Wide-Range Load Shift of Combined Aortic Valvuloplasty-Arterial Vasodilation Slows Isovolumic Relaxation of the Hypertrophied Left Ventricle

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To assess the effects of left ventricular (LV) load on isovolumic relaxation rate of the hypertrophied LV, wide range LV load shifts were imposed by the sequential use of balloon aortic valvuloplasty (BAV) and arterial vasodilation in 14 patients with severe sclerocalcific aortic stenosis (aortic valve area, 0.45±0.16 cm^2). Micromanometer tip–catheter LV pressure recordings (n=14) and simultaneous LV angiograms (n=9) were obtained before BAV, during nitroprusside infusion (NIT) before BAV, 48 hours after BAV, and 48 hours after BAV during NIT. LV peak systolic pressure (LVPSP) decreased from 237±33 mm Hg before BAV to 200±33 mm Hg (p<0.01) during NIT before BAV, to 201±27 mm Hg (p<0.01) after BAV and to 165±26 mm Hg (p<0.01) during NIT after BAV. LV end-systolic volume (LVESV) decreased from 55±34 ml before BAV to 25±23 ml (p<0.01) during NIT before BAV, to 30±32 ml (p<0.025) after BAV and to 15±12 ml (p<0.025) during NIT after BAV. LV end-systolic wall stress (LVESs) decreased from 90±30.10^3 dyne/cm^2 before BAV to 41±13.10^3 dyne/cm^2 (p<0.01) during NIT before BAV, to 55±16.10^3 dyne/cm^2 (p<0.025) after BAV and to 26±6.10^3 dyne/cm^2 (p<0.01) during NIT after BAV. Only after sequential BAV-NIT was the time of LV electromechanical systole (LVEST), which marked the onset of the LV isovolumic relaxation period, significantly reduced (from 419±26 msec before BAV to 363±28 msec after BAV-NIT [p<0.01]). The time constants of LV pressure decay with zero or nonzero asymptote pressure (T_0 and T_{PB}) remained unchanged after BAV and during NIT before BAV. At the lowest LVPSP, LVESV, and LVESs after sequential BAV-NIT, both T_0 and T_{PB} significantly prolonged from 35.7±6.3 to 46.7±12.6 msec (p<0.025) and from 46.6±12.5 to 73.2±23.3 msec (p<0.01). Phase-plane plots (LV dP/dt vs. LVP) of the LV pressure (P) signal during isovolumic relaxation were constructed for the four different loading states by matching corresponding LVP and LV dP/dt points. For a given LVP value, the corresponding LV dP/dt values on the phase plane plots were comparable before BAV, during NIT before BAV, and after BAV. The corresponding LV dP/dt value was higher during NIT after BAV, implying a slower relaxation rate at the same LVP after sequential BAV-NIT. A shift in the control of isovolumic LV relaxation kinetics from myofilamentary detachment to myoplasmic calcium removal, which proceeds slower in hypertrophied myocardium, could explain the observed slowing of LV isovolumic relaxation after drastic LV unloading of sequential BAV-NIT. (*Circulation* 1990;81:886–898)

The effects of left ventricular (LV) load on the time course of isovolumic LV pressure decay remain controversial. In animal experiments, a rise of LV load by volume loading, infusion of vasopressors, or mechanical occlusion of the aorta slows isovolumic LV pressure decline.[1–4] In normal control subjects or in patients with aortic stenosis, similar interventions fail to change the time constant of isovolumic LV pressure decay.[5,6]

The effects of LV load on the onset and time course of LV pressure decline are important because they reveal whether relaxation kinetics are controlled by myofilamentary detachment or by myoplasmic calcium removal.[7] These effects, therefore, provide valuable information on the causes underlying slow

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relaxation of ischemic[8–11] or hypertrophied[12–15] hearts or on the site of action of drugs that alter relaxation kinetics.[16–22]

In humans, the effects of LV load on isovolumic LV relaxation kinetics have so far been investigated using modest LV load shifts induced by infusion of vasodilators or vasopressors either in normal subjects[5] or in patients with aortic stenosis.[6] In the present study, we reassessed the effects of LV load changes on isovolumic LV pressure decay in patients with aortic stenosis using wide-range LV load shifts obtained by a sequential use of balloon aortic valvuloplasty[23,24] and arterial vasodilation.

Methods

Patients

Fourteen patients (10 women and four men) (age range, 70–84 years; mean age, 77 years) with sclerocalcific aortic stenosis were studied. All patients were referred for balloon aortic valvuloplasty because of estimated high surgical risk of aortic valve replacement because of advanced age or concomitant debilitating noncardiac disease. At the time of referral, nine patients were in New York Heart Association (NYHA) functional class III and five patients were in functional class IV (patients 1, 5, 9, 10, and 11 in Table 1). Predominant symptoms were dyspnea ($n=9$), angina ($n=9$), and syncope or presyncope with exertion ($n=4$). No patient had more than trivial aortic regurgitation. No patient had significant mitral valve disease on the left ventricular angiogram or significant coronary artery stenoses (coronary artery luminal diameter narrowing >50%) on the coronary angiogram. Table 1 summarizes individual patient characteristics, mean transvalvular aortic gradient, aortic valve area before and after balloon aortic valvuloplasty, LV end-diastolic volume index, LV ejection fraction, and LV wall mass index derived from the LV angiogram obtained before balloon aortic valvuloplasty. Aortic valve area was calculated using the Gorlin formula.[25] The angiographic indexes were calculated from single-plane LV cineangiograms performed in 30° right anterior oblique projection[26] using an LV wall thickness measurement performed on an end-diastolic frame two thirds of the distance from the aortic valve to the apex.[26] LV pressure-overload hypertrophy was evident from the increased LV wall mass index (191±87 g/m^2). All patients were in sinus rhythm at the time of balloon aortic valvuloplasty and at the time of repeat catheterization, 48 hours after balloon aortic valvuloplasty. At the time of both studies, five patients were using digoxin and no patient was on any other positive or negative inotropic drug. There were no immediate complications as a result of the balloon aortic valvuloplasty. Two patients (patients 10 and 12 in Table 1) underwent surgical closure of the right femoral artery balloon entry site because of development of arterial pseudoaneurysm 10 and 3 days, respectively, after the balloon aortic valvuloplasty. There were no complications as a result of the repeat catheterization 48 hours after the balloon aortic valvuloplasty. Informed consent was obtained for each patient for balloon aortic valvuloplasty and repeat hemodynamic-angiographic measurements during nitroprusside infusion and after balloon aortic valvuloplasty.

Hemodynamic Studies

Diagnostic left-right heart catheterization and angiography were performed from a femoral approach using left femoral artery and vein. LV pressure was measured with a high-fidelity micromanometer-tip catheter. A second fluid-filled catheter was advanced to the LV from the right femoral artery. After performing baseline prevalvuloplasty hemodynamic measurements ($n=14$) (Table 2, column A) and an LV angiogram ($n=12$), a nitroprusside infusion was started at an infusion rate of 0.5 μg/kg/min. The infusion rate was increased by 0.5 μg/kg/min every 3 minutes until mean aortic pressure had fallen by 20–30 mm Hg as compared with baseline prevalvuloplasty measurements. At that time, repeat hemodynamic measurements ($n=14$) (Table 2, column B) and a second LV angiogram ($n=9$) were obtained. After cessation of the nitroprusside infusion and return of mean aortic pressure to baseline value, the second fluid-filled LV catheter was exchanged for a 0.038-in. exchange guide wire and a balloon dilation catheter (20 mm or 23 mm Mansfield) was advanced across the valve. The high-fidelity micromanometer-tip catheter was kept in the LV to continuously monitor LV performance during the balloon inflations.[27] Fifteen minutes after balloon dilation of the aortic valve, repeat hemodynamic measurements were obtained. At this instant, LV contractile performance was still depressed[28,29] because of residual myocardial ischemia incurred during the valvuloplasty balloon inflations.[27,30,31] This depression of LV function offsets hemodynamic measurements[28,32] obtained shortly after balloon aortic valvuloplasty. Left-right heart catheterization was, therefore, repeated 48 hours after balloon aortic valvuloplasty at a time when LV function had recovered.[28] Repeat hemodynamic measurements ($n=14$) (Table 2, column C) and an LV angiogram ($n=9$) were obtained. After these measurements, nitroprusside was again administered at a rate that was identical to the prevalvuloplasty infusion, and a fourth set of hemodynamic measurements ($n=14$) (Table 2, column D) and LV angiograms ($n=9$) were performed.

All pressures were referenced to atmospheric pressure at the level of the midchest. LV pressure was measured with a micromanometer-tip catheter calibrated externally against a mercury reference and matched against luminal pressure. An LV dP/dt signal was derived from the high-fidelity LV pressure signal with an electronic differentiator (100 Hz high-cut filter). The pressure signals, the LV dP/dt signal, and a bipolar standard lead of the electrocardiogram were recorded on a Gould ES 1000 multichannel

recorder. Pressure signals were digitized on line with a Hewlett-Packard 9836 computer. All hemodynamic data (Table 2) were averaged throughout a complete respiratory cycle during normal sinus rhythm. Cardiac outputs were measured with Fick or thermodilution techniques (average of at least three values, 9520A Cardiac Output Computer, Edwards Laboratories).

Data Analysis

Two time constants of LV pressure decay (T_0 and T_{PB}) (Table 4) were derived from the digitized pressure data points of isovolumic LV relaxation. The time constant T_0 was derived from an exponential curve fit with zero asymptote pressure,[33] and the time constant T_{PB} was derived from an exponential curve fit with variable asymptote pressure.[13,34] Pressure data points were obtained at 3-msec intervals by digitizing the LV pressure signal from the moment of LV dP/dt min to a time at which LV pressure equaled LV end-diastolic pressure plus 5 mm Hg. When drastically altering LV load, the start and end point of the time constant analysis shift widely. This causes erroneous reductions or prolongations of the time constant value.[35] To avoid this mathematical pitfall, individual time constants (T_0 and T_{PB}) for the four different LV loadings (Table 4, columns A, B, C, and D) were calculated using the same starting point (the lowest pressure at which LV dP/dt min occurred) and the same end point (the pressure that equaled the highest LVEDP+5 mm Hg). The mean correlation coefficients for the exponential curve fits of the time constant analysis using a zero asymptote pressure (T_0) (Table 4) were 0.995 (range, 0.989–0.998), 0.992 (range, 0.983–0.998), 0.996 (range, 0.994–0.999), and 0.992 (range, 0.983–0.997). The mean correlation coefficients for the exponential curve fits of the time constant analysis using a nonzero asymptote pressure (T_{PB}) (Table 4) was 0.996 (range, 0.991–0.999), 0.994 (range, 0.985–0.998), 0.997 (range, 0.995–0.999), and 0.994 (range, 0.987–0.997). Phase plane plots of the LV pressure signal during isovolumic relaxation[36] were constructed by matching corresponding LV pressure and LV dP/dt data points (see Figure 4). Data processing for the calculation of the time constants of LV pressure decay and for the construction of the phase-plane plots was performed using an Apple M0001WP512K computer (Cupertino, California). To assess upward or downward convexity of the negative dP/dt upstroke pattern, a dP/dt (20/60) ratio was calculated[37] by dividing the negative dP/dt value at 20 msec after the onset of LV isovolumic relaxation by the negative dP/dt value at 60 msec after the onset of LV isovolumic relaxation. The lower the dP/dt (20/60) ratio, the more downward the convexity of the negative dP/dt upstroke pattern.[37]

LV end-diastolic volume index, ejection fraction, and LV wall mass index (Table 1) were calculated from single-plane LV cineangiograms performed in 30° right anterior oblique projection using the area-length method and a regression equation.[26] LV wall thickness was measured on an end-diastolic frame at the LV free wall, two thirds of the distance from the aortic valve to the apex in right anterior oblique projection. For all frames subsequent to end diastole, LV wall thickness was calculated assuming a constant mass for each frame.[38] LV end-diastolic and LV end-systolic volumes were identified by cine frame markers on the simultaneously recorded LV pressure tracing as these volumes that corresponded respectively with LV end-diastolic pressure and LV dP/dt min. LV dP/dt min was used as a marker of end systole to calculate myocardial load at the onset of isovolumic LV pressure decay. LV circumferential end-systolic wall stress (Table 2) was computed using a thick wall ellipsoid model of the LV,[39] as follows:

$$S = PD/2h * [1 - (h/D) - (D^2/2L^2)] * 1{,}332 \text{ dyne/cm}^2$$

where P is LV pressure, h is LV wall thickness, and D and L are LV diameter and length at the midwall.

Myocardial oxygen supply-demand balance was assessed by DPTI:SPTI ratio (Table 3).[31,40] Systolic pressure time index (SPTI) was calculated from the area under the LV pressure trace extending from the onset of LV isovolumic contraction to the onset of LV isovolumic relaxation multiplied by heart rate. Diastolic pressure time index (DPTI) was calculated from the area between aortic pressure and LV pressure during diastole multiplied by heart rate.

All data were reported as mean±SD. Statistical significance was set at p values less than 0.05 and was obtained by a multiple comparison analysis (Bonferroni method) and Student's t test of paired data.

Results

Effects of Combined Aortic Valvuloplasty-Arterial Vasodilation on Left Ventricular Hemodynamics

Figure 1 shows LV pressure, peripheral artery pressure, and LV dP/dt recorded in a representative patient with aortic stenosis (patient 5 in Table 1) before aortic valvuloplasty, during nitroprusside infusion before aortic valvuloplasty, after aortic valvuloplasty, and during nitroprusside infusion after aortic valvuloplasty. Table 2 shows the effects of sequential aortic valvuloplasty–arterial vasodilation on LV hemodynamics. Administration of nitroprusside before aortic valvuloplasty and aortic valvuloplasty, itself, both resulted in a comparably modest decline in LV peak systolic pressure (LVPSP) from 237±33 to 200±33 mm Hg ($p<0.01$) and 201±27 mm Hg ($p<0.01$), respectively. Administration of nitroprusside after aortic valvuloplasty resulted in a further decrease of LVPSP to 165±26 mm Hg ($p<0.01$). During nitroprusside infusion, LV end-systolic pressure (LVESP) decreased from 96±14 to 72±19 mm Hg ($p<0.01$) before aortic valvuloplasty, and from 90±15 to 58±12 mm Hg ($p<0.01$) after aortic valvuloplasty.

LV end-systolic volume (LVESV) decreased from 55±34 ml in control conditions to 25±23 ml ($p<0.01$) during infusion of nitroprusside before

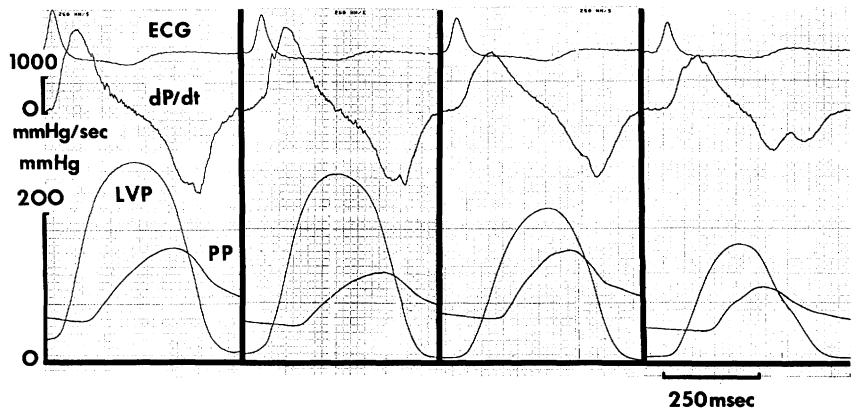

FIGURE 1. *Recordings of left ventricular pressure (LVP), peripheral artery pressure (PP), and LV dP/dt in a patient with aortic stenosis (Table 1, patient 5) before balloon aortic valvuloplasty, during nitroprusside infusion before balloon aortic valvuloplasty, after balloon aortic valvuloplasty, and during nitroprusside infusion after balloon aortic valvuloplasty.*

aortic valvuloplasty, to 30±32 ml ($p<0.025$) after aortic valvuloplasty, and to 15±12 ml ($p<0.025$) during infusion of nitroprusside after aortic valvuloplasty. LV end-systolic wall stress (LVESs) declined from 90 ± 30.10^3 dyne/cm^2 before aortic valvuloplasty to 41 ± 13.10^3 dyne/cm^2 ($p<0.01$) during infusion of nitroprusside before aortic valvuloplasty, to 55 ± 16.10^3 dyne/cm^2 ($p<0.025$) after aortic valvuloplasty, and to 26 ± 6.10^3 dyne/cm^2 ($p<0.01$) during infusion of nitroprusside after aortic valvuloplasty. Because of a simultaneous decrease of LVESP and of LVESV after combined aortic valvuloplasty–arterial vasodilation, the relative reduction of LVESs (71%) exceeded the relative reduction of LVESP (40%). The value of LVESs calculated during infusion of nitroprusside after aortic valvuloplasty (26 ± 6.10^3 dyne/cm^2) was very low because of a near-normal LVESP (58±12 mm Hg) in the presence of a small LVESV (15±12 ml) and a thick hypertrophied LV wall (14±4 mm). LV hypertrophy was evident from an increased LV muscle mass index (LVMI=191±87 g/m^2) (Table 1).

Nitroprusside infusion changed RR interval from 830±156 to 756±92 msec (p=NS) before aortic valvuloplasty and from 786±141 to 727±111 msec ($p<0.01$) after aortic valvuloplasty. Nitroprusside infusion caused a similar decrease in LV end-diastolic pressure (LVEDP) from 23±8 to 13±5 mm Hg ($p<0.01$) before aortic valvuloplasty and from 23±12 to 14±8 mm Hg ($p<0.01$) after aortic valvuloplasty. In these patients, in whom repeat LV angiograms were performed, LV end-diastolic volume (LVEDV)

TABLE 1. Patient Characteristics

Pt	Age	Sex	AVA		Gradient		LVEDVI (ml/m^2)	LVEF	LVMI (g/m^2)
			Before	After	Before	After			
1	75	F	0.7	1.0	75	53	68	55	152
2	72	F	0.4	0.6	70	42	68	72	162
3	76	M	0.5	0.9	69	30	108	57	169
4	79	F	0.5	0.8	81	44	64	69	93
5	84	F	0.3	0.5	97	30	54	66	100
6	79	F	0.2	0.4	97	39	39	42	131
7	70	M	0.5	0.8	72	41	121	47	422
8	75	F	0.4	1.0	100	20	40	74	211
9	75	F	0.8	1.5	45	15	...	...	...
10	83	F	0.3	0.7	79	30	114	58	253
11	77	M	0.4	0.7	94	45	57	85	165
12	77	M	0.5	0.9	81	36	98	59	214
13	82	F	0.4	0.9	71	36	93	41	219
14	75	F	0.4	1.0	66	19	...	...	...
Mean	77		0.45	0.84*	78	34*	77	60	191
SD	4		0.16	0.27	15	11	29	13	87

Pt, patient number; F, female; M, male; AVA, aortic valve area before and after balloon aortic valvuloplasty; Gradient, mean transvalvular aortic gradient before and after balloon aortic valvuloplasty; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; SD, standard deviation.

*$p<0.01$ vs. before balloon aortic valvuloplasty.

TABLE 2. Effects of Balloon Aortic Valvuloplasty and Arterial Vasodilation on Left Ventricular Hemodynamics

	LVPSP (mm Hg)				LVESP (mm Hg)				LVESs (10^3 dyne/cm^2)				LVEDP (mm Hg)				dP/dt max (mm Hg/sec)			
Patient	A	B	C	D	A	B	C	D	A	B	C	D	A	B	C	D	A	B	C	D
1	262	191	242	202	110	104	116	74	115	43	73	34	24	10	26	10	2,260	1,680	2,440	2,700
2	222	183	193	176	105	54	72	50	87	33	44	25	30	10	23	20	1,860	2,040	1,660	1,780
3	246	196	220	168	105	64	116	74	109	51	84	34	28	10	48	24	1,780	1,920	1,520	1,800
4	276	198	232	197	112	93	93	57	124	58	58	23	24	12	24	10	2,200	2,080	2,120	2,320
5	271	258	204	158	100	75	84	48	99	43	48	19	30	22	16	10	2,200	2,300	1,560	1,476
6	294	229	222	178	114	94	103	80	109	41	51	28	28	20	24	10	2,086	2,760	2,100	1,960
7	212	200	171	154	101	89	84	64	87	55	66	28	39	23	12	5	1,260	1,620	1,220	1,380
8	254	258	232	196	84	84	82	58	34	23	37	23	11	12	30	20	2,520	2,640	2,480	2,800
9	177	147	151	127	83	58	74	41	...	...	...	...	19	16	19	5	1,600	1,840	1,580	1,640
10	243	209	183	153	94	59	69	49	94	...	...	...	10	7	5	7	2,200	2,020	1,720	1,460
11	231	215	209	192	72	43	82	65	30	20	36	18	25	16	42	26	1,800	1,880	1,840	1,840
12	204	148	204	155	74	44	104	50	76	...	...	...	12	5	22	11	1,680	1,400	1,520	1,560
13	225	185	192	141	99	76	87	55	115	...	...	...	25	12	15	9	1,800	1,600	1,680	1,280
14	204	185	164	120	90	65	90	52	...	...	...	...	15	15	12	15	1,680	1,800	1,520	1,240
Mean	237	200*	201*	165*	96	72*	90	58*	90	41*	55†	26*	23	13*	23	14*	1,922	1,970	1,782	1,802
±SD	±33	±33	±27	±26	±14	±19	±15	±12	±30	±13	±16	±6	±8	±5	±12	±8	±332	±385	±370	±494

LVPSP, left ventricular peak systolic pressure; LVESP, left ventricular end-systolic pressure; LVESs, left ventricular end-systolic stress; LVEDP, left ventricular end-diastolic pressure; LVEST, time of left ventricular electromechanical systole; RR, RR interval; A, before balloon aortic valvuloplasty; B, before balloon aortic valvuloplasty+nitroprusside infusion; C, after balloon aortic valvuloplasty; D, after balloon aortic valvuloplasty+nitroprusside infusion.

*$p<0.01$ vs. A; †$p<0.025$ vs. A.

changed from 125±39 ml before aortic valvuloplasty to 104±24 ml (p=NS) during infusion of nitroprusside before aortic valvuloplasty, to 122±52 ml (p=NS) after aortic valvuloplasty and to 102±48 ml ($p<0.05$) during infusion of nitroprusside after aortic valvuloplasty. LV dP/dt max remained unchanged after any of the LV unloading interventions probably because of balancing effects on LV dP/dt max of changes in LVEDV and heart rate. The time of LV electromechanical systole (LVEST), which was measured as the interval from the Q wave on the electrocardiogram to the moment of LV dP/dt min and which indicated the onset of LV isovolumic relaxation, was significantly reduced after sequential aortic valvuloplasty–arterial vasodilation (from 419±26 to 363±28 msec [$p<0.01$]). The reductions of LVEST during nitroprusside infusion before aortic valvuloplasty and after aortic valvuloplasty failed to reach statistical significance on multicomparison analysis. The individual changes of LVPSP, LVESs, and LVEST before aortic valvuloplasty, during nitroprusside infusion before aortic valvuloplasty, after aortic valvuloplasty, and during nitroprusside infusion after aortic valvuloplasty are shown in Figure 2.

Effects of Combined Aortic Valvuloplasty-Arterial Vasodilation on Myocardial Oxygen Supply-Demand Balance

Myocardial oxygen supply-demand balance was assessed by DPTI:SPTI ratio[40] (Table 3). Aortic valvuloplasty favorably influenced myocardial oxygen supply-demand balance[31] by increasing DPTI:SPTI ratio from 0.43±0.17 to 0.50±0.15 ($p<0.05$). During nitroprusside infusion, a similar improvement of DPTI:SPTI ratio from 0.41±0.17 to 0.51±0.18 ($p<0.05$) was observed after aortic valvuloplasty.

Effects of Combined Aortic Valvuloplasty-Arterial Vasodilation on Isovolumic Left Ventricular Relaxation

During nitroprusside infusion LV dP/dt min increased from −2,057±399 to −1,612±497 mm Hg/sec ($p<0.01$) before aortic valvuloplasty and to −1,318±317 mm Hg/sec ($p<0.01$) after aortic valvuloplasty. The individual values of LV dP/dt min in all four loading states are shown in Figure 3 (left-hand panel) and in Table 4. In 10 of the 14 patients (patients 2, 4–6, 8–12, and 14 in Table 1) LV pressure decay shifted to a pattern of two phases of fast decay interrupted by a phase of slow decay after sequential aortic valvuloplasty–arterial vasodilation (see Figure 1). This caused a characteristic bimodal appearance of the negative dP/dt signal after sequential aortic valvuloplasty–arterial vasodilation.

Phase-plane plots of the LV pressure signal during isovolumic relaxation[36] were constructed by matching corresponding LV pressure and LV dP/dt points. Figure 4 shows a representative set of phase-plane plots derived from the LV pressure and LV dP/dt recordings shown in Figure 1 (patient 5 in Table 1). Phase-plane plots of LV isovolumic relaxation pressure were constructed before aortic valvuloplasty (A), during nitroprusside infusion before aortic valvuloplasty (B), after aortic valvuloplasty (C), and during nitroprusside infusion after aortic valvuloplasty (D). For a range of LV pressure values, for which there is overlap in all four loading states, a comparable LV dP/dt value is observed in the first

TABLE 2. Continued

LVEST (msec)				RR (msec)			
A	B	C	D	A	B	C	D
451	390	380	356	980	810	770	710
432	395	424	420	916	755	908	880
416	412	414	378	752	850	796	708
448	335	396	340	868	725	824	715
428	424	408	396	780	808	792	728
444	430	390	360	696	740	628	580
424	376	412	376	808	600	730	740
382	374	384	346	620	624	684	632
384	366	382	348	864	856	808	792
377	362	343	329	724	764	700	720
406	407	350	332	800	695	712	628
454	394	436	406	1,252	928	1,169	956
408	380	359	346	692	660	600	560
410	384	408	348	872	768	884	832
419	388	392	363*	830	756	786	727*
±26	±26	±28	±28	±156	±92	±141	±111

three loading states (A, B, and C) but a higher LV dP/dt value in the last loading state (D) (i.e., during nitroprusside infusion after aortic valvuloplasty). Deviations of isovolumic LV pressure decay from a monoexponential course can be appreciated on the phase-plane plots of LV isovolumic relaxation pressure as deviations from a linear relation between LV pressure and LV dP/dt. These deviations were more prominent during nitroprusside infusion after aortic valvuloplasty (D). The negative dP/dt upstroke pattern was assessed using the dP/dt (20/60) ratio.[37] The dP/dt (20/60) ratio observed before aortic valvuloplasty (2.8±0.8) was comparable with the dP/dt (20/60) ratio observed during nitroprusside infusion before aortic valvuloplasty (2.8±0.9) and with the dP/dt (20/60) ratio after aortic valvuloplasty (2.7±0.5). Only during nitroprusside infusion after aortic valvuloplasty was the dP/dt (20/60) ratio significantly lower (1.7±0.5; $p<0.005$) than before aortic valvuloplasty. The lower dP/dt (20/60) ratio implies a shift in the negative dP/dt upstroke pattern from convex-upward before aortic valvuloplasty to convex-downward during nitroprusside infusion after aortic valvuloplasty (see Figure 1).

Effects of Combined Aortic Valvuloplasty-Arterial Vasodilation on Time Constants of Isovolumic Left Ventricular Pressure Decay

The time constants of LV pressure decay with zero asymptote or nonzero asymptote pressures (T_0 and T_{PB}) remained unchanged after aortic valvuloplasty and during nitroprusside infusion before aortic valvuloplasty. During nitroprusside infusion after aortic valvuloplasty, the time constant of LV pressure decay with zero asymptote (T_0) showed a significant prolongation from 35.7±6.3 to 46.7±12.6 msec ($p<0.025$). The time constant of LV pressure decay (T_{PB}) with

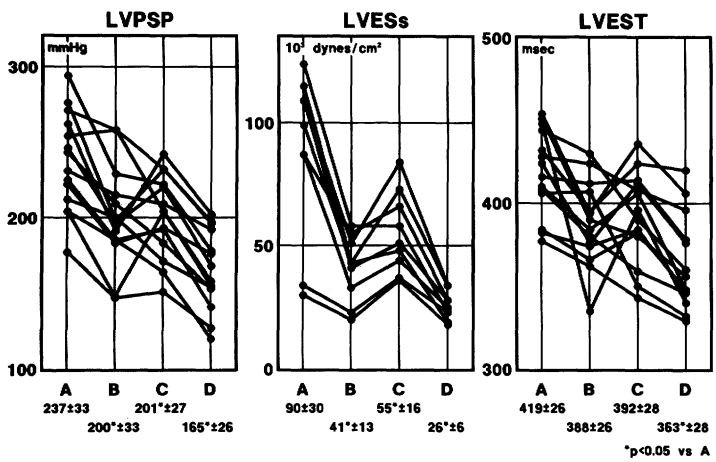

FIGURE 2. *Graphic plotting of individual changes of left ventricular peak systolic pressure* (LVPSP), *left ventricular end-systolic stress* (LVESs), *and time of left ventricular electromechanical systole* (LVEST) *before balloon aortic valvuloplasty* (A), *during nitroprusside infusion before balloon aortic valvuloplasty* (B), *after balloon aortic valvuloplasty* (C), *and during nitroprusside infusion after balloon aortic valvuloplasty* (D).

TABLE 3. Effects of Balloon Aortic Valvuloplasty and Arterial Vasodilation on Myocardial Oxygen Supply-Demand Balance

	A	B	C	D
DPTI (mm Hg·sec/min)	1,850±559	1,437±340*	1,950±535	1,415±392†
SPTI (mm Hg·sec/min)	4,485±1,067	3,783±1,206*	3,977±870	2,939±805‡†
DPTI:SPTI	0.43±0.17	0.41±0.17	0.50±0.15*	0.51±0.18‡
AoEDP (mm Hg)	59±13	45±10*	58±13	45±11†

A, before balloon aortic valvuloplasty; B, before balloon aortic valvuloplasty+nitroprusside infusion; C, after balloon aortic valvuloplasty; D, after balloon aortic valvuloplasty+nitroprusside infusion; DPTI, diastolic presure time index; SPTI, systolic pressure time index; DPTI:SPTI, DPTI:SPTI ratio; AoEDP, aortic end-diastolic pressure.
*$p<0.05$ vs. A; †$p<0.05$ vs. C; ‡$p<0.05$ vs. B.

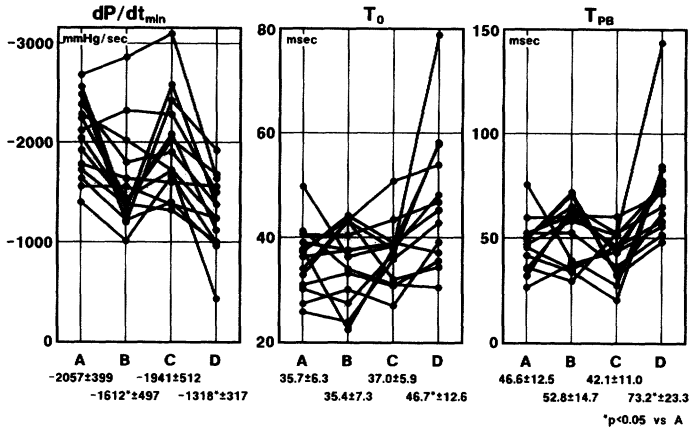

FIGURE 3. *Graphic plotting of individual changes of left ventricular (LV) dP/dt min, of T_0 (time constant of LV pressure decay with zero asymptote pressure) and of T_{PB} (time constant of LV pressure decay with nonzero asymptote pressure) before balloon aortic valvuloplasty* (A)*, during nitroprusside infusion before balloon aortic valvuloplasty* (B)*, after balloon aortic valvuloplasty* (C)*, and during nitroprusside infusion after balloon aortic valvuloplasty* (D).

nonzero asymptote pressure showed a similar prolongation from 46.6±12.5 to 73.2±23.3 msec ($p<0.01$) during nitroprusside infusion after aortic valvuloplasty. The individual changes of T_0 and T_{PB} before aortic valvuloplasty, during nitroprusside infusion before aortic valvuloplasty, after aortic valvuloplasty, and during nitroprusside infusion after aortic valvuloplasty are shown in Figure 3 (middle and righthand panels) and in Table 4. Three patients (patients 5, 11, and 14 in Table 1) had a marked prolongation of T_0 and T_{PB} during nitroprusside infusion after aortic valvuloplasty. To exclude a disproportionate weight of these patients on the statistical results, the statistical analysis of T_0 and T_{PB} was repeated without these three patients. When data obtained before aortic valvuloplasty are compared with data obtained during nitroprusside infusion after aortic valvuloplasty for the reduced patient population ($n=11$) after exclusion of the three patients with the most marked response, T_0 and T_{PB} prolonged, respectively, from 35.1±5.2 to 41.6±7.0 msec ($p<0.02$) and from 44.1±10.3 to 64.8±10.5 msec ($p<0.005$). During nitroprusside infusion after aortic valvuloplasty, the most marked prolongation of T_{PB} was observed in patients with the lowest LVESs. In the four patients with the lowest LVESs after sequential aortic valvuloplasty-arterial vasodilation (21±3.10^3 dyne/cm^2) (patients 4, 5, 8, and 11 in Table 2), T_{PB} (72.0±14.1 msec) was significantly higher than T_{PB} (65.1±11.6 msec; $p<0.05$) in the five patients with the highest LVESs after sequential aortic valvuloplasty-arterial vasodilation (30±4.10^3 dyne/cm^2) (patients 1, 2, 3, 6, and 7 in Table 2). Only after combined aortic valvuloplasty–arterial vasodilation was there a significant decline of the asymptote pressure (PB) from −15±10 to −26±4 mm Hg ($p<0.025$).

TABLE 4. Effects of Balloon Aortic Valvuloplasty and Arterial Vasodilation on Left Ventricular Relaxation Indexes

	dP/dt min (mm Hg/sec)				T_0 (msec)				T_{PB} (msec)				PB (mm Hg)			
Patient	A	B	C	D	A	B	C	D	A	B	C	D	A	B	C	D
1	2,480	1,200	2,420	1,920	37.2	44.2	39.0	37.1	49.4	70.5	32.1	48.0	−19	−30	1	−23
2	2,240	1,440	1,720	1,240	39.0	37.6	38.9	45.2	59.7	60.1	45.9	58.1	−28	−30	−8	−17
3	2,380	1,800	1,900	1,380	37.7	43.3	50.8	53.9	35.1	61.1	45.6	75.0	−14	−29	7	−28
4	2,560	1,320	2,580	1,380	30.9	33.1	30.7	35.5	26.4	37.6	43.5	55.6	7	−6	−18	−26
5	2,280	2,020	1,720	428	30.1	27.4	36.9	58.2	41.6	33.8	20.3	84.6	−8	−10	22	−23
6	2,120	2,320	2,280	1,500	37.5	22.3	37.9	48.2	45.6	35.1	46.3	73.0	−13	−30	−16	−30
7	1,560	1,560	1,380	1,240	40.5	40.4	43.4	46.8	52.2	60.7	60.2	71.3	−14	−26	−20	−27
8	2,680	2,860	3,100	1,640	25.7	23.8	35.8	42.8	35.7	29.4	52.4	64.9	−22	−14	−26	−29
9	1,640	1,220	1,400	960	36.3	37.5	38.8	45.3	31.8	64.6	42.9	77.7	4	−30	−3	−29
10	1,720	1,380	1,320	1,000	27.3	30.0	26.9	39.1	47.0	58.2	51.4	76.0	−22	−28	−27	−27
11	1,780	1,640	1,600	1,560	49.8	36.3	38.4	57.8	75.7	39.3	27.4	82.9	−27	−6	15	−23
12	1,400	1,010	1,660	996	32.8	43.2	31.9	34.3	49.6	72.0	32.8	61.8	−18	−22	−2	−26
13	1,920	1,400	2,020	1,680	41.2	33.9	31.0	30.4	52.2	52.4	36.3	51.6	−13	−23	−9	−29
14	2,040	1,400	2,080	1,120	34.0	43.1	37.8	79.0	50.8	65.1	52.3	144.0	−17	−17	−12	−28
Mean	2,057	1,612*	1,941	1,318*	35.7	35.4	37.0	46.7†	46.6	52.8	42.1	73.2*	−15	−22	−7	−26†
±SD	±399	±497	±512	±317	±6.3	±7.3	±5.9	±12.6	±12.5	±14.7	±11.0	±23.3	±10	±9	±15	±4

T_0, time constant of left ventricular pressure decay with zero asymptote pressure; T_{PB}, time constant of left ventricular pressure decay with nonzero asymptote pressure (PB); A, before balloon aortic valvuloplasty; B, before balloon aortic valvuloplasty+nitroprusside infusion; C, after balloon aortic valvuloplasty; D, after balloon aortic valvuloplasty+nitroprusside infusion.

*$p<0.01$ and †$p<0.025$ vs. A.

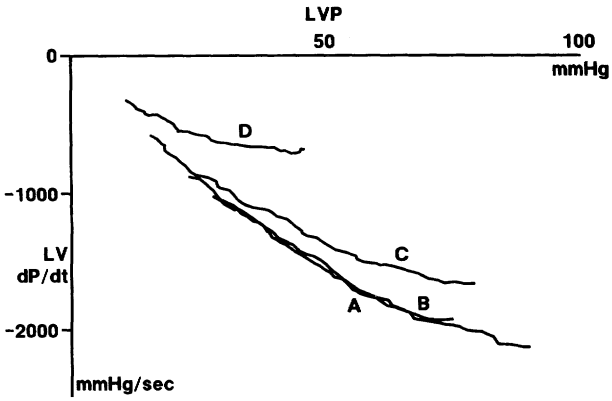

FIGURE 4. *Individual set (Table 1, patient 5; see also Figure 1) of phase-plane plots (left ventricular [LV] dP/dt vs. LVP) of LV isovolumic relaxation pressure before balloon aortic valvuloplasty* (A), *during nitroprusside infusion before balloon aortic valvuloplasty* (B), *after balloon aortic valvuloplasty* (C), *and during nitroprusside infusion after balloon aortic valvuloplasty* (D). *For given LVP value, corresponding LV dP/dt value was similar for curves A, B, and C but higher for curve D.*

Discussion

In the present study, wide range LV load drops were obtained by the sequential use of balloon aortic valvuloplasty and arterial vasodilation. The peak and end-systolic LV pressure shifts observed in the present study exceeded peak and end-systolic LV pressure changes observed in previous studies on isovolumic relaxation kinetics in patients with aortic stenosis.[6] In a subset of nine patients, LV angiograms were obtained, which allowed calculation of LVESs. The percentage of reduction of LVESs after sequential aortic valvuloplasty–arterial vasodilation (71%) was larger than the percentage of reduction of LV end-systolic pressure (40%) because of a simultaneous reduction of the LV end-systolic volumes. At the lowest LVESs after combined aortic valvuloplasty–arterial vasodilation, a significant reduction of isovolumic LV relaxation rate was observed both by time constant analysis and phase-plane plots.

Cardiac Muscle Load and Isometric Tension Decay

The effects of altered muscle load on isometric relaxation rate have been investigated in isolated cardiac muscle strips using physiological sequence relaxation (isometric relaxation preceding isotonic lengthening). When total load was reduced in physiological sequence relaxation experiments,[41] normalized peak isometric relaxation rate remained unchanged as long as end-systolic muscle length exceeded 0.94 lmax but decreased progressively at smaller end-systolic muscle lengths. Phase-plane plots of cardiac muscle force decay (dF/dt versus F plots)[42] confirmed these findings and observed a lower force decay rate at each isometric relaxation force level once end-systolic muscle length had declined below a critical value.[43] These findings could be explained by the following mechanism: when contraction load is reduced, crossbridge cycling proceeds faster, possibly, because of reduced affinity of troponin-C for calcium.[44] Isometric relaxation of a contraction with low muscle load, therefore, starts earlier than isometric relaxation of a contraction with high muscle load. When muscle load is sufficiently lowered so that end-systolic muscle length drops below 0.94 lmax, isometric relaxation will start at a time when calcium removal is still incomplete. This incomplete myoplasmic calcium removal allows for renewal of crossbridge-cycling and consequent slowing of isometric relaxation at low muscle loads. Administration of isoproterenol hastens myoplasmic calcium removal. This explains why, after administration of isoproterenol,[41] peak isometric relaxation rates remained constant with end-systolic lengths as small as 0.90 lmax. On the contrary, cardiac hypertrophy slows myoplasmic calcium removal[45] and, although experimental evidence is missing, it seems likely that isometric relaxation rates will start to decline from end-systolic muscle lengths longer than 0.94 lmax. These experiments on physiological sequence relaxation of isolated mammalian cardiac muscle, which show a significant fall of isometric tension decay if isometric relaxation occurs at small end-systolic muscle length, are consistent with the present results. In the present study, LV isovolumic relaxation rate declines, once LV end-systolic volume decreases to a small value, after drastic LV afterload reduction obtained by aortic valvuloplasty–arterial vasodilation.

A variable control of isometric relaxation by myoplasmic calcium removal and myofilamentary detachment clarifies the previously reported effects of LV load shifts on LV isovolumic relaxation rate. LV isovolumic relaxation encompasses both an initial phase during which there could still be residual myoplasmic calcium removal and a terminal phase during which relaxation kinetics are only determined by crossbridge detachment (see Figure 5). The presence and the duration of an initial phase depends on modulators of myoplasmic calcium removal such as catecholamines or myocardial hypertrophy. In anesthetized dogs, adrenergic tone is high. Hence, myoplasmic calcium removal starts earlier and proceeds faster. The time constant of isovolumic LV pressure decay, therefore, measures relaxation kinetics, which are only determined by crossbridge detachment (see Figure 5) even after an earlier onset of LV isovolumic relaxation at a lower LV load. Because of lower crossbridge cooperative activity at low muscle loads,[44] crossbridge detachment occurs faster, leading to an abbreviation of the time constant of LV pressure decay. An abbreviation of the time constant of LV pressure decay on reduction of LV peak systolic pressure was, indeed, reported in most experiments on dog hearts,[1–4] although one study observed this abbreviation only after release of an occluded descending aorta and not with other loading interventions,[46] and one recent study[47] attributed this abbreviation to the computing methods.

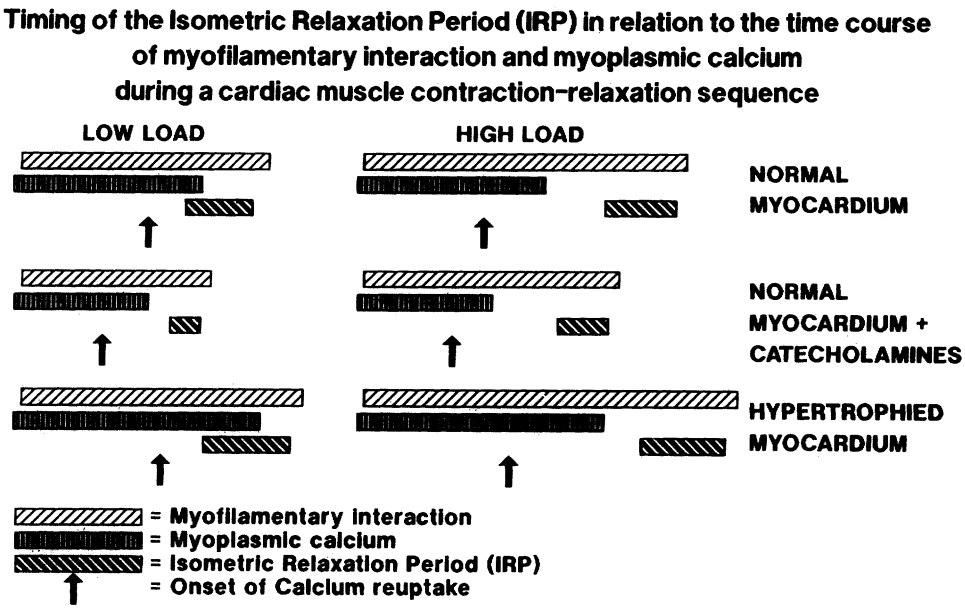

FIGURE 5. *Proposed mechanism for diverging effects of left ventricular (LV) load on LV isovolumic relaxation rate in normal human LV, during hyperadrenergic state (e.g., open-chest anesthetized dogs) and in pressure-overload hypertrophy of aortic stenosis. Timing of isometric relaxation period (IRP) is shown in relation to time course of myofilamentary interaction and myoplasmic calcium during cardiac muscle contraction-relaxation sequence at low and high muscle load. Once myoplasmic calcium reuptake (see arrows) has started, imbalance between muscle load and muscle force can trigger onset of isometric relaxation period.*[7,43] *Because of reduced calcium sensitivity of crossbridges at lower muscle load, onset of isometric relaxation occurs earlier at lower muscle load. In normal myocardium, in myocardium stimulated by catecholamines and in hypertrophied myocardium, earlier timing of IRP as result of lowered muscle load causes different shifts of isometric relaxation period in relation to myofilamentary detachment and myoplasmic calcium removal. In normal myocardium, lower contraction load causes earlier onset of IRP and initial phase of IRP could, therefore, coincide with terminal phase of myoplasmic calcium removal. Incomplete calcium removal and reduced calcium sensitivity of crossbridges at lower load could have balancing effect on relaxation rate and explain constancy of time constant of isovolumic relaxation after LV unloading in normal human LV.*[5] *In normal myocardium stimulated by catecholamines, calcium reuptake occurs earlier and faster. Myofilamentary detachment remains control mechanism of isovolumic relaxation even after reduction of LV load and earlier onset of LV relaxation. Reduced calcium sensitivity of crossbridges at lower load could explain faster relaxation rate and abbreviation of time constant observed after LV unloading in experiments on anesthetized dogs.*[1,2] *In hypertrophied myocardium, calcium reuptake from myoplasm starts later and is slower than in normal myocardium.*[45] *Reduction of LV load and earlier onset of IRP could, therefore, cause largest portion of IRP to coincide with myoplasmic calcium removal phase. This could slow isovolumic relaxation rate and explain prolongation of time constant of LV pressure decay, which was observed in present study after wide range LV load drops of combined balloon aortic valvuloplasty–arterial vasodilation.*

In hypertrophied myocardium, slower myoplasmic calcium removal has been observed during cardiac muscle relaxation using aequorin light emission signals.[45] Unloading the hypertrophied left ventricle causes an earlier onset of LV relaxation, thereby increasing the relative portion of isovolumic relaxation that coincides with the calcium removal phase (see Figure 5). This effect will tend to slow relaxation kinetics on LV unloading. On the other hand, at a lower load, crossbridge detachment proceeds faster because of reduced cooperative activity. Because of the opposite effects of LV unloading on these dual controls, the overall effect on isovolumic relaxation depends on the magnitude of the load shift. In the present and previous studies[6] on patients with aortic stenosis and LV hypertrophy, modest changes of LV afterload, imposed by either vasodilation or valvuloplasty, left the time constant of isovolumic relaxation unaltered, possibly because of balancing effects on myoplasmic calcium removal and myofilamentary detachment. After large changes of LV afterload imposed by a sequential use of aortic valvuloplasty and arterial vasodilation, the time constant of LV relaxation prolonged because the onset of isovolumic relaxation occurred so early that isovolumic relaxation kinetics were predominantly controlled by myoplasmic calcium removal.

The proposed mechanism of a shift in the control of isovolumic LV relaxation from crossbridge detachment to myoplasmic calcium removal also explains the changes of the time constant of LV pressure decay that are caused by sudden increments in late systolic LV load. A sudden increment of late systolic LV load by synchronized pressure or volume clamps induces an earlier onset of LV isovolumic relaxation, which proceeds at a slower speed in most studies[48–50]

except one,[51] in which it proceeds at a faster speed. The slower speed of LV isovolumic relaxation after a late systolic load clamp is explained by both the earlier start and the higher initial load of LV isovolumic relaxation. The earlier start of LV relaxation could slow initial isovolumic LV pressure decay if myoplasmic calcium removal was not yet finished. The higher initial load could slow isovolumic LV relaxation because of slower myofilamentary detachment induced by increased crossbridge cooperative activity at a higher load.

The wide range load shifts of sequential aortic valvuloplasty–arterial vasodilation induced significant changes of LV end-diastolic pressure. Recent studies on physiological sequence relaxation either in normal or hypertrophied muscle strips showed no effect on isovolumic relaxation rate of an isolated preload change if total muscle load was kept constant.[52,53] From these experiments, it seems that the changes in isovolumic relaxation rate observed in the present study are related to the decrease in end-systolic rather than end-diastolic wall stress.

Assessment of Left Ventricular Isovolumic Relaxation Rate

The partitioning of the isovolumic relaxation period into an initial phase of residual calcium removal and a terminal phase of crossbridge detachment is consistent with the biphasic course of isovolumic LV pressure decay, which has been observed in some studies[16,54] and which led these investigators to use a biexponential rather than a monoexponential curve fit to describe isovolumic LV pressure decay. This biphasic course of isovolumic LV pressure decline is characterized by a slower initial and a faster terminal LV pressure decay rate. The faster terminal isovolumic LV pressure decay is evident from phase-plane plots of isovolumic LV pressure versus its corresponding first derivative (dP/dt) as a terminal deviation from the initially linear course of isovolumic relaxation on the phase-plane plot (see Figure 4). Extending this terminal and faster portion of isovolumic LV pressure decay by lowering mitral valve–opening pressure leads to an erroneous reduction of the time constant of isovolumic LV pressure decay calculated from a single exponential curve fit.[35] Because of this mathematical pitfall, time constants of isovolumic LV pressure decay, which have been measured under different hemodynamic conditions, are best calculated over the same range of isovolumic LV relaxation pressure data points. This avoids erroneous reductions or prolongations of the time constant introduced by changes in either starting point pressure (pressure at peak negative dP/dt) or end-point pressure (mitral valve–opening pressure+5 mm Hg). In the present study, time constants (T_0 and T_{PB}) of isovolumic LV pressure decay were calculated using isovolumic pressure data points that covered that portion of the isovolumic relaxation period, which was overlapping for all four loading states. Moreover, phase-plane plots were constructed, which allowed comparison of isovolumic relaxation rates at the same LV pressure levels in the four different loading states (see Figure 4).

Relevance to Hypertrophic Cardiomyopathy

The presence of LV hypertrophy, which was evident from an increase in LV muscle mass, could have influenced the observed effects of LV afterload reduction on isovolumic relaxation rates. The wall stress values calculated after sequential aortic valvuloplasty–arterial vasodilation (26 ± 6.10^3 dyne/cm^2) are much lower than normal (124 ± 20.10^3 dyne/cm^2)[55] because of the reduced LV systolic pressures in the presence of a small LV cavity volume and a thick hypertrophied LV wall. In the normal nonhypertrophied left ventricle, a similar low value of systolic LV wall stress would require lowering of systolic LV pressure to an unphysiological level. In patients with nonobstructive hypertrophic cardiomyopathy, however, a similar low value of LV systolic wall stress could be observed. Normal LV systolic pressures, small end-systolic volumes, and a thick hypertrophied LV wall are indeed characteristic features of most patients with nonobstructive hypertrophic cardiomyopathy. The mechanism of slow LV relaxation in patients with hypertrophic cardiomyopathy could, therefore, be similar to the mechanism of slow LV relaxation in patients with aortic stenosis after sequential unloading of aortic valvuloplasty–arterial vasodilation, namely, slow myoplasmic calcium removal, which interferes with relaxation kinetics because of the early onset of LV relaxation induced by the low systolic wall stress. After sequential unloading of aortic valvuloplasty and arterial vasodilation, the rate and time course of isovolumic LV pressure decay, indeed, approached the rate and time course of isovolumic LV pressure decay of patients with hypertrophic cardiomyopathy. After sequential aortic valvuloplasty–arterial vasodilation, the value of T_{PB} significantly increased to 73 ± 23 msec and equaled the high values of T_{PB}, which have previously been seen in patients with hypertrophic cardiomyopathy (81 ± 10 msec,[36] 79 ± 37 msec,[14] and 74 ± 18 msec[15]).

After sequential aortic valvuloplasty–arterial vasodilation, 10 of the 14 patients developed an LV pressure decay consisting of two phases of fast decay interrupted by a shoulder of slow decay (see Figure 1). This led to a characteristic bimodal appearance of the negative dP/dt signal, which has previously been recorded in patients with hypertrophic cardiomyopathy.[36] When this bimodal negative dP/dt wave form occurred after sequential aortic valvuloplasty–arterial vasodilation, an LV angiogram revealed obliteration of the LV cavity at end ejection, such as occurs in patients with hypertrophic cardiomyopathy. This LV cavity obliteration prematurely terminated LV ejection and led to a phase of isometric myocardial force development, which preceded aortic valve closure and the onset of isovolumic LV relaxation. This phase corresponded to the shoulder of slow LV

pressure decay on the downslope of the LV pressure tracing. A similar prolongation of the interval between minimal LV cavity size and aortic valve closure has also been observed in patients with hypertrophic cardiomyopathy, irrespective of the presence or absence of an LV outflow tract gradient.[56] To calculate LV ESs, the onset of isovolumic LV relaxation was used as a marker of end systole because the present study dealt with the effects on isovolumic LV relaxation rate of myocardial wall stress at the onset of isovolumic LV relaxation. When end ejection would be used as a marker of end systole, ESs would be higher than the value reported in the present study because end ejection would occur earlier than the onset of isovolumic LV relaxation, especially after drastic LV unloading by sequential aortic valvuloplasty–arterial vasodilation.

Inversion of the Negative dP/dt Upstroke Pattern

The slow isovolumic LV pressure decay observed after sequential aortic valvuloplasty–arterial vasodilation deviates from an exponential course. This is evident from the downward convexity of the negative dP/dt upstroke pattern (Figure 1, right-hand panel), from the nonlinear course of the phase-plane plot (Figure 4, curve D), and from the lower dP/dt (20/60) ratio.[37] A similar downward convexity of the negative dP/dt upstroke pattern was observed in animal models immediately after coronary artery occlusion[57] and after intracoronary infusion of isoproterenol.[58–60] In patients with an old myocardial infarct,[37] angina pectoris,[37] or hypertrophic cardiomyopathy,[36,59,61] the same negative dP/dt upstroke pattern was reported. This negative dP/dt upstroke pattern interferes with calculations of the time constants of LV pressure decay (T_0 and T_{PB}) because of the deviations of isovolumic LV relaxation pressure from a monoexponential course. The mean correlation coefficients of the exponential curve fits used to calculate the time constants of LV pressure decay were, indeed, lowest after sequential balloon aortic valvuloplasty–nitroprusside infusion (T_0, 0.992; range, 0.983–0.997 and T_{PB}, 0.994; range, 0.987–0.997). These values, however, exceeded the value of 0.95, which was previously proposed as the critical limit for the use of a monoexponential curve fit to calculate the time constants of LV pressure decay.[14] In animal models, the downward convexity of the negative dP/dt upstroke pattern was explained by dyssynchronous onset of isovolumic relaxation in different LV segments because of segmental ischemia or segmental administration of isoproterenol. In patients with hypertrophic cardiomyopathy, the inversion of the negative dP/dt upstroke pattern was explained by dyssynchronous onset of isovolumic relaxation of hypertrophied and normal segments. Dyssynchronous LV filling in patients with hypertrophic cardiomyopathy was favorably influenced by the administration of verapamil.[62]

In the present study, an inversion of the negative dP/dt upstroke pattern was observed after drastic LV unloading of sequential aortic valvuloplasty–arterial vasodilation. Segmental myocardial ischemia caused by regional coronary hypoperfusion could explain the inversion of the negative dP/dt upstroke pattern and the slowing of isovolumic LV relaxation. The absence of significant coronary artery stenoses and a more favorable myocardial oxygen supply-demand balance after balloon aortic valvuloplasty argue against this mechanism. In the present and previous studies[31] myocardial oxygen supply-demand balance was assessed by DPTI:SPTI ratio. The lowest DPTI:SPTI ratio was observed during nitroprusside administration *before* aortic valvuloplasty and was not accompanied by a change in negative dP/dt upstroke pattern or isovolumic relaxation rate. Aortic valvuloplasty favorably influenced myocardial oxygen supply-demand ratio, which explains the symptomatic improvement frequently observed after the procedure despite incomplete correction of the valvular stenosis.[31] Nitroprusside administration *after* aortic valvuloplasty had no effect on myocardial oxygen supply-demand balance, and the DPTI:SPTI ratio significantly exceeded the values observed during nitroprusside administration before aortic valvuloplasty. Despite the favorable effect of aortic valvuloplasty on DPTI:SPTI ratio, regional myocardial ischemia cannot be excluded as a cause of the slow isovolumic relaxation after sequential aortic valvuloplasty–arterial vasodilation. Regional subendocardial myocardial ischemia could have occurred because of the association of subcritical coronary narrowing and reduced coronary perfusion at the low diastolic aortic pressure observed after sequential aortic valvuloplasty–arterial vasodilation.

The inversion of the negative dP/dt upstroke pattern could also be explained by a dyssynchronous onset of segmental isovolumic relaxation because of nonuniform LV loading[43,44] related to nonconcentric LV hypertrophy or to asymmetric LV cavity shape. In the present study, no patient with aortic stenosis had coexistent asymmetric LV hypertrophy[63,64] on two-dimensional echocardiographic examination. This, however, does not exclude nonuniform LV hypertrophy, especially in the apical segments. Regional differences in LV ESs could become more pronounced after sequential aortic valvuloplasty–arterial vasodilation because of a different shape of the LV cavity as a result of obliteration of midventricular and apical segments. A shift in the control of LV isovolumic relaxation from crossbridge detachment to myoplasmic calcium removal could also explain deviations of LV pressure decay from an exponential course. When crossbridge detachment controls relaxation kinetics, isometric force decays exponentially because the number of crossbridges detaching per unit time is proportional to the instantaneous number of crossbridges. Reattachment of crossbridges because of persistent myoplasmic calcium could interfere with this relation and could cause relaxation kinetics to deviate from an exponential course.

Conclusion

Modest changes of LV afterload imposed by either arterial vasodilation or balloon aortic valvuloplasty failed to alter isovolumic relaxation rate of the hypertrophied LV. Only after sequential balloon aortic valvuloplasty–arterial vasodilation was there significant slowing of LV isovolumic relaxation, as assessed by both time constant analysis and phase-plane plots (LVdP/dt vs. LVP) of isovolumic LV relaxation pressure. The early onset of isovolumic relaxation after combined balloon aortic valvuloplasty–arterial vasodilation could explain the slower isovolumic relaxation rate by a shift in the control of isovolumic relaxation kinetics from myofilamentary detachment to myoplasmic calcium removal, which proceeds slower in hypertrophied myocardium. The low values of LV wall stress observed in an acutely unloaded but still hypertrophied LV and the increased nonuniformity of LV wall stress after drastic LV unloading could explain the earlier onset of LV isovolumic relaxation and the convex-downward negative dP/dt upstroke pattern, which were observed after sequential balloon aortic valvuloplasty–arterial vasodilation.

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KEY WORDS • left ventricular wall stress • crossbridge detachment • myoplasmic calcium reuptake • hypertrophic cardiomyopathy

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