Cyclooxygenase contracting factors and altered pulmonary vascular responses in chronically hypoxic newborn pigs

CANDICE D. FIKE,1 SANDRA L. PFISTER,2 MARK R. KAPLOWITZ,1 AND JANE A. MADDEN2

1Department of Pediatrics, Wake Forest University School of Medicine, Winston-Salem, North Carolina 27157; and 2Departments of Neurology and Pharmacology, Medical College of Wisconsin, Milwaukee, Wisconsin 53226

Received 7 June 2001; accepted in final form 23 August 2001

PULMONARY HYPERTENSION DEVELOPS when newborn pigs are exposed to chronic hypoxia for either 3 days (short hypoxia) or 10 days (long hypoxia) (10). Identifying the changes in the pulmonary circulation that occur with chronic hypoxia may be key to understanding the pathogenesis of pulmonary hypertension and to developing therapies to intervene with its progression (17). We have previously found that ACh dilation is blunted in newborn pigs with pulmonary hypertension resulting from short hypoxia (7, 18). Another possibility is that vasoconstrictor responses to hypoxia are involved in the development of thromboxane-mediated constriction may contribute to the pathogenesis of chronic hypoxia-induced pulmonary hypertension in newborns. Therefore, for this study, most (n = 40) of the control piglets were studied on the day of arrival from the farm at 5–7 days of age.

METHODS

Animals. A total of 40 hypoxic piglets and a total of 45 control piglets were studied. For the hypoxic piglets, newborn pigs (2–3 days old; both sexes; Yorkshire, Landrace, or mixed York-Landrace) were placed in a hypoxic normobaric chamber for 3–4 days so that they were 5–7 days old when studied. Normobaric hypoxia was produced by delivering compressed air and N2 to an incubator (Thermocare). O2 content was regulated at 10–11% O2 (PO2 66–74 Torr), and CO2 was maintained at 3–6 Torr by absorption with soda lime. The chamber was opened two times per day for cleaning and to weigh the piglets. The animals were fed ad libitum with an artificial sow milk replacer from a feeding device attached to the chamber. We have previously found no differences in vascular responses between piglets raised in a room-air environment for 3–5 days and piglets raised on a farm (10, 11).

Vessel preparation. On the day of study, the piglets were preanesthetized with ketamine (30 mg/kg im) and acepromazine (1 mg/kg im) and then anesthetized with pentobarbital sodium (10 mg/kg iv). All animals were given heparin (1,000 IU/kg iv) and then exsanguinated. The thorax was opened, and the lungs were removed and placed in cold (4°C) physiological saline solution (PSS) until use. The PSS had the following composition (in mM): 141 Na+, 4.7 K+, 125 Cl−, 2.5 Ca2+, 0.72 Mg2+, 1.7 H2PO4−, 25 HCO3−, and 11 glucose. Immediately before use, segments of 100- to 400-μm-diameter pulmonary arteries were dissected from a lung lobe.

Supportive of this latter possibility is evidence that contracting metabolites of the cyclooxygenase (COX) pathway underlie the altered responses to ACh seen in a number of vascular beds of adult animals with systemic hypertension (13, 14, 22, 31). Whether a similar mechanism is operative in lungs of newborns with pulmonary hypertension is not known. The purpose of this study was to test the hypothesis that a COX-dependent contracting factor, such as thromboxane, is involved with the altered pulmonary vascular responses to ACh that develop in newborn piglets with pulmonary hypertension resulting from short hypoxia.
The system used to study cannulated arteries has been described in detail previously (20). Briefly, it consists of a water-jacketed plastic chamber in which proximal (inflow) and distal (outflow) cannulas were mounted. An arterial segment was threaded onto the proximal cannula and tied in place with a 10-0 monofilament nylon suture. The distal end of the artery was then tied onto the distal cannula, and the artery was filled with PSS and all side branches tied off. The distance between the cannula tips was adjusted with a micrometer connected to the proximal cannula so that the slack was taken out of the artery. The exterior of the artery was suffused with PSS from a reservoir at 37°C and aerated with a gas mixture containing O2, CO2, and N2, giving a PO2 of 140 Torr, a PCO2 of 38 Torr, and a pH of 7.37. The arterial lumen was filled from a syringe containing PSS, aerated with the same gas mixture as the reservoir, and connected to the cannula with polyethylene tubing. Gas concentrations and pH were monitored in all solutions (reservoir, vessel chamber, and infusion syringes) by using a blood-gas analyzer.

Inflow pressure was adjusted by changing the height of the infusion pressure transducers were placed both on the inflow side between the syringe and the artery and at the outflow end of the system. Both inflow and outflow pressures were monitored continuously on a recorder, and the artery was discarded if the pressures were not equal (indicates leak in vessel). The external diameter of the artery was observed continuously with a video system containing a color camera (Panasonic 5000) and television monitor. Vessel diameters were measured with a videocabler (FORA IV).

Protocols. Each artery was allowed to equilibrate for 40–60 min to establish basal tone. The arteries were equilibrated at transmural pressures similar to those in vivo (11): 15 cmH2O for control arteries and 25 cmH2O for hypoxic vessels. After equilibration and establishment of basal tone, the arteries were tested for viability by contraction to either KCl (10−4 M) or U-46619 (10−7 M). The arteries were then washed with fresh PSS and allowed to return to their precontracted diameter, i.e., allowed to reestablish basal tone.

In one series of studies, the diameter of control and hypoxic arteries was continuously monitored while cumulative doses of ACh (10−8 to 10−5 M) were added to the reservoir at 15-min intervals. Reproducibility of the ACh dose responses was tested in some arteries. To do this, after the first set of responses, the arteries were washed with fresh PSS and allowed to equilibrate for 15 min, and a second dose-response curve to ACh (10−8 to 10−5 M) was performed. Because the hypoxic arteries constricted to ACh, the presence of a functional endothelium was verified by assessing dilatory responses to cumulative doses (10−8 to 10−5 M) of the calcium ionophore, A-23187, administered at 15-min intervals. Responses to A-23187 were also evaluated in control arteries.

In another series of studies, the influence of transmural pressure on ACh responses was determined. Once the arteries had established basal tone at their starting pressures, 15 cmH2O for control arteries and 25 cmH2O for hypoxic arteries, the transmural pressure was increased to 25 cmH2O in the control arteries and reduced to 15 cmH2O in the hypoxic arteries. After 15 min at these pressures, the ACh dose-response curves were performed.

The influence of elevated tone on ACh responses in control and hypoxic arteries was assessed in another series of studies. Tests for viability and a functional endothelium were done as described above, and then either endothelin or the thromboxane mimetic, U-44619, was added in increasing doses until the arterial diameter had decreased by 30–40%. After equilibration at the elevated tone, the dose-response curves to ACh were performed.

To determine whether arteries from control and hypoxic piglets dilate differently because of impaired smooth muscle dilation, responses to the non-endothelium-dependent dilator, the nitric oxide (NO) donor S-nitroso-N-acetylpenicillamine (SNAP), were determined. Because vessels at basal tone dilate minimally to SNAP, tone was first elevated 30–40% by using either U-44619 or endothelin before the addition of SNAP (10−8 to 10−5 M).

The contribution from all COX metabolites and from the specific COX metabolite thromboxane to ACh responses in control and hypoxic arteries at basal tone was determined. These studies were performed with the vessels at basal tone to avoid any confounding influence from use of vasoconstrictors (4, 19). Cumulative doses of ACh were added (10−8 to 10−5 M) before and then 20 min after the addition of one of the following: the COX synthase inhibitor indomethacin (10−5 M); the thromboxane synthase inhibitor dazoxiben (10−5 M); the thromboxane synthase inhibitor feregrelate (10−5 M); or the thromboxane-receptor antagonist SQ-29548 (10−5 M). For the studies with SQ-29548, at the completion of the ACh dose responses, the thromboxane mimetic U-46619 was added to assess the effectiveness of receptor blockade by SQ-29548.

To determine the influence of the endothelium on ACh responses, the endothelium was disrupted by infusing air into control and hypoxic arteries at basal tone (15). Functional disruption of the endothelium was verified by loss of dilation to ACh and/or A-23187 in the control arteries and to A-23187 in the hypoxic arteries. Reactivity to either KCl or U-46619 was used to confirm viability of the arteries. Then, the diameter of control and hypoxic arteries was continuously monitored while cumulative doses of ACh were added before and 20 min after the addition of either indomethacin (10−5 M) or dazoxiben (10−5 M). In some of the hypoxic arteries, responses to cumulative doses of ACh were measured before and after air infusion.

After all of the above studies, vessel viability was retested by using KCl or U-44619. In addition, in some studies, vessel responses to the vehicle used for solubilization of each agent were evaluated.

Materials. Concentrations for each drug listed in Protocols were expressed as final molar concentrations in the vessel bath. ACh, A-23187, and indomethacin were obtained from Sigma Chemical. Feregrelate was from Cayman Chemicals. SNAP and SQ-29548 were from Biomol. Dazoxiben was from Pfizer. ACh, SNAP, and dazoxiben were solubilized in distilled H2O. Indomethacin was solubilized in a mixture of equal parts saline and 8% NaHCO3. Feregrelate and A-23187 were solubilized in DMSO. SQ-29548 was solubilized in ethanol.

Statistics. Data are means ± SE. One-way ANOVA with post hoc multiple-comparison test was used to compared changes in vessel diameter between control and hypoxic arteries at the different transmural pressures for each dose of ACh. An unpaired t-test was used to compare changes in vessel diameter between control and hypoxic arteries for each dose of A-23187 or SNAP. A paired t-test was used to compare changes in vessels diameters before and after treatment with indomethacin, dazoxiben, feregrelate, or SQ-29548 for each dose of ACh for both control and hypoxic arteries. P < 0.05 was considered significant.

RESULTS

After equilibration at basal tone, the mean diameter of all vessels used in these studies were 240 ± 6 μm for control arteries and 250 ± 6 μm for hypoxic arteries.
None of the vehicles significantly changed arterial diameter in the concentrations used to solubilize any of the agents.

In control arteries at normal (15 cmH₂O) and elevated (25 cmH₂O) transmural pressures, vessel diameter increased to all but the highest dose of ACh (Fig. 1). In hypoxic arteries, the diameter decreased to all doses of ACh at both normal (25 cmH₂O) and reduced (15 cmH₂O) transmural pressure. When tone was elevated with either U-46619 or endothelin, arteries from both hypoxic and control piglets dilated to all doses of ACh (Fig. 2), although the dilation to each dose of ACh was less in the hypoxic arteries. For both control and hypoxic arteries, results were similar for arteries with tone elevated with either endothelin or U-46619 so that they were combined (Fig. 2).

Both control and hypoxic arteries dilated to the calcium ionophore, A-23187 (Fig. 3), until the highest dose, whereupon the diameters returned to control values. At 10⁻⁶ M, the hypoxic arteries had dilated significantly more than the control arteries. Both artery types dilated similarly to all doses of SNAP (Fig. 4). The dilations to A-23187 (Fig. 3) and SNAP (Fig. 4) by the hypoxic arteries indicate respectively that the endothelium can release dilators and that smooth muscle cell dilation is unaltered.

Table 1 summarizes the changes in pulmonary arterial diameter by control and hypoxic vessels in which the dose responses to ACh were repeated. In both control and hypoxic arteries, the magnitude of the ACh dilation at each dilation was similar in both trials. Therefore, differences in responses to ACh measured before and after addition of inhibitors as described below cannot be attributed to tachyphylaxis.

Indomethacin reversed the ACh-induced response from dilation to constriction in control arteries (Fig. 5), whereas indomethacin reversed the ACh response from constriction to dilation in hypoxic arteries (Fig. 5). In control arteries, the magnitude of ACh-induced dilation tended to be blunted after the thromboxane synthase inhibitor, dazoxiben, or the thromboxane-receptor antagonist SQ-29548 but was unaffected by...
the thromboxane synthase inhibitor feregrelate (Fig. 6A). By comparison, the two thromboxane synthesis inhibitors feregrelate or dazoxiben and the thromboxane receptor antagonist SQ-29548 nearly abolished the ACh-induced constriction of hypoxic arteries (Fig. 6B). After treatment with SQ-29548, U-46619 elicited no change in either control or hypoxic arterial diameter. For purposes of illustration and because of their similarity, the responses to ACh measured before the addition of either of the thromboxane inhibitors or the receptor antagonist were combined for all control arteries in Fig. 6A and for all hypoxic arteries in Fig. 6B.

After air infusion, both control (Fig. 7A) and hypoxic (Fig. 7B) arteries constricted to all doses of ACh. In hypoxic arteries, the magnitude of constriction to ACh was similar to that before air infusion (Table 2). In both artery types, dazoxiben and indomethacin diminished, but did not abolish, the constriction (Fig. 7, A and B).

**DISCUSSION**

The findings of diminished dilation to ACh but preserved dilation to the non-endothelium-dependent dilator SNAP by small, 100- to 400-μm-diameter, pulmonary arteries from newborn piglets exposed to short hypoxia are consistent with our previous findings in isolated lungs showing blunted pulmonary vascular responses to ACh but unaltered responses to the non-endothelium-dependent dilators, sodium nitroprusside and papaverine (10, 11). Thus impaired smooth muscle dilation does not appear to contribute to altered ACh responses in the pulmonary vasculature of piglets exposed to short hypoxia.

The major new finding of this study is that a COX-dependent, vascular wall-derived contracting factor, most likely thromboxane, appears to be at least partly responsible for the abnormal pulmonary vascular responses to ACh that develop when newborn piglets are exposed to short hypoxia.

The major new finding of this study is that a COX-dependent, vascular wall-derived contracting factor, most likely thromboxane, appears to be at least partly responsible for the abnormal pulmonary vascular responses to ACh that develop when newborn piglets are exposed to short hypoxia. In addition, these impaired responses may involve receptors and/or G proteins (3, 9).

Besides our studies, there are only a few others in which pulmonary vascular responses to ACh have been...
evaluated in newborn animals with chronic hypoxia-induced pulmonary hypertension. Similar to our results, dilation to ACh was blunted in rings of 2- to 3-mm-diameter pulmonary arteries from piglets raised in hypobaric hypoxia for 3 days (30), and ACh responses were reduced in lobar pulmonary arteries isolated from calves exposed to high-altitude hypoxia (23). Of note, the latter group of investigators found greater pulmonary vascular responses to ACh in high-altitude calves in vivo than in comparably aged control calves (23). The discrepancy between the in vivo results and those in lobar pulmonary arteries from high-altitude calves could be due to inherent differences in the two preparations or to a difference in the influence of hypobaric hypoxia on conduit-level (as reflected by results of lobar pulmo-

Fig. 6. A: ACh-induced changes in diameter for control arteries before and after treatment with dazoxiben (n = 16 arteries from 9 piglets), feregrelate (n = 10 arteries from 9 piglets), or SQ-29548 (n = 15 arteries from 11 piglets). Values are means ± SE. Note that, for the sake of illustration, values for control arteries before treatment with dazoxiben, feregrelate, or SQ-29548 are combined. *Different from control arteries before dazoxiben; **different from control arteries before SQ-29548, P < 0.05 (paired t-test). B: ACh-induced changes in diameter for hypoxic arteries before and after treatment with dazoxiben (n = 8 arteries from 5 piglets), feregrelate (n = 11 arteries from 7 piglets), or SQ-29548 (n = 7 arteries from 6 piglets). Values are means ± SE. Note that, for the sake of illustration, values for hypoxic arteries before treatment with dazoxiben, feregrelate, or SQ-29548 are combined. *Different from hypoxic arteries before feregrelate; **different from hypoxic arteries before dazoxiben; ***different from hypoxic arteries before SQ-29548, P < 0.05 (paired t-test).

Fig. 7. A: ACh-induced changes in diameter for air-infused control arteries before and after indomethacin (n = 9 arteries from 7 piglets) or dazoxiben (n = 12 arteries from 8 piglets). Values are means ± SE. Note that, for the sake of illustration, values for air-infused control arteries before indomethacin or dazoxiben are combined. *Different from control air-infused arteries before dazoxiben; **different from control air-infused arteries before indomethacin, P < 0.05 (paired t-test). B: ACh-induced changes in diameter for air-infused hypoxic arteries before and after indomethacin (n = 5 arteries from 5 piglets) or dazoxiben (n = 5 arteries from 5 piglets). Values are means ± SE. Note that, for the sake of illustration, values for air-infused hypoxic arteries before indomethacin or dazoxiben are combined. *Different from hypoxic air-infused arteries before dazoxiben; **different from hypoxic air-infused arteries before indomethacin; ***different from hypoxic air-infused arteries before dazoxiben, P < 0.05 (paired t-test).
Table 2. Change in vessel diameter in response to ACh in hypoxic vessels before and after air infusions

<table>
<thead>
<tr>
<th>Change in Diameter, %</th>
<th>10^{-6} M ACh</th>
<th>10^{-7} M ACh</th>
<th>10^{-6} M ACh</th>
<th>10^{-5} M ACh</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before air infusion</td>
<td>-1.5 ± 0.5</td>
<td>-2.4 ± 0.9</td>
<td>-2.3 ± 0.8</td>
<td>-4.1 ± 0.4</td>
</tr>
<tr>
<td>After air infusion</td>
<td>-1.0 ± 0.5</td>
<td>-3.6 ± 1.0</td>
<td>-4.4 ± 0.7</td>
<td>-4.4 ± 0.7</td>
</tr>
</tbody>
</table>

Values are means SE for 3 vessels.

monary arteries) vs. resistance-level (as reflected by in vivo results with whole lungs) pulmonary arteries (23). Nonetheless, the combined results from studies with newborn piglets and newborn calves suggest that exposure to chronic hypoxia impairs ACh responses in some, if not all, segments of the newborn pulmonary circulation.

ACh responses are mediated by muscarinic receptors coupled to G proteins (9). Because dilation to the non-receptor-dependent, non-G-protein-dependent agent A-23187 was preserved (Fig. 3), we found that impaired ACh responses might involve either muscarinic receptors or G proteins. In particular, it is possible that chronic in vivo hypoxia alters the density and/or the subtypes of muscarinic receptors on either endothelial or smooth muscle cells. Consistent with our findings, ACh dilation was blunted but responses to A-23187 were unaltered in 2- to 3-mm-diameter pulmonary artery rings of piglets raised in hypobaric hypoxia from birth to 2.5 days of age (30). However, the same group of investigators found diminished responses to both ACh and A-23187 in pulmonary artery rings of piglets raised in hypoxia from 3 to 6 days of age (30). Thus the involvement of receptors and/or G proteins with altered ACh responses might vary with length of hypoxia, the age at which the animal is exposed to hypoxia, and the size of the pulmonary artery studied. Moreover, it is possible, as suggested by studies with adult rats, that other receptor G protein-coupled pathways are also affected with chronic hypoxia (28). All these issues will require future clarification.

Because ACh stimulates the endothelium to release NO, it has been suggested that altered production of, or responsiveness to, NO might contribute to abnormal ACh responses in newborn pulmonary hypertension. Moreover, our study with newborns is the first to show that the COX-dependent contracting factors contribute to abnormal ACh responses in a newborn model of pulmonary hypertension. Therefore, the contribution from the contracting factor occurs within a time period as short as 3 days of hypoxia.

Because of its known potent vasoconstrictive effects in the neonatal pulmonary circulation (6, 25), we pursued the possibility that thromboxane might be the COX-dependent contracting factor underlying altered pulmonary vascular ACh responses in short-hypoxic piglets. We found that ACh-induced constriction of small pulmonary arteries from piglets exposed to short hypoxia was nearly abolished by two different thromboxane synthesis inhibitors and by a thromboxane-PG_H2-receptor antagonist. However, on the basis of the observation that nonspecific COX inhibition with indomethacin appears to have a greater inhibitory effect on ACh induced constriction (Fig. 5) does either selective thromboxane synthesis inhibition or thromboxane-PG_H2-receptor antagonism (Fig. 6B), an additional COX-dependent contracting factor might also be involved. Also, COX inhibition does not completely restore ACh-induced dilation in short hypoxic piglets; i.e., there is less ACh-induced dilation in arteries of piglets exposed to short hypoxia after nonspecific COX inhibition than in untreated arteries from control piglets (Fig. 5). The concomitant inhibition of COX-dependent dilators along with the constrictors might explain why ACh-induced dilation was not restored by indomethacin. However, there is also the possibility that, in addition to COX products, a yet-to-be-identified, non-COX-dependent contracting factor contributes to the blunted ACh responses in pulmonary arteries of piglets exposed to short hypoxia.

Because our conclusions are based on results using pharmacological inhibition, we must consider that there could also be non-COX- or non-thromboxane-mediated effects. Precursor arachidonate might be shunted to non-COX-mediated pathways. COX is only one of a number of enzyme pathways in the pulmonary...
circulation known to synthesize vasoactive agents from the precursor arachidonate. Indeed, the constrictor response to ACh in control arteries after COX inhibition with indomethacin could be explained by the shunting of arachidonate to the lipoxygenase pathway. Another possibility is that inhibiting COX dilators and constrictors might unmask the effects from some nonarachidonic vasoconstrictors, such as endothelin. However, such an effect from COX inhibition in the hypoxic arteries would lead to an enhanced, not lessened, constriction to ACh.

Evidence that the thromboxane synthesis inhibitors and the receptor antagonist might have some nonthromboxane-mediated effects, including a possible effect on COX-dependent dilators, is suggested by findings with control arteries. Dazoxiben and SQ-29548 tended to blunt ACh-induced dilation in control arteries (Fig. 6A). Yet, a similar effect by these agents in hypoxic arteries would be expected to augment, not diminish, the ACh-induced constriction. Moreover, the marked and similar ability of more than one thromboxane synthesis inhibitor as well as the PGH2-thromboxane-receptor antagonist to blunt the ACh-induced constriction in hypoxic arteries adds strength to the argument that thromboxane mediates the constrictor response.

Our studies in hypoxic arteries provide evidence regarding possible cellular source(s) of thromboxane. The ability to reduce ACh-induced constriction by treatment with either a COX inhibitor or a thromboxane synthesis inhibitor was similar in both endothelium intact arteries and those in which the endothelium had been disrupted by air infusion (Figs. 6B and 7B). In addition, the magnitude of ACh-induced constriction was similar before and after endothelial disruption (Table 2). If the endothelium were the major source of the contracting factor(s), then endothelial disruption and/or removal should have diminished both the magnitude of ACh-induced constriction and the effectiveness of contracting factor inhibitors in reducing ACh-induced constriction. Thus our findings with air-infused hypoxic arteries suggest that, rather than the endothelium, cells in the vascular wall are the major source of the contracting factor(s), including thromboxane.

It is of interest that our findings suggest that, when the endothelium of small pulmonary arteries from control piglets is disrupted, ACh stimulates the release of COX-dependent contracting factor(s) from cells in the vascular wall and that thromboxane is one of these contracting factors. Consistent with this finding, recent studies have shown that thromboxane synthase is found in cells in the vascular wall, including smooth muscle cells, but not in the endothelium, of pulmonary vessels from normal rats (8). Moreover, members of our group have provided evidence that, rather than endothelial or smooth muscle cells, platelets adherent to endothelial cells are the cellular source of thromboxane synthase in intrapulmonary arteries of adult rabbits and that thromboxane production requires an interaction between platelets and endothelial cells (5, 24). The precise cellular source(s) of thromboxane production in the vascular wall of resistance-level pulmonary arteries from newborn piglets remains to be determined.

Unlike our findings in newborn piglets, when adult rats are exposed to 10 days of hypoxia, the endothelium, not the vascular wall, is the source of the COX-dependent constrictor PGH2 that underlies the development of ACh-induced constriction in conduit-level pulmonary arteries (21). Differences between species, size of arteries studied, and length of hypoxia could contribute to the variability between studies with adult rats and newborn piglets.

Altogether, our findings with newborn piglets show that COX-dependent agents are involved in ACh responses in small pulmonary arteries from both control and hypoxic animals. However, it is important to note that the COX metabolites that play the most important roles in mediating ACh responses appear to differ between arteries from control and hypoxic piglets. Specifically, our findings indicate that the influence from COX-dependent dilators predominates in control arteries, whereas the influence from COX-dependent contracting factors predominates in hypoxic arteries. In other words, one possible explanation for our findings is that both dilators and contracting factors are produced by control arteries but that the influence from dilators produced by the endothelium overrides the constrictors produced by the smooth muscle. During hypoxia, it is possible that the influence of dilators from the endothelium is lost, thereby unmasking the contractile response. Another explanation for the change with hypoxia could be that COX-dependent contracting factor production increases with short hypoxia. Yet another possibility is that sensitivity to the COX-dependent dilators and/or contracting factors is altered by exposure to short hypoxia. These possibilities merit further investigation.

To summarize, our findings indicate that a COX-dependent, vascular wall-derived contracting factor, most likely thromboxane, is at least partly responsible for the abnormal pulmonary vascular responses to ACh that develop when newborn piglets are exposed to short hypoxia. These findings have important implications for the pathogenesis of hypoxia-induced pulmonary hypertension in newborns. In addition to its vasoconstrictive effect, thromboxane is a smooth muscle cell mitogen (26). Thus intervening with thromboxane at an early time point may not only diminish the early elevation in pulmonary arterial pressure but also may inhibit progressive smooth muscle hypertrophy and thereby ameliorate the progression of hypoxia-induced pulmonary hypertension. Future studies are needed to evaluate these possibilities.

This work was supported by a March of Dimes Research Grant (to C. D. Fike).

REFERENCES


