Quantitative Analysis of Left Ventricular Function by Cold Pressor Two-Dimensional Echocardiography in Patients with Coronary Artery Disease

Takanori FUJITA, M.D., Ryuichi AJISAKA, M.D.,
Kimihiko YUKISADA, M.D., Yasuro SUGISHITA, M.D.,
and Iwao ITO, M.D.

SUMMARY

Quantitative assessment of left ventricular function in patients with coronary artery disease was made by computer analysis of two-dimensional echocardiography performed during a cold pressor test. Short-axis cross-sectional images of the left ventricle at the levels of the mitral valve and chordae tendineae were recorded by a phase array sector scanner in 12 patients with coronary artery disease and 11 normal controls. Endocardial outlines at end-diastole and end-systole were traced and analyzed by a computer system. The short-axis cross-sectional images were divided into octants and were analyzed. The segmental area and its changes during the cardiac cycle were measured and calculated for each octant. Regional function of the left ventricle was evaluated by percent changes of segmental area. The regional segmental area changes in patients with coronary artery disease were compared with those in normal controls. Similar increments were achieved in rate pressure product in the 2 groups. In relation to the perfusing coronary arteries, 8 segments were integrated arbitrarily into 3 walls (anteroseptal wall, lateral wall, and posterior wall and posterior septum). The cold pressor test induced wall motion abnormalities in 12 of 16 walls which were supplied by stenosed coronary arteries. In contrast, wall motion abnormalities were detected in only 5 of 38 walls which were supplied by coronary arteries without significant stenotic lesions. The sensitivity of cold pressor test-induced wall motion abnormalities in detecting coronary artery disease was 75% and the specificity was 87%. No serious complications were encountered in this study.

In conclusion, computer-aided cold pressor two-dimensional

From the Department of Internal Medicine, Institute of Clinical Medicine, University of Tsukuba, Ibaraki, Japan.

Address for reprint: Takanori Fujita, M.D., Department of Internal Medicine, Institute of Clinical Medicine, University of Tsukuba, Niihari-gun, Ibaraki-ken 305, Japan.

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echocardiography is a safe and sensitive method for the assessment of left ventricular function and diagnosis of coronary artery disease.

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TWO-DIMENSIONAL echocardiography represents a noninvasive approach to real time visualization of left ventricular motion. With this method, it is possible to detect stress induced left ventricular motion abnormalities.[1),2)] Some patients, especially elderly patients, however, are unable to perform an exercise test. The cold pressor ECG test has demonstrated its usefulness in the diagnosis of coronary artery disease.[3)-5)] In this study, using a computer aided system, we evaluated the usefulness of combined two-dimensional echocardiography and the cold pressor test in patients with coronary artery disease.

METHODS

Study subjects (Table I)

The study group comprised 11 normal controls (NC) (5 men and 6 women) and 12 patients with significant coronary artery disease (CAD) (10 men and 2 women). NC were patients with chest pain and normal coronary anatomy. No patients in the control group had electrocardiographic evidence of myocardial infarction. All subjects were in normal sinus rhythm without electrocardiographic conduction abnormalities. CAD had 50% or greater narrowing in at least 1 major coronary artery. Most of the patients with CAD (≥50% diameter stenosis) had a defect on either the rest or exercise thallium 201 image.[6)] Patients with valvular or congenital heart disease were excluded. Triple vessel disease was present in 1 patient, double vessel disease in 6 patients and single vessel disease in 5 patients. Informed consent for the examination was obtained from all subjects.

Table I. Subjects

	No.	Age (years)	Sex	
			M	F
CAD	12	51.3±9.8	10	2
NC	11	43.9±10.0	5	6

CAD=coronary artery disease; NC=normal coronary artery; M=male; F=female.

Cold pressor two-dimensional echocardiography

All patients underwent two-dimensional echocardiography during cold pressor testing. After the baseline two-dimensional echocardiogram and ECG were recorded and blood pressure was measured, one hand of the subject was immersed up to the level of the styloid process in a bucket of ice water (temperature 0 to 4°C) for 2 min. One precordial ECG lead was monitored continuously.

Two-dimensional echo views and wall motion analysis

Two short-axis views from the base of the left ventricle were obtained using a Toshiba SSH-11A sonolayergraph, with an electrically phased array transducer operating at 2.5-MHz. Studies were performed with the subjects in the left lateral position. During the cold pressor test, the echocardiographic transducer was constantly held on the patient's precordium in order to visualize the same left ventricular view. Short-axis parasternal images were obtained at the level of mitral valve leaflets and chordae tendineae. Two-dimensional echocardiograms were recorded at 30 frames/sec on a video recorder and transferred to a minicomputer via interface circuits, as we previously described.[7] The data flow system is shown in Fig. 1. The end-diastolic frame was chosen as the largest and most circular short-axis section, and the end-systolic as the smallest area, using the ECG as a guide. The largest end-diastolic areas generally coincided with the peak of the R wave, and the end-systolic frames were usually near the end of the T wave. The

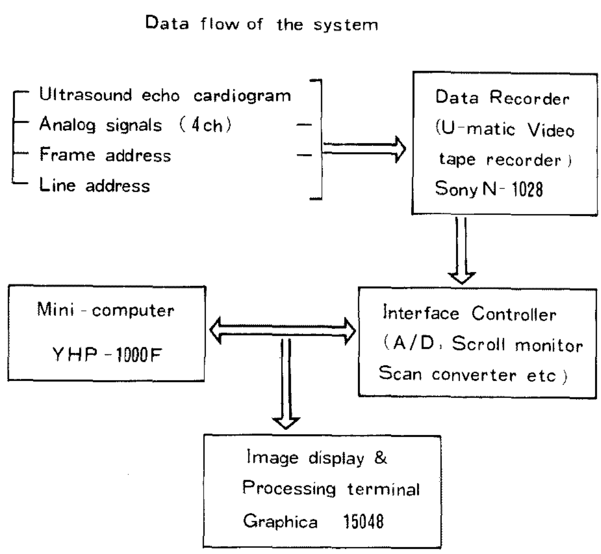

Fig. 1. Data flow of the system.

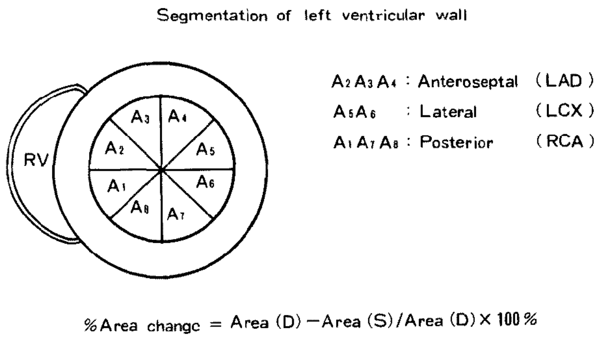

Fig. 2. Segmentation of left ventricular wall on two-dimensional echocardiogram. A = area; D = end-diastole; S = end-systole; LAD = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery; RV = right ventricle; Anteroseptal = anteroseptal wall; Lateral = lateral wall; Posterior = posterior wall.

images were manually traced and then digitized into a computer (YHP 1000F). We traced the inner borders of the endocardium. Each short-axis section was then subdivided into 8 equal angle segments, as shown in Fig. 2. A landmark in each image was the posterior junction of the right ventricular free wall and septum. The geometric center of the short-axis section of the left ventricle and the axis connecting this with the posterior end of the right side of the septum were used as the reference point and line. Floating axis systems were used for wall motion studies. End-diastolic and end-systolic segmental area changes (%area change = EDA − ESA/EDA × 100%, where EDA = end-diastolic area and ESA = end-systolic area) during a cardiac cycle were measured in each segment using a computer. Regional contractility of the left ventricle was evaluated by percent systolic changes of the segmental area. Regional wall motion abnormalities (WMA) were defined as positive when the segmental % area changes fell below 2 standard deviations (SD) of the normal control. For analysis of ventricular wall motion in relation to the perfusing coronary arteries, each segment was regarded arbitrarily to be supplied by vessels as follows (Fig. 2): anteroseptal wall by the left anterior descending artery, lateral wall by the left circumflex coronary artery and posterior wall and posterior septum by the right coronary artery, using a modification of the segment by Roberts et al,[8] Lewis et al,[9] and Ogawa et al.[10]

Evaluation of the results of the cold pressor two-dimensional echocardiography

Sensitivity of the test was calculated by a/b × 100(%), where a is the number of subjects with positive test results and b is the number of patients with significant coronary artery disease (CAD). Specificity of the test was

determined by c/d×100(%), where c is the number of patients with negative stress tests and d is the number of subjects without CAD.

Student's t-test was used to evaluate the statistical significance of the results. A probability (p) value of <0.05 was considered significant.

Results

1. Blood pressure, heart rate, and rate pressure product (Table II)

The cold pressor test (CPT) resulted in a significant increase in systolic pressure and rate pressure product (heart rate×peak systolic pressure), compared with the measurements at rest (Table II). Systolic pressure increased by an average of 33 mmHg in CAD ($p<0.005$) and 25 mmHg in NC ($p<0.01$). Heart rate did not increase in either CAD or NC. Rate pressure product (RPP) increased by an average of 3510 (35%) in CAD ($p<0.005$) and 2230 (20%) in NC ($p<0.01$). The increments with cold pressor testing did not differ significantly between the 2 groups. Neither chest pain nor electrocardiographic ST segment changes suggestive of myocardial ischemia developed during the cold pressor test in any patients.

2. Ventricular wall motion changes during cold pressor testing

Clear images were obtained in 10 of 11 normal controls, and the images were analyzed in each of 8 segments. An example of a normal control is shown in Fig. 3. No asynergy was induced during the test. Coronary arteriography showed no significant coronary artery disease in this subject. Individual segmental % area changes are shown in Fig. 4. The segmental % area changes tended to increase during cold pressor testing, but not significantly.

Table II. Hemodynamic Response to Cold Pressor Test

	HR (bpm)	SBP (mmHg)			RPP (×100)		
A. Control							
CAD	73.1±12.1	140.7±25.6			101.9±30.1		
	↕ NS	↕ NS	*	**	↕ NS	*	**
NC	71.8±12.8	127.1±12.9			91.7±22.6		
B. CPT							
CAD	78.3±10.4	174.0±20.8			137.3±27.9		
	↕ NS	↕ **			↕ ***		
NC	74.8±12.9	152.6±20.7			114.0±23.9		

* $p<0.0005$, ** $p<0.01$, *** $p<0.05$.

Abbreviations: CPT=cold pressor test; RPP=rate pressure product; NS=not significant; HR=heart rate; SBP=systolic blood pressure. Other abbreviations as in Table I.

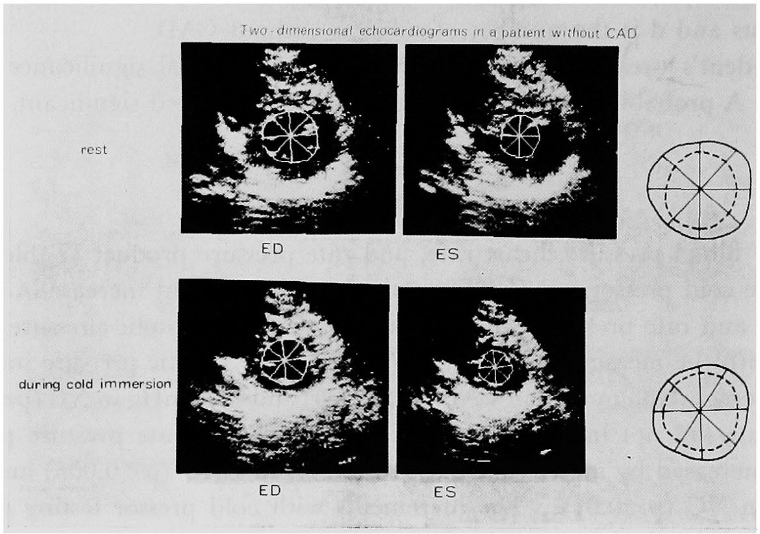

Fig. 3. Two-dimensional echocardiograms of a normal control. Right are schematic representations of echocardiograms, solid lines indicate end-diastole and broken lines indicate end-systole. No asynergy was revealed by the cold pressor test. CAD = coronary artery disease; ED = end-diastole; ES = end-systole.

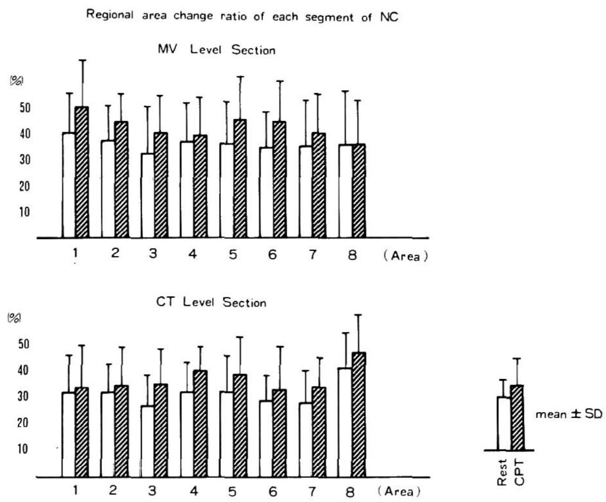

Fig. 4. Regional area changes of each segment of normal controls. Each column represents mean ± standard deviation (SD). White columns indicate resting values. Slant line columns indicate values during cold pressor testing. MV = mitral valve; CT = chordae tendineae.

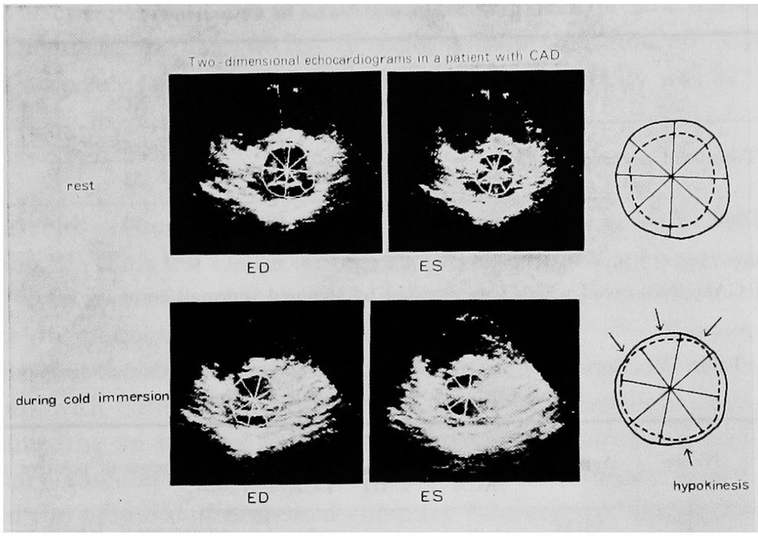

Fig. 5. Two-dimensional echocardiograms of a case with coronary artery disease (CAD). This patient had LAD and LCX lesions on coronary arteriograms. The arrow shows left ventricular regional asynergy. Abbreviations as in Figs. 2 and 3.

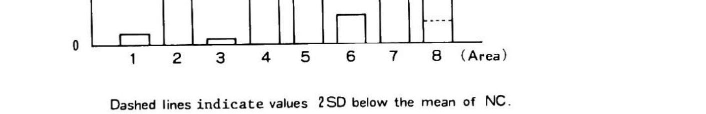

Fig. 6. Regional area change of each segment of a patient with CAD. Areas 1, 2, 3, and 6 showed 2 SD below the mean of normal control values.

3. Case presentation

Fig. 5 shows the cold pressor-induced WMA in a 40 year old male patient with CAD. Cold pressor testing induced left ventricular regional asynergy (hypokinesis) of segments #1, #2, #3, and #6 (indicated by arrows) but no electrocardiographic ST-T changes in any leads. Therefore, the cold pressor two-dimensional echocardiogram was considered to be positive. Fig. 6 shows the schematic presentation of regional area changes in each

Table III. Diagnostic Value of CPT-2DE

		Wall of CAD	Wall of NC	Total
CPT-induced asynergy	+	12	5	17
	−	4	33	37
Total		16	38	54

Sensitivity 75% (12/16); Specificity 87% (33/38).
Wall of CAD (NC) = wall which was supplied by stenosed (normal) coronary artery.

Table IV. Correlation of Cold Pressor Two-Dimensional Echocardiography and Coronary Arteriographic Findings

Patient No.	Name	Age/Sex	CAG findings RCA	LAD	LCX	Segments of positive test
1	IT	53/M	−	−	+	anteroseptal, lateral posterior
2	AY	46/M	−	+	+	anteroseptal, lateral posterior
3	AN	47/F	+	+	−	anteroseptal
4	YT	67/F	+	−	−	posterior
5	KY	40/M	−	+	+	anteroseptal, lateral
6	KA	64/M	+	−	+	anteroseptal, lateral posterior
7	YK	53/M	+	+	−	—
8	HY	63/M	−	+	+	anteroseptal, lateral posterior
9	ST	44/M	−	+	−	—
10	HK	54/M	−	+	−	anteroseptal

Segmentation of left ventricle as in Fig. 2.
Abbreviations: CAG = coronary arteriogram; RCA = right coronary artery; LAD = left anterior descending artery; LCX = left circumflex artery; M = male; F = female.

segment in this patient. Broken lines show the values of 2 standard deviations below the means of NC. Coronary arteriography demonstrated 50% stenosis at the proximal portion (segment 7) of the left anterior descending artery and 75% stenosis at the midportion (segment 13) of the left circumflex artery.

4. WMA induced by the cold pressor test (Table III)

The diagnostic accuracy of two-dimensional echocardiography was evaluated by the relationship between left ventricular wall motion of each wall and coronary artery lesions which supply the wall. Of the 38 walls which were supplied by vessels without significant stenotic lesions, cold pressor test-induced WMA were detected in only 5 walls. Clear images were obtained in 10 of 12 patients with CAD. Table IV shows the correlation between cold pressor two-dimensional echocardiography and coronary arteriographic findings in 10 patients. Of the 16 walls which were supplied by stenosed

coronary arteries, WMA were demonstrated during cold pressor testing in 12 walls. Therefore, the sensitivity of cold pressor test-induced WMA in detecting coronary artery disease was 75% and the specificity was 87%.

Discussion

The cold pressor test simply and effectively induces alpha-adrenergic stimulation.[11] This test characteristically increases blood pressure and heart rate.[11),12] It is known that a cold stimulus increases coronary vascular resistance in patients with coronary artery disease.[12),13] Raizner et al reported[14] that the cold pressor test could provoke focal coronary artery spasm in patients with coronary artery disease. Such hemodynamic changes are accompanied by an increase in myocardial oxygen requirement, an increase in coronary vascular resistance and provocation of coronary artery spasm, which, in the presence of decreased coronary flow reserve, may induce myocardial ischemia. Therefore, cold pressor testing has been used in the diagnosis of coronary artery disease (both effort angina and vasospastic angina).[3)-5] However, there may be no correlation between CPT-induced WMA and the location of fixed coronary stenosis.[5]

It is well known that left ventricular WMA are induced or exaggerated by myocardial ischemia.[15),16] It has also been reported that left ventricular regional function is a more sensitive and reliable parameter of myocardial ischemia than are electrocardiographic, ST-segment changes at the initiation of myocardial ischemia,[17)-19] since the former preceded the latter. In our patients, neither chest pain nor specific electrocardiographic ST-segment changes suggestive of myocardial ischemia developed during the cold pressor test. It is generally agreed that the cold pressor test can rarely induce angina or electrocardiographic ST-segment changes as ischemic manifestations.[3),5] With respect to collateral circulation, this was detected by coronary angiography in 5 of 10 patients (Table IV). WMA was not induced due to the presence of collateral circulation in 1 patient (case 7, Table IV).

Wainwright et al[3] evaluated left ventricular function in patients with coronary artery disease by performing radionuclide angiography during cold pressor testing. In patients with coronary artery disease, reduction in ejection fraction and development of regional wall motion abnormalities were observed. Ahmad et al[4] reported that myocardial scintigraphy during cold pressor testing offered promise in detecting abnormal myocardial perfusion and was highly sensitive in identifying patients with severe coronary artery disease. M-mode echocardiography during cold pressor testing has been described as a useful technique for detecting latent WMA in patients with CAD.[20] Ko-

dama et al reported that the sensitivity of the cold pressor test with two-dimensional echocardiography was not related to the type of angina, but to the severity of CAD.[21] Gondi et al[5] reported that two-dimensional echocardiography during cold pressor testing had a high specificity in the identification of patients with significant coronary artery disease. The sensitivity of cold pressor test-induced WMA in detecting coronary artery disease was 69% and the specificity was 86%. However, their methods were not quantitative.

In this study, we used quantitative analysis of left ventricular regional motion. Percent area changes in septal areas (segments #1 and #8) at rest in this study were greater than those reported in previous studies.[22),23] The reason for the difference is thought to be that a floating-axis system was applied in this study, while a fixed-floating system was used in the other studies. Since we used quantitative methods, the diagnostic sensitivity was superior to the previous report,[5] enabling us to make an objective analysis.

The advantages of cold pressor two-dimensional echocardiography in general subjects are: 1) the test is easily performed and repeated, 2) it is applicable to those patients who have limitations of physical activity, and 3) desirable echocardiographic images can be obtained. Thus, the cold pressor test may play a diagnostic role in those in whom exercise stress testing is not feasible. In our experience, the cold pressor test is safe and effective and can be performed easily.

Limitations of the method: Our method had some limitations in the diagnosis of coronary artery disease. The limited echocardiographic field of view might miss other ischemic events. The quantitative methods of this study require measurements in standardized locations, and the apical portions of the left ventricle, which are usually involved in ischemia, are not well represented in the analysis. In some patients, because of hypersensitivity to a cold stimulus, the test cannot be performed easily.

In conclusion, two-dimensional echocardiography during cold pressor testing is a simple, safe, and sensitive method for the assessment of left ventricular function and diagnosis of coronary artery disease.

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