NO and prostaglandin interactions during hemodynamic stress in the fetal ovine pulmonary circulation

JEANNE P. ZENGE,1 ROBYN L. RAIRIGH,1 THERESA R. GROVER,1 LAURENT STORME,2 THOMAS A. PARKER,1 JOHN P. KINSELLA,1 AND STEVEN H. ABMAN1
1Sections of Neonatology and Pulmonary Medicine, Pediatric Heart Lung Center, Department of Pediatrics, University of Colorado School of Medicine, Denver, Colorado 80262; and 2Department of Neonatology, Centre Hospitalier Regional Universitaire de Lille, Lille Cedex 59037, France

Received 14 February 2001; accepted in final form 29 May 2001

Zenge, Jeanne P., Robyn L. Rairigh, Theresa R. Grover, Laurent Storme, Thomas A. Parker, John P. Kinsella, and Steven H. Abman. NO and prostaglandin interactions during hemodynamic stress in the fetal ovine pulmonary circulation. Am J Physiol Lung Cell Mol Physiol 281: L1157–L1163, 2001.—Nitric oxide (NO) and prostacyclin (PGI2) are potent fetal pulmonary vasodilators, but their relative roles and interactions in the regulation of the perinatal pulmonary circulation are poorly understood. We compared the separate and combined effects of nitric oxide synthase (NOS) and cyclooxygenase (COX) inhibition during acute hemodynamic stress caused by brief mechanical compression of the ductus arteriosus (DA) in chronically prepared fetal lambs. Nitro-L-arginine (L-NNA; NOS antagonist), meclofenamate (Mec; COX inhibitor), combined drugs (L-NNA-Mec), or saline (control) was infused into the left pulmonary artery (LPA) before DA compression. In controls, DA compression decreased pulmonary vascular resistance (PVR) by 43% (P < 0.01). L-NNA, but not Mec, treatment completely blocked vasodilation and caused a paradoxical increase in PVR (+31%; P < 0.05). The effects of L-NNA-Mec and L-NNA on PVR were similar. To determine if the vasodilator effect of PGI2 is partly mediated by NO release, we studied PGI2-induced vasodilation before and after NOS inhibition. L-NNA treatment blocked the PGI2-induced rise in LPA blood flow by 73% (P < 0.001). We conclude that NO has a greater role than PGI2 in fetal pulmonary vasoregulation during acute hemodynamic stress and that PGI2-induced pulmonary vasodilation is largely mediated by NO release in the fetal lung.

Address for reprint requests and other correspondence and present address of J. P. Zenge: 1056 E. 19th Ave., B070, Denver, CO 80262 (E-mail: parkzenge@qwest.net).

PULMONARY VASCULAR RESISTANCE (PVR) decreases dramatically during the normal transition from the fetal to neonatal circulation at birth. During this transition, several physiological stimuli, including drainage of fetal lung fluid, rhythmic distension of the lung, and increased oxygen, contribute to the fall in PVR (3, 12, 18, 19, 22). Past studies have shown that these stimuli act in part by the release of nitric oxide (NO) and vasodilator prostaglandins (PGs) (3, 18, 20). Although nitric oxide synthase (NOS) inhibition blocks vasodila-

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
vascular tone. To further evaluate the interactions between NO and PGs, particularly PGI₂, we examined whether PGI₂-induced pulmonary vasodilation is partly mediated by NO.

**METHODS**

**Animal Preparation**

The Animal Care Committee at the University of Colorado Health Sciences Center reviewed and approved all procedures and protocols used in these studies. Pregnant Columbia-Rambouillet ewes between 125 and 130 days gestation (147 days = term) were fasted for at least 24–48 h before surgery. Each animal was sedated with pentobarbital sodium (2–4 g for total dose) and anesthetized with a lumbar injection of 1% tetracaine hydrochloride (3 mg). Animals received prophylactic antibiotics (penicillin and gentamicin) before surgery. During anesthesia, the ewes breathed spontaneously. A hysterotomy was performed using the sterile technique, and the fetal left forelimb was externalized. After local anesthesia, the amniotic cavity was opened with cotton-tip swabs. A final catheter was placed in the amniotic cavity before closure of the hysterotomy and the amnion was sutured. A hysterotomy was performed using the sterile technique, and the fetal left forelimb was externalized. After local anesthesia, the amniotic cavity was opened with cotton-tip swabs. A final catheter was placed in the amniotic cavity before closure of the hysterotomy and the amnion was sutured.

**Physiological Measurements**

The flow transducer cable was connected to an internally calibrated flowmeter (Transonic Systems, Ithaca, NY) as previously described (3). An ultrasonic flow transducer (Transonic Systems) placed around the LPA was used to measure blood flow to the left lung. To maintain patency of the left pulmonary artery (MPA), and left atrium were cannulated by direct puncture through purse-string sutures placed loosely around the MPA as previously described (25). An inflatable vascular occluder (In Vivo Metric, Healdsburg, CA) was placed loosely around the DA after gentle dissection with cotton-tip swabs. A final catheter was placed in the amniotic cavity to measure pressure. The fetus' left forelimb was gently placed back in the uterus. Amoxicillin (500 mg) was infused into the amniotic cavity before closure of the hysterotomy. The flow transducer cable, catheters, and occluder tubing were exteriorized through a subcutaneous tunnel to an external pouch on the maternal flank. Animals were allowed 48 h of recovery from surgery before any studies were performed. Amoxicillin (500 mg) was infused into the MPA and amniotic catheters for 2 days postoperatively. Food and water were given ad libitum. Catheters were kept patent with daily infusions of heparinized saline (2–3 ml).

**Drug Preparation**

Fresh solutions of nitro-l-arginine hydrochloride (l-NNA; Sigma Chemical, St. Louis, MO) were made immediately before each study. l-NNA (30 mg) was dissolved with HCl and diluted with 1 ml of normal saline. NaOH was used to correct the solution to physiological pH (~7.40). Meclomenamate (Mec; Sigma Chemical) was prepared by dissolving 60 mg in 20 ml of normal saline. Before each study, a fresh sample of a 1:10 dilution with normal saline was prepared. PGI₂ (1 mg) was dissolved in 1 ml of 100% ethanol and was diluted with 1 ml of normal saline. 8-Bromo-cGMP (8-BrcGMP) and 8-bromo-cAMP (8-BrcAMP; 0.5, 1.5, or 3 mg; Sigma) were dissolved in 1 ml of normal saline under light-sensitive conditions. Study drugs were infused at a rate of 0.1 ml/min into the LPA. The dose of l-NNA was chosen from extensive published studies that have demonstrated effective blockade of NOS activity (9, 30). The dose of Mec was chosen from previously published studies from our laboratory (1) and others (31, 33).

We studied the hemodynamic response to acute DA compression after treatment with different doses of Mec (3, 30, and 60 μg/min). Compared with the 3 μg/min dose, we found a greater reduction in pulmonary blood flow during DA compression with the 30 and 60 μg/min doses. However, there was no difference observed between these two doses. Thus the minimum Mec dose used in this study was 30 μg/min (see below).

**Experimental Design**

The following four main experimental protocols are included in this study: 1) the separate and combined pulmonary vascular effects of NOS and COX inhibition during acute compression of the DA; 2) the separate and combined pulmonary vascular effects of NOS and COX inhibition during rapid incremental increases in PAP; 3) the effects of exogenous 8-BrcGMP and 8-BrcAMP on fetal pulmonary vasodilation; and 4) the effects of NOS inhibition on PGI₂-induced pulmonary vasodilation.

**Protocol 1: Separate and combined pulmonary vascular effects of NOS and COX inhibition during acute compression of the DA.** To study the separate and combined effects of NOS and COX inhibition on the hemodynamic response to DA compression, we partially inflated the DA occluder after treatment with l-NNA, Mec, or both agents. Control studies (n = 7) were performed using a normal saline infusion at 6 ml/h starting 10 min before occlusion until the occluder was deflated. l-NNA (30 mg over 10 min) was infused into the LPA 30 min before DA compression (n = 7). Mec (30 or 60 μg/min) was infused into the LPA starting 10 min before DA compression until the compression was released (n = 4). In another group, l-NNA and Mec were both infused into the LPA (n = 7). After stable hemodynamic measurements, the DA occluder was partially inflated for 30 min. The degree of DA compression was determined by targeting an increase in the mean PAP 35% above baseline values. Elevated mean PAP was maintained at a constant value throughout the compression period (Fig. 1). For each study, serial hemodynamic measurements were made at 10-min intervals throughout the baseline period (30 min), during drug infusion, and during DA compression. Arterial blood gas tensions were measured during baseline periods, as previously described (20). The following four main experimental protocols are included in this study: 1) the separate and combined pulmonary vascular effects of NOS and COX inhibition during acute compression of the DA; 2) the separate and combined pulmonary vascular effects of NOS and COX inhibition during rapid incremental increases in PAP; 3) the effects of exogenous 8-BrcGMP and 8-BrcAMP on fetal pulmonary vasodilation; and 4) the effects of NOS inhibition on PGI₂-induced pulmonary vasodilation.
compared the effects of exogenous 8-BrcGMP and 8-BrcAMP on fetal pulmonary blood flow. After 30 min of stable baseline hemodynamic measurements, 8-BrcAMP or 8-BrcGMP \((n = 4\) for each group; 0.5, 1.5, and 3 mg) was infused into the LPA at 10-min intervals serially. Hemodynamic measurements were recorded at 10-min intervals throughout the experiment. Arterial blood gas tensions and pH were measured at baseline and after the last drug infusion.

Protocol 4: Effects of NOS inhibition on PG\(_I\)_\(_2\)-induced fetal pulmonary vasodilation. To determine if PG\(_I\)_\(_2\)-induced vasodilation is partly mediated by NO release, we infused PG\(_I\)_\(_2\) before and after treatment with the NOS antagonist L-NNA. After 30 min of stable baseline measurements, PG\(_I\)_\(_2\) (400–500 \(\mu\)g; \(n = 4\)) was infused over 10 min into the LPA. A second dose of the study drug was repeated 30 min after the L-NNA infusion (30 mg over 10 min). To determine whether the effects of L-NNA were specifically the result of NOS inhibition, we compared the response to 8-BrcGMP \((n = 5\) ), an endothelium-independent vasodilator that acts downstream to NOS blockade. Hemodynamic measurements were recorded at 10-min intervals throughout the experiment. Arterial blood gas tensions and pH were measured at baseline and after the last drug infusion.

Data Analysis

Data are presented as means ± SE. Statistical analysis was performed with the Prism software package. A one-way ANOVA for repeated measures was used to compare between-group or between-time points. One-way ANOVA with the Newman-Keuls post hoc multiple comparison test was used for comparison between groups at different time points. \(P < 0.05\) was considered significant.

RESULTS

Protocol 1: Separate and Combined Effects of NOS and COX Inhibition on the Hemodynamic Response to Acute Compression of the DA

In control animals, DA occlusion increased LPA blood flow by 128% above baseline values during the 30-min compression period (Fig. 1). PVR decreased by 42% \((P < 0.05\) vs. baseline; Fig. 2). COX inhibition reduced the effects of DA compression seen in the control group by only 14% and attenuated the fall in PVR by 33%. The effects of COX inhibition were not different from those in control studies. After L-NNA treatment, the rise in LPA blood flow was blocked, and PVR increased by 31% \((P < 0.05\) ). After combined L-NNA-Mec infusions, LPA blood flow did not increase during DA compression. This response was not different from that observed after L-NNA infusion alone. Mean aortic pressure (AoP), HR, LAP, pH, and blood gas parameters did not change during the study period or between study groups (Tables 1 and 2).

Protocol 2: Separate and Combined Effects of NOS and COX Inhibition on PVR During Serial Increases in DA Compression (Myogenic Response)

In control and Mec-treated animals, LPA blood flow progressively increased with each incremental change in MPA pressure (Fig. 3A). After treatment with L-NNA or L-NNA-Mec, LPA blood flow did not change despite progressive increases in MPA pressure (Fig. 3B).
3A). In contrast to the fall of PVR in control and in Mec-treated animals, PVR actually increased with increasing MPA pressure after L-NNA and L-NNA-Mec treatment (Fig. 3). Arterial blood gas tensions and pH, mean AoP, HR, and LAP did not change from baseline values during brief DA occlusions.

Protocol 3: Effects of Exogenous 8-BrcGMP and 8-BrcAMP on Fetal Pulmonary Vasodilation

Infusion of 8-BrcGMP increased pulmonary blood flow by 188% (P < 0.01; Fig. 4) and decreased PVR by 65% (P < 0.01; Table 3). In contrast to the vasodilator effects of 8-BrcGMP, 8-BrcAMP (0.5–3 mg) did not increase pulmonary blood flow (Fig. 4) or PVR (Table 3). Arterial blood gas tensions, pH, and HR did not differ between either treatment group (Table 3).

Protocol 4: Hemodynamic Effects of PGI2 Before and After NOS Inhibition

In control animals, PGI2 infusion increased pulmonary blood flow by more than twofold (85 ± 30 to 183 ± 47; P < 0.001) without changes in MPA pressures. After recovery, a repeat infusion of PGI2 caused the same magnitude of vasodilation. PGI2-induced pulmonary vasodilation was attenuated by 74% after NOS inhibition (P < 0.01; Fig. 5A). In contrast, the pulmonary vasodilator response to 8-BrcGMP remained intact after L-NNA (Fig. 5B), demonstrating selectivity.

### Table 1. Serial measurements of arterial blood gas tensions and pH at baseline and after 30 min of DA compression in each study group

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Mec</th>
<th>l-NNA</th>
<th>l-NNA-Mec</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.38 ± 0.01</td>
<td>7.37 ± 0.02</td>
<td>7.36 ± 0.01</td>
<td>7.37 ± 0.01</td>
</tr>
<tr>
<td>PCO2, mmHg</td>
<td>46 ± 0.9</td>
<td>47 ± 1.0</td>
<td>48 ± 1.3</td>
<td>46 ± 2.2</td>
</tr>
<tr>
<td>Pao2, mmHg</td>
<td>19 ± 1.2</td>
<td>23 ± 1.2</td>
<td>21 ± 0.8</td>
<td>22 ± 0.5</td>
</tr>
</tbody>
</table>

Values are means ± SE. Mec, meclofenamate; l-NNA, nitro-l-arginine; Pao2, arterial Pao2; DA, ductus arteriosus.

### Table 2. Comparison of hemodynamic variables at baseline and after 30 min of DA compression between study groups

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Mec</th>
<th>l-NNA</th>
<th>l-NNA-Mec</th>
</tr>
</thead>
<tbody>
<tr>
<td>AoP, mmHg</td>
<td>42 ± 1.8</td>
<td>41 ± 1.3</td>
<td>40 ± 1.9</td>
<td>44 ± 1.2</td>
</tr>
<tr>
<td>LAP, mmHg</td>
<td>2.9 ± 0.3</td>
<td>2.3 ± 0.5</td>
<td>3.1 ± 0.9</td>
<td>2.7 ± 0.6</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>173 ± 7.0</td>
<td>140 ± 6.0</td>
<td>162 ± 9.0</td>
<td>175 ± 14.0</td>
</tr>
</tbody>
</table>

Values are means ± SE. AoP, aortic pressure; LAP, left arterial pressure; HR, heart rate. *P < 0.001 vs. baseline.
for NOS inhibition. Arterial blood gas tensions, pH, and HR did not change throughout the different treatments, whereas PAP and AoP did increase after L-NNA infusion (Table 4).

**DISCUSSION**

Although NO and vasodilator PGs modulate the pulmonary vascular tone in the developing lung, their relative roles in vasoregulation and potential interactions have not been studied. Therefore, we performed a series of experiments to investigate the separate and combined effects of NOS and COX inhibition on pulmonary vasoreactivity during brief DA compression in the chronically prepared fetal lamb. We report that NOS inhibition completely blocked the rise in pulmonary blood flow during DA occlusion and caused a paradoxical increase in PVR. In contrast, COX inhibition did not attenuate the rise in pulmonary blood flow and fall in PVR during acute DA compression. The combination of NOS and COX inhibition did not cause a further increase in PVR during DA compression from that achieved during NOS blockade alone. In addition, we found that NOS, but not COX, inhibition during incremental increases in partial DA compression unmasked a vasoconstrictor, or myogenic, response. Combined NOS and COX inhibition did not further augment the myogenic response beyond that observed with NOS inhibition alone.

To better understand the lack of an additive effect of combined COX and NOS inhibition during hemodynamic measurements, we performed additional experiments to investigate the effects of NOS and COX inhibition on prostacyclin (PGI2)- and 8-BrcGMP (B)-induced vasodilation. Values are expressed as means ± SE. A: PGI2-induced pulmonary blood flow is attenuated after L-NNA treatment. *P < 0.05 for PGI2 after L-NNA treatment compared with control. B: L-NNA treatment did not affect the increase in 8-BrcGMP-induced LPA blood flow. *P < 0.001 for 8-BrcGMP vs. baseline and 8-BrcGMP after L-NNA treatment vs. baseline 2. Baseline 2 represents baseline values after recovery from initial PGI2 or 8-BrcGMP infusion. NS, not significant.

**Table 3. Comparison of hemodynamic variables and arterial blood gas tensions at baseline and after 30 min of 8-BrcGMP and 8-BrcAMP infusions**

<table>
<thead>
<tr>
<th></th>
<th>8-BrcGMP</th>
<th>8-BrcAMP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>30 Min</td>
<td>Baseline</td>
</tr>
<tr>
<td>PVR, mmHg·ml⁻¹·min⁻¹</td>
<td>0.98 ± 0.2</td>
<td>0.34 ± 0.1*</td>
</tr>
<tr>
<td>PAP, mmHg</td>
<td>47 ± 2</td>
<td>44 ± 2</td>
</tr>
<tr>
<td>AoP, mmHg</td>
<td>46 ± 0.5</td>
<td>43 ± 2</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>177 ± 15</td>
<td>199 ± 14</td>
</tr>
<tr>
<td>pH</td>
<td>7.35 ± 0.01</td>
<td>7.35 ± 0.01</td>
</tr>
<tr>
<td>PaO₂, mmHg</td>
<td>19 ± 0.5</td>
<td>20 ± 0.6</td>
</tr>
<tr>
<td>PoO₂, mmHg</td>
<td>46 ± 2</td>
<td>49 ± 3</td>
</tr>
</tbody>
</table>

Values are means ± SE. 8-BrcGMP, 8-bromo-cGMP; 8-BrcAMP, 8-bromo-cAMP; PVR, pulmonary vascular resistance; PAP, pulmonary artery pressure. *P < 0.05 vs. other treatment groups.

**Table 4. Comparison of hemodynamic variables during PGI2 treatment before and after L-NNA infusion**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>L-NNA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>PGI2</td>
</tr>
<tr>
<td>PAP, mmHg</td>
<td>43 ± 2</td>
<td>42 ± 2</td>
</tr>
<tr>
<td>AoP, mmHg</td>
<td>41 ± 1</td>
<td>42 ± 1</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>160 ± 8</td>
<td>169 ± 11</td>
</tr>
<tr>
<td>PaO₂, mmHg</td>
<td>21 ± 1</td>
<td>20 ± 1</td>
</tr>
</tbody>
</table>

Values are means ± SE. *P < 0.05 vs. control and L-NNA baseline values.
namic stress, we studied the effects of NOS inhibition on PGI2-induced fetal pulmonary vasodilation. We re-
port that NOS inhibition blocked the vasodilator ef-
effets of PGI2 by 73%, suggesting that NO mediates most of the PGI2 response in the fetal lung. In addition, 8-BrcGMP, but not 8-BrcAMP, caused marked pulmonary
vasodilation. Overall, these findings demonstrate that the NO-cGMP cascade is a more potent modulator of pulmonary vascular tone during acute hemodynamic stress than dilator PGs in the fetus.

Previous studies that have examined the roles of NO and PGs in modulating the response to shear stress in
the postnatal circulation are conflicting. Abrupt in-
creases in flow stimulate both NO and PG release in
isolated endothelial cells in culture (5, 8, 11, 13, 24, 32).
In isolated neonatal lamb lungs, NOS inhibition during
normoxia increased PVR more than COX inhibition,
but during hypoxia, COX inhibition augmented PVR
more than NOS inhibition (15). Barnard et al. (6) com-
pared the effects of NO and PG inhibition on the pulmonary vascular response to shear stress in iso-
lated rat and dog lungs. They found that NO plays a
greater role than PGs in mediating vasodilation during
shear stress in the isolated perfused adult rat lung, but
there is a greater role for PGs than NO in isolated dog
lungs (6). Both NO and vasodilator PG inhibition in-
creased vasoconstriction during shear stress in isolated
dog lungs (6). These findings suggest that, in the normal
fetal pulmonary circulation, mechanisms exist that
oppose vasodilation and maintain high PVR, which
may reflect a potent myogenic response in the fetal
lung (1, 7, 17). The myogenic response is partly de-
 fined as the ability of the vasculature to contract in response to an increase in transmural pressure (7). Recently, we have shown that the myogenic response is normally
present in the high-resistance fetal pulmonary circu-
lation in vivo and is unmasked by NOS inhibition (30).
Our current study extends these observations by dem-
onstrating that COX inhibition did not cause a similar
response and did not alter the effects of NOS inhibition
alone.

Several potential mechanisms may underlie our ob-
servations that combined treatment with COX and
NOS inhibitors does not have additive effects on shear
stress-induced pulmonary vasodilation or on the vaso-
constrictor response during increases in DA compres-
son. First, dilator PGs, especially PGI2, may act in
part through stimulation of NOS and increased NO
production. Second, fetal vascular smooth muscle cells
may be more responsive to cGMP than to cAMP, as
suggested by our findings that 8-BrcGMP, but not
8-BrcAMP, causes fetal pulmonary vasodilation. Third,
“cross talk” between these cyclic nucleotides can modu-
late the effects of the two dilator systems in the
smooth muscle cell. For example, in the systemic cir-
culation, interactions between the NO and PG path-
ways have been demonstrated at the level of cyclic
nucleotides (23). In the cerebral circulation, cAMP may
increase cGMP levels directly by inhibiting cGMP hy-
drolysis or indirectly through the activation of cGMP-
dependent protein kinases (23). Fourth, PG-induced
vasodilation may be partly mediated by the stimula-
tion of NO release. We found that PGI2-induced vaso-
dilation is blocked by nearly 75% after NOS inhibition.

In conclusion, we found that NOS inhibition com-
pletely blocked shear stress-induced pulmonary vaso-
dilation, whereas COX inhibition had no effect. NOS,
but not COX, inhibition uncovered a myogenic re-

dence during hemodynamic stress in the fetal pulmo-

nary circulation. In addition, NOS inhibition attenu-
ated PGI2-induced pulmonary vasodilation, suggesting
that PGI2 acts largely by NO release, and 8-BrcGMP,
but not 8-BrcAMP, caused fetal pulmonary vasodila-
tion. Thus the NO-cGMP cascade appears to play a
more critical role than dilator PGs in the modulation of
the vascular response to acute hemodynamic stress in
the fetal lung, and NO may mediate PGI2 pulmonary
vasodilation.

REFERENCES
1. Abman SH and Accurso FJ. Acute effects of partial compres-
sion of ductus arteriosus on fetal pulmonary circulation. Am J
2. Abman SH and Accurso FJ. Sustained fetal pulmonary vasodila-
tion with prolonged atrial natriuretic factor and GMP infu-
3. Abman SH, Chatfield BA, Hall SL, and McMurry IF. Role of
endothelium-derived relaxing factor during transition of pulmo-
nary circulation at birth. Am J Physiol Heart Circ Physiol
4. Accurso FJ, Alpert E, Wilkening RB, Peterson RB, and
Meschia G. Time-dependent response of fetal pulmonary blood
flow to an increase in fetal oxygen tension. Respir Physiol 63:
5. Alshihabi SN, Chang YS, Frangos JA, and Tarbell JM. Shear
stress-induced release of PGE2 and PGI2 by vascular smooth
6. Barnard JW, Wilson PS, Moor TM, Thompson WJ, and
Taylor AE. Effect of nitric oxide and cyclooxygenase products
on vascular resistance in dog and rat lungs. J Appl Physiol 74: