Comparison between invasive hemodynamic measurements and noninvasive assessment of left ventricular diastolic function by use of Doppler echocardiography in healthy anesthetized cats

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Objective—To compare Doppler echocardiographic variables of left ventricular (LV) function with those obtained invasively via cardiac catheterization under a range of hemodynamic conditions.

Animals—7 healthy anesthetized cats (1 to 3 years of age).

Procedure—Cats were anesthetized and instrumented to measure the time constant of isovolumic relaxation (tau [τ]), LV end-diastolic pressure (LVEDP), peak negative and positive rate of change of LV pressure, arterial blood pressure, and cardiac output. Echocardiographic variables of diastolic function (isovolumic relaxation time [IVRT], early LV flow propagation velocity [Vp], transmitral and pulmonary venous flow velocity indices, and LV tissue Doppler imaging indices) were measured simultaneously over a range of hemodynamic states induced by treatments with esmolol, dobutamine, cilobradine, and volume loading. Correlation between invasive and noninvasive measures of LV filling was determined by univariate and multivariate regression analyses.

Results—Significant correlations were found between τ and IVRT, peak Vp, peak late transmitral flow velocity, and peak systolic pulmonary venous flow velocity. A significant correlation was found between LVEDP and early diastolic transmitral flow velocity (peak E) and the ratio of peak E to peak Vp, but not between LVEDP and peak Vp.

Conclusions and Clinical Relevance—IVRT and Vp can be used as noninvasive indices of LV relaxation; Vp was independent of preload and heart rate in this study. The E:Vp ratio may be useful as an indicator of LV filling pressure. (*Am J Vet Res* 2003; 64:93–103)

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Diastolic dysfunction of the **left ventricle (LV)** is an important cause of cardiac disease and appears to be 1 of the earliest detectable functional abnormalities in a number of cardiovascular disorders in humans,[1-4] dogs,[5] and cats.[6,7] It contributes substantially to the pathophysiologic and clinical features in hypertrophic cardiomyopathy,[3,8-10] aortic stenosis,[5,11] ischemic heart disease,[12] and dilated cardiomyopathy[4-6,13] and may occur before the onset of abnormal systolic cardiac performance.[1,3,5,14] Left ventricular diastolic function has been described conceptually by 2 distinct components, relaxation and compliance.[4,15-19] Ventricular relaxation under physiologic conditions is an active process that begins in midsystole, includes the entire period of isovolumic relaxation, and ends with the onset of rapid diastolic filling.[15,17,18,20,21] However, myocardial relaxation does not necessarily terminate at the time of mitral valve opening. Under pathologic conditions, relaxation may extend throughout the entire period of diastole and may even be incomplete.[4,11,16,17] Relaxation is most commonly characterized by tau (τ), the calculated time constant of isovolumic relaxation.[15,18,21-25] Ventricular compliance is a passive, dynamic process that impacts ventricular filling. Compliance predominantly reflects the mechanical properties of the ventricular chamber but may also be influenced by constraining forces related to the right ventricle and the pericardium. It may be described in terms of LV pressures or wall stiffness by traditional pressure-volume relationships.[15-18,26] Until the advent of echocardiography, quantitative assessment of LV diastolic function generally required cardiac catheterization with direct measurement of intracardiac pressures. Echocardiography can be used to assess diastolic function of the left heart noninvasively.[4,10,19,21,27] Doppler indices of diastolic function include measurements of mitral inflow and pulmonary venous flow.[5,10,16,28,29] Recently, complementary indices of diastolic performance have been identified by use of color M-mode Doppler echocardiography or **tissue Doppler imaging (TDI)**.[7,8,19,21,30-34] However, clinical and experimental studies in humans,[16,28,35,36] dogs,[20,26,29,37] and cats[27] have revealed a complex interplay among the multiple cardiac and hemodynamic events that affect Doppler indices of LV diastolic function. Doppler velocity spectra are determined not only by intrinsic LV diastolic properties but also by loading conditions, **heart rate (HR)**, systolic ventricular function, atrioventricular conduction interval, ventricular interdependence, atrial function, pericardial restraint, and other hemodynamic

variables.[16,19,21,38] This makes the interpretation of Doppler variables of diastolic function quite challenging.

Studies comparing invasive with echocardiographic indices of diastolic LV function in humans[3,8,9,28,30,35] and dogs[20,34,37,39-43] are numerous, and reasonable correlations between selected variables have been found. In contrast, such studies in cats[6,18] are rare, and to the authors' knowledge, comparisons of hemodynamic and Doppler variables of diastolic performance in feline species are limited. Myocardial diseases with potential to impair diastole are common in cats. Therefore, an understanding of the factors that influence Doppler indices of diastolic function is essential for appropriate clinical assessment of cats. Furthermore, such data could be important to understanding noninvasive assessment of treatments designed to improve diastolic dysfunction of the LV.

The objectives of the study reported here were to compare simultaneously obtained invasive measurements with Doppler echocardiographic variables of LV diastolic function in clinically normal cats under various hemodynamic and inotropic conditions. We examined the hypothesis that τ is reflected strongly in Doppler indices of diastolic function in healthy anesthetized cats. In addition, we explored the association between ventricular filling pressures and a number of Doppler indices of ventricular filling and relaxation.

Materials and Methods

The study protocol was approved by the Animal Care and Use Committee and the Institutional Review Board of the Department of Veterinary Medicine and Surgery, College of Veterinary Medicine, University of Missouri-Columbia.

Anesthesia, instrumentation, and hemodynamic measurements—Seven domestic shorthair cats that weighed 3.6 to 4.5 kg and were 1 to 3 years old were used for these studies. Three cats were males and 4 were females. The cats were sedated with acepromazine[a] (0.1 mg/kg, SC), butorphanol[b] (0.4 mg/kg, SC), and atropine[c] (0.03 mg/kg, SC). An IV catheter was placed in the right cephalic vein. General anesthesia was induced approximately 45 minutes later with propofol[d] (5 µg/kg, IV). After endotracheal intubation, anesthesia was maintained with isoflurane[e] (0.5 to 3.0%) in 100% oxygen using mechanical ventilation with a tidal volume of 10 to 15 mL/kg and a respiratory frequency of 12 breaths/min. Lactated Ringer's solution was infused at a rate of 10 mL/kg/h. The cats were positioned in left lateral recumbency on a fluoroscopy table designed with a lateral aperture to allow continuous echocardiographic examinations with the transducer from underneath during cardiac catheterization. Drugs and fluids were infused into the right cephalic vein as boluses or at a constant rate by use of a syringe pump.[f] Cefazolin[g] (20 mg/kg, IV) was administered immediately before and 90 minutes and 8 hours after induction of anesthesia. Heparin[h] (100 U/kg, IV) was given once after completion of instrumentation.

The right external jugular vein and the right carotid artery were surgically exposed with aseptic surgical technique. Lidocaine (2%)[i] was used to irrigate the surgical fields, reduce vessel spasm, and provide additional local anesthesia. A 3-F, high-fidelity, dual micromanometer-tipped catheter (pressure transducers 4 cm apart)[j] was advanced into the LV through the right carotid artery under fluoroscopic guidance and positioned to simultaneously record left ventricular and aortic pressures. The catheter was sutured to the carotid artery and was not moved during the studies. The micromanometer catheter was connected to a digital physiologic recording system[k] for continual recording of left ventricular and aortic pressures. A 4-F, flow-directed, fluid-filled, thermistor-tipped catheter[l] connected to a pressure transducer[m] and a **cardiac output (CO)** computer[n] was positioned in the pulmonary artery by use of the right external jugular vein. The proximal catheter port was positioned in the right atrium or distal cranial vena cava, the thermistor in the main pulmonary artery, and the distal tip in the main or proximal left or right pulmonary artery. This catheter was used to measure CO and pulmonary artery pressure. Body temperature of the cats was monitored from the Swan-Ganz catheter thermistor and maintained with a circulating warm water blanket beneath the cat.

The transducers were balanced at atmospheric pressure, calibrated against a mercury manometer, and zero-referenced to midventricular level immediately prior to use. Calibrations were repeated at frequent intervals during the experimental manipulations. The CO meter was calibrated prior to instrumentation of each cat. At the end of the experiments, the micromanometer-tipped catheter was placed in saline (0.9% NaCl) solution, kept at room temperature (22°C), and exposed to air to confirm accurate registration of zero pressures.

Body temperature, ECG, **LV pressure (LVP)** and its **first derivative with respect to time (dP/dt)**, **aortic pressure (AoP)**, and pulmonary artery pressure were monitored continuously and recorded simultaneously during each treatment period. Cardiac output values measured by use of thermodilution were obtained during each intervention concurrently with echocardiographic recording of aortic outflow velocities.

At the conclusion of the study, the jugular vein and carotid artery were ligated, and the incision was closed via standard surgical methods. Butorphanol was administered for 24 hours for postoperative control of pain. Subsequently, the cats were transferred to another protocol and eventually placed in adoption homes.

Echocardiography—All cats underwent repeated transthoracic **2-dimensional (2-D)**, spectral Doppler, color flow Doppler, and TDI echocardiographic examinations[o] with a transducer array of 5.0[p] to 7.0[q] MHz.[10,27,44] Cats were allowed to ventilate spontaneously during echocardiographic recordings and assisted only if respiratory rate decreased to < 8 breaths/min. Echocardiography was performed by a single operator. The diameter of the aortic valve ring and the peak velocity of aortic outflow were measured from a left apical 3- or 5-chamber view as described.[44] To record images for measurement of **isovolumic relaxation time (IVRT)**, a large pulsed wave sample volume (axial dimension of 6 to 10 mm) was placed in an intermediate position between the LV inflow and outflow tract.[10,12,21] Pulsed Doppler echocardiography of transmitral flow and pulmonary venous flow and recordings of color M-mode Doppler wavefront propagation of early transmitral flow were done from a left parasternal apical 4-chamber view via described methods.[19,27,30,32-34,45] All flow patterns of pulmonary venous flow were recorded from the pulmonary vein of the left caudal lung lobe. Doppler echocardiographic interrogation of optimal sample volume position and alignment with the inflow streamline was guided by the simultaneous display of real-time 2-D and color Doppler echocardiographic images. Oblique or angled views were avoided. To generate the most optimal Doppler angle and to reduce translational effect, Doppler low-velocity tissue signals arising from the myocardial movement were also generated from an apical 4-chamber view, with a sample volume (axial dimension of 3 to 7 mm) placed in the septal or lateral corners of the mitral annulus.[7,46-48] Sweep speed during

recordings was 100 mm/s. In all instances, a simultaneous 1-lead ECG was recorded. Data were stored on video tape[r] for subsequent analysis.

Hemodynamic interventions—To study a wide range of hemodynamic states in order to generate additional data points for comparison, HR, systolic and diastolic function, and preload were pharmacologically manipulated. Because of the hemodynamic and HR effects of the chosen drugs, order of drug administration was not randomized. After baseline measurements had been made, 5 treatment periods were studied. The ultrashort-acting β-blocker, esmolol[s] (50 µg/kg/min, IV), was administered to decrease HR and systolic function.[49,t] Dobutamine[u] (2.5 to 5.0 µg/kg/min, IV) was administered to increase HR and improve systolic and diastolic function.[43,50] The experimental drug DK-AH 269 CL[v] (0.2 mg/kg as a single bolus, IV) was administered to reduce HR. This drug is a highly selective inhibitor of the inward funny-current channel (I_f, also called I_h) in cardiac pacemaker tissues.[51] The effects of cilobradine persisted over the next 2 treatment periods, and the cats were treated subsequently with dobutamine (1.25 to 2.50 µg/kg/min, IV) and dobutamine (1.25 to 2.50 µg/kg/min, IV) plus lactated Ringer's volume loading[w] (6 to 8 mL/kg/min, IV) to increase the **LV end-diastolic pressure (LVEDP)** by 5 to 10 mm Hg greater than the previous recording.[18,23,28,41]

After steady-state HR, blood pressure, and LVEDP had been obtained for each intervention, invasive measurements and echocardiographic recordings were made simultaneously, with data collection taking approximately 15 minutes for each period. Thereafter, drug administration was stopped. A period of hemodynamic stabilization was allowed between each stage (ranging from 8 to 16 minutes in duration).

Data analyses—Pressures and a single ECG lead were continuously recorded[k] and stored digitally[x] for subsequent analysis. Digital sampling rate for the micromanometer catheter was 500 samples/s (ie, 1 sample every 2 ms). Pressures and computations were measured from the digitized recordings at end-expiration. Measurements included HR per minute, **LV systolic pressure (LVSP)**, LVEDP, **aortic systolic pressure (AoSP)**, **aortic diastolic pressure (AoDP)**, mean AoP, **peak rate of LVP increase (dP/dt_{max})**, **peak rate of LVP decline ($-dP/dt_{max}$)**, CO, and **pulmonary artery diastolic pressure (PADP)**. The means of 3 or 5 measurements were calculated for CO or pressures, respectively. The LVEDP was defined as the LVP immediately preceding the onset of ventricular contraction, used as an estimate of LV compliance.[9,11,19,28] τ As calculated by the method of Weiss et al[24] in which the LVPs decline from aortic valve closure to mitral valve opening is fit to a monoexponential equation assuming a zero asymptote (**Figs 1–3**). This time constant was used as the gold standard of LV relaxation.[15,16,23-25] To determine the variability involved in the calculation of τ, the **coefficients of variation (CV)** for τ were computed for repeated digitization of a single beat and also between 6 consecutive beats. Repeated injections of 0.5 mL of cold saline solution and a computation constant of 0.055 allowed measurement and computerized calculation of CO by the method of thermodilution.[52-54] Results were recorded on paper tracings with a strip chart recorder.[y] **Body surface area (BSA)** was calculated (BSA = 10 × [body weight × 1,000]$^{2/3}$/10,000).[55] From the measured data, it was possible to calculate the **cardiac index (CI)** by use of the formula CI = CO/BSA.[56]

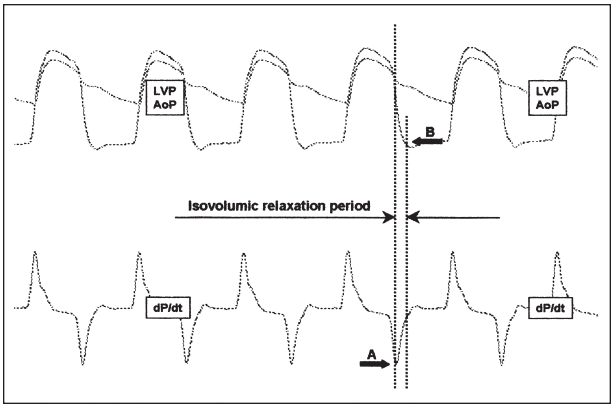

Figure 1—Simultaneous recordings of left ventricular pressure (LVP), aortic pressure (AoP), and the first derivative of the LVP curve (dP/dt) from an anesthetized cat. Pressures were recorded by a high-fidelity double catheter-tip pressure transducer. The period of isovolumic relaxation is represented by the period during which LVP decreases from point A (peak negative rate of change of LVP [$-dP/dt_{max}$]), which is coincident with the time of aortic valve closure, to point B (5 mm Hg greater than LV end-diastolic pressure [LVEDP]), which is the assumed time of mitral valve opening.

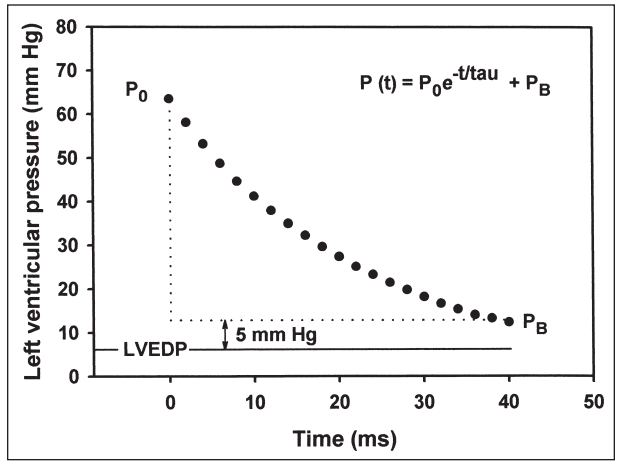

Figure 2—Digitized LVP values obtained during isovolumic relaxation in a clinically normal anesthetized cat. The pressure signal was digitized every 2 milliseconds from the $-dP/dt_{max}$ to 5 mm Hg greater than the LVEDP of the preceding beat. Nonlinear regression with a monoexponential decay model with zero asymptote (equation in top right of figure)[24] can be used to produce values for the time constant for decrease in LVP (tau). t = Time. P_0 = Pressure value at t = 0. P_B = Baseline pressure.

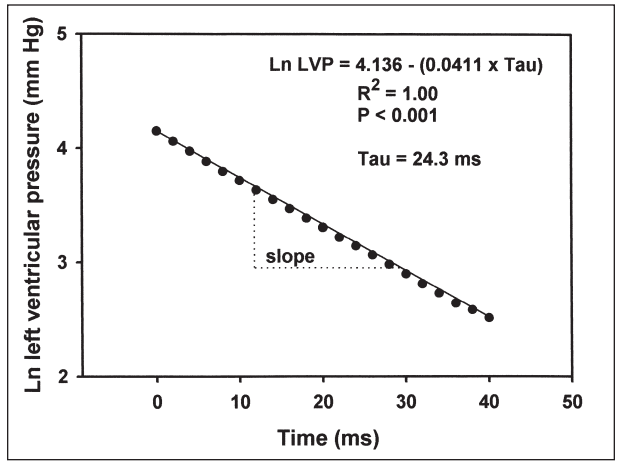

Figure 3—Plot of decrease in isovolumic LVP after natural logarithm transformation (ln LVP) versus time for the same data in Figure 2. The slope of the linear regression line, which uses a monoexponential decay model with zero asymptote, represents –1/tau.

All echocardiographic measurements were made by 1 operator who was unaware of the results of the invasive studies. The mean of 5 consecutive measurements was considered the mean of each variable, irrespective of the respiratory phase. Heart rate was calculated from the interval between successive R-waves. The **diameter of the aorta (d)** was measured at the level of the aortic annulus by use of the inner-edge method[44] to calculate the **cross-sectional area (CSA)** of the aortic valve [$CSA = \pi \times (d/2)^2$]. The Doppler aortic flow signal was planimetered to determine the **velocity time integral (VTI)** and to calculate the **stroke volume (SV**; SV = CSA × VTI). Cardiac output was calculated by a formula (CO = SV × HR[56]) and used to obtain the CI. The IVRT (ie, the period from closure of the aortic valve to opening of the mitral valve) was calculated as the time interval between the end of the LV outflow tract Doppler signal and the onset of transmitral Doppler flow.[10,38] Measurement of variables of mitral inflow, pulmonary venous flow, LV flow propagation velocity, and TDI were made in accordance with recommendations for measurement of those variables in humans,[19,30,33,46-48] dogs,[29,45] or cats.[10,27] Pulsed wave Doppler curves of mitral inflow were created to determine peak velocities of **early diastolic mitral flow wave (E-wave)** and **late diastolic mitral flow wave (A-wave)**, the **ratio of E-wave to A-wave (E:A)**, **deceleration time of the E-wave (DT_E)**, and **duration of the A-wave (A duration)**. The E:A was not calculated when the E-wave and the A-wave were completely fused, or when they were partially fused with an E-at-A velocity > 20 cm/s. For measurement of A-wave duration with partial fusion of both waves (E-at-A wave velocity < 20 cm/s), a vertical line was drawn from the junction of E-wave and A-wave fusion to the baseline.[19] Pulsed Doppler curves of pulmonary venous flow were created for the instantaneous highest velocity spectra to determine peak velocities of **systolic pulmonary venous flow wave (S-wave)**, **early diastolic pulmonary venous flow wave (D-wave)**, and **late diastolic atrial reversal of pulmonary venous flow (AR-wave)**, the ratio of **S-wave velocity to D-wave velocity (S:D)**, and the **duration of the AR-wave (AR duration)**. In addition, the ratio between **duration of the A-wave to duration of the AR-wave (A duration:AR duration)** was calculated. Color M-mode flow **propagation velocity (Vp)** of early diastolic flow into the LV was obtained by manually tracing the Vp line over a distance of 1 to 3 cm, starting at the mitral valve tips, along the transition zone in which velocity aliasing occurs.[30,34] The slope of the first aliasing isovelocity line (red-blue interface), measured in centimeters per second, was also used to calculate the **ratio between transmitral E-wave to Vp (E:Vp)**. Tissue Doppler imaging, recorded both from the septal and lateral corners of the mitral annulus, was used to determine peak velocities of **systolic mitral annulus motion (Sa-wave)**, **early diastolic mitral annulus motion (Ea-wave)**, and **late diastolic mitral annulus motion (Aa-wave)**, the ratio of **Ea-wave to Aa-wave (Ea:Aa)**, and **deceleration time of the Ea-wave (DT_{Ea})**. The Ea:Aa was not determined when both waves were completely or partially fused. In addition, the ratio of **transmitral E-wave velocity to tissue Doppler Ea-wave velocity (E:Ea)** was calculated. Local IVRT was calculated as the interval between the baseline intercepts of the end of the systolic excursion and the start of the diastolic excursion of the pulsed wave TDI signal.[7,19]

Statistical analyses—Descriptive statistics were calculated for all invasive and Doppler echocardiographic variables of LV diastolic function. Data are reported as mean, median, and either SD (for data distributed normally) or range. Differences between baseline values and values of variables after hemodynamic interventions were examined by use of a 1-way repeated measures ANOVA and Dunnett test.[z]

Pooled data from all experimental stages in all cats were used to test the relationship between invasive and Doppler echocardiographic data. Simple linear regression analysis was used to identify correlations between τ and pressures, pressure derivatives, HR, or invasively obtained CO. Simple linear regression analysis was also used to test for correlation between τ and LVEDP, HR, and Doppler

Table 1—Invasively derived indices of left ventricular diastolic and systolic function under different hemodynamic conditions in 7 clinically normal anesthetized cats*

Variable	Baseline	Esmolol	Dobutamine	Cilobradine	+ Dobutamine Cilobradine	+ Volume + Dobutamine Cilobradine
HR (bpm)	123 (127) (± 18)	135 (130) (± 23)	177 (177) (± 19)	115 (119) (± 17)	124 (130) (83–137)	122 (122) (± 11)
Tau (ms)	38 (36) (34–49)	45 (44) (± 8)	21 (21)† (± 2)	42 (45) (33–47)	27 (26)† (± 7)	39 (32) (± 16)
LVSP (mm Hg)	95 (88) (± 20)	81 (81) (± 10)	108 (107) (± 15)	81 (80) (± 12)	105 (115) (± 27)	101 (98) (± 17)
LVEDP (mm Hg)	10.0 (9.6) (± 3.1)	9.2 (9.3) (± 2.7)	6.2 (4.6)† (± 4.3)	10.3 (12.2) (± 4.6)	9.9 (13.5) (± 7.8)	16.7 (16.8)† (± 3.1)
dP/dt_{max} (mm Hg/s)	1,737 (1,563) (± 437)	1,301 (1,321) (± 280)	2,696 (2,742)† (± 717)	1,360 (1,256) (± 428)	2,395 (2,299) (± 850)	1,687 (1,752) (± 470)
$-dP/dt_{max}$ (mm Hg/s)	1,450 (1,463) (± 369)	1,100 (1,101) (± 228)	2,137 (1,978)† (± 628)	1,155 (1,077) (± 314)	2,075 (2,150) (± 918)	1,430 (1,343) (± 356)
AoSP (mm Hg)	97 (96) (± 21)	76 (77)† (± 5)	100 (103) (± 16)	79 (77)† (± 12)	104 (116) (± 26)	93 (91) (± 17)
AoDP (mm Hg)	63 (57) (± 15)	50 (49) (± 9)	51 (47) (± 9)	48 (46)† (± 10)	57 (57) (± 13)	52 (49) (± 11)
Mean AoP (mm Hg)	75 (67) (60–104)	63 (62) (± 6)	74 (71) (± 12)	64 (63) (± 12)	80 (86) (± 21)	72 (71) (± 14)
PADP (mm Hg)	8.3 (9.0) (± 5.8)	9.0 (10.0) (± 3.8)	7.6 (6.1) (± 5.9)	8.4 (9.8) (± 5.3)	9.5 (10.8) (± 5.7)	11.4 (12.0) (± 7.2)
CI (l/min/m^2)	3.44 (3.27) (± 0.84)	2.88 (2.59) (± 0.74)	4.75 (4.78)† (± 0.56)	2.83 (2.92)† (± 0.58)	4.22 (4.62) (2.61–4.82)	4.10 (3.60) (± 1.22)

*Values are expressed as mean (median) (SD or range). †Significant ($P \leq 0.05$) difference from baseline value.
HR = Heart rate. Bpm = Beats per minute. Tau = Time constant of left ventricular isovolumic relaxation. LVSP = Left ventricular systolic pressure. LVEDP = Left ventricular end-diastolic pressure. dP/dt_{max} = Maximum rate of increase in left ventricular pressure. $-dP/dt_{max}$ = Maximum rate of decrease in left ventricular pressure. AoSP = Aortic systolic pressure. AoDP = Aortic diastolic pressure. Mean AoP = Mean aortic pressure. PADP = Pulmonary artery diastolic pressure. CI = Cardiac index (using CO determined by thermodilution).

Table 2—Echocardiographically derived indices of left ventricular diastolic and systolic function under different hemodynamic conditions in 7 clinically normal anesthetized cats*

Variable	Baseline	Esmolol	Dobutamine	Cilobradine	+ Dobutamine Cilobradine	+ Volume + Dobutamine Cilobradine
HR (bpm)	132 (139) (± 15)	131 (132) (± 8)	167 (172)† (± 23)	119 (126) (± 13)	126 (129) (± 9)	126 (126) (± 8)
IVRT (ms)	71 (75) (± 17)	75 (69) (± 19)	51 (50)† (± 15)	74 (68) (± 25)	59 (54) (± 27)	61 (59) (± 7)
Peak Vp (cm/s)	64 (62) (± 20)	45 (42)† (± 7)	78 (80) (± 19)	46 (45)† (± 16)	77 (71) (± 23)	62 (61) (± 23)
HR (bpm)	137 (131) (± 28)	136 (128) (104–198)	176 (176)† (± 21)	115 (121) (± 15)	125 (132) (± 16)	133 (126) (± 15)
Peak E (m/s)	0.67 (0.69) (± 0.14)	0.62 (0.69) (0.40–0.81)	0.80 (0.81) (± 0.15)	0.65 (0.62) (± 0.17)	0.81 (0.89) (± 0.25)	0.73 (0.62) (± 0.17)
DT_E (ms)	66 (66) (± 13)	63 (64) (± 15)	69 (56) (± 17)	71 (76) (± 13)	61 (60) (± 7)	70 (70) (± 10)
Peak A (m/s)	0.33 (0.39) (± 0.11)	0.29 (0.28) (± 0.05)	0.53 (0.53)† (± 0.13)	0.28 (0.28) (± 0.09)	0.49 (0.48)† (± 0.06)	0.40 (0.38) (± 0.10)
E:A	2.27 (2.03) (± 1.00)	2.16 (2.11) (± 0.80)	1.38 (1.38)† (± 0.31)	2.79 (3.00) (± 1.09)	1.79 (1.84) (± 0.60)	1.90 (1.74) (± 0.57)
E/Vp	1.20 (1.02) (0.82–2.10)	1.32 (1.31) (± 0.50)	1.07 (1.03) (± 0.36)	1.59 (1.45)† (± 0.75)	1.68 (1.45)† (± 0.79)	1.52 (1.49)† (± 0.42)
HR (bpm)	135 (126) (± 35)	134 (130) (± 25)	178 (178)† (± 15)	117 (116) (± 23)	120 (129) (± 24)	122 (122) (± 11)
Peak S (m/s)	0.25 (0.26) (± 0.07)	0.24 (0.24) (± 0.04)	0.49 (0.51)† (± 0.10)	0.24 (0.22) (± 0.08)	0.38 (0.37) (± 0.13)	0.44 (0.41)† (± 0.09)
Peak D (m/s)	0.23 (0.23) (± 0.04)	0.18 (0.13) (± 0.09)	0.30 (0.31)† (± 0.07)	0.23 (0.23) (± 0.08)	0.32 (0.31)† (± 0.11)	0.32 (0.26) (± 0.14)
Peak AR (m/s)	0.18 (0.15) (0.10–0.39)	0.13 (0.14) (± 0.04)	0.17 (0.17) (± 0.02)	0.13 (0.13) (± 0.05)	0.15 (0.14) (± 0.04)	0.16 (0.15) (0.13–0.25)
S:D	1.14 (1.14) (± 0.32)	1.53 (1.36) (± 0.53)	1.77 (1.56)† (± 0.55)	1.15 (1.07) (± 0.43)	1.20 (1.28) (± 0.26)	1.47 (1.58) (± 0.45)
A duration:AR duration	1.71 (1.60) (± 0.31)	1.59 (1.60) (± 0.19)	1.41 (1.38) (± 0.25)	1.58 (1.42) (± 0.46)	1.63 (1.59) (± 0.41)	1.59 (1.68) (± 0.36)
HR (bpm)	130 (117) (± 37)	134 (125) (± 27)	176 (180)† (± 19)	115 (114) (± 23)	121 (129) (± 23)	125 (123) (± 10)
Peak Sa septal (cm/s)	4.19 (4.30) (± 0.82)	4.17 (4.40) (±1.15)	6.74 (7.30)† (± 1.69)	3.88 (4.10) (± 0.87)	5.62 (5.30) (± 1.05)	5.92 (6.00)† (± 1.22)
Peak Ea septal (cm/s)	6.42 (6.50) (± 1.25)	6.54 (6.00) (± 1.64)	7.56 (6.80) (± 2.09)	6.10 (6.00) (± 1.92)	6.33 (7.40) (± 2.53)	8.36 (7.40)† (± 1.34)
DT_{Ea} septal (ms)	61 (56) (± 14)	52 (47) (± 15)	44 (45)† (± 11)	62 (63) (± 15)	62 (59) (± 10)	57 (56) (± 12)
Peak Aa septal (cm/s)	3.64 (3.60) (± 1.47)	4.14 (4.30) (± 1.07)	8.15 (8.00)† (± 1.64)	3.26 (3.20) (± 0.73)	5.60 (5.65)† (± 0.55)	5.80 (6.00)† (± 0.51)
Ea:Aa septal	1.93 (1.84) (1.12–3.06)	1.57 (1.40) (± 0.27)	0.79 (0.77)† (± 0.21)	1.81 (1.76) (± 0.88)	0.99 (0.99) (± 0.41)	1.46 (1.54) (± 0.35)
E:Ea septal	10.87 (10.30) (± 2.67)	10.33 (9.76) (± 3.07)	10.55 (8.54) (± 3.65)	11.11 (10.00) (8.67–16.30)	13.75 (12.85) (9.43–21.30)	8.68 (8.62) (± 1.19)
IVRT septal (ms)	62 (64) (± 17)	62 (64) (± 11)	48 (45)† (± 15)	73 (70) (± 25)	63 (56) (± 29)	51 (52) (± 12)
Peak Sa lateral (cm/s)	3.99 (4.00) (± 0.41)	4.00 (4.00) (± 0.88)	6.34 (6.30)† (4.30–10.00)	3.83 (3.80) (± 0.54)	5.77 (5.30)† (± 1.74)	5.16 (5.00) (± 1.36)
Peak Ea lateral (cm/s)	8.34 (7.90) (± 2.04)	7.88 (7.20) (± 1.50)	10.69 (10.25) (± 2.80)	7.80 (7.40) (± 2.88)	8.92 (9.05) (± 3.95)	10.42 (11.00)† (± 2.13)
DT_{Ea} lateral (ms)	50 (52) (± 9)	49 (48) (± 9)	48 (49) (±11)	52 (51) (± 5)	47 (46) (± 8)	44 (42) (± 5)
Peak Aa lateral (cm/s)	4.01 (4.00) (± 1.65)	4.30 (4.00) (± 1.48)	7.13 (7.60)† (5.80–8.00)	3.59 (3.40) (± 0.80)	5.90 (5.90)† (± 1.37)	6.70 (6.30)† (± 0.98)
Ea:Aa lateral	2.25 (2.25) (± 0.62)	1.89 (1.93) (± 0.32)	1.13 (1.17)† (± 0.17)	2.09 (2.06) (± 0.89)	1.50 (1.69) (± 0.51)	1.55 (1.49) (± 0.17)
E:Ea lateral	8.23 (8.21) (± 1.59)	8.28 (7.14) (± 2.41)	7.66 (6.77) (± 3.50)	8.67 (8.54) (± 1.50)	10.25 (8.69) (± 4.16)	7.00 (7.36) (5.45–7.56)
IVRT lateral (ms)	64 (68) (± 14)	65 (68) (± 10)	48 (46)† (± 16)	69 (65) (± 24)	62 (52) (± 26)	49 (53)† (± 10)
HR (bpm)	134 (129) (± 36)	136 (130) (± 23)	177 (178)† (± 19)	119 (119) (± 23)	124 (130) (± 20)	118 (119) (± 3)
CI (l/min/m^2)	4.43 (4.30) (± 1.75)	3.64 (3.41) (± 1.07)	5.79 (5.59)† (± 1.44)	3.98 (3.08) (2.44–6.34)	5.10 (5.46) (± 2.01)	4.11 (3.71) (3.19–6.57)

IVRT = Isovolumic relaxation time. Peak Vp = Peak flow propagation velocity. Peak E = Peak velocity of early diastolic mitral flow wave (E-wave). DT_E = Deceleration time of E-wave. Peak A = Peak velocity of late diastolic mitral flow wave (A-wave). E:A = Ratio between Peak E to Peak A. E:Vp = Ratio between Peak E to Peak Vp. Peak S = Peak velocity of systolic pulmonary venous flow wave (S-wave). Peak D = Peak velocity of early diastolic pulmonary venous flow wave (D-wave). Peak AR = Peak velocity of late diastolic atrial reversal of pulmonary venous flow (AR-wave). S:D = Ratio between Peak S to Peak D. A duration:AR duration = Ratio between A duration to AR duration. Septal = Measured at the septal corner of the mitral annulus. Lateral = Measured at the lateral corner of the mitral annulus. Peak Sa = Peak velocity of systolic mitral annulus motion (Sa-wave). Peak Ea = Peak velocity of early diastolic mitral annulus motion (Ea-wave). DT_{Ea} = Deceleration time of Ea-wave. Peak Aa = Peak velocity of late diastolic mitral annulus motion (Aa-wave). Ea:Aa = Ratio between Peak Ea to Peak Aa. E:Ea = Ratio between Peak E to Peak Ea. CI = Cardiac index (using CO determined by echocardiography and the equation. CO = aortic valve area × velocity time integral × HR).

See Table 1 for remainder of key.

echocardiographic variables of LV function. If data were not normally distributed, a Spearman rank order correlation was used. Scatter plots of predicted values IVRT, and Vp in relation to τ and E:Vp in relation to LVEDP were reported as means with 95% confidence intervals for the regression lines.

Multiple linear regression analysis was used to predict Doppler-derived values from independent, invasively derived hemodynamic variables. A forward stepwise procedure allowed evaluation of the contribution of each independent variable (τ, LVSP, LVEDP, AoSP, AoDP, mean AoP, PADP, dP/dt_{max}, $-dP/dt_{max}$, CO, and HR) in the total variance of Doppler-derived indices of LV diastolic function. A partial correlation coefficient (R^2) indicating the proportion of variance explained by inclusion of a single variable in the regression analysis was calculated. Values of $P \leq 0.05$ were regarded as significant.[57]

Results

Hemodynamics—A wide range of hemodynamic conditions was created in this study. Changes in HR, ventricular systolic function (LV dp/dt_{max}), and arterial blood pressure were as expected on the basis of the treatments used to alter the hemodynamic state (**Table 1**). Volume infusion led to a predictable increase in filling pressures estimated by PADP and LVEDP. Heart rate varied from 79 to 211 beats/min, τ from 19 to 53 millisecond, LVEDP from –1.8 to 22.0 mm Hg, peak dP/dt_{max} from 808 to 4,067 mm Hg/s, and CI from 1.96 to 5.56 L/min/m^2.

Reproducibility of calculated values for τ was considered acceptable with the time constant ranging from 28.8 to 32.3 millisecond (mean,

30.4 ± 0.88 milliseconds) for repeated digitization of the same heart beat (CV, 2.9%). Digitization of 6 consecutive beats yielded values of τ between 42.2 and 46.8 milliseconds (CV, 4.1%).

Significant ($P < 0.001$) correlation was found between τ (the estimate of LV relaxation) and LVEDP (an estimate of LV compliance) and several other hemodynamic variables. In particular, there were associations between τ and peak dP/dt_{max} ($r = –0.82$), peak $–dP/dt_{max}$ ($r = 0.72$), LVSP and AoSP (each $r = –0.68$), CI ($r = –0.58$), HR ($r = –0.55$), and mean AoP ($r = –0.41$). The LVEDP, the PADP, and the AoDP were not correlated with τ. As expected, LVEDP correlated with PADP ($r = 0.71$).

Echocardiography—The simultaneous echocardiographic data obtained during each treatment period were tabulated (**Table 2**). Correlation coefficients were evaluated via linear regression analysis of each echocardiographic index against the independent variables τ or LVEDP (**Table 3**).

Effect of LV relaxation—An association was found between τ and IVRT (**Fig 4**), peak Vp (**Fig 5**), peak A, peak S, peak E, peak D, HR, and selected variables of TDI (Table 3). τ Was not correlated with E:A, DT_E, S:D, A duration:AR duration, E:Vp, or Ea:Aa. There was also significant correlation between IVRT, measured at the septal and lateral corner of the mitral annulus by use of TDI ($r = 0.94$), and IVRT, measured by use of mitral inflow and aortic outflow variables and IVRT septal ($r = 0.67$) or IVRT lateral ($r = 0.70$). The absolute values of IVRT, measured at 3 locations, were not significantly different.

Effect of LVEDP— Significant correlation was evident between LVEDP, an index of LV compliance, and E:Vp (**Fig 6**), peak E, IVRT, and selected variables of TDI (Table 3). There was no association between LVEDP and DT_E, Vp (**Fig 7**), and A duration:AR duration (**Fig 8**). However, the cat with the most increased LVEDP (22.0 mm Hg) had the lowest A duration:AR duration ratio (1.07). There was also a correlation between PADP and E:Vp ($r = 0.61$; $P \leq 0.05$).

Multivariate analysis—Results of stepwise multiple linear regression analysis that compared τ, LVEDP, PADP, HR, and peak dP/dt_{max} to echocardiographic variables were summarized (**Table 4**). As each echocardiographic variable was entered into the regression at each step, the **correlation coefficient** (r), R^2, and the **increase in** R^2 (ΔR^2) attributable to the entered variable were determined, as well as the P value.

Table 3—Univariate correlation coefficients for tau and LVEDP versus Doppler-derived estimates of left ventricular diastolic function in 7 clinically normal anesthetized cats by use of pooled data. Only variables with significant ($P \leq 0.05$) correlations are indicated

Variable	Tau	LVEDP
IVRT (ms)	0.78	–0.31
Peak Vp (cm/s)	–0.68	NS
Peak A (m/s)	–0.67	NS
Peak S (m/s)	–0.67	NS
Peak Sa lateral (cm/s)	–0.67	NS
Peak E (m/s)	–0.62	0.48
Peak Aa septal (cm/s)	–0.62	NS
Peak Sa septal (cm/s)	–0.62	NS
IVRT septal (ms)	0.57	–0.48
Peak D (m/s)	–0.56	NS
IVRT lateral (ms)	0.55	–0.46
HR (bpm)	0.53	NS
Peak Aa lateral (cm/s)	–0.48	NS
Peak Ea lateral (cm/s)	–0.47	0.33
DT_{Ea} septal (ms)	0.38	NS
Peak Ea septal (cm/s)	–0.36	0.44
E:Vp	NS	0.64
DT_{Ea} lateral (ms)	NS	–0.35

NS = Not significant.
See Tables 1 and 2 for key.

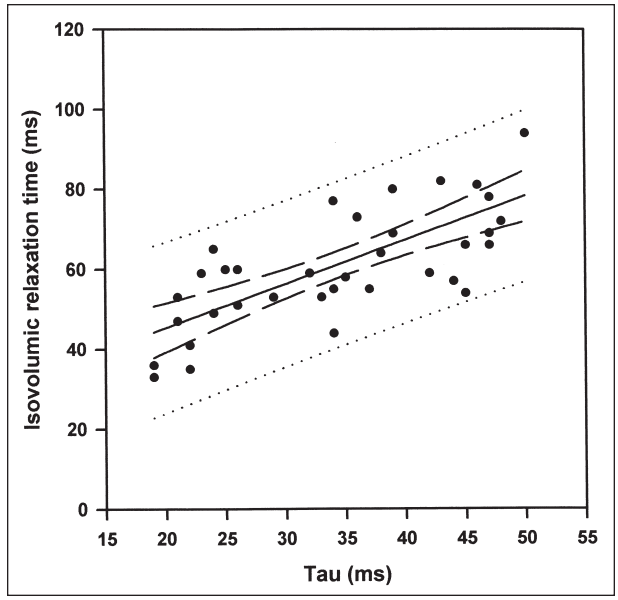

Figure 4—Scatter plot of left ventricular isovolumic relaxation time (IVRT) versus tau in 7 clinically normal anesthetized cats. Notice the linear relationship between the variables. Equation for the regression line ($r = 0.78$; $P < 0.001$) is IVRT = 23.399 + (1.098 × tau).

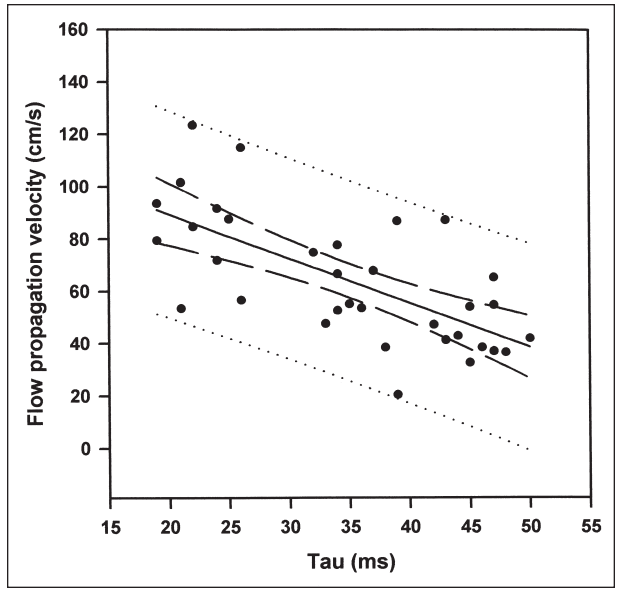

Figure 5—Scatter plot of left ventricular flow propagation velocity (Vp) versus tau in 7 clinically normal anesthetized cats. Equation for the regression line ($r = –0.68$; $P < 0.001$) is Vp = 123.196 – (1.690 × tau).

Multicolinearity was present among the independent variables. In the pooled data, τ alone accounted for up to 61% of the variance in IVRT, 46% of the variance in peak Vp, 45% of the variance in peak S and peak A, 39% of the variance in peak E, and 32% of the variance in peak D. The LVEDP alone accounted for up to 29% of the variance in IVRT septal and lateral, 21% of the variance in peak Ea septal, 13% of the variance in peak Ea lateral, and 10% and 8% of the variance in peak D and IVRT, respectively. The LVEDP had no effect on Vp. The PADP, another estimate of preload, accounted for 38% of the variance in E:Vp and for 25% of the variance in peak E. Heart rate alone accounted for up to 53% of the variance in Aa septal, 50% of the variance in DT_{Ea}

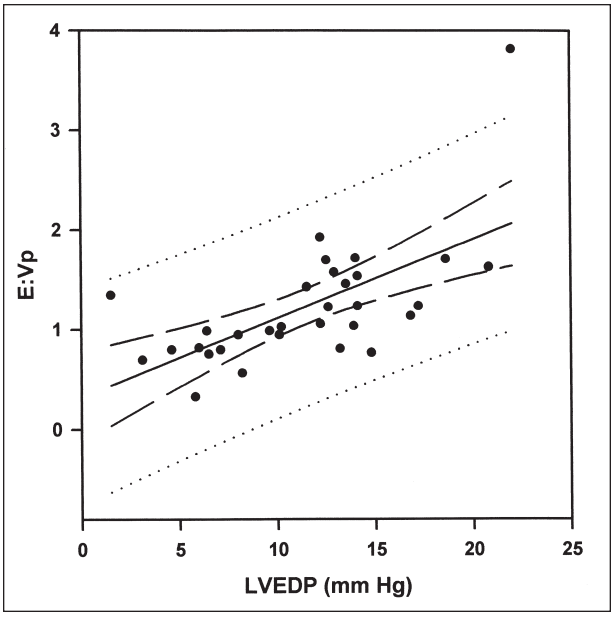

Figure 6—Scatter plot of the ratio between peak velocity of early diastolic mitral flow wave to left ventricular flow propagation velocity (E:Vp) versus LVEDP in 7 clinically normal anesthetized cats. Equation for the regression line ($r = 0.64$; $P < 0.001$) is E:Vp = 0.325 + (0.0792 × LVEDP).

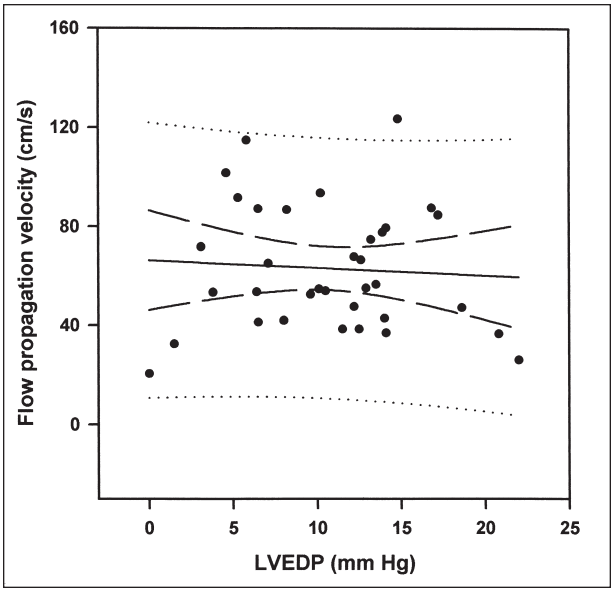

Figure 7—Scatter plot of left ventricular flow propagation velocity (Vp) versus LVEDP in 7 clinically normal anesthetized cats. There was no correlation between variables ($P = 0.715$).

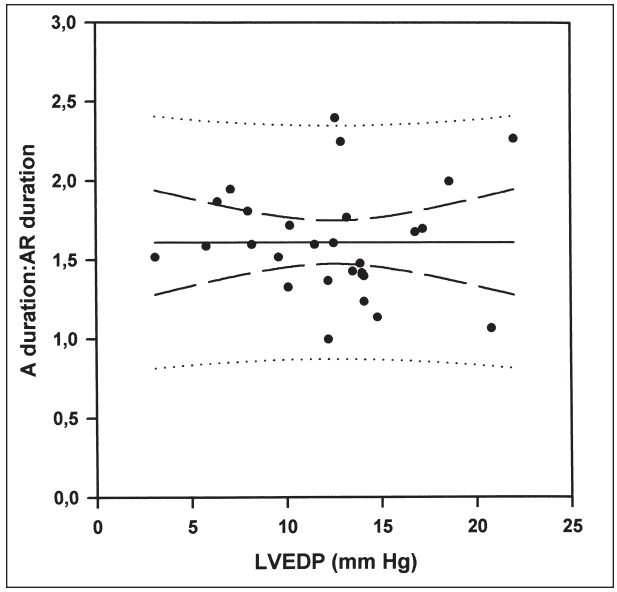

Figure 8—Scatter plot of the ratio between duration of late diastolic mitral A-wave to duration of late diastolic atrial reversal of pulmonary venous flow (A duration:AR duration) versus LVEDP in 7 clinically normal anesthetized cats. There was no correlation between variables ($P = 0.997$).

Table 4—Results of multivariate forward stepwise regression analysis between independent factors (HR, tau, LVSP, LVEDP, Peak dP/dt_{max}, CO, Peak $-dP/dt_{max}$, AoSP, AoDP, Mean AoP, and PADP) and Doppler-derived variables of left ventricular diastolic function

Variable	Independent factor	*r*	R^2	ΔR^2	*P*
IVRT	Tau	0.78	0.61	0.61	< 0.001
	LVEDP	0.83	0.69	0.08	< 0.001
Peak Vp	Tau	0.68	0.46	0.46	< 0.001
Peak E	Tau	0.62	0.39	0.39	< 0.001
	PADP	0.81	0.65	0.25	< 0.001
DT_E	HR	0.54	0.29	0.29	< 0.001
Peak A	Tau	0.67	0.45	0.45	< 0.001
$E:V_p$	PADP	0.61	0.38	0.38	< 0.001
Peak S	Tau	0.67	0.45	0.45	< 0.001
Peak D	Tau	0.56	0.32	0.32	< 0.001
	LVEDP	0.65	0.42	0.10	< 0.001
Peak AR	HR	0.39	0.15	0.15	0.020
S:D	HR	0.62	0.38	0.38	< 0.001
Peak Sa septal	Tau	0.62	0.38	0.38	< 0.001
Peak Ea septal	Peak dP/dt_{max}	0.54	0.29	0.29	< 0.001
	LVEDP	0.71	0.50	0.21	< 0.001
DT_{Ea} septal	HR	0.71	0.50	0.50	< 0.001
Peak Aa septal	HR	0.73	0.53	0.53	< 0.001
	Mean AoP	0.77	0.59	0.06	< 0.001
Ea:Aa septal	HR	0.46	0.21	0.21	0.012
IVRT septal	LVEDP	0.54	0.29	0.29	< 0.001
	HR	0.79	0.62	0.33	< 0.001
Peak Sa lateral	Tau	0.67	0.45	0.45	< 0.001
Peak Ea lateral	Peak dP/dt_{max}	0.65	0.42	0.42	< 0.001
	LVEDP	0.74	0.55	0.13	0.004
DT_{Ea} lateral	HR	0.40	0.16	0.16	< 0.001
	LVEDP	0.63	0.39	0.23	0.002
Peak Aa lateral	HR	0.52	0.27	0.27	0.002
Ea:Aa lateral	AoDP	0.38	0.14	0.14	0.004
	HR	0.58	0.34	0.20	0.010
IVRT lateral	LVEDP	0.54	0.29	0.29	< 0.001
	HR	0.78	0.61	0.32	< 0.001

r = Correlation coefficient. R^2 = Partial correlation coefficient. ΔR^2 = Increase in R^2 attributable to the entered variable.
See Tables 1 and 2 for key.

septal, 38% of the variance in S:D, 33% and 32% of the variance in IVRT septal and lateral, respectively, 29% of the variance in DT_E, and 27% of the variance in Aa lateral. Peak positive dP/dt_{max} accounted for up to 42% of the variance in peak Ea lateral and for 29% of the variance in peak Ea septal. For E:A, A duration:AR duration, and E:Ea septal or lateral, all independent variables have been eliminated from the regression model. The LVSP, peak $-dP/dt_{max}$, AoSP, mean AoP, AoDP, and CO did not enter into the regression.

Discussion

Before measures of LV diastolic function derived from Doppler echocardiography can be optimally useful in clinical situations, these variables must be related to established measures of diastolic function. Furthermore, one must consider the interrelated properties that affect diastole. Using simultaneous high-fidelity pressure recordings of LV and aortic pressures together with the pulsed Doppler technique, the study reported here examined the relationship between several hemodynamic variables of LV diastolic function and echocardiographic correlates in healthy anesthetized cats. The results reaffirm previous observations in dogs[20,34,37,39,41,42,58] but may also provide new insights into the origins of mitral inflow, pulmonary venous flow, and tissue Doppler components.

Impaired relaxation is one of the earliest detectable diastolic abnormalities in cardiac disease.[1-5] The time constant of isovolumic exponential pressure decline, τ, was used as an index of myocardial relaxation.[15,21,24,25,41] This index represents the time for LV pressure to decrease from its initial value to –1/e of that value.[3,15,22-24] More rapid myocardial relaxation results in lower values for τ, and prolonged relaxation leads to increased values for τ.[24,41]

Our study revealed that there is an association between myocardial systolic function and τ in healthy cats. Forward stepwise regression analysis detected dP/dt_{max} (an index of LV contractility)[59] as the single main variable that influenced τ. Similar observations have been reported elsewhere.[23,24,60] Systolic and diastolic cardiac function are related; therefore, interpretation of echocardiographic variables used to assess relaxation should always be made in concert with information on systolic ventricular performance in each individual cat.[24,25] However, although there was a close association between LV systolic function and relaxation, this association may in part be related to the specific methods used to induce hemodynamic alterations. Dobutamine and esmolol, for example, do not solely influence the inotropic state of the myocardium but also affect relaxation and HR.[16,20,23-25] Volume loading to increase preload may cause alterations of other hemodynamic determinants as well as via reflex mechanism[16,36,41] that were not specifically addressed in the study reported here.

Our findings were similar to those in clinically normal dogs[25,34,61] and humans with or without cardiac diseases,[21,31,32,34,36,58,62,63] indicating that IVRT and Vp in particular are useful indices of LV relaxation. There were linear and moderately strong correlations between the monoexponential τ and the temporal indices of relaxation Vp and IVRT. However, because of multicolinearity observed between τ and LV dP/dt_{max}, HR, and afterload, these independent factors may have influenced IVRT and Vp indirectly.[23,31] In addition, IVRT was related to LVEDP ($r = -0.31$; $P \leq 0.05$), and impaired relaxation as assessed by use of IVRT may be masked by increased LV filling pressures.[4,9,12] A similar close relationship between τ and Vp has been found in experimental studies in dogs after administration of esmolol, dobutamine, or preload reduction ($r = 0.78$)[34] and humans with various cardiac diseases during partial cardiopulmonary bypass ($r = 0.86$).[34] τ Was the only independent determinant of Vp in those studies, suggesting that Vp may be useful in the routine clinical evaluation of diastolic function by providing a relatively preload-independent estimate of LV relaxation.

Transmitral peak E and pulmonary venous flow peak D were also affected by LV relaxation, although preload also seemed to influence both variables. The preload sensitivity of early diastolic LV filling has also been reported in numerous animal[37,39-42] and human studies,[16,35,64,65] leading to the conclusion that Doppler filling parameters must be interpreted cautiously when used as indices of LV diastolic function.[33,37,41,66] Abnormal diastolic performance itself and the complication of systolic dysfunction with heart failure may cause an increase in filling pressure resulting in pseudonormalization of the transmitral flow pattern, which can confound evaluation of LV diastolic function.[8,16,19,66] Concurrent analysis of Vp, pulmonary venous flow, or TDI may be used to interpret transmitral flow pattern more reliably.[8,19,33,47,67]

Tissue Doppler peak Ea is a relatively preload-independent echocardiographic correlate of τ in human studies.[46-48] Regression analysis in our study revealed only a weak association between Ea and LV relaxation. Peak Ea was also influenced by peak dP/dt_{max} and LVEDP.

Left ventricular relaxation may not only be delayed or prolonged in cardiac disease, it may also be asynchronous. Diastolic asynchrony has been reported in ischemic myocardial disease and hypertrophic cardiomyopathy,[9,63,68] diseases that are also common in cats. Tissue Doppler imaging can be useful to detect asynchrony of relaxation.[7,47,48] Results of the study reported here suggested that isovolumic relaxation of the LV in healthy cats is synchronous. The values of global and local IVRT were not different, and close correlations were found between the 3 measurements. Similar results were detected in clinically normal awake cats,[7] whereas regional heterogeneity of IVRT has been detected in cats with hypertrophic or unclassified cardiomyopathy.[7] Future studies on regional asynchrony are needed to fully understand its importance for LV diastolic function.

Indices of left ventricular and left atrial systolic performance such as peak S-wave of pulmonary venous flow, peak Sa-wave of TDI, and peak A-wave of transmitral flow were also moderately related to LV relaxation. τ Alone accounted for up to 45% of the variance in these variables. Although unexpected, this finding is not surprising because of the close relationship between LV systolic function and LV relaxation, which influences those echocardiographic vari-

ables.[64,65,69] In addition, systolic LV function tends to parallel left atrial systolic performance.[37,65,69] This was particularly obvious with the inverse relationship between peak A and τ in this study. Impairment of relaxation because of LV myocardial disease causes an increase of late diastolic filling in the presence of preserved left atrial function (shift of filling from early to late diastole).[3,5,9,10,58] In our study, however, because of multicolinearity observed between indices of LA function, LV relaxation, and LV systolic function, and the use of clinically normal cats, a negative correlation between peak A and τ was found. Similar observations were reported in healthy experimental dogs.[37]

Knowledge of LV filling pressures is important for the diagnosis, prognosis, and treatment of patients with cardiac disease.[4,19,28] Abnormally increased LVEDP may be associated with clinical signs of congestion and exercise intolerance. The commonly used variables to estimate LVEDP such as E:A or DT_E may not be reliable indices of LV filling pressures in patients with diastolic abnormalities and normal or borderline systolic ventricular function.[3,8,9] The A duration:AR duration is a more important indication of increased LVEDP and decreased myocardial compliance.[19,35,45,70-72] When pulmonary venous AR-wave duration exceeds transmitral A-duration, an increased LVEDP (≥ 20 mm Hg) may be predicted with high sensitivity and specificity in humans with cardiac disease,[58,72,73] and close correlation between LVEDP and A duration:AR duration has been reported (r = 0.80).[35] Results of our study did not indicate an association between LVEDP and A duration:AR duration in healthy cats. One reason may be that this study was done in healthy cats with normal LV myocardium. Moreover, the range of LV end-diastolic pressures (–1.8 to 22.0 mm Hg) was rather low, with many pressure values within the reference range. The use of A-duration with partially fused E- and A-waves (which occurred in only 4 measures) was not found to be a reason for lack of correlation between LVEDP and A duration:AR duration. In contrast, the E:Vp ratio was significantly related to LVEDP or PADP, and thus to preload. In combining a preload- and relaxation-dependent variable such as peak E with a relaxation-dependent but preload-independent Doppler index such as Vp, the effects of change in relaxation can be minimized. Previous studies[8,30,73] in humans with or without cardiac disease have also revealed the clinical usefulness of E:Vp as a relaxation-corrected index of LV filling pressure, and close correlations between E:Vp and pulmonary capillary wedge pressure or pre-A pressure have been found (r = 0.67 to 0.81). Other investigators have shown that the E:Ea relationship is also valid for determining filling pressures in various patient populations with underlying cardiac disease.[8,48] In our study with clinically normal cats, no relation was observed between either E:Ea septal or E:Ea lateral and LVEDP. These results are in agreement with findings in healthy humans.[73]

High HR and sympathetic stimulation enhance isovolumic relaxation, reduce diastolic filling times, and accelerate early diastolic LV recoil.[16,19,21] The HR dependency of many Doppler diastolic variables can confound the clinical assessment of echocardiographic findings.[7,29,39,42] Heart rate influenced DT_E, S:D, peak AR, and several variables of TDI in our study. However, stepwise regression analysis revealed that HR alone did not affect diastolic Doppler variables such as IVRT, Vp, or E:Vp in the range of HRs between 79 and 211 beats/min. Only weak associations between HR and relaxation half-time, another index of isovolumic LVP decline, or IVRT were also reported in 10 clinically normal anesthetized cats (HR, 162 to 217 beats/min)[18] and 92 clinically normal awake dogs (HR, 67 to 162 beats/min).[29] Despite these findings in healthy animals, the relaxation-frequency relationship and its effects on Doppler variables should always be considered in the interpretation of echocardiographic variables in individual patients.[19,21]

The study reported here did have limitations. The number of cats was low, and this could have affected the power of statistical tests used to determine differences and associations between variables. Furthermore, we used only healthy anesthetized cats. It is uncertain whether our findings can be extrapolated to awake cats with myocardial disease. Therefore, these results must be interpreted with caution relative to the clinical setting.

We altered hemodynamics by administering a number of drugs and with fluid volume loading. Although it was not the intent of this study to compare the effects of these drugs on diastolic function, there is clearly the possibility that Doppler or invasive estimates of relaxation and filling might differ under the influence of different drugs, as well as in various hemodynamic states. For example, it is well known that catecholamines not only change contractility, HR, and blood pressure, but also improve myocardial relaxation in a healthy heart. Because it was our intent to compare invasive and noninvasive estimates of diastolic function, the effects of individual drugs were not analyzed.

We used τ as the gold standard of LV relaxation and LVEDP as a surrogate for LV compliance. Reliable determination of τ is not only affected by the method used for mathematical calculation[15,22,24,28] but also by the position of the catheter tip in the LV, from which the appropriate pressure curve is recorded.[11,22] The LVEDP is only 1 of several factors that influence LV compliance.[16,19,26] It was not possible to measure true chamber stiffness or myocardial stiffness to obtain variables such as the constant of chamber stiffness k or pressure-volume relations,[4,11] because wall thickness and absolute LV volume were not determined. Therefore, echocardiographic indices of myocardial stiffness such as the DT_E or the A duration:AR duration[26,71] could not be comprehensively evaluated. The manual method of Vp slope measurement is problematic, especially when the slope is too vertical (high Vp). Using a high sweep speed for Vp recording (150 to 200 mm/s) and the mean of 5 or more measurements to determine Vp may improve the accuracy flow propagation analysis.

The 95% confidence limits of diastolic Doppler estimates of LV relaxation or filling pressures were wide. This may limit the accuracy of an individual estimate, although trends in individual animals may be useful. Additional studies that use these techniques in awake cats are needed to assure the clinical applicability of these examinations.

The study reported here revealed that Doppler variables such as color M-mode LV flow propagation velocity, Vp, and IVRT provide useful estimates of LV relaxation in healthy cats. By combining the Doppler peak E velocity with Vp, better estimates of LV filling pressures may be obtained than those of any other conventional Doppler measurement. These findings have implications for the interpretation of LV diastolic function and filling pressures by use of current Doppler echocardiographic techniques in cats, which require further clinical investigation.

[a]Acepromazine maleate injection, Boehringer Ingelheim Vetmedica Inc, St Joseph, Mo.
[b]Torbugesic, Fort Dodge Laboratories, Fort Dodge, Iowa.
[c]Atropine sulfate, Phoenix Pharmaceutical Inc, St Joseph, Mo.
[d]PropoFlo, Abbott Laboratories, North Chicago, Ill.
[e]Isoflurane, Abbott Laboratories, North Chicago, Ill.
[f]Model 901 infusion/withdrawal pump, Harvard Apparatus Co, Dover, Mass.
[g]Cefazolin, 500 mg, Marsam Pharmaceuticals Inc, Cherry Hills, NJ.
[h]Heparin, Elkins-Sinn Inc, Cherry Hill, NJ.
[i]Lidocaine HCL 2%, Abbott Laboratories, North Chicago, Ill.
[j]Model SPC-75I Millar Mikro-tip catheter pressure transducer and Model TCB-600 control unit, Millar Instruments Inc, Houston, Tex.
[k]DATAQ work station, DATAQ Instruments Inc, Akron, Ohio.
[l]Model F 04 TBN 003, Edwards Swan-Ganz thermodilution catheter, Baxter Healthcare Corp, Edwards Critical-Care Division, Irvine, Calif.
[m]Disposable pressure transducer, Baxter Healthcare Corp, Edwards Critical-Care Division, Irvine, Calif.
[n]Model Solar 7000/8000 patient monitoring system, Marquette Medical Systems Inc, Milwaukee, Wis.
[o]SSA-380A Powervision, Toshiba Corp, Shimoishigami, Japan.
[p]PSK-70 LT, Toshiba Corp, Shimoishigami, Japan.
[q]PSK-50 LT, Toshiba Corp, Shimoishigami, Japan.
[r]Model SVO-9500 MD videocassette recorder, Sony Corp, City, Japan.
[s]Brevibloc, Baxter Healthcare Corp, Deerfield, Ill.
[t]Bonagura JD, Stepien RL, Lehmkuhl LB. Acute effects of esmolol on left ventricular outflow obstruction in cats with hypertrophic cardiomyopathy: a Doppler-echocardiographic study (abstr). *J Vet Intern Med* 1991;5:123.
[u]Dobutamine hydrochloride, Abbott Laboratories, North Chicago, Ill.
[v]Cilobradine, supplied for investigational drug use by Boehringer Ingelheim Vetmedica Inc, St Joseph, Mo.
[w]0.9% Sodium chloride injection, Baxter Healthcare Corp, Deerfield, Ill.
[x]WINDAQ/200, Windows Acquisition and Analysis Software and Advanced CODAS,
DATAQ Instruments Inc, Akron, Ohio.
[y]Model 7100 DDW, Solar and Tram monitoring systems, Marquette Medical Systems Inc, Milwaukee, Wis.
[z]SigmaStat, version 2.0 for Windows 95, Jandel Scientific, San Rafael, Calif.

References

1. Dougherty AH, Naccarelli GV, Gray EL, et al. Congestive heart failure with normal systolic function. *Am J Cardiol* 1984;54:778–782.
2. Soufer R, Wohlgelernter D, Vita NA, et al. Intact systolic left ventricular function in clinical congestive heart failure. *Am J Cardiol* 1984;53:567–571.
3. Briguori C, Betocchi S, Losi MA, et al. Noninvasive evaluation of left ventricular diastolic function in hypertrophic cardiomyopathy. *Am J Cardiol* 1998;81:180–187.
4. Grossman W, McLaurin LP, Ellis L. Alterations in left ventricular relaxation and diastolic compliance in congestive cardiomyopathy. *Cardiovasc Res* 1979;13:514–522.
5. Schober KE, Luis Fuentes V. Zur quantitativen Doppler-echokardiographischen Beurteilung der linksventrikulären diastolischen Herzfunktion beim Hund. *Tieraerztl Prax* 1998;26:13–20.
6. Novotny JM, Hogan PM, Paley DM, et al. Systolic and diastolic dysfunction of the left ventricle induced by dietary taurine deficiency in cats. *Am J Physiol* 1991;261:H121–H127.
7. Gavaghan BJ, Kittleson MD, Fisher KJ, et al. Quantification of left ventricular diastolic wall motion by Doppler tissue imaging in healthy cats and cats with cardiomyopathy. *Am J Vet Res* 1999;60:1478–1486.
8. Nagueh SF, Lakkis NM, Middleton KJ, et al. Doppler estimation of left ventricular filling pressures in patients with hypertrophic cardiomyopathy. *Circulation* 1999;99:254–261.
9. Nishimura RA, Appleton C, Redfied MM, et al. Noninvasive Doppler echocardiographic evaluation of left ventricular filling pressure in patients with cardiomyopathies: a simultaneous Doppler echocardiographic and cardiac catheterization study. *J Am Coll Cardiol* 1996;28:1226–1233.
10. Bright JM, Herrtage ME. Pulsed Doppler assessment of left ventricular diastolic function in normal and cardiomyopathic cats. *J Am Anim Hosp Assoc* 1999;35:285–291.
11. Pak PH, Maughan WL, Baughman KL, et al. Marked discordance between dynamic and passive diastolic pressure-volume relations in idiopathic hypertrophic cardiomyopathy. *Circulation* 1996;94:52–60.
12. Mulvagh S, Quinones MA, Kleiman NS, et al. Estimation of left ventricular end-diastolic pressure from Doppler transmitral flow velocity in cardiac patients independent of systolic performance. *J Am Coll Cardiol* 1992;20:112–119.
13. St Goar FG, Masuyama T, Alderman EL, et al. Left ventricular diastolic dysfunction in end-stage dilated cardiomyopathy: simultaneous Doppler echocardiography and hemodynamic evaluation. *J Am Soc Echocardiogr* 1991;4:349–360.
14. Litwin SE, Grossman W. Diastolic dysfunction as a cause of heart failure. *J Am Coll Cardiol* 1993;22:49a–55a.
15. Constable P, Muir III W, Sisson D. Clinical assessment of left ventricular relaxation. *J Vet Intern Med* 1999;13:5–13.
16. Thomas JD, Weyman AE. Echocardiographic Doppler evaluation of left ventricular diastolic function. Physics and physiology. *Circulation* 1991;84:978–990.
17. Gilbert JC, Glantz SA. Determinants of left ventricular filling and the diastolic pressure-volume relation. *Circ Res* 1989;64:827–852.
18. Golden AL, Bright JM. Use of relaxation half-time as an index of ventricular relaxation in clinically normal cats and cats with hypertrophic cardiomyopathy. *Am J Vet Res* 1990;51:1352–1356.
19. Appleton CP, Firstenberg MS, Garcia M, et al. The Echo-Doppler evaluation of left ventricular diastolic function. A current perspective. *Cardiol Clin* 2000;18:513–546.
20. Raff GL, Glantz SA. Volume loading slows left ventricular isovolumic relaxation rate. Evidence of load-dependent relaxation in the intact dog. *Circ Res* 1981;48:813–824.
21. Banerjee A. Impaired left ventricular relaxation is an early manifestation of diastolic dysfunction: can non-invasive indices be of help? *Prog Pediatr Cardiol* 1999;10:65–74.
22. Davis KL, Mehlhorn U, Schertel ER, et al. Variation in Tau, the time constant for isovolumic relaxation, along the left ventricular base-to-apex axis. *Basic Res Cardiol* 1999;94:41–48.
23. Gaasch WH, Blaustein AS, Andrias CW, et al. Myocardial relaxation. II. Hemodynamic determinants of rate of left ventricular isovolumic pressure decline. *Am J Physiol* 1980;239:H1–H6.
24. Weiss JL, Frederiksen JW, Weisfeldt ML. Hemodynamic determinants of the time-course of fall in canine left ventricular pressure. *J Clin Invest* 1976;58:751–760.
25. Yellin EL, Hori M, Yoran C, et al. Left ventricular relaxation in the filling and nonfilling intact canine heart. *Am J Physiol* 1986; 250:H620–H629.
26. Little WC, Ohno M, Kitzman DW, et al. Determination of left ventricular chamber stiffness from the time for deceleration of early left ventricular filling. *Circulation* 1995;92:1933–1939.
27. Santilli RA, Bussadori C. Doppler echocardiographic study of left ventricular diastole in non-anaesthetized healthy cats. *Vet J* 1998;156:203–215.
28. Hurrell DG, Nishimura RA, Ilstrup DM, et al. Utility of preload alteration in assessment of left ventricular filling pressure by Doppler echocardiography: a simultaneous catheterization and Doppler echocardiographic study. *J Am Coll Cardiol* 1997;30:459–467.
29. Schober KE, Luis Fuentes V. Effects of age, body weight, and heart rate on transmitral and pulmonary venous flow in clinically normal dogs. *Am J Vet Res* 2001;62:1447–1454.
30. Garcia MJ, Ares MA, Asher C, et al. An index of early left ven-

tricular filling that combined with pulsed Doppler peak E velocity may estimate capillary wedge pressure. *J Am Coll Cardiol* 1997;29:448–454.

31. Takatsuji H, Mikami T, Urasawa K, et al. A new approach for evaluation of left ventricular diastolic function: spatial and temporal analysis of left ventricular filling flow propagation by color M-mode Doppler echocardiography. *J Am Coll Cardiol* 1996;27:365–371.

32. Brun P, Tribouilloy C, Duval AM, et al. Left ventricular flow propagation during early filling is related to wall relaxation: a color M-mode Doppler analysis. *J Am Coll Cardiol* 1992;20:420–432.

33. Pasquet A, Garcia M, Thomas JD. New approaches to the Doppler echocardiographic assessment of diastolic function: from research laboratory to clinical practice. *Prog Pediatr Cardiol* 1999;10:105–112.

34. Garcia M, Smedira NG, Greenberg NL, et al. Color M-mode Doppler flow propagation velocity is a preload insensitive index of left ventricular relaxation: animal and human validation. *J Am Coll Cardiol* 2000;35:201–208.

35. Appleton CP, Galloway JM, Gonzales MS, et al. Estimation of left ventricular filling pressures using two-dimensional and Doppler echocardiography in adult patients with cardiac disease. *J Am Coll Cardiol* 1993;22:1972–1982.

36. Thomas JD, Flachskampf FA, Chen C, et al. Isovolumic relaxation time varies predictably with its time constant and aortic and left atrial pressures: implications for the noninvasive evaluation of ventricular relaxation. *Am Heart J* 1992;124:1305–1313.

37. Choong CY, Abascal VM, Thomas JD, et al. Combined influence of ventricular loading and relaxation on transmitral flow velocity profile in dogs measured by Doppler echocardiography. *Circulation* 1988;78:672–683.

38. Appleton CP, Jensen JL, Hatle L, et al. Doppler evaluation of left and right ventricular diastolic function: a technical guide for obtaining optimal flow velocity recordings. *J Am Soc Echocardiogr* 1997;10:271–291.

39. Steen T, Voss BMR, Smiseth OA. Influence of heart rate and left atrial pressure on pulmonary venous flow pattern in dogs. *Am J Physiol* 1994;266:H2296–H2302.

40. Akita S, Ohte N, Hashimoto T, et al. Comparative effects of volume loading on pulmonary venous flow in dogs with normal heart and with myocardial ischemia. *Angiology* 1997;48:401–411.

41. Nishimura RA, Abel MD, Hatle LK, et al. Significance of Doppler indices of diastolic filling of the left ventricle: comparison with invasive hemodynamics in a canine model. *Am Heart J* 1989;118:1248–1258.

42. Appleton CP. Hemodynamic determinants of Doppler pulmonary venous flow velocity components: new insights from studies in lightly sedated normal dogs. *J Am Coll Cardiol* 1997;30:1562–1574.

43. Novotny MJ, Hogan PM. Inotropic interventions in the assessment of myocardial failure associated with taurine deficiency in domestic cats. In: Huxtable E, ed. *Taurine 2*. New York: Plenum Press, 1996;305–314.

44. DeMadron E, Bonagura JD, Herring DS. Two-dimensional echocardiography in the normal cat. *Vet Radiol Ultrasound* 1985; 26:149–158.

45. Schober KE, Luis Fuentes V, McEwan JD, et al. Pulmonary venous flow characteristics as assessed by transthoracic pulsed Doppler echocardiography in normal dogs. *Vet Radiol Ultrasound* 1998;39:33–41.

46. Nagueh SF, Huabin S, Kopelen HA, et al. Hemodynamic determinants of the mitral annulus diastolic velocities by tissue Doppler. *J Am Coll Cardiol* 2001;37:278–285.

47. Sohn DW, Chai IH, Lee DJ, et al. Assessment of mitral annulus velocity by tissue Doppler imaging in the evaluation of left ventricular diastolic function. *J Am Coll Cardiol* 1997;30:474–480.

48. Nagueh SF, Middleton KJ, Kopelen HA, et al. Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. *J Am Coll Cardiol* 1997;30:1527–1533.

49. Tripathi CB, Bhattacharya P, Bhatt JD. Comparative study of beta-adrenoceptor blocking efficacy of two formulations of esmolol in vivo and in vitro. *Indian J Physiol Pharmacol* 1999;43:255–258.

50. McPherson GA, Malta E, Raper C. Effects of some catecholamines on the cat cardiovascular system: interactions with adrenoceptor antagonists. *J Cardiovasc Pharmacol* 1981;3:739–752.

51. Gargini C, Demontis GC, Bisti S, et al. Effects of blocking the hyperpolarization-activated current (I_h) on the cat electroretinogram. *Vision Res* 1999;39:1767–1774.

52. Dyson DH, Allen DG, McDonell WN. Comparison of three methods for cardiac output determination in cats. *Am J Vet Res* 1985; 46:2546–2552.

53. Arvidsson S, Bergqvist D, Haglund U, et al. Cardiac output measurements with thermodilution and radioactive microspheres. A comparative study in cats. *Scand J Clin Lab Invest* 1983;43:617–620.

54. Schuster AH, Nanda NC. Doppler echocardiographic measurement of cardiac output: comparison with a non-golden standard. *Am J Cardiol* 1984;53:257–258.

55. Brody S. Basal energy and protein metabolism in relation to body weight in mature animals of different species. In: Brody S, ed. *Bioenergetics and growth*. New York: Reinhold, 1945;352–403.

56. Bonagura JD, Luis Fuentes V. Echocardiography. In: Ettinger SJ, Feldman EC, eds. *Textbook of veterinary internal medicine*. Philadelphia: WB Saunders Co, 2000;834–873.

57. *SigmaStat user's manual*. San Rafael, Calif: Jandel Scientific, 1995;9-1-12-187.

58. Appleton CP, Hatle LK, Popp RL. Relation of transmitral flow velocity patterns to left ventricular diastolic function: new insights from a combined hemodynamic and Doppler echocardiographic study. *J Am Coll Cardiol* 1988;12:426–440.

59. Quinones MA, Gaasch WH, Alexander JK. Influence of acute changes in preload, afterload, contractile state and heart rate on ejection and isovolumic indices of myocardial contractility in man. *Circulation* 1976;53:293–302.

60. Li LL, Desantiago J, Chu G, et al. Phosphorylation of phospholamban and troponin I in beta-adrenergic-induced acceleration of cardiac relaxation. *Am J Physiol* 2000;278:H769–H779.

61. Stugaard M, Risöe C, Ihlen H, et al. Intracavitary filling pattern in the failing left ventricle assessed by color M-mode Doppler echocardiography. *J Am Coll Cardiol* 1994;24:663–670.

62. Nishihara K, Mikami T, Takatsuji H, et al. Usefulness of early diastolic flow propagation velocity measured by color M-mode Doppler technique for the assessment of left ventricular diastolic function in patients with hypertrophic cardiomyopathy. *J Am Soc Echocardiogr* 2000;13:801–808.

63. Oki T, Mishiro Y, Yamada H, et al. Detection of left ventricular regional relaxation abnormalities and asynchrony in patients with hypertrophic cardiomyopathy with the use of tissue Doppler imaging. *Am Heart J* 2000;139:497–502.

64. Nishimura RA, Abel MD, Hatle LK, et al. Relation of pulmonary vein to mitral flow velocities by transesophageal Doppler echocardiography. *Circulation* 1990;81:1488–1497.

65. Basnight MA, Gonzales MS, Kershenovich SC, et al. Pulmonary venous flow velocity: relation to hemodynamics, mitral flow velocity and left atrial volume, and ejection fraction. *J Am Soc Echocardiogr* 1991;4:547–558.

66. Oh JK, Appleton C, Hatle L, et al. The noninvasive assessment of left ventricular diastolic function with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr* 1997;10:246–270.

67. Sohn DW, Kim YJ, Lee MM, et al. Differentiation between reversible and irreversible restrictive left ventricular filling patterns with the use of mitral annulus velocity. *J Am Soc Echocardiogr* 2000; 13:891–895.

68. Severino S, Caso P, Galderisi M, et al. Use of pulsed Doppler tissue imaging to assess regional left ventricular diastolic dysfunction in hypertrophic cardiomyopathy. *Am J Cardiol* 1998;82:1394–1398.

69. Barbier P, Solomon S, Schiller NB. Determinants of forward pulmonary vein flow. An open pericardium pig model. *J Am Soc Echocardiogr* 2000;35:1947–1959.

70. Rossvoll O, Hatle LK. Pulmonary venous flow velocities recorded by transthoracic Doppler ultrasound: relation to left ventricular diastolic pressures. *J Am Coll Cardiol* 1993;21:1687–1696.

71. Abdalla I, Murray RD, Lee JC, et al. Duration of pulmonary venous atrial reversal flow velocity and mitral inflow A wave: new measure of severity of cardiac amyloidosis. *J Am Soc Echocardiogr* 1998;11:1125–1133.

72. Sohn DW, Choi YJ, Oh BH, et al. Estimation of left ventricular end-diastolic pressure with the difference in pulmonary venous and mitral A durations is limited when mitral E and A waves are overlapped. *J Am Soc Echocardiogr* 1999;12:106–112.

73. Firstenberg MS, Levine BD, Garcia MJ, et al. Relationship of echocardiographic indices to pulmonary capillary wedge pressures in healthy volunteers. *J Am Coll Cardiol* 2000;36:1664–1669.