An Analysis of Regional Left Ventricular Function Utilizing Pressure-Length Relationship in Patients with Coronary Artery Disease

HIROSHI NONOGI, M.D*, SHIGETAKE SASAYAMA, M.D.*, SHUNICHI MIYAZAKI, M.D.
AND CHUICHI KAWAI, M.D.

Mechanisms related to increased left ventricular filling pressure associated with myocardial ischemia were studied in 13 patients with coronary artery disease. Single-plane left ventriculograms were obtained using a high fidelity micromanometer-tipped catheter in the control and post-pacing periods. All patients developed typical anginal pain during pacing tachycardia. Seven patients (group I) demonstrated no significant changes in ejection fraction (EF) and peak systolic pressure-end-systolic volume ratio (P/Ves) after rapid pacing. End-diastolic pressure (EDP), however, increased significantly from 14.9 ± 4.9 to 24.4 ± 8.5 mmHg ($p < 0.01$). Six patients (group II) exhibited significant decreases in EF and P/Ves. Here again, EDP increased significantly from 14.0 ± 7.6 to 28.0 ± 7.7 mmHg ($p < 0.01$). The regional myocardial function was expressed by a radial coordinate system with its origin at the center of gravity of the end-diastolic contour. In the normal segment, the end-diastolic length (EDL) was augmented by 13.6%, associated with a 22.4% increase in stroke excursion with pacing stress. In the ischemic segment, EDL remained unchanged, but stroke excursion was significantly reduced. The diastolic pressure-volume curve shifted directly upward or more to the right, while the diastolic pressure-length curve moved up on the single curve in the normal segment and shifted directly upward in the ischemic segment, so that pressure was higher at any given segment length in the ischemic segment, indicating regional alteration of the diastolic properties.

Thus, an ischemic response to pacing tachycardia involves both systolic and diastolic impairment, but the latter is more sensitive. Changes in the regional myocardial performance are consistent and the global function is determined by the interaction of changes in regional function of both normal and ischemic myocardium.

CHANGES induced in left ventricular contraction as a consequence of an imbalance between myocardial oxygen requirements and coronary blood flow are essentially regional in nature, and the precise identification of such regional contraction abnormalities is necessary

Key words:

Automatic processing of left ventriculogram
Pacing-induced ischemia
Pressure-length loop
Diastolic property

for a comprehensive understanding of the mechanics of myocardial ischemia. Many methods have been used to quantitate ventricular wall motion in animal experiments; however, considerable limitations in the clinical setting in assessing localized abnormalities in the ventricle still remain¹⁻³. To ease these limitations, we developed a computer-assisted image-processing system of cine ventriculograms for the analysis of segmental ventricular wall motion⁴⁻⁷. The purpose of the present study was to assess both

*The Third Division, Department of Internal Medicine, Kyoto University, Kyoto; *Otowa Hospital, Kyoto; **The Second Department of Internal Medicine, Toyama Medical and Pharmaceutical University, Toyama, Japan*

Mailing address: Shigetake Sasayama, M.D., The Second Department of Internal Medicine, Toyama Medical and Pharmaceutical University, 2630 Sugitani, Toyama 930-01, Japan

TABLE I HEMODYNAMIC FINDINGS IN THE CONTROL AND POST-PACING STATE (n = 13)

	control	post-pacing	p
HR (beats/min)	56 ± 10	57 ± 10	NS
LVSP (mmHg)	120 ± 21	149 ± 29	NS
LVEDP (mmHg)	14 ± 7	26 ± 9	< 0.05
LVEDV (ml)	103 ± 21	112 ± 22	< 0.05
LVESV (ml)	42 ± 18	54 ± 24	< 0.01
SV (ml)	62 ± 14	58 ± 14	NS
EF (%)	61 ± 11	53 ± 13	< 0.05
P/Ves	4.2 ± 1.7	3.2 ± 1.4	< 0.05
Normal segment			
EDL (mm)	25.8 ± 5.3	29.3 ± 6.0	< 0.001
ESL (mm)	16.0 ± 6.5	17.2 ± 6.6	< 0.02
ΔL (mm)	9.8 ± 2.3	12.0 ± 3.4	< 0.01
Ischemic segment			
EDL (mm)	31.3 ± 6.5	31.3 ± 5.8	NS
ESL (mm)	22.1 ± 9.7	27.6 ± 7.0	< 0.001
ΔL (mm)	9.2 ± 5.2	3.7 ± 2.1	< 0.001

abbreviations: ΔL = segment shortening, EDL = end-diastolic length, ESL = end-systolic length, EF = ejection fraction, HR = heart rate, LVEDP = left ventricular end-diastolic pressure, LVEDV = left ventricular end-diastolic volume, LVESV = left ventricular end-systolic volume, LVSP = left ventricular systolic pressure, NS = not significant, p = statistically significant difference between control and post-pacing, P/Ves = ratio of peak systolic pressure to end-systolic volume, SV = stroke volume.

global and regional function simultaneously and to relate changes in the former to those in the latter during pacing induced angina in patients with coronary artery disease.

In addition, an attempt was made to elucidate the dissociation of effect of transient ischemia on global systolic and diastolic function and the relative role of these dysfunctions in producing hemodynamic alterations during angina precipitated by pacing tachycardia.

METHODS

We studied 13 patients (7 males and 6 females), mean age 61 years (range 37–64 years) who had distinct effort induced angina pectoris. All patients were in sinus rhythm, and all medications were discontinued 12 hours before the study. Informed consent was obtained from each patient and there were no complications.

Fig. 1. Ejection fraction (EF), ratio of peak systolic pressure to end-systolic volume (P/Ves) and left ventricular end-diastolic pressure (EDP) in the control state (C) and during angina in the immediate post-pacing period (P) in patients with coronary artery disease. Group I consisted of 7 patients with no changes in systolic function, while Group II was composed of 6 patients with significant depression of systolic function in post-pacing beats. EDP increased markedly during angina in both groups.

Catheterization procedure

Cardiac catheterization was performed during the fasting state after premedication with diazepam (5 mg orally) using the brachial approach. Left ventricular pressure was measured using a high fidelity micro-manometer tipped angiographic catheter (Mikro-Tip, Millar Instruments, Houston, Texas). A pacing catheter was positioned in the right atrium or the right ventricle.

Coronary arteriography was performed using Sones technique. Single plane left ventricu-

logram was performed at a 30 degree right anterior oblique projection using 25 to 30 ml of Angiografin injected through the Millar angiographic catheter at 10 to 12 ml per second. Cineangiograms were recorded at 48–60 frames per second on 35 mm film, and numbered cine frame markers were simultaneously recorded with pressure measurements at 100 mm/sec paper

DIASTOLIC PRESSURE-VOLUME RELATIONSHIP

N=13, mean $\pm$ S

Fig.2. Left ventricular diastolic pressure-volume relationship in 13 patients. A mean diastolic pressure-volume curve was constructed. Average values of pressures and volumes were derived from three diastolic points: early, the point at the lowest diastolic pressure; mid, at mid-diastole; and ED, at end-diastole. The diastolic pressure-volume curve shifted upward in post-pacing beats.

speed. After left ventricular pressure had returned to baseline, atrial pacing was initiated at a rate of 90 beats/min and was increased in increments of 30 beats/min every two minutes. In patients in whom atrioventricular block developed during atrial pacing, right ventricular pacing was substituted. Pacing was stopped with the occurrence of chest pain. If well tolerated, pacing was continued at a rate of 150 beats/min for 6 min. The second angiogram was obtained immediately after cessation of pacing in the same manner as with the control ventriculogram.

To exclude "drift" in the micromanometer system, the pressure registered by the transducer tip catheter was equilibrated with that recorded through the fluid-filled catheter immediately before intervention.

Analysis of data

The method of automatic processing of cine-angiography has been described elsewhere.⁴⁻⁷ Briefly, the left ventricular images on cine film were transferred to a computer through a flying spot scanner and were stored on a magnetic disk. Each digitized image consisted of 128×128 pixels with gray levels of 256 values. A gradient image was then obtained by spatial differentiation of gray levels. The points with the maximal gradient value were traced to delineate the ventricular boundary. The left ventricular volumes were calculated by the area-length method modified by Kennedy et al.⁸ The calculated volume of each frame was synchronized to the corresponding pressure by a simultaneously recorded exposure marker throughout diastole to obtain the diastolic

Fig.3. Left ventricular diastolic pressure-volume relationships in the control state (open circles) and after rapid cardiac pacing (closed circles) in two patients with coronary artery disease. The curve shifted more to the right in one patient (left panel) and directedly upward in the other (right panel).

Fig.4. Mean values of left ventricular pressure against normal (left panel) and ischemic (right panel) segment lengths in the control state (open circles) and after rapid pacing (closed circles) in 13 patients. Despite variations in response in pressure-volume curves, there are uniform changes in the pressure-length relationship, the normal segment moving on the single curve. However, in the ischemic segment, there is an upward shift of the segment pressure-length relationship during angina.

pressure-volume curve. Sequential ventricular silhouettes were superimposed on the end-diastolic frame throughout the cardiac image, 128 radial grids were drawn from the center of gravity of the end-diastolic silhouette to the endocardial margin. Measurement of the length of each grid line throughout the cardiac cycle made it possible to analyze the contraction and relaxation of specific segments of the left ventricular myocardium. The length of each radial grid plotted against time was handled in the same way as an overall volume-time curve to construct the diastolic pressure-length curve. The pressure-length loops were originally generated for 128 radial grids. The potentially ischemic section corresponding to the known coronary lesions, in which active shortening was preserved at rest, was selected, and the response to cardiac pacing was compared with that of the normal section perfused with intact coronary arteries.

Statistical comparisons were made by a paired t-test.

RESULTS

All thirteen patients had significant stenosis in one of the major branches of the coronary artery, and all experienced typical anginal pain during pacing tachycardia. The hemodynamic measures

obtained during the control and post-pacing periods are averaged in all 13 patients (Table I). In the post-pacing beats, the heart rate did not change significantly. There was a substantial increase in end-diastolic pressure (EDP) (14 ± 7 mmHg to 26 ± 9 mmHg, $p < 0.001$). Peak systolic pressure remained unchanged (150 ± 21 mmHg to 149 ± 29). The end-diastolic volume also increased from 103 ± 21 ml to 112 ± 22 ml ($p < 0.01$). The ejection fraction (EF) was reduced significantly from $61 \pm 11\%$ to $53 \pm 13\%$ ($p < 0.05$). The ratio of peak systolic pressure to end-systolic volume (P/Ves) decreased significantly from 4.2 ± 1.7 to 3.2 ± 1.4 ($p < 0.05$).

We then, divided these patients into two groups according to the magnitude of changes in the systolic function. Group I included 7 patients in whom there were no significant changes in EF (62.1 ± 1.6 vs $62.7 \pm 7.2\%$, N.S.) and P/Ves (3.7 ± 0.7 vs 3.7 ± 1.4 , N.S.) and Group II included 6 patients in whom EF was reduced more than 5% (from 59.3 ± 14.8 to $44.3 \pm 11.2\%$, $p < 0.01$) and P/Ves decreased significantly from 4.2 ± 1.8 to 3.2 ± 1.4 ($p < 0.05$). There was a substantial increase in EDP in both groups (from 14.9 ± 4.9 to 24.4 ± 8.5 mmHg, $p < 0.01$, in group I and from 14.0 ± 7.6 to 28.0 ± 7.7 mmHg, $p < 0.01$, in group II). These data suggest that left ventricular global distensibility uniformly decreased

regardless of the magnitude of systolic failure.

To evaluate the regional myocardial response to pacing tachycardia, we selected two representative radial grids for the normal and ischemic regions (Table I). In the normal segment, the end-diastolic length (EDL) was augmented by 13.6% from the control value of 25.8 ± 5.3 mm, with a significant increase in stroke excursion (ΔL) of 22.4% in response to the pacing stress. In the ischemic segment, EDL remained unchanged while ΔL was reduced by 59.8% ($p < 0.01$) from the control value. Although the mean diastolic pressure-volume (P-V) curves averaged for all 13 patients shifted upward in the post-pacing beat (Fig. 2), we observed two different types of response. The curve shifted upward in the post-pacing beat in one group (Fig. 3, right panel) while the curve shifted more to the right in the other group (Fig. 3, left panel). Plots of left ventricular pressure against normal and ischemic segment length throughout passive ventricular filling are shown in Fig. 4. An increase in diastolic pressure was accompanied by comparable changes in the diastolic length of the normal segment and the segment appeared to have moved up on the single diastolic pressure-length (P-L) curve. In the ischemic segment, the P-L curve shifted directly upward, so that pressure was higher at any given segment length in the post-pacing beat, indicating regional alteration of the diastolic property.

DISCUSSION

Left ventricular end-diastolic pressure characteristically increases during attacks of angina in patients with coronary artery disease⁹⁻¹². However, there is still controversy as to the underlying mechanisms of this change, whether it results from an increase in diastolic volume due to an impaired contractile performance or it represents altered diastolic properties with a substantial shift of the entire pressure-volume relation. The relative contributions of these mechanisms have been assessed in both clinical⁹⁻¹² and experimental settings^{13,14} and these studies demonstrated that diastolic left ventricular pressure-volume curves were shifted upward and end-diastolic and end-systolic volumes tended to be somewhat higher during myocardial ischemia. Thus, it was concluded that the increased filling pressure in the ischemic ventricle was the result of both impaired left ventricular systolic performance and altered left ventricular diastolic properties.¹²

Present results also confirm the results reported previously in the literature. In addition, we assessed the effect of rapid cardiac pacing on systolic and diastolic function separately in patients with coronary artery disease. Left ventricular end-diastolic pressure invariably increased in postpacing beats in all 13 patients, although this increase was accompanied by a comparable increase in volume in some and was out of proportion to changes in end-diastolic volume in others. Systolic functions measured by ejection fraction and P/Ves were depressed in only 7 patients in group II. Accordingly, it is probable that in group I patients, the diastolic properties of the ventricle were altered as a primary ischemic response to pacing stress and not as a secondary event to systolic failure with increases in ventricular volume.

Aroesty et al¹⁵ also analyzed pressure-volume relations serially during the development of angina pectoris with pacing stress using radio-nuclide ventriculography in conjunction with pressure recordings, and demonstrated similarly that an ischemic response to pacing tachycardia involves both systolic and diastolic dysfunction, but diastolic impairment precedes systolic depression, suggesting that impaired diastolic performance is the first manifestation of ischemia. Several mechanisms have been proposed for the increase in left ventricular end-diastolic pressure during acute myocardial ischemia^{9-12,16,17} including altered diastolic myocardial stiffness, impaired left ventricular relaxation, changes in coronary artery perfusion, alterations of intrapericardial pressure and altered right ventricular loading conditions. However, it is difficult to define the contribution of each of these mechanisms with certainty at the present time.¹⁹⁻²⁵

In the ischemic ventricle, regional dysfunction of ventricular wall motion occurs in an area supplied by an obstructed coronary artery, while the normally perfused myocardium augments shortening to compensate for the dysfunction in the ischemic area with an early use of the Frank-Starling mechanism.¹⁻³

Consequently, when the ventricle adapts sufficiently to the ischemic insult by an increased mechanical load of the normal myocardium, ejection and contractility²⁶⁻²⁸ measures of the whole heart can be maintained normally. Thus, in the presence of regional myocardial ischemia, global ventricular function alone can be misleading and an analysis of regional myocardial function is necessitated. The computer-assisted

image processing system we developed provided a quantitative expression of segmental wall motion as changes of the radial grids drawn from the center of the gravity of the end-diastolic silhouette to the endocardial margin.⁴⁻⁷ Time-length plots of a given radial grid allowed for characterization of the contraction and relaxation of the specific region of the left ventricular wall in accurate temporal and spatial relations. The diastolic pressure-length curves constructed simultaneously in multiple portions of the same ventricle revealed that despite a considerable variation in response of the diastolic pressure-volume curve, the displacement of the segmental diastolic pressure-length relation during pacing induced ischemia was remarkably consistent depending on the segment's ischemic status.

In the ischemic region, there was an upward shift of the left ventricular diastolic pressure-segment length relation so that, for any given length, pressure was higher, indicating substantial alteration in the diastolic properties of the regional myocardium.^{6,7} In the normally perfused region of the same ventricle, the elevation of end-diastolic pressure was accompanied by a comparable increase in segment length and the segment appeared to have moved up on the single pressure-length curve to the higher and steeper portion.^{6,7} This change is mediated largely by decreased myocardial distensibility in the ischemic region, being driven out along the augmented preload to compensate for dysfunction in the ischemic myocardium.

Increased stiffness of the ischemic myocardium is assumed to result from raised cytosolic calcium surrounding the contractile proteins and decreased availability of adenosin triphosphate for actin-myosin cross bridge dissociation.^{6,17,21} With this in mind, we studied the effects of nifedipine on regional dysfunction during pacing induced ischemia in patients with coronary artery disease.⁷ With nifedipine, symptomatic and hemodynamic responses to pacing stress were favorably modified with marked attenuation of the post-pacing increase in end-diastolic pressure. The upward shift of the diastolic pressure-length relation of the regional ischemic segment was attenuated or abolished.

Henry et al²⁹ also demonstrated that an isolated rabbit heart subjected to ischemia underwent progressive contracture with an accumulation of calcium in the mitochondrial cell fraction and that these changes were prevented by a calcium antagonist. When internal calcium seque-

stration by the sarcoplasmic reticulum was blocked by caffeine, the pacing induced impairment of ventricular distensibility was markedly potentiated.¹⁴ All of these data support the concept that calcium overload of myocardial cell is the major factor for increased diastolic stiffness in the ischemic myocardium.

In conclusion, an ischemic response to pacing tachycardia is expressed by both systolic and diastolic measures as an impairment of global function. However, analysis of diastolic properties is more sensitive than that of systolic dysfunction, because augmented shortening in the normally perfused area can compensate sufficiently for the dysfunction in the ischemic area. Despite considerable variations in the global function, the regional changes of the normal and ischemic myocardial performance are consistent in both systolic and diastolic function, and the complex interaction of the different regions of the ventricle determines the net global changes in the ventricular function.

REFERENCES

1. THEROUX P, FRANKLIN D, ROSS J Jr, KEMPER WS: Regional myocardial function during acute coronary artery occlusion and its modification by pharmacologic agents in the dog. *Circ Res* 35: 896, 1974
2. THEROUX P, ROSS J Jr, FRANKLIN D, KEMPER WS, SASAYAMA S: Regional myocardial function in the conscious dog during acute coronary occlusion and responses to morphine, propranolol, nitroglycerin, and lidocaine. *Circulation* 53: 302, 1976
3. SASAYAMA S, FRANKLIN D, ROSS J Jr, KEMPER WS, McKOWN D: Dynamic changes in left ventricular wall thickness and their use in analyzing cardiac function in the conscious dog. *Am J Cardiol* 38: 870, 1976
4. FUJITA M, SASAYAMA S, KAWAI C, EIHO S, KUWAHARA M: Automatic processing of cine-ventriculograms for analysis of regional myocardial function. *Circulation* 63: 1065, 1981
5. SASAYAMA S, NONOGI H, FUJITA M, SAKURA I, WAKABAYASHI A, KAWAI C, EIHO S, KUWAHARA M: Analysis of asynchronous wall motion by regional pressure-length loops in patients with coronary artery disease. *J Am Coll Cardiol* 4: 259, 1984
6. SASAYAMA S, NONOGI H, MIYAZAKI S, SAKURAI T, KAWAI C, EIHO S, KUWAHARA M: Changes in diastolic properties of the regional myocardium during pacing-induced ischemia in human subjects. *J Am Coll Cardiol* 5: 599, 1985
7. NONOGI H, SASAYAMA S, MIYAZAKI S, ASANOI H, YAMANISHI K, KAWAI C, EIHO S, KUWAHARA M: Modification of pacing-induced alterations in diastolic properties of the regional myocardium by nifedipine in patients with coro-

- nary artery disease. *Heart Vessels* 1: 232, 1985
8. KENNEDY JW, TRENHOLME SE, KASSER IS: Left ventricular volume and mass from single plane angiogram. A comparison of anteroposterior and right anterior oblique methods. *Am Heart J* 80: 343, 1970
9. DWYER EM Jr: Left ventricular pressure-volume alterations and regional disorders of contraction during myocardial ischemia induced by atrial pacing. *Circulation* 42: 1111, 1970
10. MANN T, GOLDBERG S, MUDGE GH Jr, GROSSMAN W: Factors contributing to altered left ventricular diastolic properties during angina pectoris. *Circulation* 59: 14, 1979
11. McLAURIN LP, ROLETT EL, GROSSMAN W: Impaired left ventricular relaxation during pacing-induced ischemia. *Am J Cardiol* 32: 751, 1973
12. MANN T, BRODIE BR, GROSSMAN W, McLAURIN LP: Effect of angina on the left ventricular diastolic pressure-volume relationship. *Circulation* 55: 761, 1977
13. SERIZAWA T, CARABELLO BA, GROSSMAN W: Effects of pacing-induced ischemia on left ventricular diastolic pressure-volume relations in dogs with coronary stenosis. *Circ Res* 46: 430, 1980
14. PAULUS WJ, SERIZAWA T, GROSSMAN W: Altered left ventricular diastolic properties during pacing-induced ischemia in dogs with coronary stenosis. Potentiation by caffeine. *Circ Res* 50: 218, 1982
15. AROESTY JM, McKAY RG, HELLER GV, ROYAL HD, ALS AV, GROSSMAN W: Simultaneous assessment of left ventricular systolic and diastolic dysfunction during pacing-induced ischemia. *Circulation* 71: 889, 1985
16. BARRY WH, BROOKER JF, ALDERMAN EL, HARRISON DC: Changes in diastolic stiffness and tone of the left ventricle during angina pectoris. *Circulation* 49: 255, 1974
17. GROSSMAN W, McLAURIN LP: Diastolic properties of the left ventricle. *Ann Intern Med* 84: 316, 1976
18. TEMPLETON GH, WILDENTHAL K, MITCHELL JH: Influence of coronary blood flow on left ventricular contractility and stiffness. *Am J Physiol* 223, 1216, 1972
19. GROSSMAN W, MANN JT: Evidence for impaired left ventricular relaxation during acute ischemia in man. *Eur J Cardiol* 7 (Suppl): 239, 1978
20. GLANTZ SA, PARMLEY WW: Factors which affect the diastolic pressure-volume curve. *Circ Res* 42: 171, 1978
21. GROSSMAN W, BARRY WH: Diastolic pressure-volume relations in the diseased heart. *Fed Proc* 39: 148, 1980
22. GLANTZ SA, MISBACH GA, MOORES WY, ET AL: The pericardium substantially affects the left ventricular diastolic pressure-volume relationship in the dog. *Circ Res* 42: 433, 1978
23. ROSS J Jr: Acute displacement of the diastolic pressure-volume curve of the left ventricle: role of the pericardium and the right ventricle. *Circulation* 59: 32, 1979
24. PALACIOS I, JOHNSON RA, NEWELL JB, POWELL WMJ Jr: Left ventricular end-diastolic pressure volume relationships with experimental acute global ischemia. *Circulation* 53: 428, 1976
25. HESS OM, OSAKADA G, LAVELLE JF, GALLAGHER KP, KEMPER WS, ROSS J Jr: Diastolic myocardial wall stiffness and ventricular relaxation during partial and complete coronary occlusions in the conscious dog. *Circ Res* 52: 387, 1983
26. SUGA H: Left ventricular pressure-volume ratio in systole as an index of inotropism. *Jpn Heart J* 12: 153, 1971
27. EL-TOBGI S, FOUAD FM, KRAMER JR, RINCON G, SHELDON WC, TARAZI RC: Left ventricular function in coronary artery disease. Evaluation of slope of end-systolic pressure-volume line (Emax) and ratio of peak systolic pressure to end-systolic volume (P/Ves). *J Am Coll Cardiol* 3: 781, 1984
28. NIVATPUMIN T, KATZ S, SCHEUER J: Peak left ventricular systolic pressure/end-systolic volume ratio: a sensitive detector of left ventricular disease. *Am J Cardiol* 43: 969, 1979
29. HENRY PD, SCHUCHLIB R, DAVIS J, WEISS ES, SOBEL BE: Myocardial contracture and accumulation of mitochondrial calcium in ischemic rabbit heart. *Am J Physiol* 233: H677, 1977