Reactive Oxygen Metabolites Relax the Lamb Ductus Arteriosus by Stimulating Prostaglandin Production

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To determine whether oxygen metabolites can cause ductus relaxation, we used rings of fetal ductus obtained from 36 near-term lambs and measured the effects of the oxygen metabolites generated by the combination of hypoxanthine and xanthine oxidase. The oxygen metabolites produced by hypoxanthine plus xanthine oxidase caused relaxation of the ductus that was inhibited by catalase (hydrogen peroxide scavenger) but not by superoxide dismutase (superoxide anion scavenger). In addition, hypoxanthine plus xanthine oxidase produced a 14-fold increase in prostaglandin (PG) E₂ production with only twofold increase in 6-keto-PGF₁α (the stable metabolite of PGI₂). PGE₂ is the most potent relaxant of the ductus arteriosus. The presence of either catalase or indomethacin blocked both the increase in prostaglandin production and the relaxation. We conclude that reactive oxygen metabolites relax the ductus arteriosus and oppose the normal constriction that occurs after birth. However, the vasoactive effects of reactive oxygen metabolites in the ductus appear to be mediated exclusively through the generation of PGE₂. (Circulation Research 1989;64:1-8)

Postnatal regulation of the ductus arteriosus depends on a balance between oxygen-induced contraction and prostaglandin-induced relaxation (for review, see Clyman1). Although prostaglandin (PG) E₂ is a minor product of prostaglandin production in the lamb ductus arteriosus, the marked sensitivity of the ductus to PGE₂ indicates that PGE₂ may be the most important endogenous prostaglandin to regulate vessel patency.2-3 It has been hypothesized that reactive oxygen metabolites also may play an important role in ductus regulation; lower concentrations of antioxidants in the ductus, compared with those in neighboring vessels (thoracic aorta and pulmonary artery), make it more susceptible to the action of oxygen metabolites.4 Numerous sources of oxidants could play a role in regulating the ductus, including mitochondrial electron transport chain components, endoplasmic reticulum and nuclear membrane electron transport chain components, the xanthine dehydrogenase-oxidase system, prostaglandin synthetase and lipoxygenase systems, and reduced nicotinamide adenine dinucleotide phosphate oxidase of neutrophils.5-6

After birth, the ductus is exposed to a sudden increase in PaO₂, which leads to constriction of the vessel; this constriction produces ischemia of the inner luminal one third of the vessel wall.7 Increased PO₂ increases the production of oxygen radicals.8 In addition, ischemia and tissue hypoxia can induce reactive oxygen metabolites.9,10,11 During ischemia, there are disturbances in the intramitochondrial electron transport system with release of ubisemiquinone, flavoprotein, and superoxide radicals,6,9 increases in tissue and circulating hypoxanthine concentrations,12,13 conversion of xanthine dehydrogenase to oxidase,12 and large increases in reducing equivalents.14 Free radical production can proceed at very low oxygen tensions (50% of control values at a PO₂ of 1 mm Hg). Under ischemic conditions, there is a loss of intracellular free radical protective enzymes15,16 so that the increased concentrations of free radicals are then free to react with phospholipid membranes and disrupt cellular transport processes. Reactive oxygen metabolites have been found to alter smooth muscle tone in both pulmonary and systemic blood vessels. However, it is impossible to generalize the response from any single vascular bed to others because each bed is susceptible to a different oxygen species and has its own unique con-
contractile response. In the rabbit lung, reactive oxygen metabolites generated by xanthine oxidase produce vasoconstriction, which is mediated by a product of arachidonic acid cyclooxygenase\(^1\); in the rat lung, the same generating system produces relaxation, which is independent of cyclooxygenase.\(^18\) In systemic arteries, xanthine oxidase causes relaxation that depends on the production of the hydroxyl, hydrogen peroxide, and superoxide metabolites of oxygen\(^20,21\); in pulmonary vessels, the xanthine oxidase response is independent of superoxide anion production.\(^17\) To add to these complexities, in the brain, reactive oxygen metabolites may mediate the effects of activating the cyclooxygenase system\(^21\) rather than vice versa as found in the lung.\(^17\)

Therefore, we have investigated the effects of chemically generated oxygen metabolites on the isolated lamb ductus arteriosus. We have examined the interactions between oxygen metabolite production, oxygen-induced contraction, and PGE\(_2\)-induced relaxation.

Materials and Methods

Thirty-six late gestation (134±5 days of a 145-day term) fetal lambs were delivered by cesarean section (under maternal low spinal anesthesia) and were killed by rapid exsanguination. The ductus arteriosus was dissected free from loose adventitial tissue and divided into 1-mm thick rings (23±8 mg wet weight, \(n=36\)) that were placed in separate 150 ml organ baths kept in the dark within an enclosed box. The rings were suspended between two stainless steel hooks in a modified Krebs-Tris solution at 38° C.\(^7\) Isometric responses of circumferential tension were measured by Grass FT03C force transducers (Quincy, Massachusetts).

Each of the rings was stretched to an initial length of 7–9 mm; this length results in a maximal contractile response to increases in oxygen tension.\(^23\) The tensions that developed in the rings were expressed as force/unit cross sectional area (g/mm\(^2\)).\(^23\) Initially, the P\(_O2\) of the bath solution was maintained at 20–25 mm Hg, and the rings were allowed to equilibrate for 35–50 minutes until a steady tension developed. The bath solution then was bubbled with 100% O\(_2\) (to a P\(_O2\) of 680–700 mm Hg), and the ring was allowed to equilibrate for 60 minutes. The bath solution was changed every 30 minutes. Next, the solution was bubbled with 100% O\(_2\). The bath solution was changed and collected every 30 minutes for the next 60 minutes (collection periods 1 and 2). After the second collection period, hypoxanthine 100 \(\mu\)M and xanthine oxidase 0.01 IU/ml were added to the bath solution. The solution was collected once the ductus had developed its maximal relaxation (15-minute collection period—collection period 3). Following this collection, indomethacin 5.6×10\(^{-6}\) M was added to the bath solution in addition to hypoxanthine and xanthine oxidase. The bath solution was changed every 30 minutes for the next 60 minutes, and indomethacin, hypoxanthine, and xanthine oxidase were added to each change of solution. The bath solution from the 30-minute to 60-minute exposure of the ductus to indomethacin, hypoxanthine, and xanthine oxidase was collected (collection period 4).

To determine the effects of catalase on prostaglandin production, paired rings from the same ductus that were studied above were studied according to the same protocol, except that after the exposure to oxygen alone (collection periods 1 and 2), catalase (110 IU/ml final concentration) or boiled catalase was added to the bath solution in addition to hypoxanthine plus xanthine oxidase. In the other bath, the antioxidant was boiled for 10 seconds before its addition to the solution. In 10 experiments, two rings from the same ductus were studied in separate baths. In one bath, hydrogen peroxide (H\(_2\)O\(_2\)) was added in increments from 10\(^{-7}\) to 10\(^{-3}\) M. In the other bath, indomethacin (2 \(\mu\)g/ml [5.6×10\(^{-6}\) M]) was added prior to the addition of H\(_2\)O\(_2\). In 21 experiments, two rings from the same ductus were studied in separate baths. In one bath, hypoxanthine was added, followed by xanthine oxidase. In the other bath, indomethacin (2 \(\mu\)g/ml [5.6×10\(^{-4}\) M]) was added prior to the addition of hypoxanthine, which was followed by xanthine oxidase. 7) In 11 experiments, both hypoxanthine and xanthine oxidase were added to the bath; after the tension in the ring reached a new plateau, indomethacin was added to the bath. In all experiments, we allowed the tension in the rings to reach a new steady state plateau following an addition before another experimental agent was added to the bath. After the experiment, the rings were removed from the baths and blotted dry, and their wet weights were determined.

To measure prostaglandin production by the rings of ductus arteriosus, rings were prepared as described above and then placed in 10 ml organ baths. To measure PGE\(_2\) and 6-keto-PGF\(_\text{Ia}\) (the stable metabolite of PGI\(_2\)) production by the ductus, the 10 ml bath solution was changed and collected. Initially, the bath solution was bubbled with 100% N\(_2\) (P\(_O2\) 20–30 mm Hg), and the ring was allowed to equilibrate for 60 minutes. The bath solution was changed every 30 minutes. Next, the solution was bubbled with 100% O\(_2\). The bath solution was changed and collected every 30 minutes for the next 60 minutes (collection periods 1 and 2). After the second collection period, hypoxanthine 100 \(\mu\)M and xanthine oxidase 0.01 IU/ml were added to the bath solution. The solution was collected once the ductus had developed its maximal relaxation (15-minute collection period—collection period 3). Following this collection, indomethacin 5.6×10\(^{-6}\) M was added to the bath solution in addition to hypoxanthine and xanthine oxidase. The bath solution was changed every 30 minutes for the next 60 minutes, and indomethacin, hypoxanthine, and xanthine oxidase were added to each change of solution. The bath solution from the 30-minute to 60-minute exposure of the ductus to indomethacin, hypoxanthine, and xanthine oxidase was collected (collection period 4).

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In another experiment, we studied the effects of increasing concentrations of hypoxanthine on the rate of PGE2 production. To measure PGE2 production by the ductus, the vessel was bathed in 5 ml of Krebs-Tris solution, which was changed and collected every 30 minutes. Initially, the bath solution was bubbled with 100% N2 for 60 minutes (Po2 24-32 mm Hg). The bath solution then was bubbled with 100% O2 for two 30-minute collection periods. Next, hypoxanthine was added to the bath solution. The initial concentration was 100 μM. The solution was changed after 30 minutes; the ring then was exposed to 1 mM hypoxanthine for two 30-minute collection periods. Next, indomethacin 5.6x10^-6 M and 1 mM hypoxanthine were added to the bath solution, and the ring was allowed to achieve a new steady state tension over the next 60 minutes.

**Results**

Rings of lamb ductus arteriosus initially were incubated in a low Po2 environment until a steady tension developed (2.07±0.85 gm/mm², n=36 lambs). They were then exposed to an increased Po2 (680-700 mm Hg). All rings contracted when exposed to the high Po2. The "oxygen-induced tension" was considered to be the difference between the steady state tensions at high and low Po2 (4.79±1.63 gm/mm², n=36).

A cumulative dose response to increasing concentrations of hypoxanthine was performed in eight oxygen contracted rings (Figure 1). At concentrations of hypoxanthine ≤100 μM, there were minimal effects upon the ductus arteriosus. Concentrations greater than 100 μM were associated with significant relaxation of the ductus.

Similarly, xanthine oxidase (0.01 IU/ml) produced a minimal relaxation of the ductus (Figure 2a). However, when xanthine oxidase was combined with hypoxanthine, there were marked increases in relaxation at high concentrations. Relaxation of the ductus is expressed as the percent inhibition of the oxygen-induced tension prior to the hypoxanthine additions. The oxygen-induced tension was 5.74±1.33 gm/mm². Values are mean±SD.

![Graph showing relaxation vs. hypoxanthine concentration](http://circres.ahajournals.org/)
FIGURE 2. Effects on ductus tension of xanthine oxidase (XO) (0.01 IU/ml), hypoxanthine (Hx) (10, 100, and 1,000 μM), and xanthine oxidase plus hypoxanthine. Rings of ductus were allowed to reach a steady tension in high PO₂. a: Xanthine oxidase was added to the bath and the ductus was allowed to achieve a new steady tension (<10 minutes) (p<0.008 versus oxygen-induced tension); next, hypoxanthine 10 μM was added to the xanthine oxidase (n=12) (p<0.008 versus XO alone). b: Hypoxanthine 100 μM was first added to the bath (p<0.002 versus control); next, xanthine oxidase was added (n=13) (p<0.0001 versus Hx alone). c: Same as b except hypoxanthine 1,000 μM was used (n=11) (p<0.0001 versus control; p<0.0001 Hx plus XO versus Hx alone). Relaxation is expressed as the percent of inhibition of the oxygen-induced tension. The oxygen-induced tensions were 5.5±1.7 g/ml/mm² (n=12), 3.8±1.3 g/ml/mm² (n=13), and 5.3±1.5 g/ml/mm² (n=11) for parts a, b, and c, respectively. Values are mean±SD.

decreases in the tension of the oxygen constricted rings (Figure 2a–c). These findings suggested that the ductus relaxation might be due to the reactive oxygen metabolites produced by the hypoxanthine–xanthine oxidase reaction.

To confirm the role of oxygen metabolites in ductus relaxation, we added oxygen metabolite scavengers to the bath solution prior to the introduction of hypoxanthine and xanthine oxidase (Figure 3). Catalase, a scavenger of hydrogen peroxide, inhibited the relaxation caused by both hypoxanthine and xanthine oxidase or by 1 mM hypoxanthine alone. Superoxide dismutase did not prevent either relaxation. Neither superoxide dismutase nor catalase by itself had an effect on ductus arteriosus tension. In addition, hydrogen peroxide produced a dose dependent relaxation of the ductus arteriosus (Figure 4).

From each pair of rings obtained from 21 ductus, we pretreated one ring with indomethacin to see whether the hypoxanthine plus xanthine oxidase relaxation was mediated by prostaglandin production. As we have shown previously,1 rings exposed to oxygen plus indomethacin had a greater increase in tension above the baseline tension at low PO₂ (6.8±1.7 g/ml/mm²) than did rings exposed to oxygen alone (5.3±1.6 g/ml/mm², n=21, p<0.001). Indomethacin prevented hypoxanthine plus xanthine oxidase from relaxing the ductus (Figure 5). In addition, indomethacin was able to reverse the ductus relaxation once it had been produced by hypoxanthine plus xanthine oxidase. When hypoxanthine (100 μM) plus xanthine oxidase (0.01 IU/ml) were added to rings from 11 ductus that had previously been constricted by oxygen, the tension dropped to 63±23% of the initial “oxygen-induced tension.” When indomethacin 5.6×10⁻⁶ M was added to the bath solution containing hypoxanthine plus xanthine oxidase, the tension increased to 112±13% of the initial oxygen-induced tension (p<0.01 indomethacin-induced tension versus initial oxygen-induced tension). Similarly, indomethacin blocked the H₂O₂-induced relaxation of the ductus arteriosus (Figure 4).

Addition of hypoxanthine plus xanthine oxidase also caused a 14-fold increase in PGE₂ production.
FIGURE 4. Effects of hydrogen peroxide (H$_2$O$_2$) and indomethacin plus H$_2$O$_2$. Paired rings of ductus from the same lamb were allowed to reach a steady tension in high P$_o$2 or high P$_o$2 with indomethacin (5.6x10$^{-6}$ M). Once steady tensions were achieved, H$_2$O$_2$ was added to the baths in increasing concentrations. Relaxation is expressed as the percentage of inhibition of the oxygen or oxygen plus indomethacin–induced tension. The oxygen–induced tension was 4.00±1.52 g/ml/mm$^2$; the oxygen plus indomethacin–induced tension was 4.64±1.36 g/ml/mm$^2$, n=10. Values are mean±SD. Indomethacin significantly inhibited the H$_2$O$_2$–induced relaxation between concentrations 10$^{-6}$ to 10$^{-4}$ M (p<0.01).

while producing only twofold increase in 6-keto-PGF$_{1a}$ (the stable metabolite of PGI$_2$) in rings of ductus arteriosus (Figure 6). Additions of catalase or indomethacin inhibited the hypoxanthine plus xanthine oxidase mediated rises in PGE$_2$ and 6-keto-PGF$_{1a}$. Both catalase and indomethacin blocked the hypoxanthine plus xanthine oxidase–induced relaxation (Figure 6).

To see whether the relaxation caused by hypoxanthine at high concentrations also was related to PGE$_2$ production, we studied the effects on the ductus of different concentrations of hypoxanthine and the ability of indomethacin to reverse them (Figure 7). Under the experimental conditions in Figure 7, there was no increase in PGE$_2$ production by the ductus and no change in tension when 100 $\mu$M hypoxanthine was added to the bath. However, 1 mM hypoxanthine produced a significant increase in PGE$_2$ production and a decrease in tension. Indomethacin completely inhibited the increase in PGE$_2$ production and totally reversed the relaxation caused by 1 mM hypoxanthine.

**Discussion**

Our studies show that chemically generated oxygen metabolites can produce relaxation of the ductus arteriosus and inhibit oxygen-induced contraction. To test the effects of oxygen metabolites, we used the hypoxanthine–xanthine oxidase reaction because it has been well characterized$^{6,26,27}$ and previously used for this purpose.$^{17,18,20,21}$ This reaction results in both univalent and divalent reductions of oxygen yielding approximately 20% superoxide anion (O$_2^-$) and 80% H$_2$O$_2$, respectively.$^6$ In addition, the xanthine oxidase system, in the presence of suitable catalysts, can mediate the formation of an oxidant (or oxidants) more powerful than either O$_2^-$ or H$_2$O$_2$ alone, which, for convenience, has been "called" hydroxyl radical (OH$^{-}$).$^6$

Neither hypoxanthine, in concentrations up to 100 $\mu$M, nor xanthine oxidase (0.01 IU/ml) produced a substantial effect on ductus arteriosus tone. When both were combined, there was a significant reduction in tension. This appeared to be mediated by H$_2$O$_2$ or H$_2$O$_2$–derived products such as OH$^-$, but not by O$_2^-$, since catalase (an H$_2$O$_2$ scavenger) but not superoxide dismutase blocked the relaxation. In addition, H$_2$O$_2$ relaxed the constricted ductus when added directly to the organ bath.

In our studies, catalase by itself had no effect on the oxygen–contracted ductus arteriosus. Its inability to produce further contraction of the oxygen–constricted ductus suggests that under these experimental conditions, H$_2$O$_2$ was not being produced by the ductus in amounts that would affect the vessel’s tone, or that catalase could not get to the intracellular sites where H$_2$O$_2$ was being produced.

There are numerous ways that reactive oxygen metabolites might affect vascular tone. Meerson et al$^{11}$ have suggested that it is the "lipid triad" composed of lipid peroxidation, activation of lipases and phospholipases, and the production of free fatty acids and lyso-phospholipids that mediates oxygen radical effects. Lipid peroxidation leads to an increase in membrane fluidity and permeability.$^{11}$
FIGURE 6. Effects of catalase and indomethacin on the hypoxanthine (Hx) plus xanthine oxidase (XO)--induced generation of PGE2 and 6-keto-PGF1α as well as the relaxation of the ductus arteriosus. Paired rings of ductus from seven lambs were suspended in 10 ml organ baths as described in “Materials and Methods.” The ductus rings were exposed to (in the following order): N2, O2, O2 plus hypoxanthine (100 μM) plus xanthine oxidase (0.01 IU/ml), and O2 plus hypoxanthine (100 μM) plus xanthine oxidase (0.01 IU/ml) plus indomethacin (5.6×10⁻⁶ M). To one of the rings, catalase (110 IU/ml) was added in addition to the hypoxanthine plus xanthine oxidase and in addition to the hypoxanthine plus xanthine oxidase plus indomethacin. To the other ring, boiled catalase was added at the same time points. The bath solution was collected for measurement of PGE2 and 6-keto-PGF1α after 30 minutes of ductus exposure at each condition; the collection period for hypoxanthine plus xanthine oxidase (with or without active catalase) was 15 minutes. The tension in the ductus was measured at the end of each collection period. Prostaglandins are expressed as median values of pg released/mg wet weight/collection period. Tension is expressed as mean±SD. Comparing the values obtained when the ductus was exposed to Hx+XO versus the prior period in O2 alone: *p<0.02, **p<0.002 (n=7). Comparing the values obtained when the ductus was exposed to hypoxanthine plus xanthine oxidase plus indomethacin: †p<0.02, ‡p<0.005 (n=7).

Aldehydes formed during the peroxidation of fatty acids can cross-link primary amine groups. Oxidation of sulfhydryl groups in the calcium-ATPases of plasma membranes, mitochondria, and endoplasmic reticulum decreases their activity. Oxygen metabolites can also damage Na, K-ATPase. In addition to its ability to alter protein structure, oxidation reactions can accelerate both selective proteolysis and enzymatic function. For example, hydrogen peroxide stimulates the activity of guanylate cyclase, thus increasing cyclic GMP and causing relaxation. Oxygen-derived metabolites can either stimulate or depress endothelium-dependent relaxations. In addition, there are complex interactions between reactive oxygen metabolites and prostaglandin production. During the activation of cyclooxygenase, OH⁺ is formed. The hydroxyl radical in turn inactivates the prostaglandin synthetase. On the other hand, active oxygen species can liberate arachidonic acid by stimulating lipid peroxidation of cell membranes and activating phospholipase A₂. Oxygenases that catalyze the first committed step in eicosanoid formation have an unusual requirement for lipid hydroperoxides. Both H₂O₂ and lipid hydroperoxides can accelerate cyclooxygenase activity.

Our studies show that xanthine oxidase--derived oxygen metabolites can stimulate the production of PGE₂ and PG₁₂ in isolated lamb ductus arteriosus. The relation between oxygen metabolite--induced
PGE₂ production and vasodilation seems likely. Although basal PGE₂ production is approximately 1/50 of PGİ₁ production (reflected by its stable metabolite 6-keto-PGF₁₀), prior studies have shown that PGE₂ is approximately 1,000 times more powerful than PGİ₁ in relaxing ductus constriction.²⁻³ In addition, xanthine oxidase-derived oxygen metabolites induce a 15-fold increase in PGE₂ but only a doubling of PGİ₁. Addition of catalase completely inhibited the hypoxanthine-xanthine oxidase-induced prostaglandin production and blocked the associated relaxation of the ductus. Furthermore, indomethacin blocked both the H₂O₂ and the hypoxanthine-xanthine oxidase-induced relaxation of the ductus; in addition, indomethacin reversed the increased rate of prostaglandin production and relaxation that had been previously induced by hypoxanthine-xanthine oxidase. In some studies, indomethacin has been found to be both a weak scavenger and a weak inhibitor of free radical formation; however, under experimental conditions similar to those described in the present study, indomethacin has not been found to interfere with oxygen metabolite production.¹⁷ These results suggest that PGE₂ was the mediator of oxidant-induced vasodilation of the ductus arteriosus.

It is interesting to note that H₂O₂ or H₂O₂-derived metabolites produce opposite effects in the rabbit pulmonary circulation, namely, vasoconstriction that can be inhibited by catalase and indomethacin.¹⁷,²² The difference in the response of these two neighboring vascular beds is probably due both to differences in the local production of prostaglandins as well as to differences in the sensitivity of the vessels to the prostaglandins produced. For example, the ductus arteriosus is exquisitely sensitive to the prostaglandins produced. Indomethacin inhibited the increased production of PGE₂ and reversed the relaxation that was previously induced by 1 mM hypoxanthine. In four experiments, pretreatment of the ductus with indomethacin prevented 1 mM hypoxanthine from relaxing the tissue (data not shown).

Thus, both reactive oxygen metabolites and hypoxanthine may relax the ductus and inhibit postnatal constriction. These effects are not independent but rather work through the production of PGE₂. Reactive oxygen metabolites may account for or contribute to the increased PGE₂ production that has been observed when the ductus is exposed to elevated Pₐ.⁴¹,⁴² This PGE₂ opposes the oxygen-induced constriction of the ductus, and the final degree of ductus constriction is determined by the vessel’s sensitivity to PGE₂.

Similarly, after contraction of the ductus arteriosus, there is ischemia of the vessel wall. Generation of hypoxanthine and reactive oxygen metabolites may be responsible for the increased production of PGE₂ found in ischemic ductal tissue. This source of PGE₂ appears to be responsible for reopening of the ductus after initial closure in preterm infants.⁴³

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