The Effect of Nifedipine on Ventriculoarterial Coupling in Old Myocardial Infarction

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The effect of nifedipine on ventriculoarterial coupling was examined in 8 patients with old myocardial infarction who showed a depressed ejection fraction ($37 \pm 7\%$). Left ventricular (LV) pressure and LV volume were determined simultaneously by micromanometer and conductance catheter, respectively. We measured the slope (Ees) of the end-systolic pressure-volume relation during transient inferior vena caval occlusion, the slope (Ea) of the end-systolic pressure-stroke volume relation, the ratio of Ea to Ees (Ea/Ees), and the work efficiency (the ratio of external work to the systolic pressure-volume area) at baseline and after the sublingual administration of nifedipine (10 mg). Nifedipine slightly increased the heart rate from 71 ± 14 to 78 ± 17 beats/min. Although nifedipine had little effect on Ees (2.54 ± 0.68 vs 2.47 ± 0.62 mmHg/ml/m² ns), it significantly decreased Ea from 3.47 ± 1.16 to 2.37 ± 0.54 mmHg/ml/m². Consequently, Ea/Ees decreased from 1.42 ± 0.47 to 0.97 ± 0.31 and work efficiency increased from 48 ± 12 to $59 \pm 13\%$ after nifedipine administration. These data suggest that nifedipine reduces afterload (Ea) and improves left ventriculoarterial coupling without depressing left ventricular contractility in patients with failing hearts due to old myocardial infarction.

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THERE have been many investigations^{1–8} of the acute effects of calcium antagonists on left ventricular systolic and diastolic properties in coronary artery disease. However, there have been few studies^{9,10} of the treatment ventriculoarterial coupling in diseased hearts. Sunagawa et al¹¹ proposed a theoretical model to assess the interaction between the left ventricle (LV) and the systemic arterial system. Using the slope (Ees) of the end-systolic pressure-volume relation to LV chamber elastance and the slope (Ea) of the end-systolic pressure-stroke

volume relation to effective arterial elastance, it has been shown that the ratio of Ea to Ees (Ea/Ees: ventriculoarterial coupling) is useful for assessing LV cardiac performance under varying loading and inotropic conditions.^{12–14} Asanoi et al⁹ that Ea/Ees increased as the LV ejection fraction decreased in patients with dilated cardiomyopathy (DCM). Kameyama et al¹⁰ reported that preload reduction caused by lower negative pressure reduced Ea/Ees and that afterload reduction with nitroprusside improved Ea/Ees. However, there have been few reports of how preload or afterload affects Ea/Ees in coronary artery diseases with regional wall motion abnormalities.

Therefore, the present study was designed

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to determine how nifedipine, a powerful arterial vasodilator, affects Ea/Ees in old myocardial infarction (OMI) with depressed LV ejection fraction.

METHODS

Patient Population

The study population consisted of 8 patients who were referred for cardiac catheterization for evaluation of OMI. They included 7 men and 1 woman, with a mean age of 63 ± 10 years (range 45 to 74 years). Their electrocardiograms showed abnormal Q wave (QRS interval > 0.04 msec, Q/R > 0.25) in at least 2 leads, and a remarkable elevation of creatine kinase was ascertained in all of the patients. Their functional capacity was class II or III according to the NYHA classification. All medications were withheld for at least 24 h before the examination. Each patient also provided their written informed consent to participate in the study on forms approved by the Human Investigation Committee of Yamaguchi University.

Protocol

An 8 French (Fr) introducer sheath (USCI) was placed into the femoral artery and 8-Fr and 10-Fr introducer sheaths (USCI) were placed into the femoral vein with the Seldinger percutaneous technique, respectively. The patient received intravenous heparin (100 IU/kg), and routine catheterization including coronary angiography and ventriculography was performed. After completion of routine catheterization, a Fogarty catheter which was used to reduce preload transiently by occluding the inferior vena cava (IVC) was advanced to the right atrial-IVC junction through a 10-Fr sheath. An 8-Fr volume catheter (Dual field-conductance catheter, Leycom) was inserted through the femoral arterial sheath and advanced to the ascending aorta. A 2-Fr micromanometer-tipped pressure catheter (SPC-330A, Millar Inc, TX) was then inserted via a Y connector into the lumen of the conductance catheter and extended to its distal end. The left ventricular pressure signal from the micromanometer was adjusted to match the pressure measured through the fluid channel of this catheter by means of a Statham P 23ID transducer

(Gould Inc, Oxnard, CA), and was calibrated with a mercury manometer. The midchest level was used as the zero reference. Continuous slow infusion of heparinized 5% Dextrose through another side-port of the Y connector was maintained to prevent hemostasis.

With the pressure transducer inserted, the catheter assembly was advanced to the left ventricular apex. Proper placement of the catheter within the ventricle was determined by fluoroscopic inspection and by examining each segment of the pressure-volume loops. The catheter was straightened and extended from the aortic root to the LV apex to give little longitudinal motion throughout the cardiac cycle. The conductance catheter was connected to a stimulator/signal processor (Sigma 5, Leycom, The Netherlands).

Data were obtained at baseline and 30 min after the sublingual administration of 10 mg of nifedipine. An electrocardiogram, left ventricular pressure, left ventricular volume, aortic pressure and mean right atrium pressure were monitored using a VR 12-channel recorder (Electronics for Medicine Inc, Pleasantville, NY) and simultaneously digitized at 5-msec intervals using on-line A-D conversion with custom software (DATAQ Inc, Akron, OH) on a 32-bit microcomputer system (IBM PC/AT). Real-time pressure-volume loops were also monitored with a 16-bit microcomputer system (PC-9801 EX, NEC, Tokyo).

Determination of End-Systolic Pressure-Volume Relationships (ESPVRs)

To measure pressure-volume relationships^{15,16} the balloon of the Fogarty catheter was rapidly inflated in the right atrium and pulled back to occlude venous return. Pressure-volume loops for the sequence of beats following the reduction in LV preload were monitored and simultaneously recorded with the A-D recording system. Data were stored on a hard disk for subsequent analysis.

Data Analysis

ESPVRs were determined from the 6–10 beats following IVC occlusion. The point of the maximum pressure/volume ratio for each cardiac cycle was determined. These points were fit by linear regression to the expression $P_{es} = E_{es} (V_{es} - V_0)$, where P_{es} , V_{es} ,

Fig 1. Schematic explanation of the left ventriculoarterial coupling (left panel) and the pressure-volume area (right panel). ESPVR: end-systolic pressure-volume relation, ESPSVR: end-systolic pressure-stroke volume relation, V_0 : the volume-intercept of ESPVR, Ees: the slope of ESPVR, Ea: the slope of ESPSVR, PVA: the pressure-volume area, which consists of external work represented by trajectory (ABCD) and potential energy.

TABLE I BASELINE PATIENT CHARACTERISTICS

Patient No.	Age (yr) / Gender	MI site	infarct artery
1	68/F	A-S MI	#6 (total)
2	67/M	INF MI	#3 (90%)
3	51/M	A-S MI	#6 (total)
4	60/M	INF MI	#2 (total)
5	74/M	A-S MI	#6 (90%)
6	73/M	A-S MI	#6 (total)
7	42/M	INF+LAT MI	#3, 9 (total), #6 (90%)
8	62/M	A-S+INF MI	#3, 6 (total)

A-S; anteroapical, INF; inferior, LAT; lateral, MI; myocardial infarction, F; female, M; male, total; totally occluded coronary artery. Coronary artery segments and the severity of stenosis were determined according to the recommendations of the AHA.

and Ees are the end-systolic pressure, end-systolic volume index and the slope of the ESPVR, respectively, and V_0 is the volume-axis intercept. The initial V_0 estimate was then used in a second iteration, in which the point of max $P_{es}/(V_{es}-V_0)$ was determined for each cardiac cycle. Repeat regression led to a new V_0 estimate, and this iterative process continued (usually within 4 times) until convergence was achieved for both the slope and intercept estimates.¹⁷ Ea was determined as the ratio of P_{es} to the stroke volume index. Systemic vascular resistance (SVR) was defined as the ratio of the difference between the mean arterial pressure and mean right atrium pressure to cardiac output. Ejection fraction (EF) was defined as the ratio of the stroke volume to end-diastolic

volume. The ventricular volumes were measured by conductance catheter. The pressure-volume area (PVA) was the area circumscribed by the end-systolic pressure-volume relation, the end-diastolic pressure-volume curve and the systolic segment of the pressure-volume loop trajectory. The external work (EW) index was the area within the pressure-volume loop. The PVA and EW were measured by planimetry, and work efficiency was defined as the ratio of EW index to PVA (Fig 1). End-diastole was determined at the rapid pressure upstroke (the point at which dP/dt first exceeded 50 mmHg/sec).

Volume Signal Calibration

LV volume signals at end-diastole and

TABLE II INDIVIDUAL HEMODYNAMIC RESPONSES TO NIFEDIPINE IN 8 PATIENTS

Patient No.		HR (bpm)	AoP (mmHg)	LVEDP (mmHg)	RA (m) (mmHg)	EDVI (ml/m ²)	ESVI (ml/m ²)	SVI (ml/m ²)	EF (%)	SVR (dyne · sec · m ⁻⁵)
1.	C	92	196	18	5	90	62	28	31	2488
	N	102	156	14	9	85	43	41	49	1673
2.	C	50	142	18	5	80	43	37	46	1771
	N	52	108	16	5	79	35	44	55	1503
3.	C	66	102	18	2	95	63	32	34	1686
	N	67	98	19	3	90	59	31	34	1256
4.	C	84	124	12	4	76	40	36	47	1973
	N	94	96	12	5	78	34	44	56	1136
5.	C	78	150	12	2	80	46	34	43	2029
	N	82	126	11	2	77	40	37	48	1570
6.	C	60	170	24	4	105	65	40	38	2346
	N	75	136	20	5	90	50	40	44	1414
7.	C	74	160	22	6	129	88	41	31	1838
	N	88	144	20	5	114	72	42	37	1410
8.	C	63	135	22	1	156	116	40	26	1973
	N	63	108	20	2	145	99	46	32	1386
Mean ± SD	C	71 ± 14	145 ± 15	18 ± 4	4 ± 2	101 ± 28	65 ± 26	36 ± 4	37 ± 7	2013 ± 277
	N	78 ± 17*	125 ± 20*	17 ± 3*	5 ± 2	95 ± 24*	54 ± 22*	41 ± 5*	44 ± 9*	1419 ± 170*

AoP indicates aortic systolic pressure; C: control; EDVI: end-diastolic volume index; EF: ejection fraction; ESVI: end-systolic volume index; HR: heart rate; LVEDP: Left ventricular end-diastolic pressure; N: nifedipine; RA (m): mean right atrial pressure; SVI: stroke volume index; SVR: systemic vascular resistance.

* $p < 0.05$ vs control.

end-systole from the conductance catheter were matched to LV end-diastolic volume (EDV) and LV end-systolic volume (ESV) determined from the biplane cineventriculographic volume data using the area-length method, respectively.

Statistical Analysis

Results are expressed as mean values ± SD. The statistical significance of differences in hemodynamic variables between 2 groups was tested by the paired t test. Values of $p < 0.05$ were considered statistically significant.

RESULTS

The baseline patient characteristics are summarized in Table I. None of the patients had dyskinesia in LV wall motion. Six patients did not have postinfarct angina or ischemic ST segment changes during treadmill exercise. These patients did not have significant stenosis ($\geq 75\%$ diameter) in any other major coronary artery. Of the remaining 2 patients, No. 5 underwent angioplasty and No. 7 underwent coronary bypass surgery.

The hemodynamic data are shown in Table II. Heart rate increased from 71 ± 14 to 78 ± 17 beats/min ($p < 0.05$) in response to nifedipine. Both aortic systolic pressure (145 ± 15 to 125 ± 20 mmHg, $p < 0.05$) and LV end-diastolic pressure (18 ± 4 to 17 ± 3 mmHg, $p < 0.05$) decreased significantly with nifedipine. Mean right atrial pressure did not change relative to the control value (4 ± 2 to 5 ± 2 mmHg n.s.). Although LV EDV index (EDVI) and ESV index (ESVI) decreased after the sublingual administration of nifedipine (101 ± 28 to 95 ± 24 ml/m², 65 ± 26 to 54 ± 22 ml/m², respectively, $p < 0.05$), the stroke volume index increased from 36 ± 4 to 41 ± 5 ml/m² ($p < 0.05$). Thus, EF increased from 37 ± 7 to $44 \pm 9\%$ ($p < 0.05$). SVR decreased from the control value of 2013 ± 277 to 1419 ± 170 dynes · sec · cm⁻⁵ ($p < 0.05$).

Fig 2 shows a representative relation between Ees and Ea before and after nifedipine administration. While Ees did not change, Ea decreased with nifedipine administration. Therefore, Ea/Ees decreased from 1.5 to 1.2. Table III shows the results of ventriculoarterial coupling and work efficiency. The ESPVRs were well described by a linear relationship ($r = 0.96 \pm 0.03$). Al-

Fig 2. Representative (patient No. 7) pressure-volume loops, end-systolic elastance (Ees) and effective arterial elastance (Ea) at baseline (left panel) and after nifedipine (right panel). At baseline (control), Ea was greater than Ees. After nifedipine, although Ees did not change, Ea decreased compared to the control value.

TABLE III INDIVIDUAL DATA REGARDING VENTRICULAR AND ARTERIAL PROPERTIES

Patient No.		Ees (mmHg/ml/m ²)	Ea (mmHg/ml/m ²)	Ea/Ees	EWI (mmHg · ml/m ²)	PVA (mmHg · ml/m ²)	Efficiency (%)
1.	C	2.61	5.86	2.25	3671	6347	58
	N	2.79	2.56	0.92	3002	5048	60
2.	C	2.39	3.27	1.37	5836	10168	57
	N	2.71	2.41	0.89	3751	6058	62
3.	C	2.86	2.84	0.99	3931	6681	59
	N	2.66	2.12	0.80	3405	5086	67
4.	C	4.02	3.11	0.77	4624	6956	66
	N	4.05	1.89	0.47	4294	5188	83
5.	C	2.04	4.29	2.10	5907	13446	44
	N	2.08	3.24	1.56	6665	11522	58
6.	C	2.24	2.92	1.30	6068	16410	37
	N	2.14	2.21	1.03	6009	13002	46
7.	C	2.40	3.48	1.45	5601	16251	34
	N	2.51	2.96	1.18	7164	13414	53
8.	C	1.78	2.00	1.12	2683	8657	31
	N	1.82	1.60	0.88	2789	7227	39
Mean ± SD	C	2.54 ± 0.68	3.47 ± 1.16	1.42 ± 0.52	4790 ± 1259	10617 ± 4219	48 ± 12
	N	2.47 ± 0.62	2.37 ± 0.54*	0.97 ± 0.31*	4635 ± 1727	8318 ± 3692*	59 ± 13*

Results are expressed as mean ± SD. C indicates control; N: nifedipine; EWI: external work index; PVA: pressure-volume area; Efficiency: EWI/PVA. * $p < 0.05$ vs control.

though Ees did not change with nifedipine administration, Ea decreased significantly from 3.47 ± 1.16 to 2.37 ± 0.54 mmHg/ml/m². Consequently, Ea/Ees decreased from 1.42 ± 0.52 to 0.97 ± 0.31 ($p < 0.05$). The external work index did not change significantly after nifedipine administration. However, the systolic pressure-volume area (PVA) decreased significantly vs the control value, since end-systolic pressure decreased and Vo changed only slightly vs the control (9 ± 33 to

9 ± 35 ml, ns). Consequently, work efficiency was significantly augmented with nifedipine (48 ± 12 to $59 \pm 13\%$, $p < 0.05$).

DISCUSSION

There have only been a few studies concerning ventriculoarterial coupling in OMI because it is difficult to measure LV volume in real time. Therefore, we analyzed the changes in ventriculoarterial coupling with

failing hearts due to old myocardial infarction using a conductance catheter before and after the sublingual administration of nifedipine. The present study was performed using a dual-field conductance catheter, which can measure LV volume more accurately than a single-field conductance catheter even if the left ventricle shows regional asynergy¹⁹

Hemodynamic Response to Nifedipine in Myocardial Infarction

In the present study, nifedipine decreased aortic systolic pressure and LV filling pressure but did not significantly change right atrial pressure, as has been previously reported. Thus, nifedipine had a predominantly arteriolar and a negligible venous effect. Nifedipine decreased systemic vascular resistance, and LV end-systolic and end-diastolic volume, while enhancing LV EF. Plasma catecholamines were not examined in this study. Pederson et al¹⁹ demonstrated that the plasma concentration of norepinephrine (NA) increased after the administration of nifedipine. In this study, a reflex sympathetic stimulation due to marked dilatation of sympathetic vascular vessels could cause an abrupt increase in the concentration of NA. The improvement in LV EF might be attributed to afterload reduction and an increase in intrinsic catecholamines. Nifedipine improved the deteriorated hemodynamic state in OMI.

Ventriculoarterial Coupling and Work Efficiency

Asanoi et al⁹ reported that Ees correlated well with ejection fraction in patients with global systolic dysfunction, such as in DCM. In our study, Ees did not always decrease with EF. Sunagawa et al²⁰ showed that ESPVR in acute regional ischemia was shifted to the right without a change in Ees in excised hearts. Kass et al²¹ however, showed that the change in ESPVR in response to acute regional ischemia was not merely a parallel rightward shift; indeed, Ees frequently decreased during ischemia in open-chest dogs. This change depended on both the baseline Ees and the ratio of the size of the ischemic zone to the total LV mass. A larger ischemic zone was associated with a smaller Ees. In the natural healing

process, infarcted segments become stiffer as connective tissues replace necrotic tissue. Thus, it is reasonable to conjecture that the natural healing process would substantially decrease the volume-axis intercept and restore the slope of the overall ESPVR of the ventricle, since Ees should represent the sum of the elastance in the normal compartment and the infarct compartment²². In earlier studies^{9,10} Ees in OMI was greater than that in DCM with similar EF⁹ since the infarcted area is stiff and the total elastance of the LV is high. In addition, since most cases of OMI in our study had single-vessel coronary artery disease, the size of the infarct might not be as great as expected. Thus, Ees might not decrease in proportion to a decrease in EF.

Nifedipine did not significantly decrease Ees, but did slightly increase heart rate. There are at least two explanations why Ees did not change after nifedipine administration. First, the patients received a sublingual dose of 10 mg nifedipine. Although a 10 mg-dose is common in clinical practice, it may not have had a sufficient direct negative inotropic effect on myocardium. When nifedipine exhibited a negative inotropic effect in previous studies^{23,24} it was administered in a single dose of 20 to 50 mg. Second, a decrease in aortic systolic pressure may have caused an augmented baroreflex. Heart rate increased only slightly; less than 10 beats per min. The negative inotropic effect on myocardium by nifedipine might be offset by a reflex sympathetic stimulating action.

Nifedipine decreased arterial elastance (Ea) because it decreased end-systolic pressure and increased stroke volume. Ea also reflects the influence of the pulsatile impedance load, which cannot be measured by the mean resistance. A decrease in Ea would reflect a decrease in arterial input impedance, ie, afterload.

Sunagawa et al¹³ predicted theoretically and validated experimentally that left ventricular external work was maximized when ventricular contraction (Ees) equaled arterial input impedance (Ea) ($Ea = Ees$). Burkhoff and Sagawa¹² showed theoretically that maximal mechanical efficiency was attained when arterial elastance was half of ventricular elastance ($Ea = Ees/2$). Asanoi et al⁹ first demonstrated that normal coupling condi-

tions of nearly $Ea=Ees/2$ were needed to achieve max mechanical efficiency. A severely depressed human heart, however, can not maintain optimal external work or mechanical efficiency. In this study, baseline Ea/Ees was less than that seen in patients with DCM because Ees in this study was greater than that in earlier studies.^{9,10} Kameyama et al¹⁰ showed that the reduction in preload caused by a lower negative pressure and the reduction in afterload caused by nitroprusside appeared to have opposite effects on ventricular load coupling. The reduction in afterload, but not that in preload, plays an important role in restoring optimal ventricular load coupling in patients with heart failure. In this study, nifedipine also significantly decreased Ea/Ees relative to that at baseline without reducing LV contractility. Thus, nifedipine restored deteriorated ventriculoarterial coupling.

After the administration of nifedipine although the external work index did not change, the pressure-volume area (PVA) decreased because of a decrease in end-systolic pressure, despite a small augmentation of stroke volume. According to Suga,²⁶ the relation between PVA and myocardial oxygen consumption is linear, with a non-zero positive intercept for $PVA=0$. A decrease in PVA reflects a decrease in myocardial oxygen consumption. Thus, nifedipine decreased myocardial oxygen consumption in failing hearts. The reduction in PVA was greater than the reduction in the external work index. Consequently, work efficiency increased after nifedipine administration. These results were consistent with those of Kameyama et al.¹⁰

Clinical Implications

Since coronary artery disease is the underlying cause of chronic heart failure in 60 to 70% of patients,^{26,27} the favorable effect of calcium antagonists on ventricular arterial coupling might help to improve reduced LV ejection fraction and to achieve maximal external work by decreasing afterload while having an anti-ischemic effect in coronary artery disease.

Limitations

The population in this study was fairly small. However, all of the hemodynamic

data showed a similar trend after nifedipine. These data displayed little scatter, suggesting that a greater number of patients would probably not give different results.

Volume calibration based on ventriculography may have introduced some errors. However, when LV volume determined using a conductance catheter was compared with that determined using biplane cineventriculography at baseline, the correlation coefficient was 0.94. Furthermore, volume calibration errors would have little effect on the comparison of Ea/Ees at baseline to Ea/Ees after nifedipine administration because the same calibration was applied in the same patients.

In this study, although 2 patients had angina pectoris, the improvement of chronic ischemia by nifedipine would not be expected to alter the results, since changes in the hemodynamic data in these patients did not differ much from those in other patients.

Conclusions

The patients in this study had moderately to severely depressed LV systolic function due to OMI and high LV end-diastolic pressure. In these patients, nifedipine reduced afterload (Ea) without reducing left ventricular contractility and partially restored disturbed ventriculoarterial coupling in failing hearts ($Ea/Ees > 1$) due to coronary artery disease toward the optimal condition ($Ea/Ees < 1$).

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