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Hemodynamic Determinants of the Mitral Annulus Diastolic Velocities by Tissue Doppler

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OBJECTIVES Our goal was to identify the hemodynamic determinants of the mitral annulus (MA) diastolic velocities by tissue Doppler.

BACKGROUND The MA diastolic velocities are promising indexes of left ventricular (LV) diastolic function. However, their hemodynamic determinants have not yet been evaluated.

METHODS Ten adult mongrel dogs underwent left atrial (LA) and LV pressure measurements by Millar catheters while tissue Doppler was applied to record the MA diastolic velocities at the septal and lateral corners. Conventional transmitral flow was also obtained. Left atrial and LV pressures were modified utilizing fluid administration and caval occlusion, whereas dobutamine and esmolol were used to change LV and LA relaxation. Left ventricular filling pressures were altered during different lusitropic states to evaluate for the possible interaction of preload and LV relaxation on the early diastolic velocity (Ea).

RESULTS In the majority of dogs, a positive significant relation was observed between Ea and the transmitral pressure gradient ($r = 0.57$, $p = 0.04$). The Ea had strong correlations with tau ($r = -0.83$, $p < 0.001$), LV $-dP/dt$ ($r = 0.8$, $p < 0.001$) and minimal LV pressure ($r = -0.76$, $p < 0.01$). However, there was no relation between Ea and the transmitral pressure gradient in experimental stages where tau >50 ms. Furthermore, the late diastolic velocity at both corners of the MA had significant positive relations with LA dP/dt ($r = 0.67$, $p < 0.01$) and LA relaxation ($r = 0.73$, $p < 0.01$) but an inverse correlation with LV end-diastolic pressure ($r = -0.53$, $p = 0.01$).

CONCLUSIONS Left ventricular relaxation, minimal pressure and preload determine Ea while late diastolic velocity determinants include LA dP/dt, LA relaxation and LV end-diastolic pressure. (J Am Coll Cardiol 2001;37:278–85) © 2001 by the American College of Cardiology

Mitral annulus (MA) motion (1), which is recorded by tissue Doppler (TD) with high feasibility and reproducibility (2–6), has been studied in the evaluation of left ventricular (LV) function. It has been suggested that the movement of the annulus is dependent on the shortening and lengthening of the longitudinally oriented myocardial fibers; however, information on the hemodynamic determinants of this motion is inadequate.

Preliminary studies suggest that the MA early diastolic velocity (Ea) behaves as an index of LV relaxation (7–11) with a significant inverse correlation between Ea and tau (10,11) and with no change in Ea occurring with preload alterations (11). The later clinical observations suggest that Ea is less load-dependent than conventional Doppler parameters. There is much less information regarding the MA late diastolic velocity (Aa), which decreases as LV filling pressures increase (12). Therefore, because of the unknown simultaneous influence of multiple hemodynamic variables (i.e., heart rate, left atrial [LA] function, LV afterload and systolic function) on Ea and Aa, the relation of Ea and Aa to hemodynamics needs to be evaluated in a setting that permits controlled alteration of these variables. The purpose of this study, therefore, was to identify the hemodynamic determinants of Ea and Aa.

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METHODS

Animal preparation. The study was approved by the Baylor College of Medicine Animal Protocol Review Committee, and all animals were treated in compliance with the 1985 NIH guidelines for the care and use of laboratory animals. Ten adult mongrel dogs weighing 19 to 28 kg were anesthetized with intravenous sodium pentobarbital (30 mg/kg body weight), intubated and mechanically ventilated. Adjustment of tidal volume and oxygen concentration assured maintenance of normal arterial blood gas and pH levels.

After midline sternotomy the heart was exposed, and high fidelity pressure catheters (7F, Millar, calibrated relative to atmospheric pressure before introduction) were inserted into the LA (through its appendage) and LV (retrograde from the right femoral artery through the aortic valve) to record LA and LV pressures respectively. Throughout the procedure, surface electrocardiogram (lead II), atrial and ventricular pressure signals were simultaneously acquired on a computer based data acquisition system (MP 100 Biopac Systems, Santa Barbara, California). Left atrial and LV pressures were digitized with a 5 ms

Abbreviations and Acronyms

Aa	= late diastolic annular velocity
Ea	= early diastolic annular velocity
EDP	= end-diastolic pressure
LA	= left atrial
LV	= left ventricular
MA	= mitral annulus
SV	= stroke volume
tau	= time constant of LV relaxation
TD	= tissue Doppler

sampling frequency, and all recordings were made at end expiration.

Echocardiographic studies. Dogs were imaged epicardially with standard apical views obtained using an Acuson (Mountain View, California) 128 XP ultrasound system equipped with TD program. In the apical 4-chamber view, the pulse-Doppler sample volume was placed at the mitral valve annulus and tips to record 10 to 15 cardiac cycles at each site. The TD program was applied to record the MA velocities (15 cardiac cycles) at the lateral and septal corners. Gains and filters were carefully adjusted to eliminate background noise and allow for a clear tissue signal.

Experimental protocols. Initially, LA pressure was increased with intravenous infusion of isotonic saline and decreased with inferior vena caval external compression. Both the infusions and compressions were performed in a sequential manner with data acquired at predetermined increments and decrements of mean LA pressure. After achieving a stable hemodynamic state at each LA pressure level, the LA and the LV pressures, heart rate and Doppler data, were acquired. After a stable hemodynamic state was achieved, to evaluate the influence of LV relaxation on Ea and LA relaxation on Aa, dobutamine was administered at a dose of 5 μg/kg/min with Doppler and pressure data acquired. Dobutamine infusion was then terminated, and, after the animals returned to their baseline state, esmolol with its negative lusitropic properties was administered (0.5 mg/kg intravenously) with subsequent reacquisition of data. To assess the possible interaction between atrial pressure and ventricular relaxation on the annular velocities, fluid administration and vena caval compression were repeated during the dobutamine infusion and then with esmolol on board.

Data analysis. *Hemodynamic measurements.* The following LV pressures were monitored: minimal, LV end-diastolic pressure (EDP) (determined by the peak of the R wave on the electrocardiogram) and peak systolic pressures. Also ascertained were the first derivatives of LV pressure in systole (dP/dt) and diastole (−dP/dt), the maximal instantaneous diastolic transmitral pressure gradient and the time constant of relaxation (tau) assuming a zero and nonzero pressure asymptote (13). Left atrial pressures measured included peak v, a, x waves and mean LA pressure. Left atrial dP/dt was also determined, and LA relaxation was calculated utilizing the term: [(Pa-Px)/Pa]/(tx-ta) where Pa refers to the peak pressure of the a wave, Px refers to the trough of the x wave and (tx-ta) equals the time interval between the x trough and peak of the a wave (14).

Echocardiographic measurements. The cardiac cycles included were the same ones identified by the electrocardiogram signal for the hemodynamic measurements and represent an average of 5 to 10 cycles. Left ventricular stroke volume (SV) was calculated as the product of mitral annular area and velocity time integral at the annular level. Mitral inflow was analyzed for peak E and A velocities at valve tips. The early diastolic annular velocity (Ea) and Aa were measured at the lateral and septal corners of the MA and their peak values determined using Digisonics EC 500 (Houston, Texas), which is equipped with Doppler analysis software.

Statistical analysis. Early diastolic annular velocity and Aa were correlated with the hemodynamic parameters using regression (linear or nonlinear) analysis. Stepwise regression was then used to determine the hemodynamic parameters that correlated best with the individual Doppler variables. When pooling data from all dogs, dog specific variables (including body and heart weight) were introduced into the model to account for variance related to differences among the dogs. On multiple regression, Ea was related to LA v and mean pressure, the maximal instantaneous diastolic transmitral pressure gradient, tau, peak −dP/dt, LV peak systolic pressure and heart rate. Late diastolic annular velocity was regressed against LA peak dP/dt (as an indicator of LA systolic function), LA relaxation index (see preceding text) and LVEDP (as a surrogate for LA afterload).

The study was powered to detect a significant correlation coefficient of at least 0.4 between the transmitral pressure gradient and Ea (power = 80%, $p = 0.05$). Likewise, the study had a power of 80% to evaluate a range of correlation coefficients of 0.4 to 0.5 between Aa and the several hemodynamic parameters referred to above.

Repeated measures of analysis of variance with Bonferroni correction were used to compare Doppler velocities and hemodynamic parameters at the different lusitropic states (baseline, dobutamine and esmolol) and loading conditions. Significance was set at a p value <0.05.

RESULTS

Table 1 summarizes the hemodynamic data, transmitral flow velocities and TD derived annular velocities obtained at the different experimental stages. With caval occlusion, LV peak systolic and filling pressures decreased significantly with a large percent change, and, although tau shortened, the overall change was small. Inverse changes were present with saline infusion (increase in atrial and ventricular pressures). As expected, heart rate, LV peak systolic pressure and the first derivative of LV pressure increased with

Table 1. Hemodynamics, Transmitral Flow and TD Velocities During Volume Loading, IVC Occlusion, Dobutamine and Esmolol Infusions

Hemodynamic Parameter	Baseline	Volume Loading	IVC Occlusion	Dobutamine	Esmolol
LV peak systolic pressure (mm Hg)	118 ± 22*	130 ± 24†	94 ± 20§	168 ± 33#	75 ± 20
LV SV (ml)	20 ± 5*	28 ± 4‡	14 ± 4	23 ± 4.5	16 ± 5.4¶
Heart rate (beats/min)	115 ± 6	115 ± 8	120 ± 12	136 ± 3#	103 ± 8
LVEDP (mm Hg)	5 ± 3*	11 ± 5†	1.5 ± 0.6§	2 ± 0.8#	14.5 ± 3
LA v wave pressure (mm Hg)	7.5 ± 5*	12 ± 5†	2 ± 1§	4 ± 1#	14.8 ± 3.5
LA mean pressure (mm Hg)	7 ± 4*	11 ± 6.4†	3 ± 2§	3.5 ± 2.2#	14 ± 4
LA x wave pressure (mm Hg)	3 ± 2*	5.8 ± 3.6†	1.7 ± 2§	1 ± 1#	7.3 ± 2
Tau (ms)	42 ± 10	44 ± 9	40 ± 8	26 ± 7‡	87 ± 8¶
LA dP/dt (mm Hg/s)	135 ± 33*	143 ± 38†	118 ± 30§	258 ± 35#	94 ± 23
LV dP/dt (mm Hg/s)	1,770 ± 219*	1,854 ± 230†	1,485 ± 300§	3,360 ± 400#	825 ± 100
LV −dP/dt (mm Hg/s)	1,840 ± 365*	1,925 ± 400†	1,420 ± 400§	3,720 ± 420#	725 ± 367
Transmitral E velocity (cm/s)	46 ± 15*	78 ± 17†	24 ± 12§	65 ± 10#	30 ± 14
Transmitral A velocity (cm/s)	24 ± 10*	35 ± 12‡	17 ± 11¶	37 ± 13#	16 ± 11
Ea (cm/s)	5.2 ± 1*	5.9 ± 1.2†	4.5 ± 1§	8.8 ± 0.8#	3 ± 0.7
Aa (cm/s)	5.5 ± 1.4	5.7 ± 1.3‖	5.3 ± 1	6.8 ± 1.1#	4.2 ± 1

Data: Mean ± SD; *$p < 0.05$ vs. volume loading, IVC occlusion, dobutamine and esmolol stages; †$p < 0.05$ vs. baseline, IVC occlusion, dobutamine and esmolol stages; ‡$p < 0.05$ vs. baseline, IVC occlusion and esmolol stages; §$p < 0.05$ vs. baseline, volume loading, dobutamine and esmolol stages; ‖$p < 0.05$ vs. baseline, dobutamine and esmolol stages; ¶$p < 0.05$ vs. baseline, volume loading and dobutamine stages; #$p < 0.05$ vs. esmolol.

Aa = late diastolic annular velocity; Ea = early diastolic annular velocity; IVC = inferior vena caval; LA = left atrial; LV = left ventricular; LVEDP = left ventricular end-diastolic pressure; SV = stroke volume; TD = tissue Doppler.

dobutamine infusion, which also resulted in a significantly shorter tau. Esmolol, on the other hand, produced slower LV relaxation and heart rate, a lower LV systolic pressure but higher filling pressures. Similar to previous studies (15), transmitral E and A velocities had positive relations with filling pressures (E: LA mean pressure r value ranging from 0.46 to 0.85, for all animals $r = 0.62$, $p < 0.01$; A: LA a wave pressure r value ranging from 0.45 to 0.75 for all animals $r = 0.6$, $p < 0.01$). Furthermore, the peak E velocity was significantly related to tau (all animals $r = -0.4$, $p < 0.01$) and LV −dP/dt ($r = -0.38$, $p < 0.01$).

Relation of Ea to LV filling pressures. In the first stage of experiments, saline infusion and vena caval compression were applied to alter filling pressures. In general, Ea increased as filling pressures did, although the strength of this relation was variable in individual dogs. Importantly, in comparison with baseline values, Ea was most notably altered with large absolute changes of filling pressure. Further, in the setting of low normal values at baseline, even total caval occlusion in some animals was accompanied by minimal or no change in the Ea velocity. These observations were true for both septal and lateral velocities (Fig. 1 and 2). In individual dogs, the correlation coefficient of Ea with LA v wave pressure ranged from 0.4 to 0.66 (p value range: 0.1 to 0.03), with similar relations of Ea to LA mean pressure (r ranged from 0.36 to 0.63; p values between 0.12 and 0.02). Likewise, the maximum instantaneous transmitral pressure gradient had similar associations with Ea. Combining all experimental stages, Ea had positive, but weak, correlations with the transmitral pressure gradient ($r = 0.57$, $p = 0.04$), the LA v ($r = 0.54$, $p = 0.03$) and mean ($r = 0.52$, $p = 0.04$) pressures.

Relation of Ea to LV relaxation and early diastolic recoil. In the second group of experiments, LV relaxation and early diastolic recoil were altered with dobutamine and then esmolol. As dobutamine was administered, tau shortened,

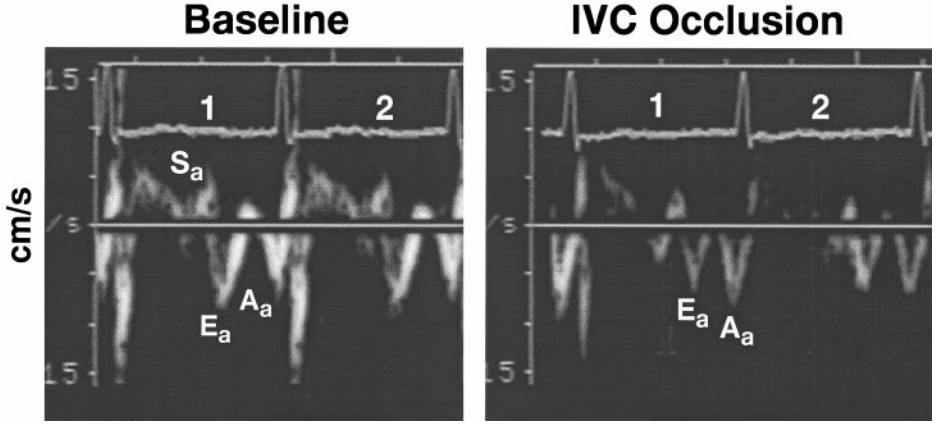

Figure 1. Lateral corner annular velocities at baseline and after interior vena caval (IVC) occlusion. Notice the decrease in early diastolic annular velocity (Ea) after IVC occlusion. Aa = late diastolic annular velocity.

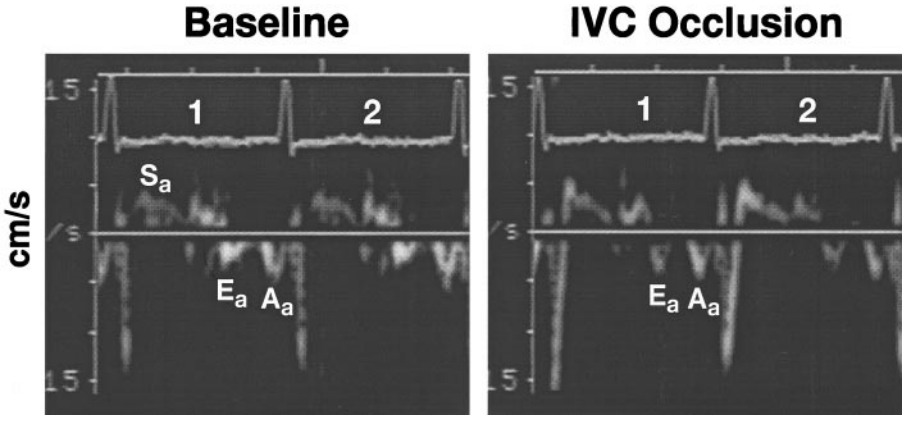

Figure 2. Septal corner annular velocities at baseline and after inferior vena caval (IVC) occlusion in another dog. Notice the minimal changes in early diastolic annular velocity (Ea). Aa = late diastolic annular velocity.

but LV peak systolic pressure, −dP/dt, LV SV and Ea increased. On the other hand, esmolol led to lengthening of tau and decrease in LV peak systolic pressure, −dP/dt and SV along with a significant decrease in Ea (Fig. 3). In general, in individual dogs as well as in the total study cohort, Ea exhibited a strong relation to both tau (zero asymptote: $r = -0.83$; nonzero asymptote: $r = -0.79$; both $p < 0.001$) and −dP/dt ($r = 0.8$, $p < 0.001$) (Fig. 4). As expected, the positive inotropic effect of dobutamine enhanced early diastolic recoil and led to low values of minimal pressure, while esmolol had the opposite effect. Again, in individual animals as well as in the whole group, both septal ($r = -0.75$, $p < 0.001$) and lateral ($r = -0.76$, $p < 0.001$) Ea had strong inverse correlations with this parameter (Fig. 4). Annular Ea related significantly to LV SV (lateral: $r = 0.6$, septal: $r = 0.54$, both: $p < 0.05$). A significant relation was also observed between minimal pressure and SV ($r = -0.67$, $p < 0.02$).

Combined influence of LV relaxation and transmitral pressure gradient on Ea. To determine whether the relation of Ea to filling pressures changes at different lusitropic states, dobutamine and esmolol were administered with subsequent alterations in load. With caval compression, peak systolic and filling pressures decreased during the dobutamine (LV systolic pressure [LVS]: 168 ± 33 to 148 ± 33; LA mean: 3.5 ± 2.2 to 1.5 ± 2.4 mm Hg; both: $p < 0.05$) and esmolol (LVS: 75 ± 20 to 60 ± 25; LA mean: 14 ± 4 to 8 ± 5 mm Hg; both: $p < 0.05$) infusions with some shortening of tau (dobutamine: 26 ± 7 to 22 ± 6 ms; esmolol: 87 ± 8 to 81 ± 7 ms) that did not reach statistical significance ($p = 0.2$). Annular Ea decreased with caval compression during the dobutamine experimental stages (8.8 ± 0.8 to 5.4 ± 1.4 cm/s, $p < 0.05$), whereas it changed minimally with esmolol on board (3 ± 0.7 to 2.8 ± 1.5 cm/s, $p = 0.3$). The relation of Ea to the transmitral pressure gradient was then evaluated in all the experimental stages where tau was ≥50 ms and in those where it was <50 ms. There was no significant relation between Ea and the pressure gradient in the first data set despite high values of transmitral pressure gradients, whereas in the latter group (tau <50 ms) a significant relationship emerged (Fig. 5). To analyze the relationship of Ea to tau at different loading conditions, the data was then redivided into two groups: experimental stages where the LA v wave pressure was <10 mm Hg and those where it was ≥10 mm Hg ($n = 30$). In the latter group, v wave pressure was >14 mm Hg in 18 data points and >18 mm Hg in 10 stages (highest values 20 to 25 mm Hg). In both situations a strong inverse relation was present. The data was best described by two separate lines (overall test of coincidence: $F = 5.1$ and exceeding the critical value of F for $p < 0.01$, with $v_n = 2$ and $v_d = 66$). This was because of a difference in the intercept of the two lines ($t = 3.41$, $p < 0.01$). Interestingly, as LV relaxation

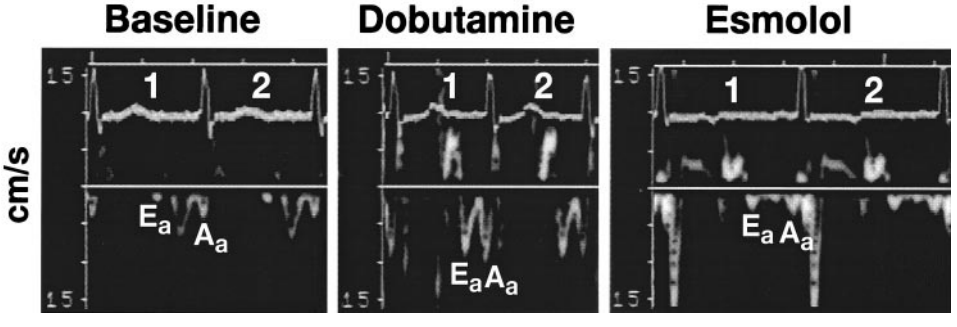

Figure 3. Lateral annular velocities at baseline, with dobutamine and with esmolol. Note the increase of the velocities with dobutamine and their reduction with esmolol. Aa = late diastolic annular velocity; Ea = early diastolic annular velocity.

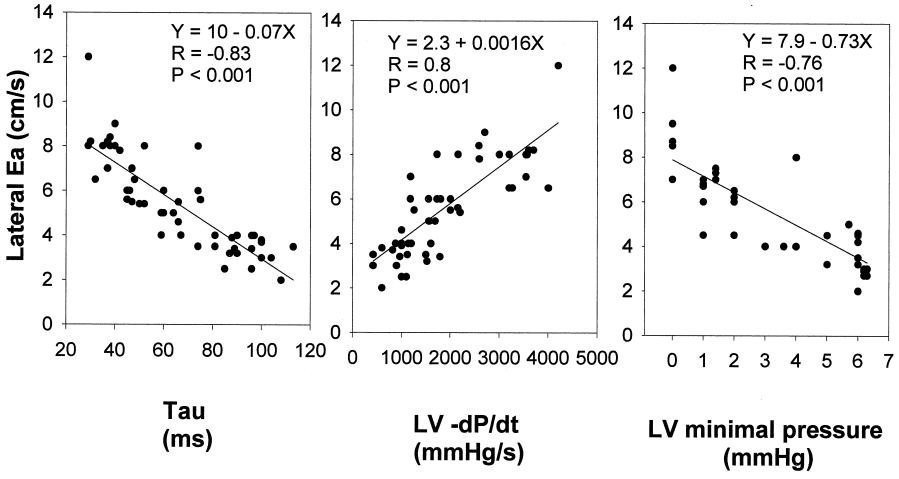

Figure 4. Relation of lateral annular Ea to tau (**left:** $R^2 = 0.69$), LV −dP/dt (**middle:** $R^2 = 0.64$) and LV minimal pressure (**right:** $R^2 = 0.55$) in all experimental stages (n = 70). Ea = early diastolic annular velocity; LV = left ventricular.

worsened, the regression lines for the two groups started to converge (Fig. 6).

Additional hemodynamic parameters related to Ea. Both heart rate and LV peak systolic pressure had weak, but significant, relations to septal and lateral Ea velocities (heart rate vs. septal Ea: $R^2 = 0.12$, $p = 0.003$; heart rate vs. lateral Ea: $R^2 = 0.09$, $p = 0.01$; LV peak systolic pressure vs. septal Ea: $R^2 = 0.12$, $p = 0.003$, LV peak systolic pressure vs. lateral Ea: $R^2 = 0.11$, $p = 0.005$).

On multiple regression analysis, the most important predictor of the lateral annular Ea velocity was tau ($b = -0.05$, standard error [SE] = 0.007, $p < 0.001$) followed by LV minimal pressure ($b = -0.31$, SE = 0.082, $p < 0.001$) and the transmitral pressure gradient ($b = 0.12$, SE = 0.067, $p < 0.05$). The model accounted well for the variance observed in Ea ($r = 0.88$, $R^2 = 0.77$, $p < 0.01$). Similar results were present for septal Ea ($R^2 = 0.71$, $p < 0.01$).

Relation of Aa to LA function and afterload. The Aa was ascertained in only 60 of 70 (86%) experimental stages due to the merging of Ea and Aa at fast heart rates, which occurred during some of the dobutamine infusion stages. Annular Aa had significant correlations with a number of hemodynamic parameters of LA function. Both septal ($R^2 = 0.44$, $p < 0.01$) and lateral ($R^2 = 0.45$, $p < 0.01$) Aa had positive significant relations with the first derivative of

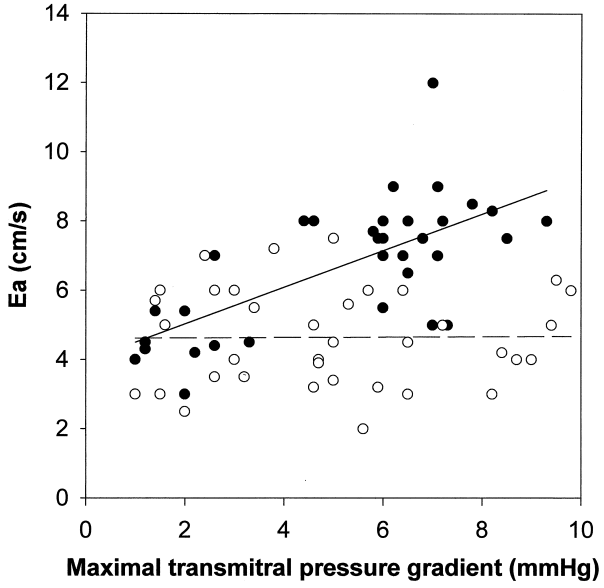

Figure 5. Lateral Ea versus maximal instantaneous transmitral pressure gradient divided according to tau. The **solid line** and **solid circles** show the relation in one group where tau was <50 ms ($y = 3.9 + 0.5x$, [$R^2 = 0.46$, $p < 0.01$]). The **dashed line** and **open circles** show the relation where tau was ≥50 ms ($y = 4.8 - 0.02x$, $R^2 = 0.0013$, $p = 0.5$). Ea = early diastolic annular velocity.

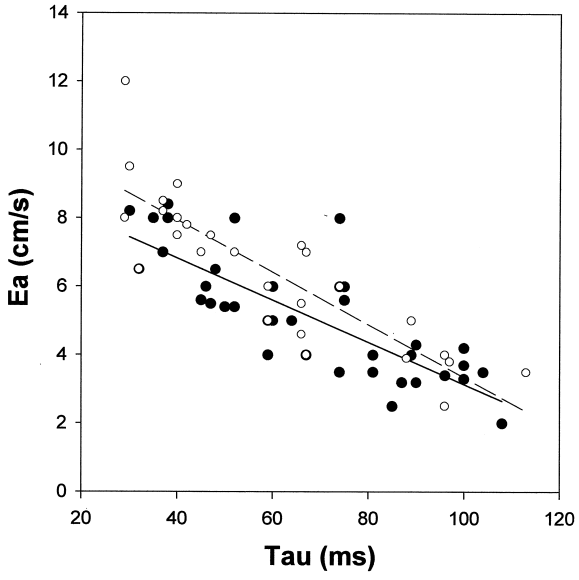

Figure 6. Lateral Ea versus tau in two groups of points divided according to left atrial v wave pressure. The **dashed line** and **open circles** ($y = 11–0.08x$, $R^2 = 0.75$, $p < 0.001$) show the data where the left atrial v wave pressure was ≥10 mm Hg. The **solid line** and **solid circles** ($y = 9.3–0.06x$, $R^2 = 0.6$, $p < 0.001$) show the relation where the pressure was <10 mm Hg. Ea = early diastolic annular velocity.

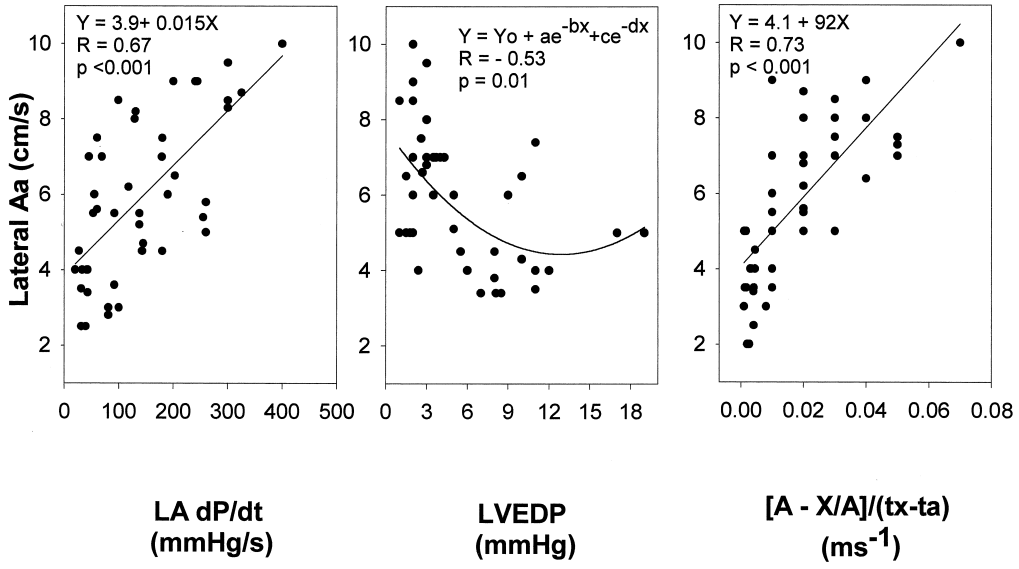

Figure 7. Relation of lateral Aa velocity to LA dP/dt **(left)**; to LVEDP **(middle)** and to LA relaxation index **(right)**. Aa = late diastolic annular velocity; dP/dt = the first derivatives of LA pressure; LA = left atrial; LVEDP = left ventricular end-diastolic pressure.

LA pressure (Fig. 7) and related inversely to LVEDP (lateral: $r = -0.53$, $R^2 = 0.28$; septal: $R^2 = 0.22$; both $p < 0.05$). Interestingly, both septal ($R^2 = 0.27$, $p < 0.01$) and lateral ($R^2 = 0.54$, $p < 0.01$) Aa velocities exhibited good relations with the calculated parameter of LA relaxation. The Aa at both corners of the MA had weak insignificant relationships with peak LV systolic pressure (septal Aa: $R^2 = 0.05$, $p = 0.07$; lateral Aa: $R^2 = 0.06$, $p = 0.06$). Heart rate had no trends for an association with Aa ($R^2 = 0.001$ and 0.004 for septal and lateral velocities, respectively). On multiple regression analysis, LA dP/dt, relaxation and LVEDP were the only predictors of Aa (lateral: $r = 0.83$, $R^2 = 0.69$; septal: $R^2 = 0.61$; both: $p < 0.01$).

DISCUSSION

These canine experiments confirm the important effect LV relaxation and early diastolic recoil have on Ea, and, in the presence of normal and enhanced relaxation states, also uncover this velocity's load dependency. However, when LV relaxation was impaired, Ea was indeed load-independent. It is interesting to note that load increase on average produced a 70% increase in transmitral E velocity, whereas the same manipulations averaged only a 13% change in Ea. Likewise, caval occlusion decreased peak E velocity an average of 48% versus 13% for Ea. On the other hand, Ea mean changes with dobutamine and esmolol (69% and 42%, respectively) were somewhat greater than those of the mitral peak E velocity (41% and 35%, respectively). Regarding Aa, it was determined mostly by hemodynamic parameters of LA function, including LA dP/dt, relaxation and afterload.

Hemodynamic determinants of Ea. We noted a significant positive relation of Ea with a number of parameters indicative of preload (transmitral pressure gradient, LA v and mean pressures). However, this influence was most noticeable with wide ranges in load alteration; in fact, small increments or decrements frequently resulted in minor or no Ea changes. Also, with LV filling pressures at baseline in the low-normal range, even extreme measures of total caval occlusion led to only small Ea changes in a number of dogs. If one were to extrapolate our present data to human physiology, these results suggest that load alteration may result in a low Ea velocity despite normal relaxation and, in this setting, would indicate the need for other clinical and echocardiographic data to infer LV relaxation. Fortunately, this situation is somewhat uncommon clinically and a normal LA size, LV mass, pulmonary artery pressures and pulmonary venous atrial reverse wave duration minus that of the antegrade mitral A wave can confirm the lack of diastolic dysfunction (16–18). Another important finding of these experiments is the lack of an influence of filling pressures on Ea once LV relaxation is impaired. Therefore, in the presence of diastolic dysfunction, low Ea values are indicative of abnormal LV relaxation even when LV filling pressures are increased. This observation is in agreement with the conclusions reached in a number of clinical investigations where Ea was found to be reduced with abnormal LV relaxation even when the mitral inflow pattern was pseudonormal or restrictive (7,10,12). It is interesting that similar results have been reported with TD derived myocardial velocity gradient in early diastole, which is an index independent of cardiac translation (19). Likewise, Ea can unmask abnormal relaxation for patients with hypertensive cardiovascular disease, hypertrophic cardiomyopathy and heart transplants where conventional mitral inflow suggests the contrary or is inconclusive (8,9,20).

The strong relation of Ea to tau and LV −dP/dt supports previous clinical investigations at other laboratories (10,11). Interestingly, as noted in Figure 6, in the presence of normal

JACC Vol. 37, No. 1, 2001
January 2001:278–85

LV relaxation, a higher transmitral pressure gradient leads to a somewhat higher Ea. However, the influence of filling pressures on the relationship between tau and Ea decreased as LV relaxation became worse and was nearly gone at extreme ranges of poor relaxation.

The relationships of Ea to the LV minimal pressure and SV were also examined in this investigation. Left ventricular minimal pressure is a very early diastolic parameter that has been shown to relate to LV end-systolic volume, decreasing as the LV cavity diminishes in systole (21). Thus, LV minimal pressure reflects the elastic energy stored in systole and then released, contributing to the early diastolic suction. Similar to previous reports, we noted a good inverse relation between minimal pressure and LV SV. More importantly, similar to clinical studies highlighting the role of the early diastolic LV recoil in determining Ea (9,22), both septal and lateral annular velocities had good inverse relations with LV minimal pressure. On multiple regression analysis only minimal pressure proved to be one of the determinants of Ea given its relation (minimal pressure) to SV.

Hemodynamic determinants of Aa. The Aa velocity is recorded at the time around LA contraction. We, therefore, sought to relate Aa to parameters of LA systolic function such as dP/dt. As expected, Aa at both corners of the MA had reasonable correlations with that index of LA systolic function. This dependency of Aa on LA dP/dt may account for the observation of higher Aa velocities in patients with impaired LV relaxation and normal filling pressures (8,12). These subjects have an increased LA preload given the reduced early diastolic LV filling. This increased LA preload, in turn, leads to increased LA dP/dt (by the Frank-Starling mechanism) and, therefore, to Aa velocity.

Other hemodynamic determinants found to influence Aa were LVEDP and LA relaxation. The relation of Aa to LVEDP is a complex one being affected by volume status and LV relaxation as well as LA function. With dobutamine infusion, LV relaxation improves with a lower LVEDP and, thus, LA afterload. Since dobutamine also augments LA contraction and relaxation, Aa increases for both reasons (enhanced LA function and decreased LA afterload). Consequently, during some of the experimental stages, lower values of LVEDP were associated with a relatively preserved Aa. Conversely, esmolol resulted in impairment in LV relaxation leading to elevated EDP and atrial afterload. This occurred alongside depression of LA function and concomitant reduction in Aa velocity. However, these relations were confounded with preload alterations. When the volume status was increased with saline infusion, an increased LVEDP was also associated with a somewhat preserved Aa. Conversely, with caval compression, reduction in both Aa and LVEDP was the case. However, the final relation was an inverse one because the highest values of EDP were present during the administration of esmolol. This observation parallels the clinical findings of lower Aa velocities in patients with a pseudonormal mitral inflow pattern in comparison with those with impaired relaxation but normal filling pressures (12).

Annular Aa was also found to have a significant relationship with the LA relaxation parameter. This may be accounted for, in part, by the interaction between LA systolic function and its subsequent relaxation, whereby the more the elastic energy stored in atrial systole, the faster the subsequent relaxation.

Study limitations. The animals were studied with the pericardium open, eliminating potential pericardial influences that were present in the intact animal. However, the pericardial effects on LV filling are minor in normal dogs. Furthermore, we were interested in evaluating the changes of TD velocities in response to different interventions. Accordingly, whatever influence (if any) the open pericardium has on TD velocities, its effect was present throughout all the experimental stages and, thus, cancels out when changes are examined. To avoid the effect of respiration on pressure and Doppler measurements, data were acquired at end expiration and, using the electrocardiogram signal, the same cardiac cycles were analyzed for hemodynamic and Doppler calculations. Although the anteroposterior motion of the heart may affect annular velocities, this most likely influences the anterior and posterior velocities rather than the septal and lateral velocities. The application of the results to the lateral and septal velocities should, therefore, hold. We used the transmitral pressure gradient and a number of LA pressures as surrogates of preload rather than LV end-diastolic volume. Given the consistency of results observed on using these different pressures, we believe that our conclusions remain valid. Also, some degree of merging of Ea and Aa was present at rapid heart rates during the dobutamine infusion stages. This limits the direct comparability of these and other similar animal experiments to human physiology.

Conclusions. Left ventricular relaxation, minimal pressure and transmitral pressure gradient determine Ea under normal lusitropic conditions. In the setting of impaired relaxation however, the influence of filling pressures appears to be minimal. This was the case despite elevated transmitral pressure gradients with values similar to those achieved in dogs with pacing induced heart failure (23). Regarding Aa, its hemodynamic determinants in these canine experiments proved to be LA dP/dt, LA relaxation and LVEDP.

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REFERENCES

1. Isaaz K, Munoz del Romeral L, Lee E, Schiller NB. Quantification of the motion of the cardiac base in normal subjects by Doppler echocardiography. J Am Soc Echocardiogr 1993;6:166–76.
2. Sutherland GR, Stewart MJ, Groundstroem KW, et al. Color Doppler myocardial imaging: a new technique for the assessment of myocardial function. J Am Soc Echocardiogr 1994;23:1441–58.
3. Miyatake K, Yamagishi M, Tanaka N, et al. New method for evaluating left ventricular wall motion by color-coded tissue Doppler imaging: in vitro and in vivo studies. J Am Coll Cardiol 1995;25:717–24.
4. Donovan CL, Armstrong WF, Bach DS. Quantitative Doppler tissue imaging of the left ventricular myocardium: validation in normal subjects. Am Heart J 1995;130:100–4.
5. Uematsu M, Miyatake K, Tanaka N, et al. Myocardial velocity gradient as a new indicator of regional left ventricular contraction: detection by a two-dimensional tissue Doppler imaging technique. J Am Coll Cardiol 1995;26:217–23.
6. Gorscan J, III, Gulati VK, Mandarino WA, Katz WE. Color-coded measures of myocardial velocity throughout the cardiac cycle by tissue Doppler imaging to quantify regional left ventricular function. Am Heart J 1996;131:1203–13.
7. Garcia MG, Rodriguez L, Ares M, Griffin BP, Thomas JD, Klein AL. Differentiation of constrictive pericarditis from restrictive cardiomyopathy: assessment of left ventricular diastolic velocities in longitudinal axis by Doppler tissue imaging. J Am Coll Cardiol 1996;27:108–14.
8. Rodriguez L, Garcia M, Ares M, Griffin BP, Nakatani S, Thomas JD. Assessment of mitral annular dynamics during diastole by Doppler tissue imaging: comparison with mitral Doppler inflow in subjects without heart disease and in patients with left ventricular hypertrophy. Am Heart J 1996;131:982–7.
9. Nagueh SF, Lakkis NM, Middleton KJ, Spencer WH, III, Zoghbi WA, Quinõnes MA. Doppler estimation of left ventricular filling pressures in patients with hypertrophic cardiomyopathy. Circulation 1999;99:254–61.
10. Oki T, Tabata T, Yamada H, et al. Clinical application of pulsed Doppler tissue imaging for assessing abnormal left ventricular relaxation. Am J Cardiol 1997;79:921–8.
11. Sohn D-W, Chai I-H, Lee D-J, et al. Assessment of mitral annulus velocity by Doppler tissue imaging in the evaluation of left ventricular diastolic function. J Am Coll Cardiol 1997;30:474–80.
12. Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quinones MA. Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. J Am Coll Cardiol 1997;30:1527–33.
13. Yellin EL, Hori M, Yoran C, Sonnenblick EH, Gabbay S, Frater RW. Left ventricular relaxation in the filling and nonfilling intact canine heart. Am J Physiol 1986;250:H620–9.
14. Barbier P, Solomon SB, Schiller NB, Glantz SA. Left atrial relaxation and left ventricular systolic function determine left atrial reservoir function. Circulation 1999;100:427–36.
15. Choong CY, Abascal VA, Thomas JD, Guerrero JL, McGlew S, Weyman AE. Combined influence of ventricular loading and relaxation in the transmitral flow velocity profile measured by Doppler echocardiography. Circulation 1988;78:672–83.
16. Rossvoll O, Hatle LK. Pulmonary venous flow velocities recorded by transthoracic Doppler ultrasound: relation to left ventricular diastolic pressures. J Am Coll Cardiol 1993;21:1687–96.
17. Appleton CP, Galloway JM, Gonzalez MS, Graballa M, Basnight MA. Estimation of left ventricular filling pressures using two-dimensional and Doppler echocardiography in adult patients with cardiac disease. J Am Coll Cardiol 1993;22:1972–82.
18. Yamamoto K, Nishimura RA, Chaliki HP, Appleton CP, Holmes DR, Jr, Redfield MM. Determination of left ventricular filling pressure by Doppler echocardiography in patients with coronary artery disease: critical role of left ventricular systolic function. J Am Coll Cardiol 1997;30:1819–26.
19. Shimizu Y, Uematsu M, Shimizu H, Nakamura K, Yamagishi M, Miyatake K. Peak negative myocardial velocity gradient in early diastole as a noninvasive indicator of left ventricular diastolic function: comparison with transmitral flow velocity indices. J Am Coll Cardiol 1998;32:1418–25.
20. Sundereswaran L, Nagueh SF, Vardan S, et al. Estimation of left and right ventricular filling pressures after heart transplantation by tissue Doppler imaging. Am J Cardiol 1998;82:352–7.
21. Udelson JE, Bacharach SL, Cannon RO, III, Bonow RO. Minimum left ventricular pressure during beta-adrenergic stimulation in human subjects: evidence for elastic recoil and diastolic "suction" in the normal heart. Circulation 1990;82:1174–82.
22. Ohte N, Narita H, Hashimoto T, Akita S, Kurokawa K, Fujinami T. Evaluation of left ventricular early diastolic performance by color tissue Doppler imaging of the mitral annulus. Am J Cardiol 1998;82:1414–7.
23. Ohno M, Cheng CP, Little WC. Mechanism of altered patterns of left ventricular filling during the development of congestive heart failure. Circulation 1994;89:2241–50.