JACC Vol. 23, No. 2
February 1994:406–16

Relation Between Ventriculoarterial Coupling and Myocardial Energetics in Patients With Idiopathic Dilated Cardiomyopathy

HITOSHI ISHIHARA, MD, MITSUHIRO YOKOTA, MD, PhD, FACC,* TOSHIKAZU SOBUE, MD, HIDEHIKO SAITO, MD, PhD

Nagoya, Japan

Objectives. **The purpose of this study was to evaluate left ventricular contractility, arterial loading conditions and the way their interaction affects myocardial energetics.**

Background. **Ventriculoarterial coupling, defined as the ratio of effective arterial elastance to left ventricular end-systolic elastance, is known to reflect the mechanoenergetic performance of the heart. However, relations between the coupling and efficiencies of energy transfer from oxygen consumption to hydraulic energy have not been fully investigated in failing hearts.**

Methods. **Pressure-volume data were measured in 23 patients with idiopathic dilated cardiomyopathy by using a conductance catheter, and myocardial oxygen consumption was obtained simultaneously in 16 patients by a double-thermistor coronary sinus catheter. End-systolic elastance was determined by transient inferior cava occlusion.**

Results. **Data are reported as mean value ± SE. Ventriculoarterial coupling at baseline was 3.24 ± 0.28. It decreased from 3.12 ± 0.43 to 1.86 ± 0.15 ($p < 0.05$) for the group receiving dobutamine infusion and from 3.16 ± 0.45 to 1.78 ± 0.22 ($p < 0.01$) for the group receiving the oral phosphodiesterase inhibitor MS-857. The ratio of pressure-volume area to myocardial oxygen consumption had a positive correlation with ventriculoarterial coupling. The ratio of external work to pressure-volume area had a hyperbolic correlation with the coupling. The mechanical efficiency defined as the ratio of external work to myocardial oxygen consumption remained within a narrow range (16.4 ± 1.2%).**

Conclusions. **The degree of ventriculoarterial coupling is far from optimal and the cardiovascular performance is severely depressed mechanically and energetically in patients with idiopathic dilated cardiomyopathy. Although inotropic agents improve the coupling, they have a minimal effect on mechanical efficiency.**

(J Am Coll Cardiol 1994;23:406–16)

Idiopathic dilated cardiomyopathy is a fatal heart disease that severely compromises cardiac performance. The main cause of death is progressive congestive heart failure; the sudden onset of critical arrhythmias is another important cause of death (1). Various aspects of this disease including the pathophysiology, hemodynamics and associated mortality have been analyzed and reported (2–8), but many problems remain unresolved. One problem is that this disease is extremely resistant to therapy and no cardiotonic agent has been reported to decrease its mortality (9–12).

Left ventricular contractility, vascular loading conditions and their interaction have been investigated recently. Investigations have focused on how these variables affect myocardial energetics because an understanding of the pathophysiology of myocardial energetics will permit a better appreciation of the mechanism of energy generation in the heart. Better understanding might promote better treatment of failing hearts and better use and development of cardiovascular drugs.

Recent studies (13–18) on myocardial energetics using pressure-volume relations have enhanced our understanding of the efficiency of energy conversion from oxygen consumption to mechanical or hydraulic output and the way that contractile state and loading conditions influence efficiency. Mechanical efficiency, a ratio of external work to myocardial oxygen consumption, is the conversion efficiency from metabolic energy to hydraulic energy that the left ventricle generates against the vascular system. This efficiency can be divided into two stages: 1) the efficiency from myocardial oxygen consumption to the pressure-volume area; and 2) the efficiency from pressure-volume area to external work, which is called cardiac work efficiency (13–15). Each stage of energy transfer varies according to changes in contractility and loading conditions.

By means of left ventricular pressure-volume relations, we investigated left ventricular contractility, arterial loading conditions and the way their interaction affects myocardial energetics in patients with idiopathic dilated cardiomyopathy.

From First Department of Internal Medicine, Nagoya University School of Medicine and *Department of Clinical Laboratory Medicine, Nagoya University Hospital, Nagoya, Japan. This study was supported in part by research grants for cardiovascular diseases (4A-4) from the Ministry of Health and Welfare, Tokyo, Japan.

Manuscript received January 29, 1993; revised manuscript received August 26, 1993, accepted September 8, 1993.

Address for correspondence: Dr. Mitsuhiro Yokota, Circulatory Physiology Section, Department of Clinical Laboratory Medicine, Nagoya University Hospital, 65 Tsurumai-cho, Showa-ku, Nagoya, Japan, 466.

0735-1097/94/$7.00

Methods

Patients. The study group consisted of 23 patients (18 men and 5 women aged 25 to 65 years [mean 53]) with mild to moderate idiopathic dilated cardiomyopathy. All patients were in normal sinus rhythm. Idiopathic dilated cardiomyopathy was defined as a decreased left ventricular ejection fraction (<50% as determined by contrast ventriculography) and a dilated left ventricular cavity in the absence of coronary or valvular heart disease, arterial hypertension or cardiac muscle disease caused by any known systemic disease (19,20). All patients had experienced cardiac failure at least once. They reported having dyspnea at rest or with exertion and had an increased cardiothoracic ratio and pulmonary congestion. All patients had received treatment and were in stable condition before admission to Nagoya University Hospital. Prior medications were digitalis in 12, diuretic drugs in 19, isosorbide dinitrate in 7, angiotensin-converting enzyme inhibitors in 15, denopamine in 2 and alpha-adrenergic blocking agents in 1. Their New York Heart Association functional class ranged from II to III at the time of this study. Some patients had a relatively small left ventricular cavity (range 90 to 351 ml). The clinical features of these patients closely resembled those of patients with typical idiopathic dilated cardiomyopathy and they could be classified as having mildly dilated cardiomyopathy (21,22).

The study protocol was reviewed and approved by the Institutional Committee on Human Investigations. Each patient gave written informed consent before entering the study.

Cardiac catheterization. All cardiac catheterization procedures were begun in the morning with the patients in a fasting state. All previous medications were withheld for ≥48 h before the investigation. Right and left heart catheterization was performed by the femoral approach. A triple-lumen thermistor Swan-Ganz catheter was positioned in the pulmonary artery to measure pulmonary artery pressure, pulmonary artery wedge pressure, right atrial pressure and cardiac output. The thermodilution method was used to determine cardiac output. The catheter was connected to a cardiac output computer (model R1-5DCP, General Scanning Inc.). A double-thermistor catheter (model CCS/GOK, Wilton-Weoster Laboratories) was placed percutaneously in the coronary sinus through the brachial or the subclavian vein to measure myocardial blood flow. After left ventriculography was performed, an eight-electrode volume conductance catheter with a micromanometer tip (Leycom, Oegstgeest, The Netherlands) was advanced to the left ventricular apex to measure left ventricular volume and pressure. A Fogarty catheter (model 62-080-8/22F, Edwards Laboratories) was placed in the inferior vena cava and was inflated transiently with 8 to 15 ml of carbon dioxide gas for the determination of left ventricular end-systolic pressure-volume relation. Baseline hemodynamic data, including left ventricular pressure, pulmonary artery pressure, pulmonary artery wedge pressure and right atrial pressure, were obtained and cardiac output was determined. Myocardial blood flow and arterial and coronary sinus blood oxygen saturation were measured. A left ventricular pressure-volume diagram was obtained by using a volumetric conductance catheter during the steady state. Transient preload reduction was produced by occluding the inferior vena cava to obtain the end-systolic pressure-volume relation.

To avoid compromising ventricular performance, selective coronary angiography and right ventricular biopsy were performed after all study protocols were complete. The cardiac biopsy was performed to support the diagnosis, and secondary dilated cardiomyopathy was excluded.

Additional investigation. After the basal measurements were complete, dobutamine was administered intravenously (2.5 to 5 μg/kg per min) in 10 patients and 10 patients received 10 to 15 mg of the oral phosphodiesterase inhibitor MS-857 (23,24). Hemodynamic measurements, coronary blood flow and the pressure-volume diagram were obtained and blood sampling was performed 1) when the hemodynamic indexes stabilized 15 min after the continuous infusion of dobutamine, or 2) 45 min after the oral administration of MS-857.

Left ventricular pressure-volume relations. The volume conductance catheter was connected to a volumetric system (model Sigma 5, Leycom) to measure left ventricular conductance and convert it to left ventricular volume (25–27). Real time pressure-volume diagram generation and eight-channel analog/digital conversion (at 200 Hz) were performed by using a 16-bit microcomputer system (PC-9801VX, NEC Co., Tokyo). The catheter had eight electrodes spaced at 1-cm intervals and was excited by an alternating current (30 μA, 20 kHz) across the distal and proximal electrodes. The catheter was placed under fluoroscopic guidance. We also confirmed that each individual segment (sequential electrode pairs) was intracavitary and that the pressure-volume loops showed counterclockwise movement. The ventricular volume obtained by conductance methods was calibrated by using biplane ventriculography (area-length methods [28]) as follows. Biplane ventriculography was performed immediately before inserting the conductance catheter. A mesh grid placed at the same distance from the body to the image intensifier was also exposed bidirectionally for each case and was used for the correction factor of ventricular volume. Both the end-systolic and end-diastolic volumes obtained by the conductance method were adjusted directly for each case by the end-systolic and end-diastolic volumes calculated from biplane ventriculography. The example in Figure 1A shows the close correlation between the angiographic left ventricular volume and that obtained by the conductance method.

Data analysis. The left ventricular pressure and volume signals were digitized at 3-ms intervals and analyzed with the PC-9801VX. An end-systolic pressure-volume line was drawn on the left upper corners of the pressure-volume loops of the initial 4 to 15 contractions during the transient decrease in preload caused by inflation of the Fogarty

JACC Vol. 23, No. 2
February 1994:406–16

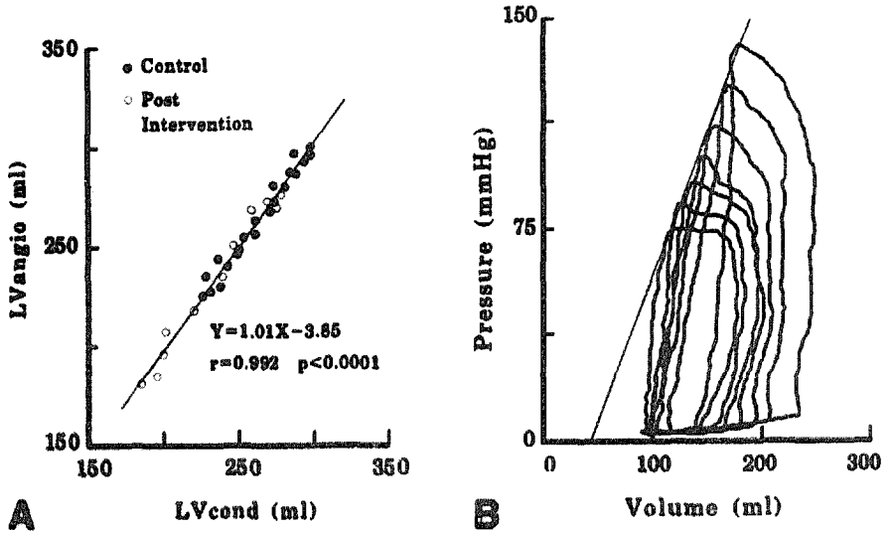

Figure 1. A, Correlation between conductance volume and angiographic volume was highly linear and the close correlation was maintained after the intervention. B, Left ventricular end-systolic pressure-volume relations during inferior vena cava occlusion were highly linear. End-systolic elastance was calculated as the slope of the end-systolic pressure-volume line. LVangio = angiographic left ventricular volume; LVcond = left ventricular volume obtained by the conductance method.

catheter (Fig. 1B). The data points were fit by linear regression ($r = 0.97 \pm 0.04$, $n = 43$).

The pressure-volume area was determined as the area under the end-systolic pressure-volume line and the systolic pressure-volume trajectory and above the end-diastolic pressure-volume relation curve. External work was determined as the area within the pressure-volume diagram. Planimetry was performed on hard copies of the pressure-volume loops drawn with an X-Y plotter (model DXY-880A, Roland Digital Group, Hamamatsu, Japan). The units of pressure-volume area and external work were measured as mm Hg·ml and were converted to the dimensions of energy as follows: 1 mm Hg·ml = 1.33×10^{-4} J (29).

The mechanical efficiency of the heart is defined as the ratio of external work to myocardial oxygen consumption. Suga et al. (13–15) have demonstrated that this efficiency can be divided into two stages: 1) the efficiency of energy transfer from the myocardial oxygen consumption to the pressure-volume area; and 2) the efficiency of energy transfer from the pressure-volume area to external work. In this study, the energy conversion efficiencies of these two stages and the mechanical efficiency as the overall energy conversion efficiency were determined at baseline and after the administration of the inotropic agents.

The effective arterial elastance was calculated as the ratio of the end-systolic pressure to the stroke volume as proposed by Sunagawa et al. (30,31):

$$Ea = Pes/SV, \quad [1]$$

where Ea is effective arterial elastance, Pes is end-systolic pressure and SV is stroke volume.

Furthermore, external work (EW) can be approximated as the stroke work, which is the product of the stroke volume and the end-systolic pressure:

$$EW = SV \cdot Pes. \quad [2]$$

In addition, pressure-volume area (PVA) can be defined as the sum of external work and the potential energy:

$$PVA = EW + 0.5Pes^2/Ees, \quad [3]$$

where Ees represents the end-systolic elastance, that is, the slope of the end-systolic pressure-volume line. Combining equations 1, 2 and 3, one obtains:

$$EW/PVA = SV/(SV + 0.5Ea/Ees) \quad [4]$$

$$= Ees/(Ees + 0.5Ea)$$

$$= 1/(1 + 0.5Ea/Ees).$$

Equation 4 indicates that the index of ventriculoarterial coupling Ea/Ees is a powerful predictor of the cardiac work efficiency EW/PVA. We tested the hypothesis that equation 4 could predict the experimentally obtained results.

Myocardial oxygen consumption. Myocardial blood flow was measured using a double-thermistor catheter (model CCS/GOK, Wilton-Webster Laboratories). The distal external thermistor was advanced to the great cardiac vein, and the proximal external thermistor was positioned under fluoroscopic guidance in the coronary sinus between the ostium and the termination of the middle cardiac vein. Coronary sinus and great cardiac vein flows were calculated according to the method of Ganz et al. (32) using a computer system (Thermo Flow, Goodman Co., Nagoya, Japan). The injectate was a normal saline solution kept at room temperature and delivered by a Harvard pump (Waters Instruments) at a flow rate of 40 ml/min. Coronary sinus and great cardiac vein flows were recorded on a six-channel recorder (Unicorder, Nippon Denshi Kagaku Co., Kyoto, J[illegible]) at a paper speed of 100 cm/min.

A sample of blood for oxygen satura[illegible] was measured in samples obtained simultaneously from the femoral artery and coronary sinus while the steady-state measurements were being collected. The blood oxygen saturation was determined with a hemoximeter (model ABL3, Radiometer, Copenhagen, Denmark). Myocardial oxygen consumption per minute ($M\dot{V}O_2$/min [ml/min]) was calculated as the product of myocardial blood flow and the arterial-coronary

Table 1. Baseline Data

Pt No.	Age (yr)/ Gender	LVEF (%)	LVEDV (ml)	Ees (mm Hg/ml)	Ea (mm Hg/ml)	Ea/Ees	$M\dot{V}O_2$ (J/beat)	EW (J/beat)	PVA (J/beat)	EW/PVA (%)	PVA/$M\dot{V}O_2$ (%)	EW/$M\dot{V}O_2$ (%)
1	53/M	0.41	90	1.65	3.38	2.05	2.06	0.27	0.79	34.9	38.2	13.3
2	65/M	0.26	192	0.74	2.94	3.97	5.08	0.59	2.34	25.4	46.1	11.7
3	60/M	0.37	175	1.53	4.56	2.98	4.18	0.63	1.95	32.1	46.7	15.0
4	61/M	0.39	150	0.97	2.28	2.35	—	0.40	1.05	38.0	—	—
5	36/M	0.39	152	0.89	3.30	3.71	5.16	1.21	2.93	41.5	56.8	23.5
6	54/F	0.46	235	0.20	1.23	6.15	11.82	1.58	9.16	17.2	77.5	13.3
7	55/M	0.33	221	0.57	1.81	3.18	4.37	0.56	2.88	19.6	65.8	12.9
8	55/M	0.24	296	0.72	2.35	3.26	8.28	0.99	3.34	29.6	40.3	11.9
9	57/M	0.24	214	0.33	1.31	3.97	9.00	1.10	5.95	18.5	66.1	12.2
10	49/M	0.22	248	1.01	3.02	2.99	2.14	0.52	1.24	41.7	58.2	24.2
11	49/M	0.22	267	0.98	3.45	3.52	2.55	0.33	0.94	35.5	37.1	13.1
12	41/F	0.23	230	0.81	2.23	2.75	—	0.59	1.71	34.5	—	—
13	25/M	0.52	154	1.10	1.18	1.07	—	1.48	2.58	57.5	—	—
14	64/M	0.46	229	1.29	2.69	2.09	6.47	0.98	1.99	49.0	30.8	15.1
15	56/M	0.28	196	0.85	2.56	3.00	3.90	0.73	2.58	28.2	66.0	18.6
16	59/M	0.22	264	1.37	3.87	2.82	2.75	0.66	1.17	56.7	42.5	24.1
17	57/F	0.34	250	1.02	1.79	1.75	5.07	1.11	2.26	49.1	44.6	21.9
18	64/M	0.32	226	1.23	2.21	1.80	4.36	0.69	2.21	31.2	50.7	15.8
19	57/F	0.28	203	0.82	2.67	3.26	4.50	0.59	2.17	27.2	48.2	13.1
20	48/M	0.19	351	0.22	1.35	6.14	—	0.54	3.33	16.2	—	—
21	45/F	0.43	189	0.31	1.73	5.58	—	0.93	4.85	19.2	—	—
22	40/M	0.41	190	0.35	1.14	3.26	4.73	0.88	3.13	28.1	66.2	18.6
23	62/M	0.32	244	0.38	1.13	2.97	—	0.61	2.78	21.9	—	—
Mean	53	0.33	216	0.84	2.36	3.24	5.08	0.78	2.75	32.7	51.9	16.4
± SE	2	0.02	12	0.09	0.20	0.28	0.67	0.09	0.39	2.6	3.4	1.2

Ea = effective arterial elastance; Ees = end-systolic elastance; Ea/Ees = the ratio of effective arterial elastance to end-systolic elastance; EW = external work; EW/$M\dot{V}O_2$ = the ratio of external work to myocardial oxygen consumption ($M\dot{V}O_2$); EW/PVA = the ratio of external work to pressure-volume area (PVA); F = female; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; M = male; Pt = patient; PVA/$M\dot{V}O_2$ = the ratio of pressure-volume area to myocardial oxygen consumption.

sinus oxygen content difference. Myocardial oxygen consumption per beat ($M\dot{V}O_2$/beat) was calculated as follows: ($M\dot{V}O_2$/beat [J/beat]) = (20 × [$M\dot{V}O_2$/min]/heart rate), where 1 ml oxygen = 20 J (33).

Statistical analysis. All data are expressed as mean value ± SE. Comparison between measurements before and after the administration of dobutamine and MS-857 were made with the paired *t* test. A p value < 0.05 was considered statistically significant. Linear regression analysis was made using the ratio of effective arterial elastance to end-systolic elastance as an independent variable and cardiac work efficiency, the ratio of pressure-volume area to myocardial oxygen consumption and the mechanical efficiency as the dependent variables. The derived regression coefficient and the regression constant were tested in the derived regression equation.

Results

Ventricular and effective arterial elastance and ventriculoarterial coupling. Baseline data from all 23 patients are provided in Table 1. The ventricular end-systolic elastance was 0.84 ± 0.09 mm Hg/ml, effective arterial elastance was 2.36 ± 0.20 mm Hg/ml and the ratio of effective arterial elastance to end-systolic elastance was 3.24 ± 0.28. For the group receiving the dobutamine infusion, the baseline end-systolic elastance increased from 0.80 ± 0.12 to 1.31 ± 0.13 mm Hg/ml ($p < 0.001$) and effective arterial elastance slightly increased from 2.14 ± 0.19 to 2.33 ± 0.22 mm Hg/ml ($p < 0.05$). The ratio of effective arterial elastance to end-systolic elastance decreased from 3.12 ± 0.43 to 1.86 ± 0.15 ($p < 0.05$, Table 2). For the group receiving MS-857, the baseline end-systolic elastance increased from 1.03 ± 0.14 to 1.39 ± 0.17 mm Hg/ml ($p < 0.01$), effective arterial elastance decreased from 2.87 ± 0.36 to 2.30 ± 0.31 mm Hg/ml ($p < 0.05$) and the ratio of effective arterial elastance to end-systolic elastance decreased from 3.16 ± 0.45 to 1.78 ± 0.22 ($p < 0.01$, Table 3).

Figure 2 shows representative sets of the pressure-volume loops, end-systolic elastance, effective arterial elastance and their changes before and after the administration of dobutamine (Fig. 2A) or MS-857 (Fig. 2B). End-systolic elastance increased after the administration of both dobutamine and MS-857. Effective arterial elastance decreased after the administration of MS-857, whereas it did not change or increased only slightly after dobutamine infusion. Effective arterial elastance was larger than end-systolic elastance in each group and the relation between them suggested that the coupling was not optimal. The ratio of effective arterial elastance to end-systolic elastance de-

Table 2. Effects of Dobutamine on Hemodynamics and Energetics

Pt No.	Ees (mm Hg/ml)		Ea (mm Hg/ml)		Ea/Ees		$M\dot{V}O_2$ (J/beat)		EW (J/beat)		PVA (J/beat)		EW/PVA (%)		PVA/$M\dot{V}O_2$ (%)		EW/$M\dot{V}O_2$ (%)	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
7	0.57	1.25	1.81	1.79	3.18	1.43	4.37	5.06	0.56	0.48	2.88	1.55	19.6	31.2	65.8	30.6	12.9	9.6
8	0.72	1.03	2.35	2.48	3.26	2.41	8.28	11.97	0.99	1.31	3.34	3.33	29.6	39.3	40.3	27.8	11.9	10.9
9	0.33	0.56	1.31	1.31	3.97	2.34	9.00	15.22	1.10	1.48	5.95	5.12	18.5	29.0	66.1	33.7	12.2	9.8
10	1.01	1.45	3.02	3.22	2.99	2.22	2.14	2.79	0.52	0.61	1.24	1.06	41.7	57.4	58.2	38.0	24.2	21.8
12	0.81	0.99	2.23	2.42	2.75	2.44	—	—	0.59	0.78	1.71	1.80	34.5	43.2	—	—	—	—
14	1.29	1.46	2.69	2.48	2.09	1.70	6.47	6.95	0.98	0.92	1.99	1.71	49.0	53.8	30.8	24.6	15.1	13.2
17	1.02	1.68	1.79	2.24	1.75	1.33	5.07	5.89	1.11	1.17	2.26	1.88	49.1	62.6	44.6	31.9	21.9	19.9
18	1.23	1.85	2.21	2.51	1.80	1.36	4.31	6.01	0.69	0.76	2.21	1.89	31.2	40.2	51.3	31.4	16.0	12.6
19	0.82	1.72	2.67	3.32	3.26	1.93	4.50	6.59	0.59	0.78	2.17	1.83	27.2	42.6	48.2	27.8	13.1	11.8
20	0.22	1.09	1.35	1.57	6.14	1.44	—	—	0.54	1.22	3.33	2.54	16.2	48.0	—	—	—	—
Mean	0.80	1.31	2.14	2.33	3.12	1.86	5.52	7.56	0.77	0.95	2.71	2.27	31.7	44.7	50.7	30.7	15.9	13.7
± SE	0.12	0.13	0.19	0.22	0.47	0.15	0.86	1.52	0.08	0.11	0.44	0.39	4.0	3.6	4.7	1.6	1.8	1.8
p value	< 0.001		< 0.05		< 0.05		< 0.05		< 0.05		< 0.05		< 0.001		< 0.001		< 0.001	

Post and Pre = after and before, respectively, dobutamine administration; other abbreviations as in Table 1.

creased and the ventriculoarterial coupling improved after the administration of both drugs, but effective arterial elastance remained far greater than end-systolic elastance. Thus, the difference between the effects of these drugs on the hemodynamics can be visualized and distinguished easily. Both dobutamine and MS-857 have a potent inotropic effect, and MS-857 reduces the arterial load, whereas dobutamine slightly increases it.

Myocardial oxygen consumption and energy conversion efficiency. The mean data at baseline from the 23 patients are provided in Table 1. Myocardial oxygen consumption was 5.08 ± 0.67 J/beat, the mean external work was 0.78 ± 0.09 J/beat, and the pressure-volume area was 2.75 ± 0.39 J/beat. In addition, cardiac work efficiency was 32.7 ± 2.6%, the ratio of pressure-volume area to myocardial oxygen consumption was 51.9 ± 3.4% and the mechanical efficiency was 16.4 ± 1.2%.

The effects of dobutamine on the energy conversion efficiency from 10 patients are provided in Table 2. Myocardial oxygen consumption analysis was available from eight patients. Myocardial oxygen consumption increased from 5.52 ± 0.86 to 7.56 ± 1.52 J/beat ($p < 0.05$), external work increased from 0.77 ± 0.08 to 0.95 ± 0.11 J/beat ($p < 0.05$), and pressure-volume area decreased from 2.71 ± 0.44 to 2.27 ± 0.39 J/beat ($p < 0.05$). As a result of these findings, cardiac work efficiency increased from 31.7 ± 4.0% to 44.7 ± 3.6% ($p < 0.001$), the ratio of pressure-volume area to myocardial oxygen consumption decreased from 50.7 ± 4.7% to 30.7 ± 1.6% ($p < 0.001$) and mechanical efficiency slightly decreased from 15.9 ± 1.8% to 13.7 ± 1.8% ($p < 0.001$).

The effects of MS-857 on the energy conversion efficiency from 10 patients are provided in Table 3. Myocardial oxygen consumption analysis was available from eight patients.

Table 3. Effects of MS-857 on Hemodynamics and Energetics

Pt No.	Ees (mm Hg/ml)		Ea (mm Hg/ml)		Ea/Ees		$M\dot{V}O_2$ (J/beat)		EW (J/beat)		PVA (J/beat)		EW/PVA (%)		PVA/$M\dot{V}O_2$ (%)		EW/$M\dot{V}O_2$ (%)	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	1.65	2.17	3.38	3.26	2.05	1.50	2.06	2.89	0.27	0.33	0.79	0.69	34.9	47.3	38.2	23.8	13.2	11.3
2	0.74	1.20	2.94	2.70	3.97	2.25	5.08	5.86	0.59	0.63	2.34	1.70	25.4	37.2	46.1	29.1	11.7	10.8
3	1.53	2.08	4.56	3.28	2.98	1.58	4.18	4.60	0.63	0.68	1.95	1.82	32.1	37.3	46.7	39.5	15.0	14.8
4	0.97	1.42	2.28	1.92	2.35	1.35	—	—	0.40	0.59	1.05	1.11	38.0	53.1	—	—	—	—
5	0.89	1.33	3.30	1.78	3.71	1.34	5.16	5.29	1.21	1.10	2.93	1.92	41.5	57.0	56.8	36.4	23.5	20.8
6	0.20	0.34	1.23	0.98	6.15	2.88	11.82	14.37	1.58	1.82	9.16	6.01	17.2	30.3	77.5	41.8	13.3	12.7
11	0.98	1.32	3.45	3.37	3.52	2.55	2.55	2.73	0.33	0.35	0.94	0.85	35.5	41.0	37.1	31.0	13.1	12.7
13	1.10	1.50	1.18	0.94	1.07	0.63	—	—	1.48	1.69	2.58	2.29	57.5	73.8	—	—	—	—
15	0.85	1.13	2.56	1.85	3.00	1.64	3.90	4.31	0.73	0.74	2.58	1.66	28.2	44.6	66.0	38.6	18.6	17.2
16	1.37	1.41	3.87	2.93	2.82	2.08	2.75	2.82	0.66	0.73	1.17	1.18	56.7	61.7	42.5	41.8	24.1	25.8
Mean	1.03	1.39	2.87	2.30	3.16	1.78	4.69	5.36	0.79	0.86	2.55	1.92	36.7	48.3	51.3	35.2	16.6	15.7
± SE	0.14	0.17	0.36	0.31	0.45	0.22	1.17	1.45	0.16	0.17	0.82	0.51	4.3	4.4	5.4	2.5	1.9	2.0
p value	< 0.01		< 0.05		< 0.01		NS		NS		NS		< 0.001		< 0.01		NS	

Abbreviations as in Tables 1 and 2.

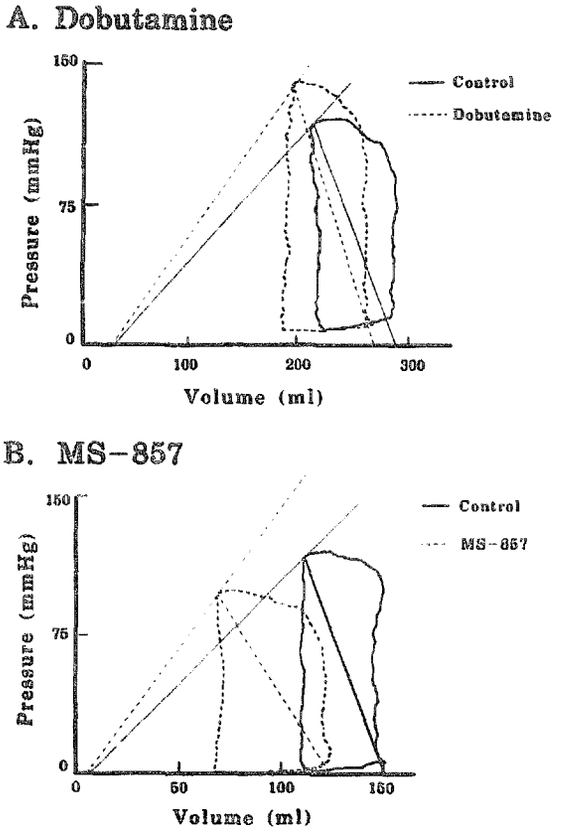

Figure 2. Pressure-volume loops, end-systolic elastance, effective arterial elastance and their changes before and after the administration of dobutamine (A) and MS-857 (B). Dobutamine and MS-857 increased end-systolic elastance but have different effects on effective arterial elastance. Effective arterial elastance is larger than end-systolic elastance in each group. The degree of ventriculoarterial coupling is far from optimal and improves after the administration of both drugs.

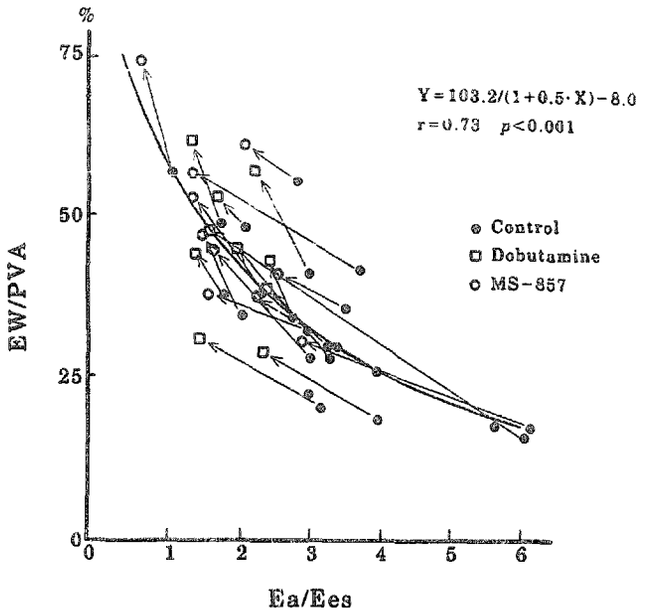

Figure 3. The transfer efficiency from pressure-volume area to external work (EW/PVA) has a hyperbolic correlation with the ratio of effective arterial elastance to end-systolic elastance (Ea/Ees). The transfer efficiency from pressure-volume area to external work increases when the ratio of effective arterial elastance to end-systolic elastance decreases (that is, ventriculoarterial coupling improves). The enhancement of contractility, a reduction in the arterial load or both of these changes improves cardiac work efficiency.

Changes in myocardial oxygen consumption, external work and pressure-volume area were minimal and statistically insignificant. Nevertheless, the energy conversion efficiencies showed significant changes. Cardiac work efficiency increased from 36.7 ± 4.3% to 48.3 ± 4.4% ($p < 0.001$), the ratio of pressure-volume area to myocardial oxygen consumption decreased from 51.3 ± 5.4% to 35.2 ± 2.5% ($p < 0.01$) and mechanical efficiency did not change significantly.

Figure 3 shows the scatter diagram of cardiac work efficiency against the ratio of effective arterial elastance to end-systolic elastance for all the data obtained (at baseline and after the administration of both drugs). A hyperbolic correlation between cardiac work efficiency and the ratio of effective arterial elastance to end-systolic elastance was found with a correlation coefficient of 0.73 ($p < 0.001$). The experimentally obtained regression equation closely resembled equation 4, which was derived theoretically.

Figure 4 shows the close positive correlation between the ratio of pressure-volume area to myocardial oxygen consumption and the ratio of effective arterial elastance to end-systolic elastance for all the data. The correlation coefficiency was 0.74 ($p < 0.001$).

The mechanical efficiency remained within a narrow range (Fig. 5), depending on the interaction of the first and second step of energy transfer.

Discussion

This study demonstrated a close relation between ventriculoarterial coupling and myocardial energetics in patients with idiopathic dilated cardiomyopathy. In the first part of this study, the hemodynamic performance and the efficiency of energy transfer for each step from the baseline values were investigated. The second part of this study examined the influence of inotropic agents on various hemodynamic and energetic variables. Finally, the interactions between ventriculoarterial coupling and the efficiencies of energy conversion were analyzed.

Ventriculoarterial coupling. By combining end-systolic elastance and effective arterial elastance in a pressure-volume diagram, the relation between the inotropic state and its interaction with afterload can be visualized easily and becomes useful for its quantitative evaluation (30,31,34). The ratio of effective arterial elastance to end-systolic elastance is also a good predictor of the efficiency of energy transfer.

This study also showed that a mismatching of the baseline ventriculoarterial coupling occurred with a large effective arterial elastance and small end-systolic elastance in all

JACC Vol. 23, No. 2
February 1994:406–16

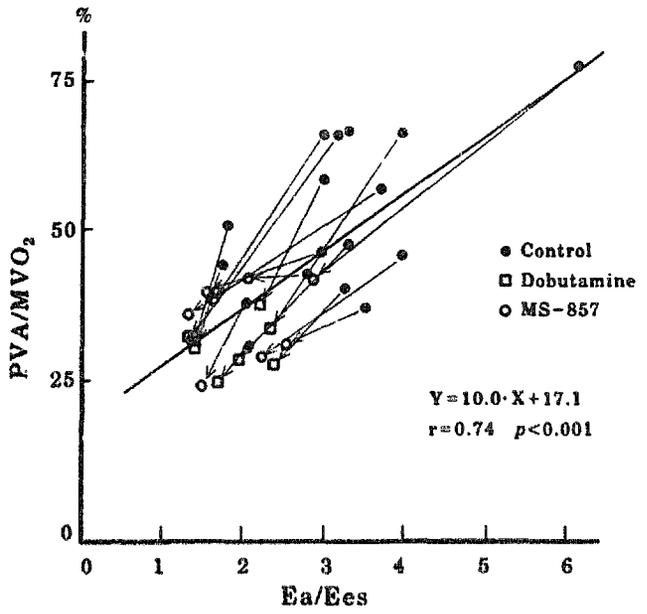

Figure 4. The transfer efficiency from myocardial oxygen consumption to pressure-volume area (PVA/MVO_2) has a close positive correlation with the ratio of effective arterial elastance to end-systolic elastance (Ea/Ees). The efficiency, of the transfer efficiency from myocardial oxygen consumption to pressure-volume area, which represents the first stage of energy transfer from metabolic energy to mechanical energy, decreases when the ratio of effective arterial elastance to end-systolic elastance decreases (that is, ventriculoarterial coupling improves).

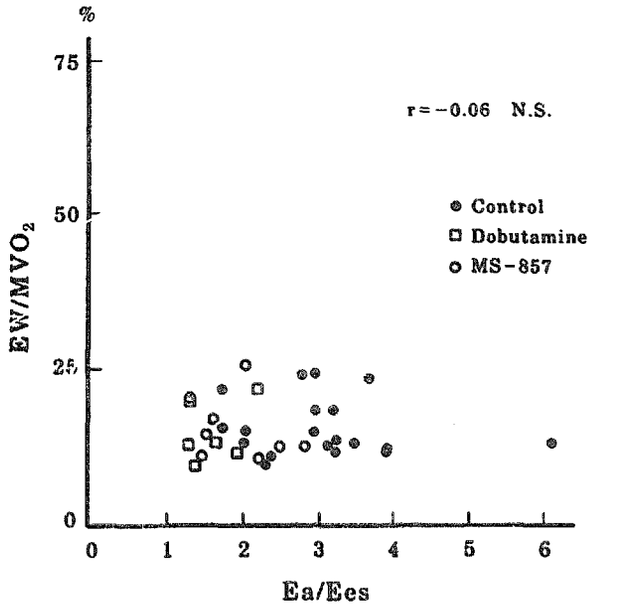

Figure 5. The mechanical efficiency (EW/MVO_2) has no significant relation with the ratio of effective arterial elastance to end-systolic elastance (Ea/Ees) and remains within a narrow range (16.4 ± 1.2%). Myocardial oxygen utilization appears to maintain a constant mechanical efficiency.

patients. The patients with idiopathic dilated cardiomyopathy had a large left ventricle with depressed contractility. To maintain the peripheral circulation, the heart must generate sufficient blood pressure and flow to overcome the peripheral resistance. The left ventricle of a failing heart (that is, end-diastolic volume to V_0, where V_0 is the volume-axis intercept of end-systolic pressure-volume line) must enlarge to maintain adequate blood pressure. Therefore, the enlarged ventricle seen in patients with idiopathic dilated cardiomyopathy could be considered to be a compensatory response to depressed contractility. Some patients who had a normal to mildly dilated left ventricle also had decreased contractility and increased afterload (that is, ventriculoarterial mismatching that resulted in depressed energetics). The pathologic enlargement of the ventricle seemed to be a consequence of compensation and not to be a limiting factor in response to depressed hemodynamics and energetics.

After the administration of dobutamine and MS-857, the ratio of effective arterial elastance to end-systolic elastance became smaller but remained >1 in most patients. In a previous study (31,34), the coupling conditions between ventricular contractility and arterial load were predicted theoretically and validated experimentally. These conditions indicated two criteria for optimal coupling: 1) External work is maximized when effective arterial elastance equals end-systolic elastance, and 2) mechanical efficiency is maximized when effective arterial elastance is nearly half of end-systolic elastance (31,34). Under normal physiologic conditions, the ventricular and arterial properties in normal patients are matched to maximize efficiency because effective arterial elastance is nearly half of end-systolic elastance. In slightly impaired hearts, these variables are such that the external work is maximized and effective arterial elastance nearly equals end-systolic elastance. Severely impaired hearts can no longer maintain either maximal external work or maximal mechanical efficiency (35–39). Our study demonstrated that the coupling conditions were far less than optimal and cardiovascular performance was severely depressed both mechanically and energetically in patients with idiopathic dilated cardiomyopathy.

Relations between ventriculoarterial coupling and energy conversion efficiencies. Mechanical efficiency, defined as the ratio of external work to myocardial oxygen consumption, is the conversion efficiency from metabolic energy to hydraulic energy that the left ventricle generates to the vascular system. As noted before, this efficiency can be divided into two stages of energy transfer (13–15). Each stage of energy transfer varies according to changes in contractility and loading conditions. In this study, we investigated how the interaction of the contractile state and the arterial load affected myocardial energetics, especially in terms of each of these energy transfer stages in patients with idiopathic dilated cardiomyopathy.

This study showed that the transfer efficiency from myocardial oxygen consumption to pressure-volume area varied over a wide range and had a close positive correlation with the ratio of effective arterial elastance to end-systolic

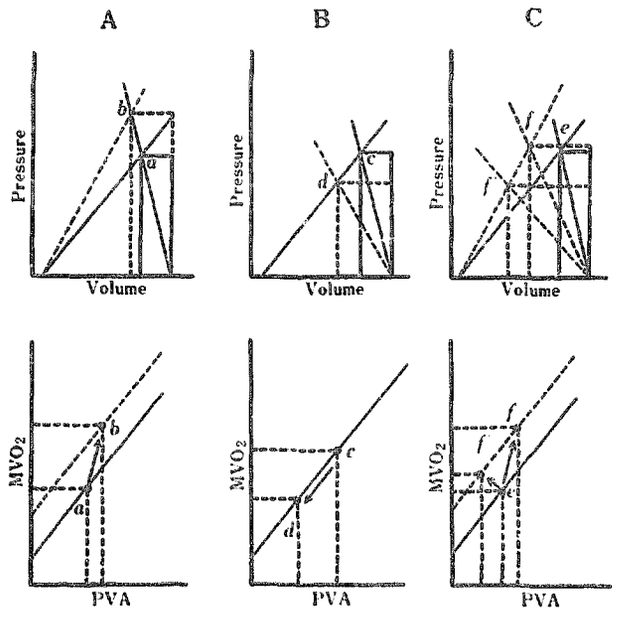

Figure 6. Changes in hemodynamics and energetics when contractility is enhanced (A), arterial load decreases (B) and contractility is enhanced and arterial load decreases (C). Contractile efficiency (that is, the slope of the transfer efficiency from myocardial oxygen consumption to pressure-volume area, line) is constant in each group, but the ratio of the transfer efficiency from myocardial oxygen consumption to pressure-volume area will change at different levels of pressure-volume area after the administration of inotropic agents.

elastance. In other words, the efficiency may decrease with improvements in ventriculoarterial coupling. This relation between the ratio of effective arterial elastance to end-systolic elastance and the ratio of pressure-volume area to myocardial oxygen consumption can be better understood if one plots pressure-volume relations and relations between pressure-volume area and myocardial oxygen consumption.

Figure 6 depicts representative changes in effective arterial elastance and end-systolic elastance. When the ratio of effective arterial elastance to end-systolic elastance improves toward 1, there are considerable changes in the relation between pressure-volume area and myocardial oxygen consumption. It is well known that the pressure-volume area has a close linear correlation with myocardial oxygen consumption and can be expressed as the equation: $M\dot{V}O_2 = A \cdot PVA + B$, where $M\dot{V}O_2$ is myocardial oxygen consumption, PVA is pressure-volume area and A and B are constants. The inverse of the slope (1/A) is considered to be the contractile efficiency (14–16). The relation between pressure-volume area and myocardial oxygen consumption is known to shift upward when contractility is enhanced and end-systolic elastance increases. The transfer efficiency from myocardial oxygen consumption to pressure-volume area changes according to changes in contractility or loading conditions, even if contractile efficiency is constant. If contractility is enhanced and end-systolic elastance increases but effective arterial elastance remains unchanged (in the case of dobutamine infusion), the end-systolic pressure-volume line and pressure–stroke volume line will move from the solid to the dotted line and point *a* will move to point *b*. If contractility remains unchanged and effective arterial elastance decreases (that is, when afterload decreases in the case of arterial vasodilator therapy), the end-systolic pressure-volume line remains unchanged, but the slope of the pressure–stroke volume line declines and point *c* moves to point *d*. In this case, the relation between myocardial oxygen consumption and pressure-volume area does not change and point *c* moves to point *d* on the same line of pressure-volume area/myocardial oxygen consumption relation. If both the contractility and the arterial load change (that is, after an inotropic and vasodilating agent is administered in the case of MS-857 administration), point *e* moves to a point between *f* and *f'*.

Suga et al. (13–15) have reported that pressure-volume area is representative of total mechanical energy generated from myocardial oxygen consumption. This implies that pressure-volume area must be smaller than myocardial oxygen consumption (that is, slope A must be >1). Intercept B is the sum of the energy that is generated from the basal metabolism and excitation-contraction coupling and is called pressure-volume area–independent myocardial oxygen consumption (15). In a previous clinical study (36), slope A was reported to be >1, whereas intercept B is a nonzero positive number. This observation suggests that a direct measurement of this efficiency will not be constant because of the nonzero positive intercept B, even if contractile efficiency (1/A) is unchanged. Furthermore, it predicts that this efficiency will decrease when the ratio of effective arterial elastance to end-systolic elastance decreases toward 1 as was observed in our study. In our study, these changes were validated in the baseline data and after the administration of dobutamine and MS-857.

The transfer efficiency from pressure-volume area to external work also varied over a wide range and had a close curvilinear correlation with the ratio of effective arterial elastance to end-systolic elastance (Ea/Ees). In our study, the experimentally derived regression equation closely resembled the equation predicted theoretically. This implies that the work efficiency can be evaluated only by measuring the ventriculoarterial coupling. Several investigators (37–39) have reported experimental results that suggest that the enhancement of the contractile state, a reduction in the arterial load or both these changes improve work efficiency. Our study confirmed not only these previous studies, but also the theoretic predictions with clinical data obtained by means of actual pressure-volume measurements.

Finally, we examined the overall efficiency from myocardial oxygen consumption to external work, that is, the mechanical efficiency. The mean value of the mechanical efficiency was 16.4 ± 1.2% and remained constant over the range of the ratio of effective arterial elastance to end-systolic elastance obtained in our study. In a previous experimental study (13), the mechanical efficiency varied

JACC Vol. 23, No. 2
February 1994:406–16

between 0 and 30% as a function of left ventricular loading conditions and contractile state. A recent experimental study (39) of the mechanical efficiency of intact dog hearts reported that an increase in the ratio of stroke work to pressure-volume area indicates that the ratio of stroke work to myocardial oxygen consumption will be higher if the contractile state is unchanged. If the contractile state is enhanced and the relation between pressure-volume area and myocardial oxygen consumption shifts upward, the ratio of external work (equivalent to stroke work) to pressure-volume area will increase and the ratio of pressure-volume area to myocardial oxygen consumption will decrease. When considering the two-stage energy transfer model, it may not be clear whether the mechanical efficiency increases or decreases with changes in loading conditions. How the enhancement of contractility or a change in the ventriculoarterial coupling affects mechanical efficiency has not been clarified. This study has shown that this efficiency remains within a narrow range under compensated stable conditions of chronic heart failure, but depends on the interaction of the first and the second stages of energy transfer.

Our study also demonstrated that different inotropic agents have similar but slightly different effects on ventriculoarterial coupling and mechanical efficiency. Both dobutamine and MS-857 improved ventriculoarterial coupling. The two agents differed mainly in their effects on arterial load. The phosphodiesterase inhibitor MS-857 had a vasodilating effect and led to a reduction in effective arterial elastance, whereas dobutamine had an opposite effect on effective arterial elastance. MS-857 did not alter mechanical efficiency; dobutamine slightly decreased it. We believe that these differences are simply the result of their differences in provoking a vasodilating effect. Both inotropic agents decreased the efficiency from myocardial consumption to pressure-volume area, increased cardiac work efficiency and consequently did not increase mechanical efficiency.

These findings indicate that a depressed heart can no longer sustain high mechanical efficiency; therefore, constant mechanical efficiency may be the result of the regulation of myocardial oxygen utilization to maximize the efficiency in patients with idiopathic dilated cardiomyopathy. Pure inotropic agents such as dobutamine require increased oxygen use to improve cardiac performance; however, they can have an oxygen wasting effect on the depressed heart with idiopathic dilated cardiomyopathy. This adverse effect can be considered to be one of the difficulties in using inotropic agents for dilated depressed hearts. Conversely, the ability of vasodilator therapy to improve hemodynamic performance without increasing myocardial oxygen requirements or with little increase in pressure-volume area–dependent myocardial oxygen consumption was confirmed in this pressure-volume analysis.

Limitations of the study. Use of the pressure-volume relation to study myocardial energetics is widely accepted because of its visual and intellectual simplicity. However, this method requires the use of several limiting assumptions when attempting a clinical study.

First, the relation between pressure-volume area and myocardial oxygen consumption was assumed to be linear. This may not be true. To verify a linear relation, one would need more than two samples under different loading conditions with the same end-systolic elastance and another two points with a different end-systolic elastance to obtain a parallel shift of this relation. In a clinical study, alterations in the hemodynamic status must be minimized to avoid reflexes that would complicate the analysis or harm the patients. In a recent clinical study (35,36), the relation between pressure-volume area to myocardial oxygen consumption was investigated by changing the arterial load before and after the administration of phenylephrine. However, this drug may also cause changes in contractility by the autonomic nerve reflex.

Second, we assumed that left ventricular volume could be obtained reliably by the conductance catheter under steady state conditions and during a transient reduction of preload. It has been reported that the conductance catheter may underestimate the real volume when calibrated by using blood conductivity and measuring the parallel conductance by injection of hypertonic saline solution. To minimize this error, we calibrated the left ventricular volume by biplane ventriculography, which was performed immediately before the control measurements. A recent study (40–42) suggests that the value of end-systolic elastance may be underestimated when measured by conductance methods. Negative V_0 could occur when linear regression was performed on curvilinear end-systolic pressure-volume relation or end-systolic elastance was underestimated. Actually, negative V_0 was obtained in three cases and the pressure-volume areas for them could be overestimated. The error originated by negative area was estimated $\leq$13% in pressure-volume areas. Other methods of measuring ventricular volume also have some limitations. Continuous two-dimensional echocardiograms are not available and would also yield some errors in measuring the ventricular volume. Radioisotope angiography can accurately assess ventricular volume, but cannot be performed continuously.

Third, the curvilinear nature of the end-systolic pressure-volume relation may produce some errors in end-systolic elastance and pressure-volume area (43). The end-systolic pressure-volume lines were obtained under steady state conditions and over 4 to 15 contractions during the transient reduction in preload and were well fit by linear regression.

Finally, the different effects of dobutamine and MS-857 would be enhanced if larger doses were used. However, most patients who received doses of these drugs larger than those we used in this study complained of severe episodes of palpitation associated with an increase in heart rate or ventricular arrhythmias including ventricular tachycardia. Because these effects could be harmful to the patients and could cause alterations in the autonomic nervous system responses, we decided not to use larger doses of these drugs.

Doses >5 μg/kg per min of dobutamine are considered high for Japanese patients with chronic mild to moderate congestive heart failure. However, this study also may suggest the significance of low doses of inotropic agents because the doses of the inotropic agents used in this study improved ventriculoarterial coupling and had only a small effect on the mechanical efficiency.

Conclusions. The coupling condition in patients with idiopathic dilated cardiomyopathy was far from "optimal." Moreover, the cardiovascular performance of these patients was severely depressed, both mechanically and energetically. Dobutamine and MS-857 similarly improved the relation between contractility and vascular load and increased the work efficiency, but not enough to optimize the coupling condition. Both inotropic agents had little effect on mechanical efficiency. It appears that myocardial oxygen utilization is regulated to maintain a constant mechanical efficiency, according to our analysis of the first (efficiency from myocardial oxygen consumption to pressure-volume area) and second (the cardiac work efficiency) stages of energy transfer.

We thank Dr. Shinichiro Morimoto (Department of Internal Medicine, Nagoya Health University, Toyoake, Japan) for his assistance on the histopathologic diagnosis of biopsy specimens. We also thank Drs. Takashi Miyahara, Yasuhiro Kodama, Tatsuyuki Matsunami, Makoto Watanabe, Mitsunori Iwase, Masahiko Ukai, Ryozo Kato, Kozo Nagata and Yasuhito Nishinaka for their cooperation and Sadako Ichihashi for preparing the manuscript.

References

1. Kuhn H, Becker R, Fisher J, et al. Studies on the etiology, the clinical course, and the prognosis of patients with dilated cardiomyopathy (DCM). Z Kardiol 1982;71:497–508.
2. Tanganelli P, Lenarda A, Bianciardi G, et al. Correlation between histomorphometric findings on endomyocardial biopsy and clinical findings in idiopathic dilated cardiomyopathy. Am J Cardiol 1989;64:504–6.
3. Figulla HR, Rahlf G, Nieger M, Luig H, Kreuzer H. Spontaneous hemodynamic improvement or stabilization and associated biopsy findings in patients with congestive cardiomyopathy. Circulation 1985;71: 1095–104.
4. Douglas PS, Morrow R, Ioli A, Reichek N. Left ventricular shape, afterload and survival in idiopathic dilated cardiomyopathy. J Am Coll Cardiol 1989;13:311–5.
5. Juilliere Y, Danchin N, Briancon S, et al. Dilated cardiomyopathy: long-term follow-up and predictors of survival. Int J Cardiol 1988;21:269–77.
6. Katz AM. Potential deleterious effects of inotropic agents in the therapy of chronic heart failure. Circulation 1986;73 Suppl III:III-184–90.
7. Hasenfuss G, Holubarsch C, Heiss HW, et al. Myocardial energetics in patients with dilated cardiomyopathy. Circulation 1989;80:51–64.
8. Caforio ALP, Stewart JT, McKenna WT. Idiopathic dilated cardiomyopathy: rational treatment awaits better understanding of pathogenesis. Br Med J 1990;300:890–1.
9. Shah PK, Amin DK, Hulse S, Shellock F, Swan HJC. Inotropic therapy for refractory congestive heart failure with oral fenoximone (MDL-17, 043): poor long-term results despite early hemodynamic and clinical improvement. Circulation 1985;71:326–31.
10. Beber KT, Janicki JS, Jain MC. Enoximone (MDL 17,043) for stable, chronic heart failure secondary to ischemic or idiopathic cardiomyopathy. Am J Cardiol 1986;58:589–95.
11. Webster MWI, Sarpe DN. Adverse effects associated with newer inotropic agents. Med Toxicol 1986;1:335–42.
12. Packer M, Medina N, Yushak M. Hemodynamic and clinical limitations of long-term inotropic therapy with amrinone in patients with severe chronic heart failure. Circulation 1984;70:1038–47.
13. Suga H, Igarashi Y, Yamada O, Goto Y. Mechanical efficiency of the left ventricle as a function of preload, afterload, and contractility. Heart Vessels 1985;1:3–8.
14. Suga H, Hayashi T, Shirahata M. Ventricular systolic pressure-volume area as a predictor of cardiac oxygen consumption. Am J Physiol 1981;240:H39–44.
15. Suga H, Hisano R, Goto Y, Yamada O, Igarashi Y. Effect of positive inotropic agents on the relation between oxygen consumption and pressure volume area in canine left ventricle. Circ Res 1983;53:306–18.
16. Suga H, Yasumura Y, Nozawa T, Futaki S, Igarashi Y, Goto Y. Prospective prediction of O_2 consumption from pressure-volume area in dog hearts. Am J Physiol 1987;252:H1258–64.
17. Suga H. Total mechanical energy of a ventricle model and cardiac oxygen consumption. Am J Physiol 1979;236:H498–505.
18. Suga H, Sagawa K, Shoukas AA. Load independence of the instantaneous pressure-volume ratio of the canine left ventricle and effects of epinephrine and heart rate on the ratio. Circ Res 1973;32:314–22.
19. Report of the WHO/ISFC Task Force on the Definition and Classification of Cardiomyopathies. Br Heart J 1980;44:672–3.
20. Goodwin JF. The frontiers of cardiomyopathy. Br Heart J 1982;48:1–18.
21. Keren A, Billingham ME, Weintraub D, Stinson EB, Popp RL. Mildly dilated congestive cardiomyopathy. Circulation 1985;72:302–9.
22. Keren A, Billingham ME, Popp RL. Features of mildly dilated congestive cardiomyopathy compared with idiopathic restrictive cardiomyopathy and typical dilated cardiomyopathy. J Am Soc Echocardiogr 1988;1:78–87.
23. Maruyama M, Kamiya J, Kaiho T, Kobari T. Cardiovascular properties of MS-857 a new and potent cardiotonic agent, on normal and failing hearts. J Cardiovasc Pharmacol 1988;12:579–86.
24. Kamiya J, Maruyama M, Kaiho T, Kobari T. Characterization of MS-857, a new and potent cardiotonic agent, in isolated mammalian cardiac muscles. J Cardiovasc Pharmacol 1989;14:790–7.
25. Baan J, van der Velde ET, de Bruin HG, et al. Continuous measurement of left ventricular volume in animals and humans by conductance catheter. Circulation 1984;70:812–23.
26. Burkoff D, van der Velde ET, Kass DA, Baan J, Maughan WL, Sagawa K. Accuracy of volume measurement by conductance catheter in isolated, ejecting canine hearts. Circulation 1985;72:440–7.
27. Kass DA, Yamazaki T, Burkhoff D, Maughan WL, Sagawa K. Determination of left ventricular end-systolic pressure-volume relationship by the conductance (volume) catheter technique. Circulation 1986;73:586–95.
28. Dodge HT, Sandler H, Baxley WA, Hawley RR. Usefulness and limitations of radiographic methods for determining left ventricular volume. Am J Cardiol 1966;18:10–24.
29. Gibbs CL. Cardiac energetics. Physiol Rev 1978;58:174–254.
30. Sunagawa K, Maughan WL, Burkhoff D, Sagawa K. Left ventricular interaction with arterial load studied in isolated canine ventricle. Am J Physiol 1983;245:H773–80.
31. Sunagawa K, Maughan WL, Sagawa K. Optimal arterial resistance for the maximal stroke work studied in isolated canine left ventricle. Circ Res 1985;56:586–95.
32. Ganz W, Tamura K, Marcus HS, Donoso R, Yoshida S, Swan HJC. Measurement of coronary sinus blood flow by continuous thermodilution in man. Circulation 1971;4:181–95.
33. Gibbs CL, Chapman JB. Cardiac energetics. In: Berne RM, Sperlakis N, Geiger SR, editors. Handbook of Physiology. The Cardiovascular System, The Heart. Washington, DC: American Physiology Society, 1979: 775–804.
34. Burkhoff D, Sagawa K. Ventricular efficiency predicted by an analytical model. Am J Physiol 1986;250:R1021–7.
35. Asanoi H, Sasayama S, Kameyama T. Ventriculoarterial coupling in normal and failing heart in humans. Circulation 1989;65:483–93.
36. Kameyama T, Asanoi H, Ishizuka S, Yamanishi K, Fujita M, Sasayama S. Energy conversion efficiency in human left ventricle. Circulation 1992;85:988–96.
37. Kameyama T, Asanoi H, Ishizuka S, Sasayama S. Ventricular load

optimization by unloading therapy in patients with heart failure. J Am Coll Cardiol 1991;17:199–207.

38. Nozawa T, Yasumura Y, Futaki S, Tanaka N, Uenishi M, Suga H. Efficiency of energy transfer from pressure-volume area to external mechanical work increases with contractile state and decreases with afterload in the left ventricle of the anesthetized closed-chest dog. Circulation 1988;77:1116–24.
39. Little WC, Cheng CP. Left ventricular-arterial coupling in conscious dogs. Am J Physiol 1991;261:H70–6.
40. Meeuw LTA, Hess OM, Nonogi H, Monrad ES, Leskosek B, Krayenbuehl HP. Left ventricular volume determination in dogs: a comparison between conductance technique and angiocardiography. Eur Heart J 1988;9:1018–26.
41. Applegate RJ, Cheng CP, Little WC. Simultaneous conductance catheter and dimension assessment of left ventricle volume in intact animals. Circulation 1990;81:638–48.
42. Boltwood C, Appleyard F, Glantz SA. Left ventricular volume measurement by conductance catheter in intact dogs. Circulation 1989;80:1360–77.
43. Van der Velde E, Burkhoff D, Steendijk P, Karsdon J, Sagawa K, Baan J. Nonlinearity and load sensitivity of end-systolic pressure-volume relation of canine left ventricle in vivo. Circulation 1991;83:315–27.