Pharmacological Strategies for Improving Diastolic Dysfunction in the Setting of Chronic Pulmonary Hypertension

Edward P. Chen, MD; Damian M. Craig, MS; Hartmuth B. Bittner, MD, PhD; R. Duane Davis, MD; Peter Van Trigt, MD

Background—Right ventricular (RV) hypertrophy is an adaptive process that occurs in the setting of chronic pulmonary hypertension (CPH) and can lead to alterations in normal RV diastolic properties. This study was designed to investigate the effects of NO and milrinone on RV diastolic dysfunction in the setting of CPH and RV hypertrophy by use of a canine model of monocrotaline pyrrole (MCTP)-induced CPH.

Methods and Results—Sixteen mongrel dogs (22 to 24 kg) were used. Animals underwent percutaneous pulmonary artery (PA) catheterization to measure pulmonary hemodynamics before and 8 weeks after injection of 3 mg/kg MCTP (n=8) or placebo (control, n=8). Eight weeks after injection, all hearts were instrumented with a PA flow probe, sonomicrometric dimension transducers, and micromanometers. Data were collected at baseline and after both NO and milrinone administration. Diastolic properties were quantified by use of the end-diastolic pressure-volume relationship and the time constant of ventricular isovolumic relaxation. Eight weeks after injection, significant increases in the PA pressure and pulmonary vascular resistance were observed in MCTP dogs. Significant worsening of RV diastolic function occurred in association with significant increases in the ratio of RV dry weight to LV+septal dry weight. NO and milrinone administration both led to significant improvements in RV diastolic properties.

Conclusions—In the setting of MCTP-induced CPH, significant worsening of RV diastolic function was observed in association with significant increases in the ratio of RV dry weight to LV+septal dry weight, suggesting that these changes are partially due to RV hypertrophy. The significant improvement in RV diastolic properties after both NO and milrinone administration suggests that these agents may be effective forms of pharmacological therapy for improving RV diastolic dysfunction in the setting of CPH. (Circulation. 1998;97:1606-1612.)

Key Words: hypertension, pulmonary • diastole • ventricles • hypertrophy
Hemodynamic parameters were permitted to stabilize for 10 minutes across the base-apex major-axis and anteroposterior minor-axis for continuous recording of intracavitary pressures.

Experimental animals (MCTP, n=8, 22 to 24 kg) received an injection of 3 mg/kg MCTP dissolved in N,N-dimethyl formamide at a concentration of 40 mg/mL, and control animals (n=8, 22 to 24 kg) received dimethyl formamide as placebo. Consequently, the volume of injectate was dependent on the individual weight of each animal and varied from 1.65 to 1.8 mL. MCTP was synthesized by a previously well-established method.11

**Instrumentation and Surgery**

Eight weeks after MCTP injection, a standard median sternotomy and an anterior pericardiotomy were performed to expose the hearts of all animals. An ultrasonic flow probe (T208X, Transonic Systems Inc) was placed around the main pulmonary trunk to measure pulmonary blood flow. Micromanometers (MPC-500, Millar Instruments Inc) were placed into the RV and LV, right and left atrium, and pulmonary artery for continuous recording of intracavity pressures. An ultrasonic flow probe (T208X, Transonic Systems Inc) was placed into the RV and LV, right and left atrium, and pulmonary artery for continuous recording of intracavity pressures.

**Experimental Protocol During Pharmacological Studies**

Eight weeks after MCTP injection, baseline functional and hemodynamic data were collected in every animal in the control and MCTP groups after the instrumentation procedure. Control animals did not receive any pharmacological treatment or undergo any further data collection. In MCTP animals, inhaled NO (NO, 777 ppm and NO1, 400 ppm) and inhalation of NO (0 ppm) were repeated every 1.5 to 3 hours in each MCTP animal. After each incremental change in the NO concentration, the animal's condition and hemodynamic parameters were allowed to equilibrate for 10 minutes before any further data collection. After data were obtained at the dose of 80 ppm, NO was stopped, and the time constant of isovolumic pressure decay (τ) was then calculated from the following monoexponential model: P = P0 e^(-t/τ), where P is ventricular pressure relative to the change in volume and represents an index of ventricular chamber stiffness, whereas A is a proportionality constant.

A parameter of myocardial stiffness was quantified according to the following equation: myocardial stiffness = αV′, where α is chamber stiffness and V′ is ventricular wall mass.14

To assess ventricular isovolumic pressure decay, the period of isovolumic relaxation was defined from the nadir of the ventricular pressure derivative (dP/dtmin) to the point at which ventricular pressure decreased to the level of atrial pressure.15 The time constant of isovolumic pressure decay (τ) was then calculated from the following monoexponential function: P(t) = Pp + (Pv - Pp) e^(-t/τ), where Pp is the initial pressure above Pp during isovolumic relaxation, t is time, Pp is the asymptote to which pressure decays, and τ is the time required for pressure at any point on the isovolumic curve to fall to 1/e of its original value.13 RV/LV model parameters were estimated by nonlinear least-squares regression.

**Assessment of Biventricular Systolic Function**

RV and LV systolic function were assessed by load-insensitive means. The highly linear relationship between stroke work and end-diastolic chamber volume was calculated from data acquired during vena cava occlusion by use of least-squares linear regression. The slope of these linear regressions is known as the PRSW and represents a left-independent index of systolic function and myocardial contractility.15

**Experimental Approval and Animal Rights**

The experimental setup and procedures conformed to the guidelines established by the American Physiological Society and the National Institutes of Health (Guide for the Care and Use of Laboratory Animals, National Institutes of Health publication 86–23, revised 1985). The experiments described in this report were approved by the Duke University Institutional Animal Care and Use Committee (DUIACUC Assigned Registry A621-95-9R1).
TABLE 2. Hemodynamic Measurements Before and 8 Weeks After MCTP or Placebo Injection

<table>
<thead>
<tr>
<th></th>
<th>HR, bpm</th>
<th>RAP, mm Hg</th>
<th>sRVP, mm Hg</th>
<th>dRVP, mm Hg</th>
<th>mPAP, mm Hg</th>
<th>PCWP, mm Hg</th>
<th>CO, mL/min</th>
<th>PVR, dyne s cm⁻²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control (n=8)</td>
<td>91 (5)</td>
<td>3.4 (0.4)</td>
<td>24.9 (0.7)</td>
<td>0.6 (0.2)</td>
<td>10.1 (0.6)</td>
<td>3.6 (0.3)</td>
<td>1278 (64)</td>
<td>407 (54)</td>
</tr>
<tr>
<td>MCTP (n=8)</td>
<td>85 (5)</td>
<td>3.1 (0.3)</td>
<td>25.0 (1.3)</td>
<td>0.8 (0.2)</td>
<td>9.7 (0.6)</td>
<td>4.1 (0.4)</td>
<td>1197 (73)</td>
<td>379 (65)</td>
</tr>
<tr>
<td>8 weeks after injection</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control (n=8)</td>
<td>94 (5)</td>
<td>3.4 (0.4)</td>
<td>24.0 (0.4)</td>
<td>0.8 (0.2)</td>
<td>10.0 (0.5)</td>
<td>3.7 (0.3)</td>
<td>1344 (76)</td>
<td>421 (37)</td>
</tr>
<tr>
<td>MCTP (n=8)</td>
<td>89 (4)</td>
<td>5.6† (0.3)</td>
<td>33.3† (1.5)</td>
<td>4.1† (0.3)</td>
<td>20.2† (1.0)</td>
<td>5.7† (0.8)</td>
<td>1256 (69)</td>
<td>988† (72)</td>
</tr>
</tbody>
</table>

HR indicates heart rate; RAP, right atrial pressure; sRVP, right ventricular systolic pressure; dRVP, right ventricular end-diastolic pressure; mPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; CO, cardiac output; and PVR, pulmonary vascular resistance. Values are mean±SEM (in parentheses).

*P<.0001 vs control.
†P<.01 vs control.

Statistical Analysis
Statistical analysis was performed with commercially available software (SigmaStat Version 2.0, Jandel Corp). Hemodynamic data obtained before and after injection of MCTP within the MCTP group were analyzed with standard two-tailed paired Student's t tests. Unpaired Student's t tests were used to compare all data between MCTP and control.

To test for significant changes in the parameters of diastolic function as well as systolic function after NO inhalation within the MCTP group, a one-way ANOVA for repeated measurements was used. Follow-up comparison of each index of ventricular diastolic properties at the individual levels of NO were done with paired Student's t tests. Comparison of changes in RV diastolic function occurring after milrinone infusion was performed in a similar fashion. The results are expressed as mean±SEM. A difference was considered statistically significant at P<.05.

Results
There was no significant difference in the baseline pulmonary hemodynamic indices between control and MCTP dogs; however, 8 weeks after MCTP injection, significant differences in these same indices were observed between the two groups (Table 1).

Diastolic Properties in MCTP-Induced CPH
The exponential EDP-EDV model accurately represented (r²>0.92) all pressure and volume data during transient vena cava occlusion in both groups. No significant differences in LV A were observed between control (.021±.005) and MCTP (.024±.005). There was, however, a significant increase in the RV A of MCTP (.070±.006, P<.05) compared with control (.046±.008). RV AV was significantly greater in MCTP (.724±.066) than in control (.383±.068, P<.005), while no significant difference was observed in LV AV between the two groups (.560±.108 versus .495±.105).

The monoexponential model of isovolumic pressure decay accurately predicted (r²>0.993) the fall of ventricular pressure during isovolumic relaxation for the RV and LV. There was no significant difference in LV τ (41±3 versus 42±3 ms) between the two experimental groups. RV τ was significantly longer, however, in MCTP (84±15 ms, P<.05) than in control (35±3 ms).

Systolic Function in MCTP-Induced CPH
Highly linear relationships (r²>0.95) were obtained between calculated RV and LV EDV and stroke work during vena caval occlusion in both control and MCTP 8 weeks after MCTP injection. There was no significant difference in LV PRSW between MCTP (94.65±6.26X10³ erg/mL) and control (87.98±7.23X10³ erg/mL). However, significant increases in RV PRSW were observed in MCTP (46.90±3.16X10³ erg/mL, P<.0005) compared with the control values (24.56±3.12X10³ erg/mL).

Effect of NO on Diastolic Properties and Systolic Function
NO led to significant improvements in pulmonary hemodynamic indices (Table 2). In addition, significant decreases occurred in RV A as well as RV AV, whereas no significant improvements in these same parameters were observed in the LV (Table 3). RV and LV τ were significantly shorter after NO inhalation; however, RV/LV PRSW was not significantly different (Table 3). Although NO did not lead to significant changes in the LV A of MCTP dogs, a substantial downward shift was observed in the LV EDP-EDV relationship of these animals (Fig 1). The changes occurring in the EDP-EDV relationship as a result of NO inhalation for both the LV and RV are illustrated in Figs 1 and 2, respectively.

TABLE 2. Effects of NO on Hemodynamic Measurements in MCTP-Induced Pulmonary Hypertension

<table>
<thead>
<tr>
<th>NO, ppm</th>
<th>RAP, mm Hg</th>
<th>sRVP, mm Hg</th>
<th>dRVP, mm Hg</th>
<th>mPAP, mm Hg</th>
<th>PCWP, mm Hg</th>
<th>CO, mL/min</th>
<th>PVR, dyne s cm⁻²</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5.6 (0.3)</td>
<td>33.3 (1.5)</td>
<td>4.1 (0.3)</td>
<td>20.2 (1.0)</td>
<td>5.7 (0.8)</td>
<td>1256 (69)</td>
<td>988 (72)</td>
</tr>
<tr>
<td>40</td>
<td>4.6† (0.2)</td>
<td>29.3* (2.2)</td>
<td>3.4 (0.4)</td>
<td>15.9† (0.9)</td>
<td>7.0 (0.4)</td>
<td>1465* (130)</td>
<td>551† (83)</td>
</tr>
<tr>
<td>80</td>
<td>4.5† (0.2)</td>
<td>31.1* (1.5)</td>
<td>3.5 (0.4)</td>
<td>15.7† (0.8)</td>
<td>7.5* (0.4)</td>
<td>1481* (102)</td>
<td>515† (60)</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1. Values are mean±SEM (in parentheses).

*P<.05 vs 0 ppm NO.
†P<.01 vs 0 ppm NO.
TABLE 3. Effects of NO on Biventricular Diastolic Properties and Systolic Function

<table>
<thead>
<tr>
<th></th>
<th>RV $\alpha$</th>
<th>LV $\alpha$</th>
<th>RV $\alpha V_w$</th>
<th>LV $\alpha V_w$</th>
<th>RV $\tau$ ms</th>
<th>LV $\tau$ ms</th>
<th>RV PRSW, erg×10⁶/mL</th>
<th>LV PRSW, erg×10⁶/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 ppm NO</td>
<td>0.070 (0.006)</td>
<td>0.024 (0.005)</td>
<td>0.724 (0.066)</td>
<td>0.560 (0.108)</td>
<td>84 (15)</td>
<td>41 (3)</td>
<td>46.9 (3.2)</td>
<td>94.7 (6.3)</td>
</tr>
<tr>
<td>40 ppm NO</td>
<td>0.039* (0.008)</td>
<td>0.019 (0.004)</td>
<td>0.406* (0.086)</td>
<td>0.454 (0.093)</td>
<td>47 (5)</td>
<td>35* (1)</td>
<td>45.8 (2.4)</td>
<td>99.0 (7.0)</td>
</tr>
<tr>
<td>80 ppm NO</td>
<td>0.035† (0.005)</td>
<td>0.020 (0.004)</td>
<td>0.365† (0.052)</td>
<td>0.459 (0.096)</td>
<td>44* (5)</td>
<td>34* (2)</td>
<td>45.7 (2.3)</td>
<td>106.6 (6.0)</td>
</tr>
</tbody>
</table>

$\alpha$ indicates chamber stiffness; $\alpha V_w$ myocardial stiffness; and $\tau$, time constant of isovolumic relaxation. Values are mean±SEM (in parentheses).

*P<.05 vs 0 ppm NO.
†P<.005 vs 0 ppm NO.

**Effect of Milrinone on Diastolic Properties and Systolic Function**

Milrinone infusion caused significant decreases in the pulmonary vascular resistance, which were associated with significant improvements in pulmonary blood flow (Table 4). Although there were decreases in the mean pulmonary artery pressure at 0.5 and 1.0 $\mu$g·kg⁻¹·min⁻¹, these differences were not statistically significant.

Milrinone infusion also led to significant improvements in RV $\alpha$, RV $\alpha V_w$, RV/LV $\tau$, and RV/LV PRSW (Table 5). There was no significant change in LV $\alpha$ after milrinone infusion; however, as with NO, a substantial downshifting of the EDP-EDV relationship was also noted (Fig 3). The changes occurring in the EDP-EDV relationship after milrinone infusion for both the LV and RV are illustrated in Figs 3 and 4, respectively.

**Tissue Analysis in the Setting of MCTP-Induced CPH**

There was a significant increase in the RV dry weight of MCTP dogs (10.29±0.55 g, $P<.05$) compared with control animals (8.40±0.51 g). Both the ratio of RV dry weight to LV+septal dry weight (0.45±0.02 versus 0.37±0.01, $P<.05$) and the ratio of RV dry weight to body weight (0.43±0.02 versus 0.36±0.02 g RV/kg body wt, $P<.05$) were also significantly elevated in MCTP animals compared with the control group. No significant differences were observed in the LV dry weights (23.3±1.4 versus 23.3±1.3 g) or in the RV (79.6±0.4% versus 78.6±0.4%) and LV (79.0±0.4% versus 78.4±0.3%) water contents between the two experimental groups.

**Discussion**

CHF represents an important clinical sequela that commonly occurs as a result of chronic obstructive pulmonary disease. It is also associated with a number of other pathological processes, including long-standing congestive heart failure, mitral valve disease, congenital heart defects, and chronic pulmonary emboli; alternatively, CPH may exist as a primary process. This state of chronically elevated pulmonary vascular pressures can lead to adaptive mechanisms in the RV and eventually result in altered systolic and diastolic mechanics.

Myocardial hypertrophy is a compensatory process of the heart that can develop in the setting of a sustained pressure overload, such as CHF, and is perhaps one of the most important causes of diastolic dysfunction.11 Hypertrophied myocardium is particularly susceptible to diastolic dysfunction as a result of structural changes (increased LV mass) and impaired ventricular relaxation.16 In a previous investigation, a significant correlation was noted between myocardial hypertrophy and diastolic dysfunction, which later improved after regression of the hypertrophy.17

Approximately 10 years ago, NO was identified as an important endogenous biological mediator of vascular tone.18,19 Since that initial discovery, clinical1 and experimental4 investigations have shown that NO is a selective pulmonary vasodilator without significant effect on the systemic circulation. Recent reports have also suggested that NO is an important regulator of cardiac diastolic function.56

Milrinone is a phosphodiesterase inhibitor that possesses positive inotropic, selective pulmonary vasodilator, and positive lusitropic effects.8 In a canine model of embolism-induced pulmonary hypertension using autologous muscle, milrinone increased cardiac index while improving mean pulmonary artery pressure and pulmonary vascular resistance.57 Clinically, in the setting of congestive heart failure, significant improvements have been observed in the indexes of LV diastolic performance as well as overall global im-

![Figure 1](chart1.png)  
**Figure 1.** Effects of NO on the LV EDP-EDV relationship, as plotted from average values of chamber stiffness, in setting of MCTP-induced CPH. There were no significant changes in LV chamber stiffness after NO inhalation at either 40 or 80 ppm compared with 0 ppm, although a substantial downward shift was observed in this relationship.

![Figure 2](chart2.png)  
**Figure 2.** Effects of NO on the RV EDP-EDV relationship, as plotted from average values of chamber stiffness, in setting of MCTP-induced CPH. Significant improvements in RV chamber stiffness were observed after NO inhalation at both 40 and 80 ppm compared with 0 ppm. There was no further significant decrease in RV chamber stiffness at 80 vs 40 ppm. $P<.05$ vs 0 ppm.
TABLE 5. Effects of Milrinone on Biventricular Diastolic Properties and Systolic Function

<table>
<thead>
<tr>
<th>Milrinone, ( \mu g \cdot kg^{-1} \cdot min^{-1} )</th>
<th>( RV \alpha )</th>
<th>( LV \alpha )</th>
<th>( RV \alpha V_m )</th>
<th>( LV \alpha V_m )</th>
<th>( RV \tau, ) ms</th>
<th>( LV \tau, ) ms</th>
<th>( RV ) PRSW, erg x 10³/mL</th>
<th>( LV ) PRSW, erg x 10³/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.070 (0.006)</td>
<td>0.024 (0.005)</td>
<td>0.724 (0.066)</td>
<td>0.560 (0.108)</td>
<td>84 (15)</td>
<td>41 (3)</td>
<td>46.9 (3.2)</td>
<td>94.7 (6.3)</td>
</tr>
<tr>
<td>0.5</td>
<td>0.045 (0.007)</td>
<td>0.024 (0.005)</td>
<td>0.463 (0.069)</td>
<td>0.573 (0.120)</td>
<td>32* (6)</td>
<td>23† (2)</td>
<td>54.7 (4.1)</td>
<td>114.5† (5.8)</td>
</tr>
<tr>
<td>1.0</td>
<td>0.033† (0.004)</td>
<td>0.019 (0.004)</td>
<td>0.342† (0.041)</td>
<td>0.443 (0.095)</td>
<td>36* (5)</td>
<td>23† (2)</td>
<td>63.6* (6.5)</td>
<td>134.3* (9.5)</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 3. Values are mean±SEM (in parentheses).
*P<.05 vs 0 \( \mu g \cdot kg^{-1} \cdot min^{-1} \) milrinone.
†P<.005 vs 0 \( \mu g \cdot kg^{-1} \cdot min^{-1} \) milrinone.

Pharmacological Strategies for Diastolic Dysfunction

TABLE 4. Effects of Milrinone on Hemodynamic Measurements in MCTP-Induced Pulmonary Hypertension

<table>
<thead>
<tr>
<th>Milrinone, ( \mu g \cdot kg^{-1} \cdot min^{-1} )</th>
<th>RAP, mm Hg</th>
<th>aRVP, mm Hg</th>
<th>dRVP, mm Hg</th>
<th>mPAP, mm Hg</th>
<th>PCWP, mm Hg</th>
<th>CO, mL/min</th>
<th>PVR, dynes x s x cm⁻²</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5.6 (0.3)</td>
<td>33.3 (1.5)</td>
<td>4.1 (0.3)</td>
<td>20.2 (1.0)</td>
<td>5.7 (0.8)</td>
<td>1256 (69)</td>
<td>988 (72)</td>
</tr>
<tr>
<td>0.5</td>
<td>5.0 (0.2)</td>
<td>36.4 (2.6)</td>
<td>3.8 (0.3)</td>
<td>18.2 (1.3)</td>
<td>7.1 (0.4)</td>
<td>1549* (72)</td>
<td>560* (95)</td>
</tr>
<tr>
<td>1.0</td>
<td>5.5 (0.3)</td>
<td>39.8† (2.8)</td>
<td>3.8 (0.3)</td>
<td>18.7 (1.9)</td>
<td>8.0* (0.5)</td>
<td>1631† (42)</td>
<td>555* (73)</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1. Values are mean±SEM (in parentheses).
*P<.05 vs 0 \( \mu g \cdot kg^{-1} \cdot min^{-1} \) milrinone.
†P<.01 vs 0 \( \mu g \cdot kg^{-1} \cdot min^{-1} \) milrinone.

Thus, NO and milrinone may both be potentially useful pharmacological strategies for improving altered RV diastolic properties in the setting of CPH. However, experience with these two agents in treating RV diastolic dysfunction is currently limited. Experimental investigation of this problem has not previously been possible because of lack of an appropriate large-animal model of CPH.

In this investigation, the effects of NO and milrinone on RV diastolic and systolic mechanics were assessed in a recently established canine model of MCTP-induced CPH. MCTP-induced CPH is characterized by a proliferative vasculitis. Pulmonary vascular injury, after the initial injection, affects the medium and small pulmonary arterioles. Subsequent vascular remodeling leads to endothelial degeneration and hyperplasia, smooth muscle hypertrophy and medial thickening, and perivascular connective tissue proliferation. The development of these microscopic changes along with the ensuing rise in pulmonary vascular pressures is gradual. In addition, the characteristic parenchymal features of this model are often observed in the pulmonary vasculature of patients with pulmonary hypertension of differing etiologies, including end-stage cardiac disease as well as a subtype of primary pulmonary hypertension known as plexogenic pulmonary arteriopathy.

MCTP-induced CPH has a significant impact on RV diastolic properties and an insignificant effect on LV diastolic function. RV \( \alpha \) and RV \( \alpha V_m \) were significantly elevated in animals with MCTP-induced CPH, whereas no significant differences were observed in LV \( \alpha \) or \( \alpha V_m \). The significant increase in RV \( \alpha \) should be interpreted with caution, because it may have been due to collagen recruitment. It is unlikely, however, that these changes were the result of MCTP-induced myocardial damage, because previous morphological analysis using light and electron microscopy suggests that monocrotaline itself has no direct toxic effect on myocardial tissue.

Ventricular chamber stiffness, as estimated by the EDP-EDV relationship, represents a useful means for quantifying diastolic function in an intact heart. Pressure-volume relationships provide important information regarding diastolic function and have been applied in clinical and experimental investigations. Another technique that is often used for assessing diastolic properties involves assessment of myocardial diastolic stiffness, as defined by use of stress-strain relations, remained relatively unchanged despite dramatic shifts in the passive pressure-volume relations. Measurement of pressure-volume relations may therefore be a more sensitive means to assess myocardial diastolic properties than estimation of stress-strain relations.

\( \tau \) represents another useful index frequently used for assessing diastolic properties that has been shown to be independent of any changes in loading conditions and is relatively insensitive to heart rate. \( \tau \) was significantly longer in the setting of MCTP-induced CPH. However, no significant differences were observed in LV \( \tau \) between the two experimental groups.

Tissue dry weight analysis revealed that the RV was significantly hypertrophied, whereas no significant change in LV muscle mass occurred. There were significant elevations in the ratio of RV dry weight to LV+ septal dry weight as well as the ratio of RV dry weight to body weight in MCTP animals compared with control animals, indicating that a significant degree of RV hypertrophy had occurred. These findings suggest that the alterations in RV diastolic and systolic properties observed in this model are at least partially...
due to hypertrophy. The significant augmentation of RV systolic function associated with the significant worsening of RV diastolic properties may provide insights into the mechanisms of myocardial dysfunction in the setting of CPH.

NO-mediated improvement of ventricular diastolic properties can occur indirectly through easing of RV loading conditions or via direct myocardial relaxation. It has previously been shown that endogenous NO released from coronary endothelial cells plays an important role in the modulation of myocardial relaxation activity. In other investigations using sodium nitroprusside as an exogenous donor, NO was shown to exert a direct myocardial relaxant effect in isolated ejecting hearts, independent of any changes in cardiac loading, as well as in isolated papillary muscles. Similar results were observed in the clinical setting of Paulus and associates, where significantly improved LV diastolic properties were observed after global intracoronary infusion of sodium nitroprusside.

In this report, however, the beneficial effects of NO appear to be related to its well-established vasodilator activity. By improving pulmonary hemodynamic indices, NO led to a significant easing of RV loading conditions, which were observed in association with significant decreases in RV diastolic properties and LV σ. Although the use of sodium nitroprusside as an exogenous NO donor might be equally effective in decreasing RV σ and RV τ in this model, such conclusions are not possible on the basis of the data presented in this study. Future studies should examine whether sodium nitroprusside would be as effective as inhaled NO for improving RV diastolic properties in MCTP-induced CPH.

Although the lusitropic effects of milrinone have been clearly demonstrated in this study in association with significant improvements in pulmonary blood flow, the vasodilatory properties of this agent can potentially play a key role in its total effects and may partially account for the observed improvements in RV σ, RV τ, and overall hemodynamic status in this model. In a previous report by Monrad and associates, the relative ratio of the lusitropic and vasodilator actions of milrinone was examined in patients with advanced congestive heart failure. In that investigation, significant improvement of LV diastolic function was observed in association with relatively small decreases in mean arterial pressure, suggesting that the influence of milrinone on cardiac relaxation at the level of the individual myocyte plays a more fundamental role in its overall effects than its vasodilator actions. In the present report, significant improvements in RV diastolic properties as well as LV σ occurred in association with slight decreases in mean pulmonary artery pressure after milrinone infusion, which would appear to be consistent with the findings of Monrad and associates. Further investigation should attempt to elucidate the relative contributions of the lusitropic and vasodilatory effects of milrinone in MCTP-induced CPH.

Evaluation of diastolic function with in vivo models necessitates careful measurement of the dynamic changes occurring in ventricular pressure and volume within an intact heart. With respect to EDP, use of transmural pressures is required for an accurate assessment of diastolic properties. Estimates of α from EDP-EDV relationships, however, generally ignore any possible restrictive effect of the pericardium and assume that no external forces are imposed on the heart when intraventricular pressure is elevated. When the pericardium is left intact, the possibility exists that pericardial pressures might exceed zero and violate these assumptions. Previous investigations have demonstrated that in the setting of pressure or volume overload, an intact pericardium contributes significantly to increases in EDP and may affect the EDP-EDV relationship independently of changes in ventricular diastolic properties. Admittedly, use of an open-chest, open-pericardium model could potentially introduce a degree of experimental artifact and might be considered a study limitation. It should be noted, however, that this type of experimental preparation allows one to obtain true transmural pressures, which, as previously discussed, are requisite for accurate assessment of ventricular diastolic properties.

It is acknowledged that the absolute level of pulmonary hypertension occurring after MCTP injection may not accurately reflect the degree of CPH observed clinically. Consequently, the amount of hypertrophy induced in this model was much less than what one would expect in the clinical setting. It is important to point out, however, that the baseline pulmonary vascular pressures observed in the dogs before drug injection were significantly lower than normal levels found in human beings and that a twofold increase in pulmonary hemodynamic indices was achieved. Even at this level of pulmonary hypertension, significant alterations in RV diastolic properties were observed, which improved significantly after pharmacological therapy. A potential way to achieve a higher degree of pulmonary hypertension would be...
to perform multiple injections of MCTP at regular intervals to theoretically cause repeated injury to the pulmonary vascular bed and produce greater scarring of the pulmonary circulation. Higher pulmonary hemodynamic indices might, in turn, lead to more severe hypertrophy. When such a model of CPH is used for basic investigation, however, it is reasonable to state that the resultant pulmonary hypertension should not be so severe that clinical right-sided heart failure would ensue and result in a highly unstable situation.

In summary, a canine model of MCTP-induced CPH provides a useful means to evaluate various pharmacological strategies for improving RV diastolic dysfunction in the setting of CPH. There was a significant worsening of RV diastolic properties, which was significantly improved after NO and milrinone administration. These data suggest that NO and milrinone may both be effective pharmacological strategies in the treatment of diastolic dysfunction in the setting of CPH.

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References


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