Hemodynamic Changes due to Afterload Reduction as a Predictor of Exercise Capacity in Patients with Dilated Cardiomyopathy

Masaki HASHIMOTO, Mitsunori OKAMOTO, Togo YAMAGATA*, Tetsuya YAMANE*, Naoko MORICHIKA*, Yukiko TSUCHIOKA* Hideo MATSUURA* and Goro KAJIYAMA*

Sixteen patients with dilated cardiomyopathy were examined hemodynamically in order to clarify the relationship between the exercise capacity and the effects of afterload reduction at rest using supine graded bicycle exercise testing before and after sublingual administration of 10 mg nifedipine. 1) The integration of work loads was weakly correlated with the stroke index ($r = 0.64$), heart rate ($r = -0.58$) and plasma norepinephrine concentration at rest ($r = 0.49$), but not with the left ventricular ejection fraction, cardiac index, pulmonary arterial diastolic pressure or the mean arterial pressure at rest. 2) Changes in stroke index and heart rate after administration of nifedipine correlated well with the integration of work loads ($r = -0.84$, $r = 0.81$, respectively). Thus, in patients with dilated cardiomyopathy changes in stroke volume and heart rate due to afterload reduction at rest were better predictors of exercise capacity than the baseline left ventricular hemodynamic parameters. (Internal Medicine 31: 344–348, 1992)

Key words: exercise testing, nifedipine, congestive heart failure

Introduction

It is well known that patients with severe left ventricular dysfunction vary widely in their exercise capacity such that their resting hemodynamic data do not provide practical information about their exercise capacity (1–3). In contrast, the improvement in symptoms and hemodynamics in patients with heart failure following acute vasodilator therapy is generally recognized both during rest and during exercise (4–6). However, the relationship between the effect of afterload reduction and exercise capacity is unclear.

We therefore conducted a study to determine whether changes in hemodynamics by afterload reduction at rest would be related to exercise capacity of patients with severe left ventricular dysfunction.

Methods

Patients

The study group consisted of 16 patients, 12 males and 4 females aged 27–67 years (mean 48.1), with idiopathic dilated cardiomyopathy. The diagnosis was established on the basis of complete medical history, physical examination, chest roentgenogram, echocardiography, ^{201}Tl myocardial images, and coronary angiography. Those patients with coronary artery disease, primary valvular heart disease, alcohol abuse, systemic hypertension, diabetes mellitus, exposure to cardiotoxic drugs or with other known causes of secondary myocardial disease were excluded from this study. Symptomatic heart failure had been present in these patients for 1 month to 6 years (mean 1.0 year). For at least three days prior to the study, digitalis, vasodilator or other cardiac drugs were discontinued. Eight patients were classified as functional class III of the New York Heart Association (NYHA) criteria, and eight were as functional class II (Table 1).

From the First Department of Internal Medicine, Hiroshima Prefectural Hiroshima Hospital, Hiroshima and *The First Department of Internal Medicine, School of Medicine, Hiroshima University, Hiroshima

Received for publication May 29, 1991; Accepted for publication October 11, 1991

Reprint requests should be addressed to Masaki Hashimoto, M.D., the First Department of Internal Medicine, Hiroshima Prefectural Hiroshima Hospital, 1–5–54 Ujinakanda, Minami-ku, Hiroshima 734, Japan

Exercise Capacity in DCM

Table 1. Summary of Integration of Work Loads, NYHA Functional Class and Changes in Hemodynamics after Administration of Nifedipine

Patient	NYHA FC	Integration of work loads (watt·min)	Δ HR (beats/min)	Δ MAP (mmHg)	Δ PADP (mmHg)	Δ CI (liters/min/m ²)	Δ SI (ml/beat/m ²)	Δ LVEF (%)	Δ PNE (pg/ml)
1	II	104	0	-6	1	0.43	5	24	-42
2	II	108	3	-12	0	0.72	7	2	53
3	II	200	16	-10	-1	0.64	0	6	-68
4	II	371	18	-9	-6	0.75	0	—	27
5	II	463	18	-18	-1	0.07	-10	7	49
6	II	562	29	-1	-2	0.66	-13	2	10
7	II	600	16	-8	-5	0.15	-9	-2	10
8	II	638	26	-4	-2	0.56	-12	-6	64
9	III	100	3	-6	-7	0.71	8	4	31
10	III	150	10	11	-1	0.42	1	2	19
11	III	150	6	-23	-3	1.03	10	6	81
12	III	225	11	-4	-1	0.41	-3	4	10
13	III	230	7	-6	-4	0.56	4	8	-22
14	III	325	9	-4	-9	0.87	7	7	-35
15	III	334	3	2	0	0.33	3	2	-23
16	III	350	8	-5	5	0.60	4	1	18
Mean ± SD		306.9 180.5	11.4 8.4	-6.4 7.7	-2.3 3.4	0.557 0.250	0.1 7.4	4.5 6.5	11.4 40.9

CI: cardiac index, HR: heart rate, LVEF: left ventricular ejection fraction, MAP: mean arterial pressure, NYHA FC: New York Heart Association functional class, PADP: pulmonary arterial diastolic pressure, PNE: plasma norepinephrine concentration, SI: stroke volume index.

All patients were in sinus rhythm and had received cardiac catheterization. Their baseline cardiac index ranged from 2.0 to 4.4 liters/min/m² (mean of 2.9 ± 0.6), stroke volume index from 27 to 62 ml/beat/m² (mean 42.4 ± 11.4), pulmonary arterial diastolic pressure from 6 to 24 mmHg (mean 13 ± 5) and left ventricular ejection fraction from 7 to 50% (mean 34 ± 14) (Table 2).

Study protocol

A Swan-Ganz catheter was inserted via the subclavian vein and placed in the pulmonary artery. The following values were determined at baseline: blood pressure, heart rate, pulmonary arterial pressure, cardiac output and left ventricular ejection fraction (using radionuclide angiography). In order to examine whether the effects of afterload reduction is related to sympathetic nerve activity, blood samples for measuring the plasma norepinephrine concentration were obtained at rest. Thereafter, exercise testing was performed with patients in the supine position using a bicycle ergometer

(Siemens). The supine position was chosen because the Swan-Ganz catheter was placed in the pulmonary artery. Exercise was begun at 25 W with the work load increased by 25 W every 4 minutes. Exercise continued until the patients developed severe fatigue, shortness of breath, or both. Exercise capacity was defined as the summation product of exercise duration (minutes) multiplied by the work loads (watts) at each level of exercise (integration of work loads). When the patients' hemodynamic parameters had almost recovered to baseline levels 40 minutes after exercise testing, they received a single dose of 10 mg nifedipine sublingually. Twenty minutes after administration of nifedipine, the hemodynamic parameters were again measured and blood was drawn for determination of plasma norepinephrine concentration.

This study protocol was approved by our ethical research committee and each patient gave informed consent.

Hemodynamic measurements

Blood pressure was measured by the standard cuff technique and cardiac output by the thermodilution method. Mean arterial pressure, stroke index and cardiac index were calculated using standard formulas.

Radionuclide angiography

To obtain the left ventricular ejection fraction, multigated radionuclide angiograms were recorded by labelling red blood cells *in vivo* with 740 MBq (20 mCi) of technetium-99m. Radionuclide angiograms were obtained using a scintillation camera (Searle) with a multipurpose collimator and hardware zoom and an R-wave triggered gate interfaced with an ADAC system I computer. The camera head was positioned in the left

Table 2. Changes in Hemodynamics after Administration of Nifedipine

	before	after	p value
HR (beats/min) [†]	72 ± 12	83 ± 8	**
MAP (mmHg)	91 ± 15	85 ± 10	**
PADP (mmHg)	13 ± 5	11 ± 6	*
CI (liters/min/m ²)	2.9 ± 0.6	3.5 ± 0.5	**
SI (ml/beat/m ²)	42.4 ± 11.4	42.5 ± 6.6	
LVEF (%)	34 ± 14	38 ± 14	*
PNE (pg/ml)	175 ± 96	187 ± 92	

* p < 0.05, ** p < 0.01 vs before nifedipine, [†] Abbreviations as table 1

anterior oblique projection to maximize the separation of the right and left ventricles (usually 45 degrees). Data were processed using conventional software programs which included calculation of the automatic left ventricular ejection fraction.

Norepinephrine levels

Mixed venous blood samples were drawn and centrifuged. Plasma was stored at -60°C for subsequent determination of plasma norepinephrine levels using a modification of the method described by Sato et al (7).

Statistics

Data are presented as mean $\pm$ standard deviation and the differences before and after administration of a single sublingual dose of nifedipine were evaluated by the paired t test. A p value of less than 0.05 was regarded as significant. The correlation between the integration of work loads and resting hemodynamics as well as changes in hemodynamics after nifedipine administration were evaluated by linear regression analysis.

Results

Exercise capacity

Of the 16 patients evaluated, eight achieved 25 W, five 50 W and three 75 W, and the integration of work loads ranged from 104 to 350 watt min (Table 1). Exercise was discontinued because of excessive fatigue in 13 patients and because of dyspnea in three.

Relationship between ventricular function at rest and exercise capacity

No significant correlation was found between the integration of work loads and mean arterial pressure, pulmonary arterial diastolic pressure, cardiac index and left ventricular ejection fraction. Stroke index, heart rate and plasma norepinephrine concentration at rest were weakly correlated with the integration of work loads ($r = 0.64$, $r = -0.58$, $r = -0.49$, respectively) (Table 3).

Table 3. Correlation Coefficient between Integration of Work Loads and Base Line Hemodynamic Values or Their Changes after Administration of Nifedipine

	Base line values vs work loads	Changes after nifedipine vs work loads
HR (beats/min) [†]	-0.58*	0.81**
MAP (mmHg)	0.13	0.05
PADP (mmHg)	-0.08	-0.08
CI (liters/min/m ²)	0.30	-0.36
SI (ml/beat/m ²)	0.64**	-0.84**
LVEF (%)	0.14	-0.55*
PNE (pg/ml)	0.49*	0.18

* $p < 0.05$, ** $p < 0.01$ [†] Abbreviations as Table 1. Work Load is Defined as Integration of Work Loads.

Hemodynamic changes following nifedipine

The heart rate and cardiac index increased significantly ($p < 0.005$, $p < 0.005$, respectively), while the mean arterial pressure and pulmonary arterial diastolic pressure decreased significantly ($p < 0.005$, $p < 0.05$, respectively) following a single dose of nifedipine. However the direction of change in the stroke index was not consistent (Table 2). Hemodynamic changes after the administration of nifedipine are presented in Table 1.

Correlation between the integration of work loads and hemodynamic changes after nifedipine administration

Fig. 1. Relationship between work load and change in stroke index following a single dose of nifedipine (10 mg). There is a close correlation between the integration work loads and changes in stroke index after nifedipine administration ($p < 0.01$). Work load is defined as the integration of work loads.

Fig. 2. Relationship between work load and change in left ventricular ejection fraction following a single dose of nifedipine. There is a close correlation between the integration work loads and change in left ventricular ejection fraction following a nifedipine administration. Work load is defined as the integration of work loads.

Discussion

Relationship between exercise capacity and resting hemodynamics

Many studies have investigated the relationship between exercise capacity and left ventricular function at rest (1–3). It has been postulated that exercise capacity is not always correlated with parameters of left ventricular function such as ejection fraction and cardiac output at rest. The present findings are in agreement with such reports. Namely, it is considered that baseline hemodynamic conditions may not be closely related to left ventricular function during exercise and anaerobic threshold. In patients with severe left ventricular dysfunction, hemodynamic parameters obtained at rest, such as cardiac output, will maintain almost normal values as a result of the compensatory mechanisms due to an activated sympathetic tone. In this study, a weak but significant inverse correlation was observed between the plasma norepinephrine concentration and the integration of work loads. In those patients with severe left ventricular dysfunction, however, the hemodynamic reserve during exercise may be so small and compensatory mechanisms linked to sympathetic activity may no longer enhance left ventricular function as found with the normal heart.

Effects of nifedipine and exercise capacity

In this study, mean arterial pressure and pulmonary arterial diastolic pressure decreased significantly following the administration of a single dose of nifedipine. A decrease of mean arterial pressure and pulmonary arterial diastolic pressure may result from this agent's vasodilator effect. These findings are also consistent with previous reports (4–6). However, a relationship between the integration of work loads and hemodynamic changes due to afterload reduction have not been elucidated. In this study, an increase in heart rate following nifedipine administration was positively correlated with the integration of work loads. Although the increase in the cardiac index did not correlate with the integration of work loads, an increase in the stroke index due to afterload reduction showed a close negative correlation with the integration of work loads ($r = -0.84$). Thus, in patients with dilated cardiomyopathy, changes in hemodynamics due to afterload reduction, especially a change in stroke volume, may be better predictors of exercise capacity than are resting hemodynamics. The reason why hemodynamic changes due to afterload reduction correlate well with exercise capacity is not clear, but one can speculate as follows. According to the theory of end-systolic pressure volume relationship, if the preload is fixed, the increase in stroke volume due to afterload reduction is greater in the heart with severely depressed contractility than in one with mildly depressed contractility (8, 9). That is, patients showing

Fig. 3. Relationship between work load and change in pulmonary arterial diastolic pressure following a single dose of nifedipine. There is no correlation between the integration work loads and change in pulmonary diastolic pressure after nifedipine administration. Work load is defined as the integration of work loads.

Fig. 4. Relationship between work load and change in plasma norepinephrine concentration following a single dose of nifedipine (10 mg). There is no correlation between the integration work loads and change in plasma norepinephrine concentration after nifedipine administration. Work load is defined as the integration of work loads.

The change in stroke index after the administration of nifedipine was inversely well correlated with work loads ($r = -0.84$, Fig. 1). Changes in heart rate and left ventricular ejection fraction were significantly correlated with the integration of work loads ($r = 0.81$, $r = -0.55$, respectively, Table 3, Fig. 2). However, changes in mean arterial pressure, cardiac index, pulmonary arterial diastolic pressure, and plasma norepinephrine concentration were not correlated with the integration of work loads (Table 3, Figs. 3, 4).

a greater increase in stroke volume after nifedipine administration would have a severely depressed left ventricular performance, which could result in poor exercise capacity.

Clinical Implications

The exercise capacity of patients with dilated cardiomyopathy may not always depend upon baseline hemodynamic values but rather upon the change in hemodynamic values following the administration of nifedipine. Although in the present study, the effects of nifedipine was determined invasively by Swan-Ganz catheter, they can be determined also noninvasively by echocardiography or radionuclide angiography. Therefore, hemodynamic changes due to afterload reduction, especially in stroke volume, may be one of the important predictors of exercise capacity in patients with dilated cardiomyopathy.

References

- 1) Francis GS, Goldsmith SR, Cohn JN. Relationship of exercise capacity to resting left ventricular performance and basal plasma norepinephrine levels in patients with congestive heart failure. *Am Heart J* **104**: 725, 1982.
- 2) Litchfield RJ, Keber RE, Bengt JW, et al. Normal exercise capacity in patients with severe left ventricular dysfunction: compensatory mechanisms. *Circulation* **66**: 129, 1982.
- 3) Latham RD, Thornton JW, Mulrow JP. Cardiovascular reserve in idiopathic dilated cardiomyopathy as determined by exercise response during cardiac catheterization. *Am J Cardiol* **59**: 1375, 1987.
- 4) Matsui S, Murakami E, Takekoshi N, et al. Hemodynamic effects of sublingual nifedipine in congestive heart failure. *Jpn, Circ J* **43**: 1081, 1979.
- 5) Ludbrook PA, Tufembrunn AJ, Reed FR, et al. Acute hemodynamic responses to sublingual nifedipine: dependence on left ventricular function. *Circulation* **65**: 489, 1982.
- 6) Miller AB, Conetta DA, Bass TA. Sublingual nifedipine: acute effects in severe chronic congestive heart failure secondary to idiopathic dilated cardiomyopathy. *Am J Cardiol* **55**: 1359, 1985.
- 7) Sato H, Inoue M, Matsuyama T, et al. Hemodynamic effects of β_1 -adrenoceptor partial agonist xamoterol in relation to plasma norepinephrine levels during exercise in patients with left ventricular dysfunction. *Circulation* **75**: 213, 1987.
- 8) Suga H, Sagawa K, Shoukas A. Load independence of instantaneous pressure-volume ratio of the canine left ventricle and effects of epinephrine and heart rate on the ratio. *Circ Res* **32**: 314, 1973.
- 9) Braunwald E, Sonnenblick EH, Ross J Jr. Mechanisms of cardiac contraction and relaxation. In: *Heart Disease: A Textbook of Cardiovascular Medicine*, Braunwald E, Ed WB Saunders Company, Philadelphia, 1988, p.383.