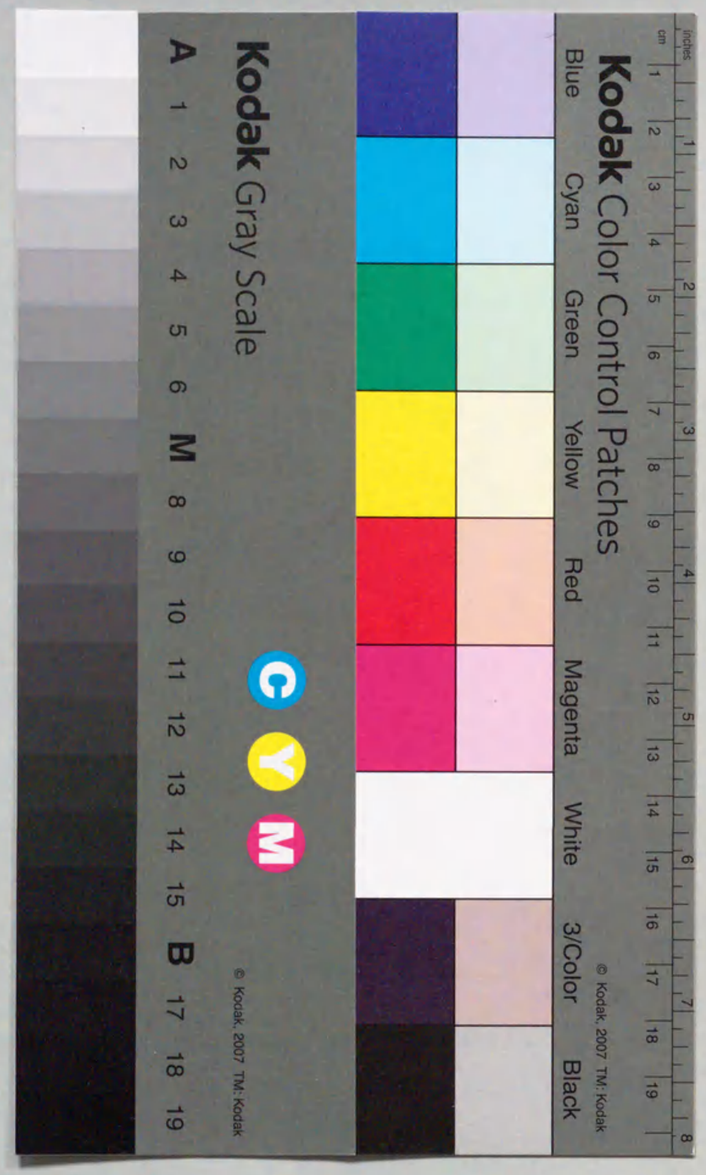

Determinants of left ventricular filling dynamics: Alteration in the Doppler-derived transmitral filling profile with progressive impairment of cardiac function in a dog preparation

(左室充満動態の規定因子：犬標本における心機能増悪過程中のドプラ経僧帽弁流入速波形の変化様式)

宮口 和彦

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Determinants of left ventricular filling dynamics : Alteration in the Doppler-derived transmitral filling profile with progressive impairment of cardiac function in a dog preparation

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①

主　論　文

Determinants of left ventricular filling dynamics: Alteration in the Doppler-derived transmitral filling profile with progressive impairment of cardiac function in a dog preparation

Short Running Title: **Determinants of transmitral filling**

Kazuhiko Miyaguchi, Shozo Ogawa, Hideo Nomura, Masatsugu Iwase, Mitsuhiro Yokota*, Hiroshi Hayashi

The First Department of Internal Medicine and the Department of Clinical Laboratory*, Nagoya University School of Medicine, Nagoya, Japan.

Correspondence to: Kazuhiko Miyaguchi, MD,
The First Department of Internal Medicine,
Nagoya University School of Medicine,
65 Tsurumai, Showa-ku, Nagoya, 466 Japan.
Tel. (052) 741-2111　Fax. (052) 741-1612

左室充満動態の規定因子：犬標本における心機能増悪過程中のドプラ経僧帽弁流入速波形の変化様式

宮口和彦、小川昭三、野村英雄、岩瀬正嗣、横田充弘、林博史

Key words:

pulsed Doppler echocardiography

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diastolic property

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Abstract

To clarify the factors determining transmitral filling, left ventricular and atrial pressures (LVP and LAP) and Doppler-derived diastolic indices were analyzed in six anesthetized dogs at various right atrial pacing rates during dextran infusion. The relationship of the late to early diastolic peak velocity ratio (A/E ratio) to end-diastolic LVP (LVEDP) showed a quadratic curve concave to the LVEDP axis in five animals (r^2=0.320-0.588). An elevation in LVEDP up to 25 mmHg accompanied an increase in A/E ratio (ascending limb), and further LVEDP elevation caused its inverse decline (descending limb). Multiple regression analysis indicated that A/E ratio correlated positively with maximal LVP, a-wave LAP, and heart rate, and negatively with v-wave LAP in both limbs. The time constant of isovolumic LVP decline, which was prolonged as LVEDP was elevated, was a positive correlate of A/E ratio in the ascending limb, but lost its influence on A/E ratio in the descending limb. An elevation in v-wave LAP must have masked the expected effect of left ventricular relaxation abnormality on A/E ratio in this limb. Thus, the transmitral filling profile did not alter unidirectionally, but returned to that seen before volume loading together with progressive impairment of cardiac function.

Introduction

Abnormalities of the Doppler-derived transmitral filling velocity indices have been previously reported in a variety of conditions associated with impaired left ventricular (LV) diastolic function, such as systemic arterial hypertension, aortic stenosis, hypertrophic cardiomyopathy, and coronary artery disease[1-5]. Most of these Doppler studies have been primarily based on the assumption that LV relaxation abnormality causes a decrease in LV early diastolic filling and exaggerates left atrial (LA) systolic filling. However, a disappointingly poor correlation has been found whenever the Doppler-derived LV diastolic indices have been compared to invasively-obtained parameters of LV diastolic properties[5-8]. Recently, some investigators have evaluated the effect of end-diastolic LV pressure and/or v-wave LA pressure on transmitral filling, and have reported a negative correlation between these pressures and LA contribution both with and without an alteration in LV relaxation[8-14]. These findings suggest that LV filling is determined in a complex manner by multiple factors including LV preload and LA driving pressure, and not only by LV relaxation.

However, the relationships of LV filling to the intrinsic properties of the heart and to hemodynamic conditions remain poorly described and imperfectly understood. This study utilized a model of acutely volume-loaded congestive heart failure, which was produced by rapid infusion of dextran into anesthetized open-chest dogs with intact pericardium. To obtain a more precise understanding of the factors determining LV filling dynamics, during progressive deterioration of cardiac function, we evaluated an alteration in the Doppler-derived transmitral fill-

ing profile and analyzed the relationships between the Doppler indices and hemodynamic parameters.

Methods

INSTRUMENTATION

This study conformed to the position of the American Heart Association on research animal use. Six adult mongrel dogs weighing between 20 and 25 kg were anesthetized with xylazene (5 mg/kg intramuscularly) and sodium pentobarbital (25 mg/kg intravenously). They were then intubated and ventilated artificially with a mixture of room air and oxygen delivered by a Harvard respirator. The animals were placed in the supine position, and a midline thoracotomy was performed with the pericardium being maintained intact. The left jugular vein was cannulated for infusion of dextran. A pacing catheter was introduced into the right appendage from the right jugular vein and connected to a pulse generator to control the heart rate (HR). A high-fidelity micromanometer-tip catheter (MODEL 16CT/7F, Gaeltec Ltd., Dunvegan, Scotland) and a fluid-filled reference catheter were inserted into the left ventricle from the right carotid artery to measure LV pressure (LVP). Before each experiment, the micromanometer signal was aligned with the pressure signal obtained from the fluid-filled catheter, which was connected to a pressure transducer (TP-200T, Nihon Kohden, Tokyo, Japan) positioned at the midthoracic level. Another fluid-filled catheter was inserted into the left atrium from the left middle pulmonary vein and connected to another pressure transducer (TP-200T) to measure LA pressure (LAP).

ECHOCARDIOGRAPHIC EXAMINATION

A commercially-available echocardiographic and Doppler system equipped with a 2.0-MHz mechanical sector transducer (SSD-730, Aloka, Tokyo, Japan) was used to evaluate the transmitral filling velocity profile. Pulsed Doppler echocardiography was performed with the transducer positioned at the cardiac apex and the Doppler beam aligned parallel to the presumed transmitral flow. The sample volume was sited in the center of the mitral annulus, and during infusion of dextran, the sampling depth was altered under B-mode guidance as changes in LV size occurred, so as to keep its spatial relation to the mitral annulus constant.

EXPERIMENTAL PROTOCOLS

To obtain a broad hemodynamic data base, LV preload was elevated progressively by infusion of low molecular dextran (10 % dextran) into the left jugular vein at an infusion rate of about 1 L/hr. During rapid infusion of dextran, the atrial pacing rate was increased above a spontaneous HR by increments of 10 bpm over the range for which the two peaks of the Doppler transmitral signal could be clearly separated. This pacing procedure was repeated at several levels of LV preload, and preload itself was elevated to the extent of its plateau level. A single-lead electrocardiogram, LVP, and LAP were monitored on a four-channel oscillograph and also recorded on magnetic tape using a tape recorder. The Doppler and pressure signals were fed to a heat-sensitive recorder attached to the ultrasound imaging system and recorded on paper at a speed of 50 mm/sec. They were obtained simultaneously at the spontaneous HR and about three minutes after starting pacing under each different level of LV preload.

All recordings were performed with respiration suspended in the end-expiratory phase.

DATA ANALYSIS

The analog pressure signals recorded on magnetic tape were digitized with an off-line analog-to-digital converter at 3 msec intervals, and the digitized data were stored on a floppy disk for analysis using a personal computer (PC-9801, NEC, Tokyo, Japan). From the LVP curve, the maximal rate of change of LVP (dP/dtmax), the time constant of isovolumic LVP decline (T_W), and maximal, minimal, and end-diastolic LVPs (LVPmax, LVPmin, and LVEDP) were calculated. T_W was calculated by the method of Weiss et al[15]. Pressures at the LA v-wave and a-wave peaks (LAPv and LAPa) were calculated from the LAP curve. As the Doppler-derived transmitral filling indices, early diastolic peak velocity (E-velocity) and late diastolic peak velocity during atrial systole (A-velocity) were measured from the darkest Doppler velocity envelope, and the ratio of A-velocity to E-velocity (A/E ratio) was calculated. The values of eight successive cardiac cycles were averaged in these determinations.

Results

RELATIONSHIP BETWEEN A/E RATIO AND LVEDP

The Doppler indices were altered substantially in each animal together with hemodynamic changes caused by rapid infusion of dextran and right atrial pacing, as shown in Table 1. A relationship of A/E ratio to LVEDP was described approximately as a non-linear quadratic curve concave to the LVEDP axis in five of

the six animals rather than being linear (Figure 1). Only animal No.6 showed a negative linear relationship ($r=-0.52$, $p<0.05$). The Doppler recordings and pressure tracings for animal No.2 are shown in Figure 2, in which heart rate was almost the same level (80-85 bpm) in these three demonstrative recordings. For each quadratic equation ($y=ax^2+bx+c$; y:A/E ratio, x:LVEDP), a significance of the coefficient of x^2 (a) was evaluated by the t-test, and this coefficient was found to be significantly less than zero in five of the six animals (Table 2). From the five quadratic equations with the negative coefficient of x^2, the maximal value of A/E ratio was calculated to be 0.99±0.31 (mean ± standard deviation) when LVEDP was 25±7 mmHg.

DETERMINANTS OF THE DOPPLER INDICES

Multiple linear regression analysis with stepwise forward selection was used to simultaneously identify the hemodynamic parameters with which each Doppler index of interest correlated significantly. The criterion variables were the Doppler-derived diastolic indices (E-velocity, A-velocity, and A/E ratio). The explanatory variables were the hemodynamic parameters (dP/dtmax, T_W, LVPmax, LVPmin, LVEDP, LAPv, LAPa, and HR). Criterion variable must be almost linearly dependent upon each explanatory variable in this type of analysis[16]. Then, the data of the five animals showing a quadratic relationship had to been divided into two parts at the value of LVEDP (=-b/2a) at which A/E ratio was calculated to be maximal for each quadratic curve. The data from these five animals were pooled separately for the ascending limb of the quadratic curve (n=49) in which an elevation in LVEDP accompanied an increase in A/E ratio, and for the descending limb

of the curve (n=84) where further elevation in LVEDP caused A/E ratio to decrease inversely. The data of the animal No.6 were included in the descending limb in this analysis. Multiple regression analysis was performed for each limb of the curve. The multiple coefficients of determination and partial correlation coefficients of each Doppler index to the hemodynamic parameters are summarized in Table 3.

CHANGES IN THE HEMODYNAMIC AND DOPPLER INDICES IN EACH LIMB

To identify a direction of change in each of the hemodynamic and Doppler indices in each limb, further analysis was performed. The data in each limb were divided into two parts at the median value of A/E ratio for each animal. Thus, there were a total of four subsets of data; the data from the initial (n=25) and peak (n=24) parts of the ascending limb, and the data from the peak (n=42) and terminal (n=42) parts of the descending limb. Scheffe's-type multiple comparison analysis was performed among these four subsets of data (Table 4).

As would be expected, A/E ratio was greater in the peak part of either limb than in the initial part of the ascending limb or in the terminal part of the descending limb. LVPmax, dP/dtmax, and A-velocity all changed in a similar manner to A/E ratio. Each of these four variables showed its maximal value in the peak part of either limb, and then, in the terminal part of the descending limb, it returned to near its initial value obtained before dextran infusion. On the other hand, T_W, LVPmin, LAPv, LAPa, and E-velocity increased unidirectionally together with a progressive elevation in LVEDP. HR did not show any significant difference among the four parts of the quadratic curve.

Discussion

QUADRATIC RELATIONSHIP BETWEEN A/E RATIO AND LVEDP

This study is the first to demonstrate a quadratic relationship between A/E ratio and LVEDP that was concave to the LVEDP axis. The scatter plots in Figure 1 and relatively low values of the coefficients of determination in Table 2 are thought to be unavoidable in the in situ experiment because of spontaneous variations in the other codeterminant factors. The validity of the quadratic relationship was supported statistically by the t-test. We expressed the statistical relationship between A/E ratio and LVEDP as a quadratic equation, however, A/E ratio in itself dose not necessarily possess a so-called "quadratic" relationship with LVEDP, physiologically. What we want to emphasize in this study is that A/E ratio was altered continuously in a biphasic manner with the progressive elevation in LVEDP.

In the first phase of the quadratic relationship, A/E ratio increased together with the hemodynamic changes caused by an elevation in LVEDP (the ascending limb of the quadratic curve). In the second phase, this ratio decreased inversely with the consequent hemodynamic changes induced by further elevation in LVEDP (the descending limb of the curve). Only animal No.6 did not show the quadratic relationship. In this animal, the initial level of LVEDP before dextran infusion was so high that a negative linear relationship, which could be interpreted as the descending limb of the curve, must have been observed.

DETERMINANTS OF LV FILLING DYNAMICS

Theoretically, the velocity of blood flow across the mitral valve is regulated by the transmitral pressure gradient (the

Bernoulli equation)[17-19]. This gradient is potentially determined by the intrinsic properties of the heart, such as the rate and extent of LV active relaxation, contractility and passive chamber stiffness of both left atrium and ventricle, pericardial constraint, and mitral orifice area[20-22]. We did not concentrate on the transmitral pressure gradient in this study, because it is clinically not interesting unless mitral stenosis exists. What we want to evaluate through the Doppler-derived transmitral filling profile are chamber properties and loading conditions. However, various hemodynamic factors affect these properties and also directly influence the transmitral pressure gradient. All of these factors are interdependent on each other. Thus, a simple correlation of one Doppler index with a single hemodynamic parameter is often poor[5-8].

Multiple linear regression analysis is able to account for the effects of multiple factors at the same time without a necessity of controlling each explanatory variable. To use this analysis, we had to separate the data into two limbs because of the quadratic relationship between A/E ratio and LVEDP[16]. Each Doppler index showed significant partial correlations with certain hemodynamic parameters in this analysis. However, some diastolic pressure variables occurring at the different diastolic phase were also selected as correlates of E- or A-velocity, i.e., a partial correlation of E-velocity with LVEDP or LAPa, and that of A-velocity with LVPmin or LAPv. We regarded these results as mis-selections occurring in the stepwise selection process for the following reason. These four diastolic pressure variables would be highly likely to be altered in the same direction and to the same degree by dextran infusion, and actually showed strong

positive linear relationships with each other (r=0.95-0.98). If there is too strong a linear relationship between explanatory variables, this can sometimes lead to erroneous results in this analysis (the problem of multi-collinearity)[23].

The transmitral pressure gradient at the time of E-velocity should be almost equal to the difference between LAPv and LVPmin. This prediction is confirmed by the findings that E-velocity showed a positive correlation with LAPv (upstream pressure) in both limbs and a negative correlation with LVPmin (downstream pressure) in the descending limb. It did not show a significant correlation with LVPmin in the ascending limb, and this result may be due in part to the problem of multi-collinearity described above[23]. Previous studies have demonstrated that LV relaxation profoundly affects the early diastolic phase and that a prolongation in T_W elevates early diastolic LVP[24,25]. However, stepwise multiple analysis selected T_W as a negative correlate of E-velocity in both limbs, suggesting that LV relaxation may affect E-velocity directly rather than only via its influence on LVPmin. It is possible that the speed of isovolumic LVP decline may have some effect on the inertial component of LV suction force[26]. Courtois et al[27] also have documented from LAP and LVP measurements combined with Doppler technique that LV early diastolic filling is augmented by the mechanical suction of blood into the LV cavity.

The late diastolic phase is more complex to understand from basic hydrodynamic principles than the early one. A-velocity correlated positively with LAPa (upstream pressure), but LVEDP, which was substituted for downstream pressure of this phase, was not selected. This lack of a correlation is considered to be

mainly because LA contraction precedes the time of occurrence of LVEDP. It is interesting that A-velocity correlated positively with dP/dtmax and LVPmax in both limbs. This suggests that LV systolic function may parallel A-velocity and also LA systolic function in a worsening course of congestive heart failure.

From partial correlations of E- or A-velocity with the hemodynamic parameters studied, it is easily understood that A/E ratio correlated positively with LAPa and negatively with LAPv. T_W was selected as a positive correlate of this ratio only in the ascending limb. Many investigators have studied the conceptual basis for using the Doppler indices to evaluate LV diastolic properties[1-6,13]. A prolongation in T_W certainly caused A/E ratio to increase, but only in the ascending limb, i.e., at relatively lower levels of LV preload. This suggests that LV relaxation may lose its influence on the transmitral filling profile at higher levels of LV preload. Previous reports have documented that LV relaxation varies directly with LV systolic pressure[28-30]. However, it is possible that LVPmax, which was selected as a positive correlate of this ratio in both limbs, may affect the transmitral filling profile independently of LV relaxation.

Furthermore, an increase in HR is well known to quicken LV relaxation[15,26,30], but showed an incremental effect on A/E ratio in both limbs. Thus, the direct effect of HR on this ratio may overcome the effect mediated through LV relaxation. An increase in HR would be expected to increase a proportion of late diastolic filling, probably as a result of decreasing the time available for early diastolic filling[31,32]. Stoddard et al[14] ruled out changes in LV stiffness and relaxation as an explana-

tion for the alteration in the transmitral filling profile, however, they failed to take into account the effect of concomitant changes in HR.

ALTERATION IN THE TRANSMITRAL FILLING PROFILE WITH PROGRESSIVE IMPAIRMENT OF CARDIAC FUNCTION

In the ascending limb, A/E ratio increased with a prolongation in T_W and moderate elevations in diastolic LAP and LVP. At the same time, LV systolic function assessed by dP/dtmax remained normal or slightly augmented. These results are in accord with previous observations that LV relaxation abnormality is usually one of the earliest manifestations of cardiac dysfunction and frequently precedes systolic dysfunction in many disease states[2-4,33]. The ascending limb is considered to represent a compensatory phase in which relative depression of LV early diastolic filling induced by LV relaxation abnormality is counteracted by an elevation in LAPa and perhaps by the consequent augmentation of LA contraction, so that LV systolic function is maintained.

In the descending limb, redistribution of diastolic filling to early diastole was accompanied by marked elevations in diastolic LAP and LVP together with LV systolic dysfunction, and occurred despite further prolongation in T_W. An elevation in LAPv must have normalized or increased the early diastolic transmitral pressure gradient and masked the expected effect of LV relaxation abnormality on this gradient and on the Doppler indices. Although we did not document the data in this study, in the descending limb, fluctuations in blood gases and pH must have induced global hypoxia or ischemia that can lessen the rate and

extent of LV relaxation and impair contractility of both left atrium and ventricle[34,35]. In the terminal part of the descending limb, all animals produced and expectorated white or pink sputum into the endotracheal tube due to pulmonary edema. The arterial P_{O2} was 40 mmHg and the pH was 7.1 in the terminal part in the animal N0.2. The descending limb can be regarded as a worsening course of congestive heart failure.

A/E ratio, which is one of the indices expressing LA contribution to LV filling, has been previously reported to be high under the condition of impaired LV relaxation[1-5]. On the other hand, this ratio has been recently reported to be low under high levels of LVEDP and/or LAPv[8-14]. We demonstrated that these two phases in the alteration of A/E ratio were continuous during progressive impairment of cardiac function. In this process, positive predictors of A/E ratio were counteracted by negative predictors, thus during volume loading, A/E ratio exhibited the biphasic alteration.

Lavine et al[36] have reported that redistribution of diastolic filling to early diastole in the acutely dilated left ventricle was mediated by pericardial constraint. However, the effect of the pericardium is itself mediated through alterations in the diastolic properties of the heart and loading conditions. The extreme elevations in diastolic LAP and LVP shown in the terminal part of the descending limb must have reflected this pericardial constraint. More recently, Myreng et al[37] have reported that this redistribution of diastolic filling was observed at markedly elevated filling pressures in an experimental open-chest, open pericardium dog model. It is still controversial whether pericardial constraint is essential for this redistribution or not.

LIMITATION OF THE STUDY

The study limitation is that it was not possible to evaluate all the potential factors that must affect LV filling dynamics. In multiple regression analysis relating to A-velocity, the multiple coefficients of determination gave relatively lower values, especially in the descending limb, and this resulted in the lower multiple coefficient of determination for A/E ratio too. LV passive chamber stiffness, pulmonary venous compliance, and LA systolic function are the three major intrinsic properties that affect the late diastolic transmitral pressure gradient[20]. Thus, these factors also have a profound effect on A-velocity. Further investigations taking into account these three factors are essential to clarify the relationship of LV filling dynamics to the intrinsic properties of the heart and to hemodynamic conditions.

The time interval between mitral valve opening and LVPmin is expected to be an another important factor of LV filling. We analyzed this interval, however, this was not selected as a significant correlate of the transmitral filling velocities in stepwise multiple linear regression analysis. It did not show any significant difference among the four parts of the curve. These results may be ascribed to that the interval is a function of the sites of intraventricular pressure measurement and increases from the LV apex to the LV base[27]. In this study, the site of the tip of the micromanometer might have been variable in the left ventricle during volume loading and right atrial pacing. Therefore, we could not separate the pure effect of the alteration in hemodynamic conditions on this parameter from its whole change including the influence of the site of LVP measurement.

Conclusions

The Doppler-derived LV diastolic indices were found to be substantially and simultaneously affected by multiple factors in addition to LV relaxation. These factors included contractility and loading conditions of both left atrium and ventricle and HR. Our model of volume-loaded cardiac failure showed that, despite the progressive impairment of LV relaxation, the transmitral filling profile returned to that seen before volume loading with severe elevations in diastolic LAP and LVP and with LV systolic dysfunction. The findings of this study urge that these multiple factors should be carefully considered when the Doppler indices are clinically used to evaluate LV diastolic function.

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Table 1 Parameters measured in each animal

Animal Number	1	2	3	4	5	6
Measurements Number	18	21	24	33	21	16
dP/dtmax(mmHg/sec)	693-3995	502-2460	1355-2625	1267-2483	1030-2720	919-2688
T_W (msec)	41-96	39-110	44-104	49-91	45-113	80-97
LVPmax (mmHg)	67-166	50-137	100-181	93-189	78-171	81-226
LVPmin (mmHg)	8-29	0-20	8-33	8-25	11-34	17-46
LVEDP (mmHg)	12-38	2-27	13-45	11-38	17-46	22-60
LAPv (mmHg)	4-30	3-20	11-37	8-31	11-46	24-64
LAPa (mmHg)	13-39	3-28	15-46	12-39	19-47	23-62
Heart Rate (bpm)	64-102	67-101	70-101	82-122	81-111	66-123
E-velocity(cm/sec)	34-59	21-40	30-62	20-58	43-67	33-88
A-velocity(cm/sec)	19-53	16-40	19-48	20-44	18-56	22-71
A/E ratio	0.44-0.99	0.78-1.79	0.34-1.58	0.45-1.85	0.30-1.06	0.52-1.18

dP/dtmax:the maximal rate of change of left ventricular pressure; T_W:the time constant of isovolumic left ventricular pressure decline; LVPmax, LVPmin, and LVEDP:maximal, minimal, and end-diastolic left ventricular pressure; LAPv and LAPa:v-wave and a-wave left atrial pressure; E- and A-velocity:early and late diastolic peak velocity; A/E ratio:the late to early diastolic peak velocity ratio.

Table 2 Coefficients for a quadratic equation of the late to early diastolic peak velocity ratio (y) to left ventricular end-diastolic pressure (x) ($y=ax^2+bx+c$) and coefficients of determination (r^2)

Animal Number	1	2	3	4	5	6
a	-0.001^{*}	-0.004^{**}	-0.001^{*}	-0.003^{*}	-0.002^{*}	0.001
b	0.053	0.110^{**}	0.061^{*}	0.121^{*}	0.095^{*}	-0.048
c	0.070	0.569^{**}	-0.051	-0.072	-0.892	1.765^{**}
r^2	0.344	0.588	0.320	0.406	0.442	0.274
p value	<0.05	<0.001	<0.05	<0.05	<0.01	0.12

*:p<0.05, **:p<0.01 coefficient different from zero.

Table 3 Multiple coefficients of determination (r^2) and partial correlation coefficients obtained by multiple regression analysis in the ascending and descending limb of a quadratic relationship between the late (A-velocity) to early diastolic peak velocity (E-velocity) ratio (A/E ratio) and left ventricular end-diastolic pressure (LVEDP)

Limb	Ascending	Descending	Ascending	Descending
Measurements Number	49	84	49	84
	E-velocity		A-velocity	
r^2	0.814	0.821	0.760	0.690
dP/dtmax	------	------	0.307^{*}	0.439^{***}
T_W	-0.597^{***}	-0.240^{*}	0.235^{+}	------
LVPmax	------	------	0.463^{**}	0.463^{***}
LVPmin	------	-0.370^{***}	-0.517^{***}	0.308^{**}
LVEDP	------	0.478^{***}	------	------
LAPv	0.774^{***}	0.554^{***}	-0.421^{**}	------
LAPa	-0.440^{**}	-0.358^{**}	0.468^{**}	0.161^{+}
Heart Rate	-0.458^{**}	-0.371^{***}	0.514^{***}	------

Table 3 (Continued)

Limb	Ascending	Descending
Measurements Number	49	84
	A/E ratio	
r^2	0.823	0.600
dP/dtmax	------	0.237^{*}
T_W	0.559^{***}	------
LVPmax	0.635^{***}	0.368^{***}
LVPmin	-0.534^{***}	0.449^{***}
LVEDP	------	-0.420^{***}
LAPv	-0.666^{***}	-0.367^{***}
LAPa	0.485^{***}	0.193^{+}
Heart Rate	0.620^{***}	0.251^{*}

dP/dtmax:the maximal rate of change of left ventricular pressure; T_W: the time constant of isovolumic left ventricular pressure decline; LVPmax and LVPmin: maximal and minimal left ventricular pressure; LAPv and LAPa: v-wave and a-wave left atrial pressure; +:$p<0.10$, *:$p<0.05$, **:$p<0.005$, ***:$p<0.001$.

Table 4 Comparison among the four parts of a quadratic relationship between the late (A-velocity) to early diastolic peak velocity (E-velocity) ratio (A/E ratio) and left ventricular end-diastolic pressure (LVEDP) (Initial and Peak Part of Ascending Limb, and Peak and Terminal Part of Descending Limb)

Limb		Ascending		Descending			
Part		Initial	Peak	Peak		Terminal	
Measurements Number		25	24	42		42	
dP/dtmax	(mmHg/sec)	1880±568	2192±680	2406±370	**	1811±598	+ $$
T_W	(msec)	38±7	47±8 *	63±11	**+	82±28	**++$$
LVPmax	(mmHg)	112±19	137±20 *	160±31	**+	129±42	$$
LVPmin	(mmHg)	9±5	13±4 *	21±6	**++	27±8	**++$$
LVEDP	(mmHg)	13±5	20±7 *	30±7	**++	38±9	**++$$
LAPv	(mmHg)	9±5	15±7 *	25±7	**++	34±13	**++$$
LAPa	(mmHg)	13±5	21±6 *	31±6	**++	38±10	**++$$
Heart Rate	(bpm)	88±11	94±13	93±11		87±13	
E-velocity	(cm/sec)	39±12	37±11	46±16	++	49±13	* ++
A-velocity	(cm/sec)	23±4	34±6 **	43±10	**++	32±10	** $$
A/E ratio		0.67±0.24	1.13±0.37**	0.99±0.26**		0.67±0.16	++$$

All values are expressed as mean ± standard deviation. dP/dtmax:the maximal rate of change of left ventricular pressure; T_W:the time constant of isovolumic left ventricular pressure decline; LVPmax and LVPmin:maximal and minimal left ventricular pressure; LAPv and LAPa:v-wave and a-wave left atrial pressure; *:$p<0.05$, **:$p<0.01$ vs the initial part of the ascending limb; +:$p<0.05$, ++:$p<0.01$ vs the peak part of the ascending limb; $$:$p<0.01$ vs the peak part of the descending limb.

Figure legends

Figure 1 The relationship of the late to early diastolic peak velocity ratio (A/E) to left ventricular end-diastolic pressure (LVEDP) as determined in each animal. This relationship showed a non-linear quadratic curve concave to the LVEDP axis, except in animal No.6. In this animal, LVEDP before infusion of dextran was so high (22 mmHg) that only the descending limb of the quadratic curve could be observed. No.1-No.6:animal number.

Figure 2 The relationship of the late to early diastolic peak velocity ratio (A/E, y) to left ventricular end-diastolic pressure (LVEDP, x) for animal No.2 (upper panel) combined with the tracings of Doppler signal, left ventricular pressure (LVP), and left atrial pressure (LAP) (lower panel), in which heart rate was almost the same level (80-85 bpm). Quadratic regression gave the following equation: $y=-0.004x^2+0.110x+0.569$ ($n=21$, $r^2=0.588$, $p<0.001$). 1,2,3:experimental stage.

Summary of main result

The Doppler-derived transmitral filling profile was simultaneously affected by multiple factors including LV relaxation, LV and LA systolic function, loading conditions, and HR. It returned to that seen before volume loading with severe elevation in diastolic chamber pressure and LV systolic dysfunction, despite the progressive impairment of LV relaxation.

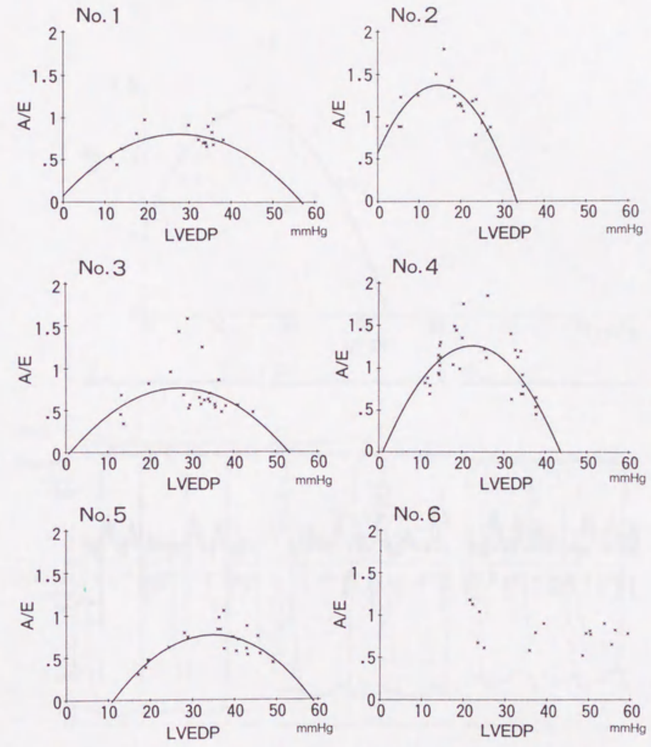

Figure 1

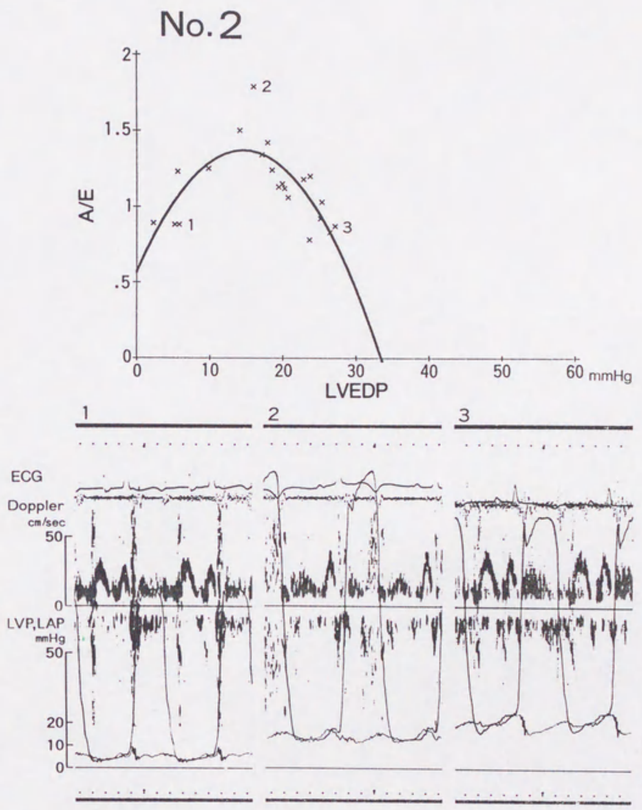
No. 2
A/E
2
1.5
1
.5
0
0
10
20
30
40
50
60 mmHg
LVEDP
1
2
3
ECG
Doppler
cm/sec
50
0
LVP,LAP
mmHg
50
20
10
0

Figure 2