Vasodilator Therapy for Right Ventricular Failure

KAZUSHIGE SAKAGUCHI, M.D., NOBUYUKI TANAKA, M.D.
MASATERU SAWADA, M.D., YOSHIHiko ARAKI, M.D.
AND KAZUSHIGE FUJITA, M.D.

The effects of PGE₁ and ISD on right ventricular performance in patients with pulmonary hypertension secondary to chronic lung disease were evaluated, and the following results were obtained.

I) Effects of PGE₁ on Right Ventricular Failure

The effects of PGE₁ (intravenous infusion, 0.01 to 0.03 μg/kg/min) on right ventricular failure were studied in 12 patients with acute exacerbation of chronic respiratory failure.

PGE₁ resulted in a significant fall in RAP (p < 0.05), PAMP (from 33.8 ± 7.6 to 29.3 ± 5.7 mmHg, p < 0.005) and TPVR (p < 0.001), whereas a significant increase in CI (from 3.4 ± 0.6 to 3.9 ± 0.6 l/min/m², p < 0.001) and SI (p < 0.005). PaO₂ was significantly decreased by PGE₁ (p < 0.02), however P<sub>F</sub>O₂ remained unchanged because of a significant increase of O₂-transport (p < 0.01).

PGE₁ induced active vasodilation of the pulmonary vascular beds and reduced a right ventricular afterload. We concluded that PGE₁ improved the right ventricular failure secondary to chronic lung disease.

II) Effects of ISD on Right Ventricular Performance

The effects of ISD (intravenous infusion, 0.05 mg/kg/hr) on right ventricular performance were studied at rest and during exercise in 11 patients with clinically stable chronic respiratory failure.

At rest and during exercise, ISD induced a significant decrease in RAP, PAMP and CI, however no change in TPVR. RVWI was reduced significantly by ISD (from 2.5 ± 0.8 to 1.9 ± 0.5 Kg-m/min/m², p < 0.01) during exercise.

ISD reduced the right ventricular preload by means of venodilation, and reduced right ventricular work. We concluded that ISD improved the right ventricular performance of cor pulmonale.

Vasodilator therapy has been applied for many years to treat patients with acute left ventricular failure due to myocardial infarction or chronic congestive heart failure!−3 However there is a little experience with the effects of vasodilators in treating right ventricular failure⁴−⁶ or cor pulmonale⁷−₁⁰ secondary to chronic lung disease.

The prognosis of cor pulmonale is generally poor. In the majority of patients with cor pulmonale the cause of death is right ventricular failure and/or respiratory failure¹¹,¹² Studies of acute exacerbation of chronic respiratory failure with right ventricular failure suggest that the treatment of low cardiac output syndrome is important to improve the prognosis of cor pulmonale.¹¹,¹² We evaluated (1) the effects of Prostaglandin E₁ (PGE₁) on right ventricular

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Key Words:
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Cor pulmonale
Prostaglandin E₁
Isosorbide dinitrate

The Third Department of Internal Medicine Osaka Prefectural Habikino Hospital, Osaka, Japan
Mailing address: Kazushige Sakaguchi, M.D., The Third Department of Internal Medicine, Osaka Prefectural Habikino Hospital, 3-7-1 Habikino, Habikinoshi, Osaka 583, Japan.

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TABLE I EFFECTS OF PGE$_1$ ON CIRCULATORY AND RESPIRATORY PARAMETERS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control Mean ± S.D.</th>
<th>PGE$_1$ Mean ± S.D.</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAP (mmHg)</td>
<td>8.6 ± 6.2</td>
<td>6.4 ± 4.0</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>PAMP (mmHg)</td>
<td>33.8 ± 7.6</td>
<td>29.3 ± 5.7</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>TPVR (unit)</td>
<td>6.6 ± 1.5</td>
<td>5.0 ± 1.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PVR (unit)</td>
<td>4.9 ± 1.7</td>
<td>3.8 ± 1.4</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>CI (l/min/m$^2$)</td>
<td>3.38 ± 0.64</td>
<td>3.89 ± 0.64</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SI (ml/beat/m$^2$)</td>
<td>40.1 ± 11.2</td>
<td>46.8 ± 10.4</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>PCWP (mmHg)</td>
<td>12.1 ± 4.4</td>
<td>10.0 ± 5.6</td>
<td>NS</td>
</tr>
<tr>
<td>HR (beat/min)</td>
<td>85.8 ± 15.1</td>
<td>85.3 ± 14.0</td>
<td>NS</td>
</tr>
<tr>
<td>mAP (mmHg)</td>
<td>87.8 ± 10.0</td>
<td>82.6 ± 9.2</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>SVR (unit)</td>
<td>17.1 ± 4.5</td>
<td>14.1 ± 2.9</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>pHa</td>
<td>7.418 ± 0.093</td>
<td>7.428 ± 0.092</td>
<td>NS</td>
</tr>
<tr>
<td>PaCO$_2$ (torr)</td>
<td>50.5 ± 12.3</td>
<td>48.2 ± 9.4</td>
<td>NS</td>
</tr>
<tr>
<td>PaO$_2$/FIO$_2$ (torr)</td>
<td>285.2 ± 81.5</td>
<td>245.1 ± 93.6</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>A-aDO$_2$ (torr)</td>
<td>121.2 ± 56.4</td>
<td>142.3 ± 72.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Qs/Qt (%)</td>
<td>8.9 ± 3.5</td>
<td>11.4 ± 5.6</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>$O_2$-transport (ml/min)</td>
<td>821 ± 266</td>
<td>919 ± 257</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Fig.1. Effects of PGE$_1$ on right atrial pressure (RAP), pulmonary arterial mean pressure (PAMP), cardiac index (CI) and total pulmonary vascular resistance (TPVR).

failure and (2) the effects of isosorbide dinitrate (ISD) on right ventricular performance of cor pulmonale.

METHODS

1) Effects of PGE$_1$ on Right Ventricular Failure

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Twelve patients with right ventricular failure were admitted to the Intensive Care Unit because of acute exacerbation of chronic respiratory failure. Seven were male and five female with a mean age of 62.6 years (range, 48 to 81 years). Ten had old pulmonary tuberculosis, two had chronic obstructive pulmonary disease. Three patients were treated with controlled oxygen therapy¹³ nine had to be intubated and ventilated mechanically.

As soon as their condition was stabilized, hemodynamic measurements were performed using a Swan-Ganz flow directed thermodilution catheter (93A-131-7F). Cardiac output was measured by the thermodilution method, using Cardiac Output Computer 9510 (Edwards). Blood gas was measured using ABL2 (Astrup).

PGE₁ was then infused into the right atrium at a rate of 0.01 to 0.03 µg/kg/min for 30 minutes, and hemodynamic measurements were
TABLE II  EFFECTS OF ISD ON RESTING AND EXERCISE HEMODYNAMICS AND RESPIRATORY PARAMETERS

<table>
<thead>
<tr>
<th></th>
<th>Control Mean ± S.D.</th>
<th>ISD Mean ± S.D.</th>
<th>P values</th>
<th>Control Mean ± S.D.</th>
<th>ISD Mean ± S.D.</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAP (mmHg)</td>
<td>5.4 ± 3.8</td>
<td>4.0 ± 4.2</td>
<td>p &lt; 0.001</td>
<td>9.8 ± 4.4</td>
<td>8.1 ± 3.7</td>
<td>p &lt; 0.02</td>
</tr>
<tr>
<td>PAMP (mmHg)</td>
<td>20.1 ± 4.4</td>
<td>16.7 ± 3.7</td>
<td>p &lt; 0.005</td>
<td>40.3 ± 8.3</td>
<td>36.4 ± 10.8</td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td>TPVR (unit)</td>
<td>4.1 ± 1.4</td>
<td>3.9 ± 1.4</td>
<td>NS</td>
<td>4.6 ± 1.3</td>
<td>4.6 ± 1.4</td>
<td>NS</td>
</tr>
<tr>
<td>PVR (unit)</td>
<td>2.4 ± 1.2</td>
<td>2.4 ± 1.2</td>
<td>NS</td>
<td>2.8 ± 1.1</td>
<td>2.9 ± 1.1</td>
<td>NS</td>
</tr>
<tr>
<td>CI (l/min/m²)</td>
<td>3.4 ± 1.1</td>
<td>3.0 ± 0.8</td>
<td>p &lt; 0.05</td>
<td>6.1 ± 1.5</td>
<td>5.3 ± 0.9</td>
<td>p &lt; 0.025</td>
</tr>
<tr>
<td>SI (ml/beat/m²)</td>
<td>44.5 ± 16.3</td>
<td>37.6 ± 12.7</td>
<td>p &lt; 0.01</td>
<td>58.7 ± 19.4</td>
<td>52.3 ± 12.1</td>
<td>NS</td>
</tr>
<tr>
<td>PCWP (mmHg)</td>
<td>8.7 ± 3.2</td>
<td>6.7 ± 3.4</td>
<td>p &lt; 0.05</td>
<td>16.2 ± 4.3</td>
<td>14.2 ± 4.9</td>
<td>NS</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>78.6 ± 10.6</td>
<td>83.5 ± 12.5</td>
<td>p &lt; 0.005</td>
<td>106.3 ± 12.9</td>
<td>103.0 ± 13.2</td>
<td>NS</td>
</tr>
<tr>
<td>mAP (mmHg)</td>
<td>97.0 ± 12.0</td>
<td>91.1 ± 10.8</td>
<td>p &lt; 0.025</td>
<td>99.8 ± 14.3</td>
<td>96.7 ± 15.8</td>
<td>NS</td>
</tr>
<tr>
<td>SVR (unit)</td>
<td>19.0 ± 5.1</td>
<td>20.2 ± 6.1</td>
<td>NS</td>
<td>10.3 ± 3.0</td>
<td>11.5 ± 3.5</td>
<td>NS</td>
</tr>
<tr>
<td>pHa</td>
<td>7.405 ± 0.024</td>
<td>7.410 ± 0.024</td>
<td>NS</td>
<td>7.380 ± 0.028</td>
<td>7.386 ± 0.035</td>
<td>NS</td>
</tr>
<tr>
<td>PaO₂ (torr)</td>
<td>65.1 ± 7.8</td>
<td>67.0 ± 8.1</td>
<td>NS</td>
<td>56.3 ± 9.1</td>
<td>56.4 ± 9.0</td>
<td>NS</td>
</tr>
<tr>
<td>PaCO₂ (torr)</td>
<td>44.9 ± 6.9</td>
<td>44.2 ± 7.2</td>
<td>NS</td>
<td>44.2 ± 8.2</td>
<td>43.0 ± 9.6</td>
<td>NS</td>
</tr>
<tr>
<td>PaO₂ (torr)</td>
<td>36.1 ± 2.9</td>
<td>34.6 ± 3.7</td>
<td>NS</td>
<td>27.4 ± 4.3</td>
<td>26.4 ± 4.5</td>
<td>NS</td>
</tr>
<tr>
<td>Ó (Qt (%))</td>
<td>30.5 ± 6.3</td>
<td>25.6 ± 7.1</td>
<td>p &lt; 0.005</td>
<td>26.4 ± 12.8</td>
<td>24.6 ± 11.4</td>
<td>NS</td>
</tr>
<tr>
<td>O₂-transport (ml/min)</td>
<td>845 ± 288</td>
<td>761 ± 226</td>
<td>NS</td>
<td>1473 ± 490</td>
<td>1285 ± 351</td>
<td>NS</td>
</tr>
<tr>
<td>RVWI (kg·m/min/m²)</td>
<td>0.7 ± 0.3</td>
<td>0.5 ± 0.2</td>
<td>p &lt; 0.02</td>
<td>2.5 ± 0.8</td>
<td>1.9 ± 0.5</td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td>LVWI (kg·m/min/m²)</td>
<td>4.2 ± 1.6</td>
<td>3.5 ± 1.1</td>
<td>p &lt; 0.005</td>
<td>7.2 ± 2.4</td>
<td>5.9 ± 1.6</td>
<td>p &lt; 0.02</td>
</tr>
<tr>
<td>VO₂ (ml/min)</td>
<td>213.1 ± 73.4</td>
<td>218.1 ± 63.6</td>
<td>NS</td>
<td>658.5 ± 227.2</td>
<td>597.8 ± 245.7</td>
<td>NS</td>
</tr>
</tbody>
</table>
Fig. 5. Effects of ISD on right atrial pressure (RAP), pulmonary arterial mean pressure (PAMP), cardiac index (CI) and total pulmonary vascular resistance (TPVR) at rest (open circle) and during exercise (closed circle).

Fig. 6. Effects of ISD on arterial oxygen tension (PaO₂), oxygen-transport (O₂-transport), mixed venous oxygen tension (PvO₂) and right ventricular work index (RVWI) at rest and during exercise.

repeated.

The data are presented as the mean ± SD. Statistical analysis of the data was performed using the paired t test for paired data.

II) Effects of ISD on Right Ventricular Performance

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formance

Eleven patients with clinically stable chronic respiratory failure were studied. Six had chronic obstructive pulmonary disease, five had old pulmonary tuberculosis. All were male with a mean age of 58.3 years (range, 46 to 68 years).
After right heart catheterization was performed using a Swan-Ganz catheter, baseline measurements were made at rest in the supine position. Supine bicycle exercise was performed at a constant work-load of 30 to 60 Watt for five minutes. Patients were allowed to recover for at least 30 minutes until hemodynamics returned to baseline. ISD was administered intravenously at a rate of 0.05 mg/kg/hr. Resting hemodynamics were measured after 30 minutes of ISD administration. Bicycle exercise was repeated at a same workload and duration described above.

The significance of the ISD effects on these measurements at rest and during exercise was assessed by paired t test.

RESULTS

I) Effects of PGE\textsubscript{1} on Right Ventricular Failure

The effects of PGE\textsubscript{1} on circulatory and respiratory parameters are shown in Table I and Fig. 1 to 4.

Administration of PGE\textsubscript{1} resulted in a significant fall in right atrial pressure (RAP) (from 8.6 ± 6.2 to 6.4 ± 4.0 mmHg, p < 0.05), mean pulmonary arterial pressure (PAMP) (from 33.8 ± 7.6 to 29.3 ± 5.7 mmHg, p < 0.005) and total pulmonary vascular resistance (TPVR) (from 6.6 ± 1.5 to 5.0 ± 1.2 unit, p < 0.001), and a significant increase in cardiac index (CI) (from 3.4 ± 0.6 to 3.9 ± 0.6 l/min/m\textsuperscript{2}, p < 0.001) and stroke index (SI) (from 40.1 ± 11.2 to 46.8 ± 10.4 ml/beat/m\textsuperscript{2}, p < 0.005) (Fig. 1).

CI was likely to increase as RAP or TPVR was reduced by PGE\textsubscript{1} (Fig. 2). A percent change in CI after PGE\textsubscript{1} infusion did not correlate with a percent change in RAP significantly. Whereas there was a significant correlation between percent changes in TPVR and CI (Fig. 3).

After PGE\textsubscript{1} administration, pulmonary capillary wedge pressure (PCWP) and heart rate (HR) did not change significantly. But there was a significant reduction in mean arterial pressure (mAP) and systemic vascular resistance (SVR) (Table I).

The effects of PGE\textsubscript{1} on gas exchange were shown in Fig. 4. PaO\textsubscript{2} was significantly decreased by PGE\textsubscript{1} (p < 0.02), however P\textsubscript{v}O\textsubscript{2} remained unchanged because of a significant increase of O\textsubscript{2}-transport (p < 0.01) (Fig. 4).

II) Effects of ISD on Right Ventricular Performance

The effects of ISD on circulatory and respiratory parameters are shown in Table II and Fig. 5 to 6.

At rest, ISD induced a significant decrease in RAP (from 5.4 ± 3.8 to 4.0 ± 4.2 mmHg, p < 0.001), PAMP (from 20.1 ± 4.4 to 16.7 ± 3.7 mmHg, p < 0.005) and CI (from 3.4 ± 1.1 to 3.0 ± 0.8 l/min/m\textsuperscript{2}, p < 0.05), however no change in TPVR (from 2.4 ± 1.2 to 2.4 ± 1.2, NS). During exercise, RAP, PAMP and CI were also significantly decreased and TPVR unchanged by ISD (Fig. 5). There was a significant reduction in right ventricular work index (RVWVI) from 2.5 ± 0.8 to 1.9 ± 0.5 Kg·m/min/m\textsuperscript{2} (p < 0.01) (Fig. 6).

The effects of ISD on systemic circulation are shown in Table II. At rest PCWP and mAP decreased and HR increased significantly after ISD administration, whereas SVR remained unchanged. During exercise, on the other hand, ISD elicited no changes in PCWP, mAP, HR and SVR.

The effects of ISD on respiratory parameters are shown in Fig. 6. There were no significant changes in PaO\textsubscript{2}, O\textsubscript{2}-transport and P\textsubscript{v}O\textsubscript{2} after ISD administration either at rest or during exercise.

DISCUSSION

Most of the patients with chronic respiratory failure have pulmonary hypertension and elevated pulmonary vascular resistance even in a clinically stable state\textsuperscript{14} An episode of acute exacerbation might increase right ventricular afterload and result in right ventricular failure\textsuperscript{12} The low cardiac output from right ventricular failure is the most consequence of all factors that leads to a poor prognosis of cor pulmonale\textsuperscript{11,12}

It has now already won recognition that vasodilator therapy can improve refractory congestive heart failure!\textsuperscript{3} Vasodilating agents reduce the preload and/or afterload of the heart, and actually decrease myocardial work and improve metabolic efficiency!\textsuperscript{1-3} However there is a little information with these vasodilators in treating right ventricular failure\textsuperscript{4-6} and cor pulmonale?\textsuperscript{10} We evaluated the effects of vasodilators on right ventricular failure and cor pulmonale.

It has been reported that PGE\textsubscript{1} is a potent vasodilatation of all peripheral blood vessels and increases blood flow in the coronary, pulmonary and renal arteries\textsuperscript{15,16} However, there is a little experience with PGE\textsubscript{1} in treating pulmonary
hypertension secondary to chronic lung disease.\textsuperscript{4,5}

In the present study the subjects still had pulmonary hypertension even after hypoxemia and acidosis were treated with controlled oxygen therapy and mechanical ventilation, and they were in a state of right ventricular failure. After PGE\textsubscript{1} was administered intravenously at a rate of 0.01 to 0.03 $\mu$g/kg/min, they had an improvement in clinical signs, such as a significant decrease in pulmonary arterial pressure and total pulmonary vascular resistance and a significant increase in cardiac output. The fact that pulmonary arterial pressure and total vascular resistance decreased in spite of an increase of pulmonary blood flow suggested that PGE\textsubscript{1} caused active vasodilation of the pulmonary vascular beds and reduced right ventricular afterload.

After PGE\textsubscript{1} administration arterial pressure and systemic vascular resistance decreased. The reduction in arterial pressure and systemic vascular resistance is consistent with the known systemic effects of this drug, but in the absence of left ventricular dysfunction, it was not the cause of the hemodynamic improvement we observed.

Right atrial pressure also decreased significantly after PGE\textsubscript{1} infusion. This reduction may be due to the venodilating\textsuperscript{15} and diuretic effect of PGE\textsubscript{1}.\textsuperscript{16} It seems to presume that this reduction in preload of right ventricle is contributable to the improvement of right ventricular failure.

Cohn et al.\textsuperscript{3} suggested that since the vasodilators in general appeared to have a greater effect on the systemic rather than the pulmonary vascular bed, refractory hypotension became a limiting factor in the treatment of right ventricular failure. In our study, PAMP and TPVR significantly decreased after PGE\textsubscript{1} infusion, whereas arterial pressure had only a slight decrease. This fact provides supportive evidence that PGE\textsubscript{1} is of clinical benefit to patients with right ventricular failure.

$\text{QO}_2/\text{QT}$ increased significantly and $\text{PaO}_2$ decreased after PGE\textsubscript{1} infusion. This change may be considered to be an increased ventilation-perfusion mismatch. However, it should be noted that $\text{O}_2$-transport increased significantly due to the increase in cardiac output. Subsequently $\text{PvO}_2$, which indicates a tissue oxygenation,\textsuperscript{17} had no change after PGE\textsubscript{1} infusion. This fact indicates that adequate tissue oxygenation was maintained after administration of PGE\textsubscript{1}.

Naeije et al.\textsuperscript{5} studied the effects of PGE\textsubscript{1} on pulmonary hypertension. PGE\textsubscript{1} was administered intravenously at a rate of 0.02 and 0.04 $\mu$g/kg/min to 26 patients with decompensated chronic obstructive pulmonary disease. They reported a significant decrease in PAMP, TPVR and mAP, and an increase in CI and $\text{O}_2$-transport. They also recognized the beneficial effects of PGE\textsubscript{1}.

Our study suggested that PGE\textsubscript{1} caused active vasodilation of the pulmonary vascular bed and reduced right ventricular afterload. We concluded that the reduction of right ventricular afterload by PGE\textsubscript{1} is of clinical benefit to patients with right ventricular failure.

Secondly, the effects of ISD on right ventricular performance were studied in 11 patients with cor pulmonale. In patients with chronic lung disease, they may not have pulmonary hypertension at rest, but often have a remarkable rise in pulmonary arterial pressure during exercise.\textsuperscript{18} The sustained elevation in pulmonary arterial pressure increases the right ventricular work and ultimately leads to right ventricular failure.

It is well known that ISD acts predominantly on the venous system, resulting in venodilation, and decreases in preload.\textsuperscript{2} ISD is a potent dilator of the pulmonary vascular bed and causes a decrease in pulmonary arterial pressure in patients with congestive heart failure.\textsuperscript{19,20} However a little information is available about the effects of ISD on pulmonary circulation in patients with cor pulmonale.\textsuperscript{7-9}

In our study ISD induced a decrease in RAP, PAMP and CI, however no change in TPVR at rest and during exercise. The decrease in PAMP can be considered to be a reduction in cardiac output. Schüren et al.\textsuperscript{7} observed the effects of sublingual ISD in patients with cor pulmonale. They reported a significant decrease in pulmonary arterial pressure associated with no change in pulmonary vascular resistance, and suggested that the decrease in PAMP was mainly due to a reduction in cardiac output from venodilation. Konietzko et al.\textsuperscript{8} studied the changes in hemodynamics with oral ISD in patients with cor pulmonale. They described a decrease in TPVR as well as PAMP, and suggested that the reduction in PAMP might be attributable to active pulmonary vasodilation. But our data did not show active pulmonary vasodilation. It seems probable that the dose of ISD used in our study was too low to produce pulmonary vasodilation. During
exercise with ISD, the increase in PAMP was less remarkable than during exercise without ISD. The right ventricular work was significantly decreased by ISD. This fact suggests that ISD may increase exercise tolerance in patients with cor pulmonale.

It has been reported that ISD induced a fall in PaO₂ as other vasodilators. The reduction in PaO₂ may be considered to be increased ventilation-perfusion mismatch. In our study, however, PaO₂ remained unchanged after ISD infusion. It seems probable that the dose of ISD used in our study did not produce active pulmonary vasodilation, and thus failed to give rise to an increase in ventilation-perfusion mismatch. Oxygen transport showed a tendency to decline due to a decrease in cardiac output. However PO₂, which indicates a tissue oxygenation, showed no change.

The results of the present study suggested that ISD reduced PAMP and RVWI at rest and during exercise. We concluded that ISD improved the right ventricular performance in patients with cor pulmonale.

Further studied will be undertaken to determine the effects of other vasodilators such as hydralazine and nifedipine etc on disturbances in pulmonary circulation.

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