Assessment of Left Ventricular Relaxation in the Diseased Heart in Man

TOSHIAKI KUMADA, M.D., KAZUHIRO KATAYAMA, M.D., MASUNORI MATSUZAKI, M.D.
YASUO MATSUDA, M.D., AND REIZO KUSUKAWA, M.D.

To examine the exponential nature of the left ventricular pressure (LVP) fall during isovolumic relaxation (IRP) in 59 patients (normal (N), 6; angina pectoris (AP), 13; myocardial infarction (MI), 24; and congestive (CCM), 6) and hypertrophic (HCM, 10) cardiomyopathies, LVP and dP/dt were measured by a Millar's catheter-tipped transducer. In P vs time relation during IRP was reasonably fitted by a straight line ($r > 0.97$) in all cases. Time constant (msec) in CCM (56.9 ± 10.7), HCM (44.8 ± 12.4) and MI (43.8 ± 7.4) was higher ($p < 0.05$) than in N (30.3 ± 5.5), and peak ($-$) dP/dt (mmHg/sec) was lower (841 ± 171 , 1152 ± 397 and 1270 ± 211 , respectively; $p < 0.05$) than in N (1885 ± 150), suggesting impaired LV relaxation in these groups. However, ($-$) dP/dt upstroke pattern was exponential only in both N and 8 of the AP. The ($-$) dP/dt upstroke in the remaining groups lost its exponential nature, showing rather a downward-convex curvature which was especially prominent in CCM. This indicates non-exponential fall of LVP during IRP. Thus, the present results suggest that impaired relaxation disturbs the exponential nature of LV relaxation.

IN the intact isolated papillary muscle the tension decay of the relaxing muscle is exponential after the initial rapid fall of the tension.¹ Similar findings have been observed experimentally in the intact isovolumically beating left ventricle as well as in the working canine left ventricle.²⁻⁴ These results led to the conclusion that the time course of isovolumic left ventricular pressure fall could be expressed as a monoexponential function of time ($P = e^{At+B}$, where P is left ventricular pressure, t is time, and A and B are constant).^{3,4} The negative, inverse value of A ($-1/A$) is characterized as time constant.²⁻⁴

Time constant has been reported to be prolonged by pharmacologic interventions,^{1,4-6}

myocardial hypoxia or ischemia,⁵⁻¹¹ aging,^{12,13} changes in temperature¹¹ and various heart diseases,^{5,7,9,10,13-15} and minimally depends on heart rate.³ Thus, although some controversy exists regarding the effects of loading conditions on time constant,^{4,6} these data emphasized the usefulness of time constant as a measure of myocardial relaxation. However, a recent clinical study by Rousseau et al. has shown that in patients with coronary artery disease the time course of the left ventricular pressure fall during early diastole is not described by monoexponential, but at least 2 different types of exponential curve.⁵ Even in the intact human left ventricle, non-monoexponential pressure fall may occur during relaxation.⁵ This suggests that the left ventricular pressure pattern during early diastole is changed in diseased hearts.

When left ventricular pressure fall is expo-

Key Words:

Left ventricular relaxation
Negative dP/dt upstroke pattern
Time constant

The Second Division, Department of Internal Medicine, Yamaguchi University School of Medicine, Ube, Japan
Address for correspondence: Toshiaki Kumada, M.D., The Division, Department of Internal Medicine, Yamaguchi University School of Medicine, 1144 Koguchi, Ube, Yamaguchi 755, Japan

nential during relaxation, the first derivative of the pressure (dP/dt) or the upstroke of the negative dP/dt is also exponential, expressed by $dP/dt = Ae^{At+B}$. Therefore, the exponential nature of the pressure fall can be also analyzed by examining the negative dP/dt upstroke pattern.¹⁴ The purpose of the present study is, by analyzing the negative dP/dt upstroke pattern, to investigate whether the exponential nature of left ventricular pressure fall is disturbed or not during early diastole in the normal and diseased hearts, and to discuss the relation between disturbance of the exponential characteristic of the time course of the left ventricular pressure fall and impaired relaxation in man.

MATERIALS AND METHODS

Fifty-nine consecutive patients, mean age of 40 years (ranges, 21 to 69), undergoing routine cardiac catheterization were studied. Informed consent was obtained for the procedure in all cases. All were in sinus rhythm, and patients with valvular heart disease were excluded.

Six patients, being evaluated for atypical chest pain, had completely normal coronary arteries, normal routine hemodynamics and left ventriculograms. They also had normal 12 lead electrocardiograms at rest as well as during exercise-testing. This group was regarded as the normal controls. Thirteen patients had a typical anginal attack during which significant ST changes were obtained: 6 had effort angina; the remaining 7 had resting or variant angina, 4 of whom showed significant spasm of the proximal region of the main coronary artery by ergonovine maleate during the cardiac catheterization. None of them showed elevation of serum enzyme or abnormal Q waves in the resting electrocardiograms. This group was regarded as having angina pectoris. Twenty-four patients were diagnosed as having myocardial infarction according to the typical history, elevation of serum enzyme and abnormal Q waves in the electrocardiogram. They had severe stenosis (above 75%) or complete obstruction of the main coronary arteries and showed abnormal left ventricular wall motions which corresponded to the area supplied by the affected arteries. The remaining 16 of the 59 patients studied had congestive (6 cases) and hypertrophic (10 cases) cardiomyopathies. They were diagnosed by the history, echocardiography, coronary arteriogram and ventriculogram, based on the Goodwin's criteria, which was modified

by the National Study Group of Idiopathic Cardiomyopathies of Japan.^{16,17}

Cardiac catheterization was performed on the patients in a fasting state after they had received 10 mg of diazepam intramuscularly. All cardioactive drugs were withheld at least 24 hours before the procedure, and none of the interventions such as drug infusion or angiograms were induced before the left heart catheterization. The patients studied were relaxed and showed no complaint during the catheterization. After routine right heart catheterization was completed, left ventricular pressure was measured by a Millar's catheter-tipped micromanometer (Model PC-471#7F with the external fluid filled system) with Electronics for Medicine at a paper speed of 150 mm/sec. The catheter tip was inserted *via* the brachial artery and placed in the middle of the left ventricular cavity to avoid ventricular extrasystole. The micromanometer system was calibrated not only electronically against a standard mercury manometer before insertion and after withdrawal, but also by matching the pressure obtained simultaneously from the fluid filled system of the catheter connected to the Statham P23ID manometer. The first derivative of the left ventricular pressure (dP/dt) was measured electrically by the differentiating circuit (Analog Data Processor Model V-4202, Electronics for Medicine, Inc.) and calibrated by a known slope. The recording of the dP/dt was made with an electrical filter of 25 Hz. This filter system responded linearly up to 20 Hz by 20 dB/decay, smoothing the dP/dt curve.¹⁴ Comparison of the configuration of the negative dP/dt upstroke filtered at 25 Hz were made with those filtered at 50 and 100 Hz. With the decrement of the filter range from 100 to 25 Hz, the peak (—) dP/dt was progressively attenuated by 10–20%, and the maximum time delay of the occurrence of the peak (—) dP/dt was about 20 msec. This led to a slightly lower peak (—) dP/dt value than that reported by others in which the differentiating amplifier had a linear response up to 60 Hz.⁵ After pressure measurement were completed, biplane-cineventriculography and coronary arteriography were conducted. Coronary disease was considered present if there was evidence of 75% or greater luminal narrowing of the vessel as assessed independently by at least 2 observers.

Time constant was computed by Weiss's method.² In brief, left ventricular pressure was digitalized every 5 msec from the time of peak

TABLE I HEMODYNAMIC PARAMETERS

	No	AGE	HR	EDP	PSP	$\frac{peak\ dP/dt}{(+)} \quad \frac{(-)}$		T
			bts/min	mmHg	mmHg	mmHg/sec		msec
CON	6	44.0±12.0	76.1±10.7	8.6±1.7	124± 8	1665±205	1885±150	30.3± 5.5
CCM	6	54.3± 9.1	69.8± 8.5	16.8±8.9	118±20	940±328*	841±171*	56.9±10.7*
HCM	10	48.8±11.3	65.4±15.5	13.3±5.0 [#]	122±32	1397±480	1152±397*	44.8±12.4*
MI	24	53.3± 9.9	71.8±14.1	15.8±7.2 [#]	126±19	1374±277*	1270±211*	43.8± 7.4 [#]
AP	13	48.8± 8.8	68.9±10.0	8.8±3.9	141±21	1665±438	1764±324	33.0± 5.4

HR = heart rate, EDP = left ventricular end-diastolic pressure, PSP = left ventricular peak systolic pressure, T = time constant, CON = normal control, CCM = congestive cardiomyopathy, HCM = hypertrophic cardiomyopathy, MI = myocardial infarction, AP = angina pectoris. Comparisons of each parameter with those of the normal controls (CON): * = $p < 0.001$, # = $p < 0.05$.

(-) dP/dt to the time when the left ventricular pressure fell to the same level as the preceding end-diastolic pressure. Natural logarithm of the pressure (ln P) versus time data for this period was fitted into a straight line by the method of least squares. The inverse value of the slope of the straight line was the time constant.

Measured variables were heart rate, left ventricular peak systolic and end-diastolic pressures, peak positive (+) and negative (-) dP/dt and time constant. The data were averaged for 5 consecutive beats and expressed as mean ± one standard deviation. Comparisons of the variables among patient groups were made by unpaired *t*-test.

RESULTS

Routine hemodynamic parameters are shown in Table I. There was no statistically significant difference in age, PSP and HR between the control and patient groups. LVEDP was higher in HCM (13.5 ± 5.0 mmHg, $p < 0.005$) and MI (15.8 ± 7.2 mmHg, $p < 0.005$) than in the control group (8.6 ± 1.7 mmHg). Peak (+) dP/dt was lower in CCM (940 ± 328 mmHg/sec, $p < 0.001$) and MI (1374 ± 277 mmHg/sec, $p < 0.05$) than in the control group (1665 ± 205 mmHg/sec). Peak (-) dP/dt was significantly lower ($p < 0.001$) in MI (1270 ± 211 mmHg/sec), HCM (1152 ± 397 mmHg/sec) and CCM (841 ± 171 mmHg/sec), when compared to the control group (1885 ± 150 mmHg/sec).

Time constant was higher in MI (43.8 ± 7.4 msec, $p < 0.001$), HCM (44.8 ± 12.4 msec, $p < 0.05$) and CCM (56.9 ± 10.7 msec, $p < 0.001$)

than in the control group (30.3 ± 5.5 msec). There were no significant differences in peak (-) dP/dt and time constant between the angina group and the control group (Table I). The average correlation coefficient (*r*) of the linear fitting of ln P vs time was 0.998 in the control group and 0.993 in the diseased groups. In all cases studied, none of the *r* value were below 0.97. Representative examples are shown in Fig. 1. Despite such a good linear fitting, the (-) dP/dt upstroke pattern was variable among groups (Fig. 2). In the control group, (-) dP/dt upstroke was smooth and downward-concave, showing nearly an exponential configuration (Fig. 2). In the AP group, the (-) dP/dt upstroke in 8 of the 14 patients was also exponential as observed in the control group, while in the remaining 6 patients the upstroke lost its exponential smoothness and had different curvatures in the first and second phases of the early diastolic period: (-) dP/dt increased rapidly from the peak (-) dP/dt for the first 20–30 msec (the first phase) and then rose at a slightly reduced velocity in the second phase. As the result, the (-) dP/dt pattern in the first phase was straight or downward-concave, and that in the second phase was straight or downward-convex (Fig. 2). In the MI group, 2 of the 24 patients had nearly an exponential pattern in the (-) dP/dt upstroke; one of the 2 patients had an intact coronary artery and the other had 70% stenosis of the right coronary artery alone. Four of the remaining 22 patients showed a smooth, downward-convex curvature of the (-) dP/dt upstroke throughout the early diastole, which

Fig.1. Representative examples of $\ln P$ vs time in a normal (left panel) and a patient with congestive cardiomyopathy (CCM, right panel). The subjects were the same as those in Fig. 2. $\ln P$ = natural logarithm of left ventricular pressure, T = time constant

Negative dP/dt upstroke pattern

Fig.2. Representative examples of $(-)$ dP/dt upstroke pattern. N = normal control, AP = angina pectoris, MI = myocardial infarction, HCM = hypertrophic cardiomyopathy, 0 = zero level of the dP/dt . One large box of the time scale represents 50 msec.

was completely reverse compared to that of the control group. The remaining 18 patients showed the first rapid rise of the $(-)$ dP/dt upstroke for about 20–30 msec followed by the second rise with a different curvature. This biphasic configuration of the $(-)$ dP/dt pattern resembled that of the AP group, but the downward-convexity in the second phase tended to be more prominent in the MI group. In the cardiomyopathy groups, none of the patients had an exponential pattern in the $(-)$ dP/dt upstroke.

In the CCM group, all of the $(-)$ dP/dt upstrokes were completely reverse (downward-convex) compared with that of the control group. Four of the 10 patients with HCM had such a downward-convex curvature, while the remaining 6 had a biphasic upstroke similar to that observed in the MI group.

DISCUSSION

The present data demonstrated increase in time constant and decrease in peak $(-)$ dP/dt in patients with myocardial infarction and cardiomyopathy, which suggests impaired relaxation in these groups. This is consistent with the findings observed by other investigators^{5,13} Although myocardial relaxation has been evaluated by using peak $(-)$ dP/dt and time constant, peak $(-)$ dP/dt depends on loading conditions^{1,4,8,18–20} and regional wall motion⁸ This limits the use of peak $(-)$ dP/dt as an index of myocardial relaxation. On the other hand, time constant is reported to be independent of loading conditions and thus is a better index for the assessment of the myocardial relaxation^{2–4} although some have suggested dependence of time constant on afterload as well as end-systolic volume⁶

Time constant is calculated by a straight line fitting of $\ln P$ vs time provided that left ventricular pressure falls exponentially during isovolumic

relaxation^{1,2,4} Experimental^{1-4,8} and clinical^{9,10,13} studies have demonstrated that $\ln P$ vs time relation during isovolumic relaxation is reasonably fitted by a straight line with a very high correlation coefficient (usually, $r > 0.9$). This led to the conclusion that left ventricular pressure declines exponentially during isovolumic relaxation. In our cases, the r value in each patient was also over 0.97. Despite these excellent results of linear fitting, some investigators have suggested non-exponential fall of the left ventricular pressure during early diastole^{5,8,14}. In single cells in spontaneously beating monolayer cultures of chick embryo ventricle, 2-phase relaxation occurred²¹. Similarly, left ventricular relaxation was found to be biexponential in patients with coronary artery disease⁵. Experimentally-induced regional ischemia disturbed the exponential nature of the pressure fall during relaxation⁸. In addition, the conclusions derived from isolated papillary muscle experiments may not correspond to intact ventricle in man.^{22,23} Thus, whether left ventricular pressure fall during isovolumic relaxation is exponential or not remains to be further studied.

If left ventricular pressure fall during relaxation is exponential, as expressed by $P = e^{At+B}$, the upstroke of the $(-)$ dP/dt is also exponential ($dP/dt = Ae^{At+B}$). The present data documented that the $(-)$ dP/dt upstroke was nearly exponential in the normal heart but non-exponential in the diseased heart. This indicates that the exponential nature of the left ventricular pressure fall which is observed in the normal heart is disturbed in the heart with histological changes of the myocardium. Of interest is that the downward-convex curvature of the $(-)$ dP/dt upstroke, which is the reverse of the normal pattern, was most prominent in CCM, indicating that the degree of the histological change of the myocardium may affect the alteration of the $(-)$ dP/dt upstroke curvature. As myocardial damage or histological changes progress, the curvature of the $(-)$ dP/dt upstroke may alter from upward-convex (normal pattern) to downward-convex (abnormal pattern).

Our data stress the importance of the $(-)$ dP/dt upstroke pattern in assessing myocardial relaxation, and suggest that impaired left ventricular relaxation can be detected by the $(-)$ dP/dt upstroke pattern. Although heart rate and left ventricular peak systolic pressure were not significantly different among subject groups in the present study, the effect of loading conditions on

the $(-)$ dP/dt upstroke pattern remains to be clarified.

REFERENCES

1. PARMLEY WW, SONNENBLICK EH: Relation between mechanics of contraction and relaxation in mammalian cardiac muscle. *Am J Physiol* **216**: 1084, 1969
2. WEISS JL, FREDERIKSEN JW, WEISFELDT ML: Hemodynamic determinants of the time course of fall in canine left ventricular pressure. *J Clin Invest* **58**: 751, 1976
3. FREDERIKSEN JW, WEISS JL, WEISFELDT ML: Time constant of isovolumic pressure fall: Determinants in the working left ventricle. *Am J Physiol* **235**: 701, 1978
4. KARLINER JS, LeWINTER MM, MAHLER F, ENGLER R, O'ROURKE RA: Pharmacologic and hemodynamic influences on the rate of isovolumic left ventricular relaxation in the normal conscious dog. *J Clin Invest* **60**: 511, 1977
5. ROUSSEAU MF, VERITER C, DETRY JMR, BRASSEUR L, POULEUR H: Impaired early left ventricular relaxation in coronary artery disease: Effects of intracoronary nifedipine. *Circulation* **62**: 764, 1980
6. GAASCH WH, BLAUSTEIN AS, ANDRIAS W, DONAHUE RP, AVITALL B: Myocardial relaxation. II. Hemodynamic determinants of rate of left ventricular isovolumic pressure decline. *Am J Physiol* **239**: H1, 1980
7. MCLAURIN LP, ROLETT EL, GROSSMAN W: Impaired left ventricular relaxation during pacing-induced ischemia. *Am J Cardiol* **32**: 751, 1973
8. KUMADA T, KARLINER JS, POULEUR H, GALLAGHER K, SHIRATO K, ROSS JJr: Effects of coronary occlusion of early ventricular diastolic events in conscious dogs. *Am J Physiol* **237**: 542, 1979
9. SHARMA B, REED N, HODGES M, FRANCIS G: Changes in the diastolic properties of the left ventricle during spontaneous angina pectoris. *Circulation* **59**, **60** (Suppl II): 120, 1979
10. TAW RL Jr, GRIFFITH LSC, CONTI CR, DUCCI H, WEISFELDT M: Impaired isovolumic relaxation during pacing induced ischemia in man. *Circulation* **53**, **54** (Suppl II): 6, 1976
11. FRIST WH, PALACIOS I, POWELL WJJr: Effect of hypoxia on myocardial relaxation in isometric cat papillary muscle (abstr). *Am J Cardiol* **41**: 361, 1978
12. LAKKATA EG, GERSTENBLITH G, ANGELL CS, SHOCK NW, WEISFELDT ML: Prolonged contraction duration in aged myocardium. *J Clin Invest* **55**: 61, 1975
13. HIROTA Y: A clinical study of left ventricular relaxation. *Circulation* **62**: 756, 1980
14. KATAYAMA K, KUMADA T, MATSUZAKI M, FUJII Y, TOMA Y, NAITO H, OGAWA H, SASAKI T, ISHIDA K, YOROZU T, MATSUDA Y, KUSUKAWA R: Detection of impaired left ventricular relaxation by negative dP/dt upstroke pattern. *Circulation* **62** (Suppl III): 93, 1980
15. FIORETTI P, BROWER RW, MEESTER GT,

- SERRUYS PW: Interaction of left ventricular relaxation and filling during early diastole in human subjects. *Am J Cardiol* **46**: 197, 1980
16. Study group for idiopathic cardiomyopathies of Japan: The criteria for the diagnosis of idiopathic cardiomyopathies. In *A Guide for the Diagnoses of the Diseases of Unknown Etiology*, ed by the Committee for diseases of unknown etiology, Ministry of Health and Welfare of the Japanese Government, Tokyo, 1975, p 45 (in Japanese)
 17. GOODWIN JF, OAKLEY CM: The cardiomyopathies. *Br Heart J* **34**: 545, 1972
 18. WEISFELDT ML, SCULLY HE, FREDERIKSEN J, RUBINSTEIN JJ, POHOST GM, BEIERHOLM E, BELLO AG, GAGGETT WM: Hemodynamic determinants of maximum negative dP/dt and periods of diastole. *Am J Physiol* **227**: 613, 1974
 19. FREDERIKSEN J, WEISFELDT ML, SCULLY HE, BELLO AG, BEIERHOLM E, RUBERSTEIN J, DAGGETT WM: Hemodynamic determinants of maximum left ventricular relaxation rate. *Fed Proc* **32**: 332, 1973
 20. COHN PF, LIEDTKE AJ, SERUR J, SONNENBLICK EH, URSCHER CW: Maximum rate of pressure fall (peak negative dP/dt) during ventricular relaxation. *Cardiovasc Res* **6**: 263, 1972
 21. MIURA DS, BIEDERT S, SMITH TW, BARRY WH: Evidence for two phases of relaxation in cultured ventricular cells. *Circulation* **51**, **52** (Suppl II): 213, 1975
 22. ESCHMANN PE, KLAYENBUEHL HP, RUTISHAUSER W: Druckverlauf bei der isovolumetrischen Relaxation des linken Ventrikels des Menschen im Ruhezustand und unter akuter Druckbelastung. *Z Kardiologie* **64**: 444, 1975
 23. SULMAN DL, BING OHL, MARK RG, BURNS SK: Physiologic loading of isolated heart muscle. *Biochem Biophys Res Commun* **56**: 947, 1974