
LVIDs (mm)	10.05 ± 10.05	11.06 ± 1.27	9.00	13.00	8.51 to 13.63	12
LVFWd (mm)	2.16 ± 0.25	2.75 ± 0.43	2.00	3.00	1.89 to 3.63	16
LVFWs (mm)	3.48 ± 0.55	3.96 ± 0.73	3.00	5.00	2.50 to 5.43	18
Left ventricular fractional shortening (%)	30.13 ± 2.98	28.89 ± 5.63	20	45	17.63 to 40.16	19
Ejection fraction (%)	61.29 ± 4.66	59.03 ± 8.30	45	80	42.42 to 75.65	14

IVSd, interventricular wall thickness in diastole; IVSs, interventricular wall thickness in systole; lat, lateral wall; LVFWd, left ventricular free wall thickness in diastole; LVFWs, left ventricular free wall thickness in systole; LVIDd, left ventricular internal diameter at end-diastole; LVIDs left ventricular internal diameter at end-systole

[a]n = 52 except for mitral E wave velocity, mitral A wave velocity, and E/A (n = 35)

Table 2. TDI- and TV-derived parameters in New Zealand white rabbits

		Mean ± 1 SD	Minimum	Maximum	Reference range	Coefficient of variation (%)
TDI (n = 31)						
	E′ (cm/s)	7.68 ± 1.96	4.33	12.00	3.76 to 11.59	26
	A′ (cm/s)	4.47 ± 1.57	2.00	9.00	1.32 to 7.61	35
	S′ (cm/s)	5.31 ± 1.38	3.00	7.00	2.55 to 8.06	26
	E′/A′	1.84 ± 0.51	0.68	3.00	0.82 to 2.86	28
	E/E′	8.50 ± 1.77	5.11	12.13	4.95 to 12.05	21
TV (n = 24)						
	E′ lateral (cm/s)	6.46 ± 2.24	1.36	11.87	1.98 to 10.94	35
	E′ septal (cm/s)	4.64 ± 1.40	1.90	8.66	1.83 to 7.45	31
	A′ lateral (cm/s)	3.08 ± 2.28	0.38	11.48	−1.49 to 7.64	74
	A′ septal (cm/s)	2.72 ± 1.54	1.10	7.70	−0.37 to 5.80	57
	S′ lateral (cm/s)	3.76 ± 1.28	1.24	6.20	1.20 to 6.32	34
	S′ septal (cm/s)	3.73 ± 1.35	1.10	7.80	1.02 to 6.43	36
	E′/A′ lateral	2.68 ± 1.18	0.91	5.40	0.31 to 5.05	44
	E′/A′ septal	2.00 ± 0.82	0.60	4.03	0.37 to 3.63	41
	E′ lateral to E′ septal (msec)	1.67 ± 1.64	0.00	6.94	−1.60 to 4.94	98
	A′ lateral to A′ septal (msec)	1.33 ± 1.79	0.00	7.64	−2.26 to 4.92	135
	S′ lateral to S′ septal (msec)	0.71 ± 0.85	0.00	4.50	−0.99 to 2.42	120

variation in the echocardiographic M-mode measurements of various breeds and weights of rabbits, as occurs in dogs.[2]

TDI is obtained during the echocardiogram and represents tissue motion, whereas TV is obtained after the exam and refers to the tracking of the speckles within the myocardium.[13] Imaging techniques like TDI and TV have been used successfully in evaluating cardiac function in dogs,[5] cats,[4] mice,[21,22] and rabbits[16] that were healthy and in animals with specific diseases such as muscular dystrophy and hypertrophic cardiomyopathy. The results obtained (Table 2) favorably compare with the values reported for healthy cats[4] and are similar to values found in adult humans.[10]

We noted minor differences from the septal and lateral wall measurements that have been reported in previous human studies.[17] As this technology becomes more widespread, the use of these advanced echocardiographic imaging techniques likely will help advance the study of morphologic, physiologic, and rhythm disturbances in both healthy and diseased small animals. As reflected by higher values of coefficient of variation, the variability of the data is greater for TDI and TV compared with the standard echocardiographic parameters (M-mode,

2D, and Doppler). Therefore, the benefit of using the resulting reference ranges should be weighed against the variability of these data.

A limitation to the current study is the few rabbits studied. A larger sample size could have decreased the variability of the data and increased the power of the study. All rabbits were fed and housed in standard conditions, but we are uncertain whether the same values could be obtained in other rabbits under the same conditions.

The use of anesthesia could also have introduced a confounding element to the study, such that a different anesthetic protocol or the lack of anesthesia could lead to different results. However, a previous study reported only a few differences between sedated and awake rabbits.[26] These differences included lower heart rate and minor decreases in E and A wave measurements in sedated rabbits without significant differences in the TDI-derived data. Furthermore, all data obtained were evaluated for parametric distribution, with no significant outliers noted, and findings were similar to the few reports in the literature.

Despite these limitations, advanced echocardiographic imaging is feasible in healthy anesthetized rabbits. This technology can readily be used to evaluate noninvasively normal physiologic and diseased states. Because New Zealand white rabbits have been used as models to study cardiovascular disease, the similarity of the advanced echocardiographic values obtained in this species to human data adds credence to the use of this animal as a surrogate for human pathology.

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