

## Response of right ventricular systolic function to exercise stress: Effects of pulmonary vascular resistance on right ventricular systolic function

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To elucidate factors influencing responses of right ventricular systolic function to exercise stress, we evaluated the right ventricular ejection fraction and peak ejection rate with two different loading conditions, atrial septal defect and mitral stenosis, at rest and during exercise by means of gated equilibrium blood pool radionuclide ventriculography. In both atrial septal defect and mitral stenosis, strong correlations between changes in the right ventricular ejection fraction with exercise and pulmonary vascular resistance at rest ( $r = -0.97, p < 0.001$ ;  $r = -0.86, p < 0.0005$ ; respectively) were found. Significant correlations between changes in the right ventricular peak ejection rate with exercise and pulmonary vascular resistance at rest ( $r = -0.85, p < 0.05$ ;  $r = -0.75, p < 0.01$ ; respectively) were found in atrial septal defect and mitral stenosis. Both the right ventricular ejection fraction and peak ejection rate were lower during exercise than at rest when pulmonary vascular resistance at rest was more than 200 dynes-sec-cm<sup>-5</sup>-m<sup>2</sup> in both atrial septal defect and mitral stenosis. In conclusion, right ventricular systolic function responding to exercise stress was influenced by the pulmonary vascular resistance in both atrial septal defect and mitral stenosis.

**Key words:** right ventricular systolic function, mitral stenosis, atrial septal defect, pulmonary vascular resistance

### INTRODUCTION

RIGHT VENTRICULAR FUNCTION appears to be depressed during exercise in patients with certain cardiovascular abnormalities, such as coronary artery disease with right ventricular infarction,<sup>1-4</sup> acquired valvular heart disease<sup>5,6</sup> or congenital heart diseases.<sup>7</sup> Right ventricular systolic function is dependent on afterload at rest.<sup>8</sup> However, factors influencing the right ventricular systolic function during exercise have not been well elucidated.

The purpose of the present study is to examine right ventricular systolic function both at rest and during exercise in patients with right ventricular volume overload due to atrial septal defect (ASD) and in those with right ventricular pressure overload due to mitral stenosis (MS),

and to assess factors influencing responses of the right ventricle to exercise stress.

### MATERIALS AND METHODS

*Patient selection:* Twenty-one patients treated at the Osaka Police Hospital were studied: 7 with atrial septal defect (ASD group) and 14 with mitral stenosis (MS group) (Table 1). Informed consent was obtained from all the patients. The ASD group consisted of 5 females and 2 males with a mean age of  $40 \pm 17$  years. ASD was diagnosed by cardiac catheterization, oxymetry, and echo- and Doppler cardiography. No patient displayed secondary tricuspid regurgitation in either right ventriculography or Doppler cardiography, and all had normal sinus rhythm. The MS group consisted of 9 females and 5 males with a mean age of  $53 \pm 8$  years. All these patients had pure MS without mitral regurgitation or secondary tricuspid regurgitation diagnosed by cardiac catheterization, right ventriculography or echo- and Doppler cardiography. Five out of the 14 patients had normal sinus rhythm and

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**Table 1** Demographics and cardiac catheterization data of patients

| No. | Age (years) | Sex | Diagnosis | Rhythm | CI (l/m <sup>2</sup> ) | RVs (mmHg) | PAm (mmHg) | PVRI* | Qp/Qs | MV (cm <sup>2</sup> ) |
|-----|-------------|-----|-----------|--------|------------------------|------------|------------|-------|-------|-----------------------|
| 1   | 51          | F   | ASD       | NSR    | 9.8                    | 28         | 20         | 130   | 3.5   | –                     |
| 2   | 18          | M   | ASD       | NSR    | 5.8                    | 17         | 14         | 137   | 4.1   | –                     |
| 3   | 38          | F   | ASD       | NSR    | 11.1                   | 27         | 19         | 65    | 3.2   | –                     |
| 4   | 44          | F   | ASD       | NSR    | 5.6                    | 36         | 23         | 156   | 2.9   | –                     |
| 5   | 60          | F   | ASD       | NSR    | 6.1                    | 37         | 26         | 262   | 2.6   | –                     |
| 6   | 25          | F   | ASD       | NSR    | 6.1                    | 79         | 46         | 514   | 2.0   | –                     |
| 7   | 50          | M   | ASD       | NSR    | 5.0                    | 35         | 23         | 318   | 2.8   | –                     |
| 8   | 41          | F   | MS        | NSR    | 3.7                    | 31         | 14         | 86    | –     | 1.4                   |
| 9   | 50          | M   | MS        | Af     | 2.0                    | 35         | 17         | 236   | –     | 1.6                   |
| 10  | 51          | M   | MS        | Af     | 3.0                    | 24         | 18         | 162   | –     | 1.6                   |
| 11  | 40          | F   | MS        | NSR    | 3.2                    | 32         | 15         | 101   | –     | 1.2                   |
| 12  | 66          | F   | MS        | Af     | 1.9                    | 25         | 20         | 254   | –     | 0.9                   |
| 13  | 54          | F   | MS        | Af     | 2.2                    | 21         | 13         | 183   | –     | 1.0                   |
| 14  | 62          | F   | MS        | Af     | 1.8                    | 21         | 12         | 135   | –     | 1.5                   |
| 15  | 69          | M   | MS        | NSR    | 6.0                    | 36         | 25         | 68    | –     | 1.6                   |
| 16  | 58          | F   | MS        | NSR    | 2.8                    | 40         | 22         | 112   | –     | 0.9                   |
| 17  | 54          | M   | MS        | Af     | 2.8                    | 30         | 18         | 165   | –     | 1.1                   |
| 18  | 58          | F   | MS        | Af     | 4.4                    | 24         | 19         | 150   | –     | 1.6                   |
| 19  | 53          | F   | MS        | Af     | 1.5                    | 22         | 16         | 359   | –     | 1.9                   |
| 20  | 66          | F   | MS        | Af     | 2.9                    | 40         | 23         | 250   | –     | 1.1                   |
| 21  | 49          | M   | MS        | NSR    | 4.0                    | 20         | 12         | 153   | –     | 2.2                   |

\* dynes·sec·cm<sup>-5</sup>·m<sup>2</sup>

CI, cardiac index; RVs, right ventricular systolic pressure; PAm, mean pulmonary artery pressure; PVRI, pulmonary vascular resistance index; Qp/Qs, pulmonary-systemic flow ratio; MVA, mitral valve area; ASD, atrial septal defect; MS, mitral stenosis; NSR, normal sinus rhythm; Af, atrial fibrillation

the remaining nine had atrial fibrillation.

Among these 21 patients, none had previously undergone cardiac surgery. No significant coronary artery disease was detected in any patient by coronary arteriography. Moreover, all the patients had normal pulmonary function and no lung disease.

*Procedures for cardiac catheterization:* Cardiac output was determined by the dye dilution method. Indocyanine green dye solution was injected into the pulmonary artery. Blood was withdrawn continuously from the ascending aorta through a densitometer cuvette. Well-flushed fluid-filled catheters connected to a Statham P23Db transducer (Spectramed Inc., Cardiovascular Products Division, Oxnard, Calif.) were used. Left ventricular pressure and pulmonary wedge pressure were recorded simultaneously.

*Procedures for radionuclide ventriculography:* Radionuclide ventriculography was performed within 1 week before and after cardiac catheterization by using red blood cells labeled with <sup>99m</sup>Tc. To label red blood cells *in vivo*, 10 mg of sodium pyrophosphate and 2 mg of stannic chloride were injected intravenously into the right median cubital vein, and after 20 minutes, 20 mCi (740 MBq) of <sup>99m</sup>Tc-pertechnetate in 15 ml of physiologic saline was infused intravenously into the right external jugular vein. About 20 minutes later, when the administered agents

were presumed to have reached equilibrium, a parallel hole collimator was attached in a modified 40–50 degree left anterior oblique position. In each patient the degree of obliquity used was that which provided the best separation between the right and left ventricles. In addition, a 5–10 degree slant in the caudal tilt of the detector head was used to improve the separation between the right atrium and right ventricle. Radionuclide ventriculography was performed by using the multigated acquisition method in which one heartbeat is divided into 32 portions using the R wave of the electrocardiogram as a trigger, and cumulative imaging was performed on frames each consisting of a 64 × 64 matrix over 500 heartbeats with the time phase being synchronized with the frame mode. A Shimadzu Scintipac 70A and a rotary gamma camera (Shimadzu ZCL 7500) were used. The images prepared were subjected to smoothing. A region of interest was selected in each of the areas thought to be the right and left ventricles. The atrioventricular border was well visualized by the inward motion of the lateral right ventricular wall throughout systole. The right ventricular-pulmonary artery separation was chosen as the junction between the contracting and noncontracting regions of the outflow tract in which there was a differential systolic increase in counts superiorly and systolic decrease in counts inferiorly. Background was automatically assigned at end-systole and was located lateral to the left ventricle. This background region was crescent shaped, separated by two

**Table 2** Data of right and left ventricular ejection fraction (EF) and peak ejection rate (PER) of patients with atrial septal defect

| No.  | RVEF (%) |         | RVPER (EDV/sec) |              | LVEF (%) |         | LVPER (EDV/sec) |              |
|------|----------|---------|-----------------|--------------|----------|---------|-----------------|--------------|
|      | R        | Ex      | R               | Ex           | R        | Ex      | R               | Ex           |
| 1    | 45       | 46      | -1.90           | -2.10        | 59       | 77      | -2.50           | -3.70        |
| 2    | 44       | 43      | -2.10           | -2.10        | 60       | 43      | -3.25           | -2.65        |
| 3    | 61       | 65      | -2.10           | -2.70        | 82       | 83      | -3.45           | -3.55        |
| 4    | 49       | 51      | -1.90           | -2.10        | 71       | 74      | -2.50           | -3.35        |
| 5    | 40       | 37      | -1.85           | -1.75        | 70       | 59      | -3.45           | -3.05        |
| 6    | 53       | 31      | -2.00           | -1.70        | 81       | 56      | -3.25           | -3.20        |
| 7    | 49       | 41      | -2.10           | -1.85        | 65       | 58      | -3.25           | -3.05        |
| mean | 49 ± 7   | 45 ± 11 | -1.99 ± 0.11    | -2.04 ± 0.34 | 70 ± 9   | 64 ± 14 | -3.09 ± 0.42    | -3.22 ± 0.35 |

R, at rest; Ex, during exercise

**Table 3** Data of right and left ventricular ejection fraction (EF) and peak ejection rate (PER) of patients with pure mitral stenosis

| No.  | RVEF (%) |        | RVPER (EDV/sec) |              | LVEF (%) |         | LVPER (EDV/sec) |              |
|------|----------|--------|-----------------|--------------|----------|---------|-----------------|--------------|
|      | R        | Ex     | R               | Ex           | R        | Ex      | R               | Ex           |
| 1    | 33       | 33     | -1.55           | -1.60        | 47       | 46      | -2.05           | -2.40        |
| 2    | 34       | 21     | -1.55           | -0.90        | 34       | 29      | -1.70           | -1.75        |
| 3    | 42       | 42     | -2.00           | -2.00        | 42       | 41      | -2.00           | -1.90        |
| 4    | 35       | 31     | -1.70           | -1.65        | 67       | 65      | -2.80           | -3.00        |
| 5    | 42       | 35     | -2.00           | -1.75        | 39       | 39      | -2.20           | -2.40        |
| 6    | 42       | 39     | -1.85           | -1.85        | 60       | 68      | -2.50           | -3.60        |
| 7    | 36       | 36     | -1.60           | -1.90        | 42       | 41      | -2.30           | -2.45        |
| 8    | 38       | 42     | -1.80           | -2.60        | 78       | 82      | -3.00           | -3.85        |
| 9    | 48       | 50     | -2.65           | -3.30        | 48       | 60      | -2.05           | -3.60        |
| 10   | 44       | 46     | -1.85           | -2.00        | 53       | 59      | -2.40           | -2.95        |
| 11   | 46       | 48     | -2.00           | -2.40        | 46       | 56      | -2.10           | -3.45        |
| 12   | 41       | 26     | -2.00           | -1.50        | 41       | 36      | -2.35           | -2.35        |
| 13   | 37       | 29     | -1.75           | -1.50        | 56       | 55      | -2.50           | -2.70        |
| 14   | 50       | 50     | -2.45           | -3.05        | 67       | 60      | -2.95           | -2.85        |
| mean | 41 ± 5   | 38 ± 9 | -1.91 ± 0.32    | -2.00 ± 0.65 | 51 ± 13  | 53 ± 15 | -2.35 ± 0.38    | -2.80 ± 0.65 |

R, at rest; Ex, during exercise

matrix elements from the left ventricle activity, and was three to five matrix elements wide. Background counts were eliminated, and a time activity curve was prepared for each region of interest. The left and right ventricular ejection fractions (LVEF, RVEF) and peak ejection rate (PER) were measured. PER is the ejection phase index of systolic function.<sup>9-11</sup> These values were determined according to a technique reported by previous investigators.<sup>7,12,13</sup>

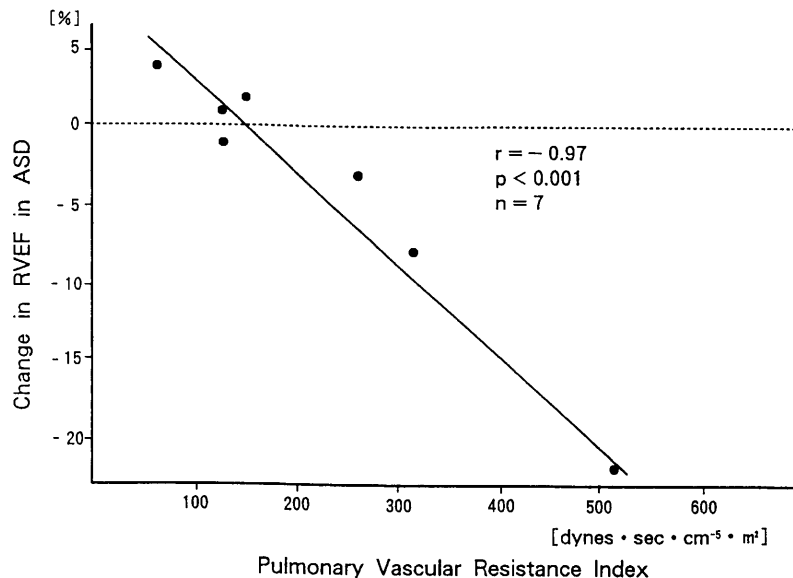
After obtaining data at rest, supine exercise was performed on a bicycle ergometer. The initial workload was 25 watts, which was increased successively by 25 watts every three minutes to 50-75 watts. At each workload, 200 heartbeats were added, this being enabled by the 3-minute interval, and imaging was performed. The image was subjected to the same treatment as applied to the image obtained at rest. The data employed were those at maximum load.

In patients with atrial fibrillation, peaks of the heart-

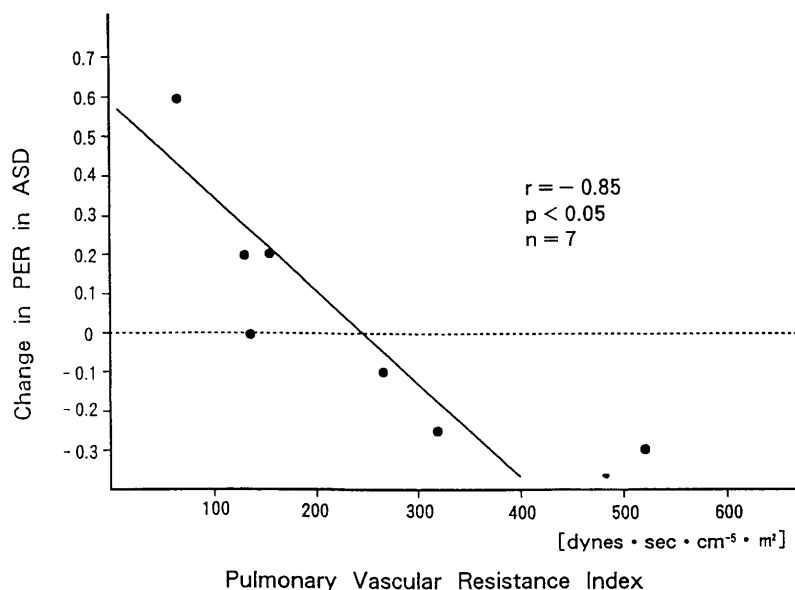
beats were identified from the distribution in a histogram of heart rates, whereby 20% of the heartbeats adjacent to each selected peak heartbeat (i.e., 10% before the peak and 10% after the peak) were selected in order to exclude a large deviation.

In subsequent studies, analysis was performed independently by two observers. The reproducibility of RVEF and LVEF was assessed in all patients. RVEF by the same observer at two different times was  $43 \pm 7\%$  and  $43 \pm 6\%$ , respectively (absolute difference:  $2.0 \pm 0.7\%$ ), and that measured by two observers was  $43 \pm 7\%$  and  $44 \pm 7\%$ , respectively (absolute difference:  $1.6 \pm 1.0\%$ ). The LVEF by the same observer at two different times was  $58 \pm 14\%$  and  $57 \pm 14\%$ , respectively (absolute difference:  $1.3 \pm 0.9\%$ ), and that measured by two observers was  $57 \pm 14\%$  and  $57 \pm 14\%$ , respectively (absolute difference:  $1.1 \pm 0.8\%$ ).

*Statistical analysis:* Data are expressed as the mean ±



**Fig. 1** Correlation between changes in right ventricular ejection fraction (RVEF) from rest to exercise and pulmonary vascular resistance (PVR) at rest in patients with atrial septal defect (ASD). There was a strong inverse correlation between changes in RVEF and PVR. When the PVR was over 200 dynes·sec·cm<sup>-5</sup>·m<sup>2</sup>, the changes with exercise in RVEF became less than "0".



**Fig. 2** Correlation between changes in right ventricular peak ejection rate (RVPER) from rest to exercise and pulmonary vascular resistance (PVR) at rest in patients with atrial septal defect (ASD). A strong inverse correlation existed between changes in RVPER and PVR. When the PVR was over 200 dynes·sec·cm<sup>-5</sup>·m<sup>2</sup>, the changes with exercise in RVEF became less than "0".

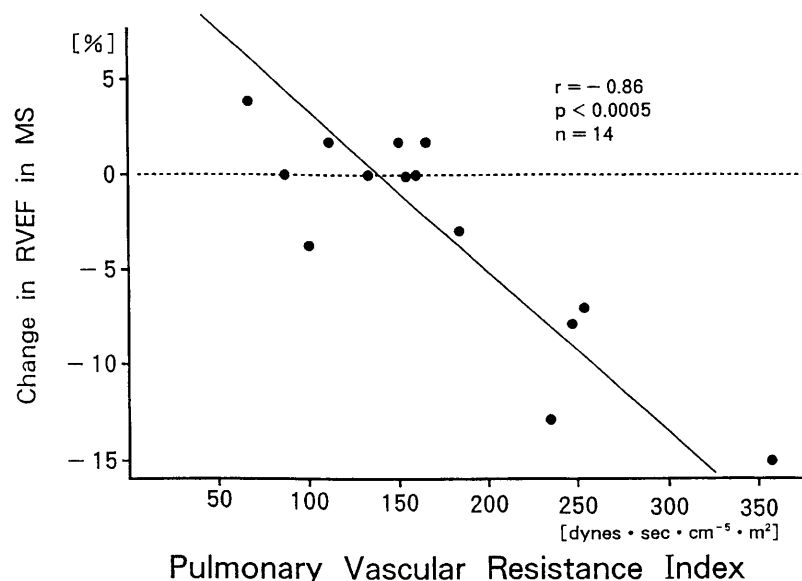
standard deviation for each variable. All the data were compared by a paired t-test. The strength of association between certain variables was evaluated by a standard linear regression analysis.

### RESULTS

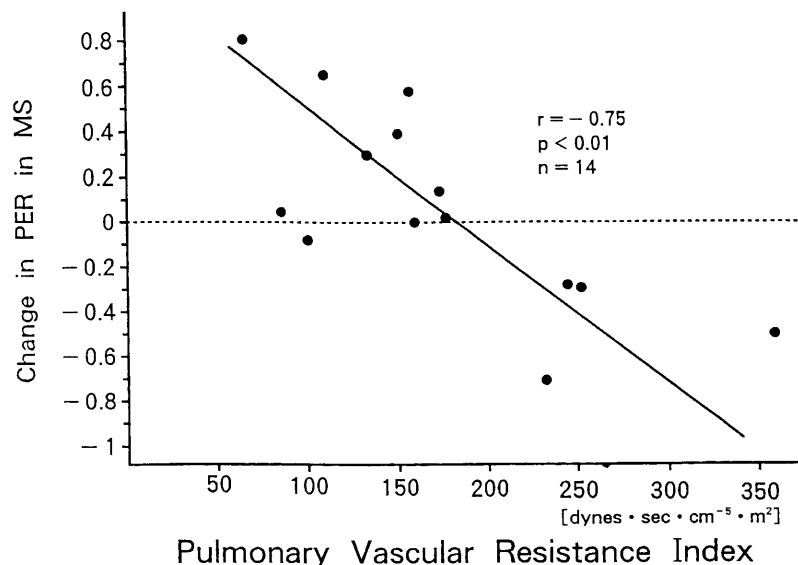
*Cardiac catheterization data and radionuclide ventriculographic data at rest* (Tables 1, 2, and 3): In ASD, cardiac catheterization revealed that the pulmo-

nary-systemic flow ratio (Qp/Qs ratio) was  $3.0 \pm 0.7$ . Right ventricular end-systolic pressure and mean pulmonary arterial pressure were  $37 \pm 20$  mmHg and  $24 \pm 10$  mmHg. Pulmonary vascular resistance was  $254 \pm 165$  dynes·sec·cm<sup>-5</sup>·m<sup>2</sup>. RVEF was  $49 \pm 7\%$  and RVPER was  $-1.99 \pm 0.11$  EDV(end-diastolic volume)/sec. Neither RVEF nor RVPER correlated with right ventricular systolic pressure, mean pulmonary arterial pressure or pulmonary vascular resistance.

In MS, right ventricular end-systolic pressure and mean



**Fig. 3** Correlation between changes in right ventricular ejection fraction (RVEF) from rest to exercise and pulmonary vascular resistance (PVR) at rest in patients with mitral stenosis (MS). A significant correlation existed between changes in RVEF and PVR. When the PVR was over 200 dynes·sec·cm<sup>-5</sup>·m<sup>2</sup>, the changes with exercise in RVEF became less than "0".



**Fig. 4** Correlation between changes in right ventricular peak ejection rate (RVPER) from rest to exercise and pulmonary vascular resistance (PVR) at rest in patients with mitral stenosis (MS). A significant correlation existed between changes in RVPER and PVR. When the PVR was over 200 dynes·sec·cm<sup>-5</sup>·m<sup>2</sup>, the changes with exercise in RVEF became less than "0".

pulmonary arterial pressure were  $29 \pm 7$  mmHg and  $17 \pm 5$  mmHg. Pulmonary vascular resistance was  $175 \pm 85$  dynes·sec·cm<sup>-5</sup>·m<sup>2</sup>. The RVEF was  $41 \pm 5\%$  and RVPER was  $-1.91 \pm 0.32$  EDV/sec. Neither RVEF or RVPER correlated with right ventricular systolic pressure, mean pulmonary arterial pressure or pulmonary vascular resistance.

*Responses of right ventricular systolic function to exercise in patients with ASD:* RVEF and RVPER were

$45 \pm 11\%$  and  $-2.04 \pm 0.34$  EDV/sec during exercise. RVEF decreased during exercise in 4 patients, while it did not decrease in the other 3. Both RVEF and RVPER during exercise correlated well with pulmonary vascular resistance at rest ( $r = -0.82$ ,  $p < 0.05$ ;  $r = -0.80$ ,  $p < 0.05$ , respectively). In addition, changes in RVEF and RVPER from rest to exercise correlated well with pulmonary vascular resistance at rest ( $r = -0.97$ ,  $p < 0.001$ ;  $r = -0.85$ ,  $p < 0.05$ , respectively) (Figs. 1 and 2). When pulmonary vascular resistance was over 200 dynes·sec·

$\text{cm}^{-5}\cdot\text{m}^2$ , changes in RVEF and RVPER with exercise became less than "0" (Figs. 1 and 2).

*Response of right ventricular systolic function to exercise in patients with MS:* RVEF and RVPER were  $38 \pm 9\%$  and  $-2.00 \pm 0.65$  EDV/sec during exercise. The RVEF decreased during exercise in 6 patients, while it did not decrease in the other 8. Changes in RVEF and RVPER from rest to exercise correlated well with pulmonary vascular resistance at rest ( $r = -0.86$ ,  $p < 0.0005$ ;  $r = -0.75$ ,  $p < 0.01$ , respectively) (Figs. 3 and 4). When pulmonary vascular resistance was over  $200$  dynes $\cdot\text{sec}\cdot\text{cm}^{-5}\cdot\text{m}^2$ , changes in RVEF and RVPER with exercise became less than "0" (Figs. 3 and 4).

*Relationship between right and left ventricular function* (Tables 2 and 3): LVEF at rest in ASD and MS was  $70 \pm 9\%$  and  $51 \pm 13\%$ , and that during exercise was  $64 \pm 14\%$  and  $53 \pm 15\%$ , respectively. LVPER at rest in ASD and MS was  $-3.09 \pm 0.42$  and  $-2.35 \pm 0.38$  EDV/sec, and that during exercise was  $-3.22 \pm 0.35$  and  $-2.80 \pm 0.65$  EDV/sec, respectively. LVEF at rest was not related to right ventricular systolic function in either ASD or MS. LVEF did not increase during exercise in 9 (90%) of 10 patients whose RVEF was depressed during exercise.

## DISCUSSION

Response of right ventricular systolic function to exercise was limited by pulmonary vascular resistance at rest. Response to exercise stress was quite similar in volume overloaded and pressure overloaded right ventricles in this study. RVEF and RVPER values were lower during exercise than at rest when pulmonary vascular resistance was over  $200$  dynes $\cdot\text{sec}\cdot\text{cm}^{-5}\cdot\text{m}^2$ .

Previous investigations have suggested that loading conditions are important determinants of right ventricular systolic function during exercise.<sup>1-7</sup> However, it has remained unclear which factors influence right ventricular systolic function. Some investigators<sup>12,13</sup> reported a significant relation between RVEF and right-sided pressures even at rest, and others<sup>14,15</sup> reported no significant relation between these two. There have been relatively few studies of right ventricular function during exercise. Generally, right ventricular function appears to be depressed during exercise in patients with volume or pressure overload on the right ventricle.<sup>5-7</sup> In agreement with these studies, right ventricular systolic dysfunction in some patients with MS and/or ASD became apparent during exercise in this study. The pulmonary vascular resistance at rest influenced right ventricular systolic function during exercise in both ASD and MS. These results are similar to those in pure mitral stenosis reported by Cohen and his colleague.<sup>5</sup> In their study there was significant correlation between responses of RVEF to exercise and total pulmo-

nary resistance. However, right ventricular function during exercise was depressed in all patients and was unlike our data, which may indicate more progressed pathological states of the mitral valve in their patients.

The present study suggests that afterload mismatch could exist in the right ventricle having pressure and/or volume overload. We have no clear data to indicate depression of right ventricular contractility. In patients whose RVEF and/or RVPER decreased during exercise, the RVEF and/or RVPER at rest were not always low. These quite similar responses to exercise stress of right ventricles under two different loading conditions might show that these phenomena were intimately related to right ventricular systolic properties. These findings may demonstrate the limitation of systolic function in the right ventricle exposed to chronic afterload.

Left ventricular systolic function at rest was not related to right ventricular function at rest. However, it was depressed during exercise in almost all the patients whose right ventricular systolic function was depressed during exercise in both ASD and MS. We think these data suggest that the right ventricle with depressed function may induce left ventricular dysfunction during exercise.<sup>16</sup>

Our analysis of right ventricular function by means of gated equilibrium blood pool radionuclide ventriculography may be limited by the variation in the R-R interval in atrial fibrillation. To exclude a large deviation, we selected the heartbeats adjacent to within  $\pm 10\%$  of the peak identified from a distribution in a histogram of heartbeats. Moreover, R-R interval irregularity decreasing during exercise. Accordingly, we think that the present method enabled evaluation of right ventricular function by averaging, in comparison with the angiographic method on the assessment of heart function with atrial fibrillation. In order to avoid changes in the heart rate just after the workload was increased to its maximum, in which the heart rate was over 100 in all patients ( $105 \pm 5$ ), 200 heartbeats during exercise were added not in the first minute but in the remaining two minutes. The changes in heart rate in this two minutes included those ranging 20% around the peak heart rate. Parts of the right atrium are behind the right ventricle and thus interfere with right ventricular activity. This leads to a slight underestimation of the RVEF.<sup>17,18</sup>

In conclusion, right ventricular systolic function responding to exercise stress was influenced by pulmonary vascular resistance in both atrial septal defect and mitral stenosis. Right ventricular systolic function during exercise deteriorated when the pulmonary vascular resistance index rose to over  $200$  dynes $\cdot\text{sec}\cdot\text{cm}^{-5}\cdot\text{m}^2$ .

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