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

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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.

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, 201Tl 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).
Exercise Capacity in DCM

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 of 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. 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. 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 |
|-------------------|-------------------|-------------------|-------------------|
| Patient | NYHA FC | Integration of work loads (watt-min) | \( \triangle HR \) (beats/min) | \( \triangle MAP \) (mmHg) | \( \triangle PADP \) (mmHg) | \( \triangle CI \) (liters/min/m²) | \( \triangle SI \) (ml/beat/m²) | \( \triangle LVEF \) (%) | \( \triangle PNE \) (pg/ml) |
| 1 | II | 104 | 0 | -6 | 1 | 0.43 | 5 | 24 | -42 |
| 2 | II | 108 | 3 | -10 | -1 | 0.72 | 7 | 2 | 53 |
| 3 | II | 200 | 16 | -4 | 0 | 0.64 | 0 | 6 | -68 |
| 4 | II | 371 | 18 | -9 | -6 | 0.75 | 0 | -2 | 27 |
| 5 | II | 463 | 18 | -10 | -1 | 0.07 | -10 | 7 | 49 |
| 6 | II | 562 | 18 | -10 | -2 | 0.66 | -13 | 2 | 10 |
| 7 | II | 600 | 16 | -8 | -5 | 0.15 | -9 | 2 | 10 |
| 8 | II | 638 | 26 | -5 | -2 | 0.56 | -12 | 2 | 31 |
| 9 | III | 100 | 3 | -6 | -7 | 0.71 | 8 | 4 | 19 |
| 10 | III | 150 | 10 | -11 | -1 | 0.42 | 1 | 2 | 19 |
| 11 | III | 150 | 6 | -13 | -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

180.5 ± 8.4

42.4 ± 11.4

13 ± 5

34 ± 14

175 ± 96

600 ± 124

3.5 ± 0.5

42.5 ± 6.6

230 ± 50

225 ± 10

100 ± 14

56 ± 20

150 ± 10

125 ± 12

60 ± 10

100 ± 14

50 ± 10

**p < 0.05, ***p < 0.01 vs before nifedipine, \(^{1}\) Abbreviations as table 1

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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 ± 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

<table>
<thead>
<tr>
<th></th>
<th>Base line values vs work loads</th>
<th>Changes after nifedipine vs work loads</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>-0.58*</td>
<td>0.81**</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>0.13</td>
<td>0.05</td>
</tr>
<tr>
<td>PAPD (mmHg)</td>
<td>-0.08</td>
<td>-0.08</td>
</tr>
<tr>
<td>CI (liters/min/m²)</td>
<td>0.30</td>
<td>-0.36</td>
</tr>
<tr>
<td>SI (ml/beat/m²)</td>
<td>0.64**</td>
<td>-0.84**</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>0.14</td>
<td>-0.55*</td>
</tr>
<tr>
<td>PNE (pg/ml)</td>
<td>0.49*</td>
<td>0.18</td>
</tr>
</tbody>
</table>

*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

![Graph showing relationship between work load and change in stroke index](image)

Fig. 1. Relationship between work load and change in stroke index following a single dose of nifedipine (10mg). 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.

![Graph showing relationship between work load and change in left ventricular ejection fraction](image)

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 changes in left ventricular ejection fraction after a nifedipine administration. Work load is defined as the integration of work loads.
Exercise Capacity in DCM

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 (10mg). 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).

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 the heart with severely depressed contractility than in one with mildly depressed contractility (8, 9). That is, patients showing
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.


