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# Effects and Interactions of Oxygen and Prostaglandins on the Tone of the Isolated Human Umbilical Artery

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## ABSTRACT

**Prostaglandin $E_2$ ($PGE_2$) and prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) were found to be equipotent contractors of the isolated human umbilical artery (HUA) in the concentration range 0.2–40 μg/ml. Prostaglandin $E_1$ ($PGE_1$) relaxed HUA at 0.1–3.0 μg/ml, whereas at 10–50 μg/ml contraction occurred. $PGE_2$ was significantly more potent at a $PO_2$ of 102 mmHg than at 27, 48 and above 400 mmHg. An increase in $PO_2$ *per se* (27–>400 mmHg) resulted occasionally in minor increases in the tone of the HUA. Such effects of oxygen had a lag period of 10–15 min. It is suggested that an increased formation of prostaglandins in the umbilical artery at birth is a more likely cause of the closure of the vessel than an increase in $PO_2$.**

## INTRODUCTION

The human umbilical artery (HUA) seems to be devoid of nervous motor regulation (for references, see 9). Hence, in studies on the regulation of the tone of this vessel, including the rapid closure at birth, interest has been focused on possible humoral mediator systems and physical factors, such as increase in oxygen tension, cooling, or stretching (1, 13, 16, 19).

It has recently been suggested that prostaglandins (PGs) may play a role in maintenance of the tone of the HUA (23). This proposition was based on the findings that human umbilical arteries are capable of synthesizing PGs (11, 24, 25) and that the resting tone of the isolated HUA is depressed by the PG synthetase inhibitors indomethacin and eicosa-5,8,11,14-tetraynoic acid and the PG antagonist polyphloretin phosphate (21).

For the closure of the HUA, as well as of the *ductus arteriosus*, the increase in oxygen tension taking place at birth is considered the major causative factor. In accordance with this concept an increase in oxygen tension has been shown to result in constriction of the *ductus arteriosus* (12, 16). On the other hand, a similar effect of oxygen on the isolated umbilical artery seems to be a less regular finding. Thus some authors have reported a constricting effect (3, 5, 16, 17) while others have demonstrated effects only in some preparations (13) or in none at all (12). In the present investigation we have compared the effects of the prostaglandins $E_1$, $E_2$ and $F_{2\alpha}$ and of changes in oxygen tension on the tone of the HUA, and also studied the interactions between these factors.

## MATERIAL AND METHODS

Human umbilical cords from infants delivered at full term were obtained immediately after cord clamping and transported to the laboratory in Krebs-bicarbonate-glucose solution (7). Spiral strips of the arteries were prepared as described elsewhere (21) and mounted in 5 ml organ baths within 20 min after delivery of the infant for isotonic recording by means of a Harvard smooth muscle transducer and a Servogor II recorder. The baths were aerated with one of four different $O_2/CO_2/N_2$ mixtures, all containing 5% $CO_2$ which resulted in a $PCO_2$ of approximately 40 mmHg in the bath fluid. These mixtures contained 0.6%, 5%, 15% or 95% $O_2$, producing a $PO_2$ in the bath fluid of 27±1.5 (Mean±S.D.), 48±0.5, 102±0.5, 102±1 and >400 mmHg, respectively. When the gas was changed from a low to a high $O_2$ content, the $PO_2$ of the bath fluid was equilibrated within 60 sec. The temperature was maintained at 37°C and the pH at 7.3–7.4.

### *Effects of PGs on the tone of HUA*

Spiral artery strips were exposed to submaximal concentrations of 5-hydroxytryptamine (5-HT) and papaverine in order to determine the contraction-relaxation span as described earlier (21). After standardization, the papaverine was washed out and the desired gas mixture was supplied. The tone of the preparation was allowed to stabilize at the level attained spontaneously. Subsequently cumulative dose–response curves for $PGE_1$ and $PGE_2$ were determined. The observed effects on tone are expressed as

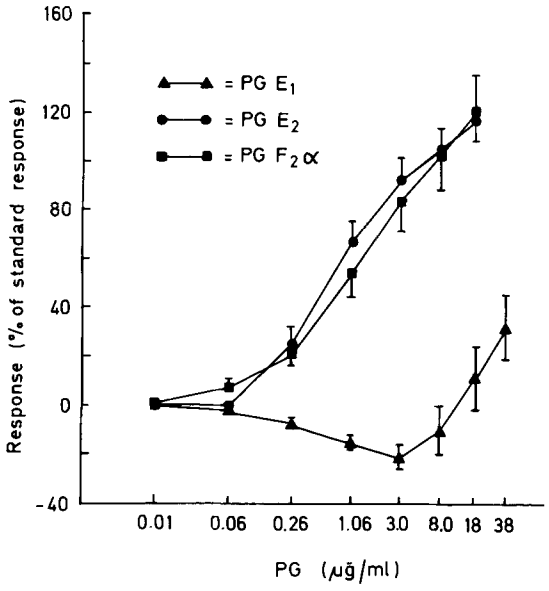


*Fig. 1.* Cumulative dose–response curves for $PGE_1$ ($n=15$), $PGE_2$ ($n=8$), and $PGF_{2\alpha}$ ($n=12$). The organ baths were aerated with a gas mixture containing 15% $O_2$. Means and S.E.M. are given.

percentages of the standard response, i.e. the contraction–relaxation span. The prostaglandins ($PGE_1$ U-10136, $PGE_2$ U-12062 and $PGF_{2\alpha}$-tromethamine salt U-14583 E) were generous gifts from Dr J. E. Pike, Upjohn. They were dissolved in $Na_2CO_3$–ethanol–water by the procedure recommended by the manufacturer. The stock solutions were diluted in distilled water. All solutions were stored at −20°C.

*Effect of oxygen on the tone of HUA*

The baths were gassed with the 0.6% $O_2$ gas mixture for 1–3 hours. After this period the $PO_2$ was abruptly increased by gas exchange. No drugs were administered to the smooth muscle preparations prior to the shift in $PO_2$. After 45–90 min 5-HT (0.2 μg/ml) was added to the bath solution to test the capacity of the preparation to contract. A response to oxygen was defined as an increase in tone of at least 5% of the response to 5-HT within 20 min after gas exchange.

Student's *t*-test was used for statistical analysis of the responses to $PGE_2$ at different oxygen tensions.

## RESULTS

*Effects of $PGE_1$, $PGE_2$ and $PGF_{2\alpha}$ on the tone of HUA*

$PGE_2$ and $PGF_{2\alpha}$ contracted the isolated HUA in the concentration range 0.2–40 μg/ml. In this respect they were about equipotent. In contrast, the cumulative dose–response curves for $PGE_1$ were biphasic in 42 of 44 preparations (Fig. 1). At concentrations of 0.1–3.0 μg/ml relaxation was obtained. Concentrations of 10–50 μg/ml produced an increase in the tone. In two preparations with very high initial tone levels (>100% of the standard response), $PGE_1$ caused no contraction.

*Effect of oxygen on the tone of HUA*

In a series of 21 experiments the smooth muscle preparations were subjected to conditions mimicking the situation present at birth in the sense that the $PO_2$ was increased from a value of approximately 27 mmHg (0.6% $O_2$ mixture). Three out of 10 preparations responded significantly to an increase in the oxygen content of the supplied gas mixture from 0.6% to 15%. Only 2 of 11 preparations showed an increase in tone when this content was raised from 0.6% to 95%. The onset of a response was recorded 10–15 min after gas exchange. The responses were all small and amounted only to 5–15% of the response to 5-HT. The most pronounced response to oxygen observed in these experiments is shown in Fig. 2.

*Prostaglandins and oxygen*

Regardless of oxygen tension, the dose–response curves for $PGE_1$, $PGE_2$ and $PGF_{2\alpha}$ showed the same pattern. The influence of oxygen on the action of $PGE_2$ was analysed in greater detail. The responses of the preparations gassed with 15% $O_2$ were significantly higher than those of the preparations gassed with 0.6% $O_2$ ($p<0.01$), 5% $O_2$ ($p<0.05$) or 95% $O_2$ ($p<0.05$). No significant difference was found between the responses of the preparations gassed with 0.6%, 5% and 95% $O_2$ (Fig. 3).

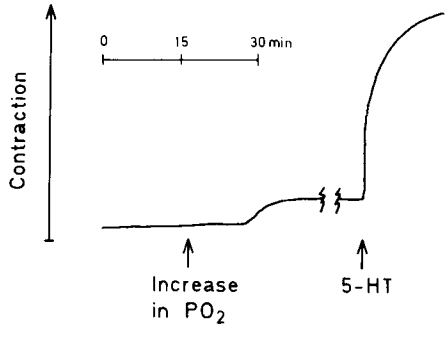


*Fig. 2.* Effect of an oxygen increase (from 0.6% to 15%) and of 5-HT (0.2 μg/ml) on an isolated human umbilical artery.

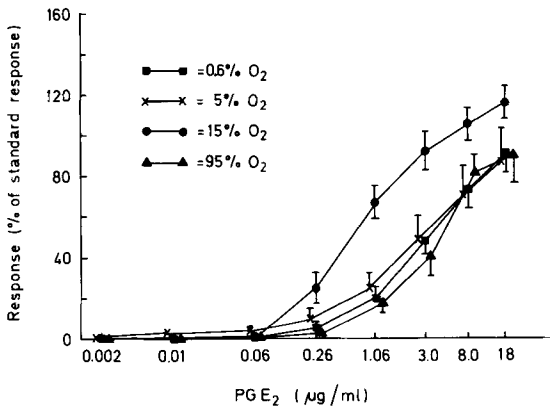


*Fig. 3.* Cumulative dose–response curves for $PGE_2$ at different oxygen tensions. Means and standard errors of the mean for preparations aerated with 0.6% $O_2$ ($n$=8), 5% $O_2$ ($n$=6), 15% $O_2$ ($n$=8), and 95% $O_2$ ($n$=4) are given.

## DISCUSSION

The contractile effects of $PGE_2$ and $PGF_{2\alpha}$ demonstrated in this study are in agreement with earlier results (1, 8, 18). The biphasic dose–response curve for $PGE_1$ explains previous, apparently contradictory statements. Thus the responses to low concentrations of $PGE_1$ are consistent with the findings of relaxation at 1 μg/ml (8), and like Park et al. (18) we observed contraction at high concentrations of $PGE_1$. In two control experiments the dose–response curve for $PGE_1$ was also biphasic at 34°C, the temperature used by Park et al. (18).

The responses to $PGE_2$ were significantly stronger at a $PO_2$ of about 102 mmHg than at 27, 48 or more than 400 mmHg. Essentially similar results have been reported for bradykinin, 5-HT and adrenalin (5, 14, 15). Neither in the studies cited nor in ours was the enhancing effect of oxygen on the response to the agonist impressive. In fact, it might merely reflect basic needs of oxygen for aerobic metabolism.

In approximately one-fourth of the isolated HUA, oxygen *per se* produced a small increase in tone. Thus 3 of 10 preparations responded 10–15 min after the $PO_2$ was increased from about 27 mmHg to 102 mmHg or more. This increase in $PO_2$ is greater and it was produced more promptly than the increase in $PO_2$ at birth, when it takes 8–10 min (10) or possibly even longer to change from 25–35 mmHg to 55–75 mmHg (6, 22).

A review of the literature shows that some of the investigators reporting significant contractile effects of oxygen have used 95–100% oxygen, producing $PO_2$ values of 400 mmHg or higher, i.e. values beyond the physiological level (3, 17). Others have not reported whether all or only some of their preparations responded to oxygen (e.g. 5). In accordance with our findings, however, Lewis (13) found contractions in only 3 of 11 isolated human umbilical arteries and in 5 of 22 lamb umbilical arteries on increasing the $PO_2$ from 25 to 120–160 mmHg. Similarly, Kovalcik (12) demonstrated contractions of the *ductus arteriosus* but no effect on the umbilical artery of guinea pig foetuses *in vitro* following an increase in $PO_2$. Oberhänsli-Weiss et al. (16) reported that oxygen altered the tone of the umbilical artery from foetal lambs 'far less' than that of the *ductus arteriosus*. Only for the *ductus arteriosus* were significant changes reported. Furthermore, an increase in arterial $PO_2$ in lamb foetuses induced by ventilation of the foetal lungs (4) or by giving the ewe hyperbaric oxygen (2) has been shown to result in a decrease in umbilical blood flow of about 10%, while ductal blood flow is reduced to one-third of the original flow or even less (2). These latter data agree with the present findings that the effects of oxygen on the human umbilical artery are inconsistent and, if present, small and with late onset. Thus it does not seem likely that the gradual increase in $PO_2$ at birth accounts for the closure of this vessel, since this process takes place within the first minute or minutes of life (20, 26). In this context it is of interest that high levels of PGs have been found in umbilical cords analysed immediately after delivery (11). Since the prostaglandins identified, i.e. $PGE_2$ and $PGF_{2\alpha}$, and in particular the precursor PG endoperoxides, are potent contractors of the HUA (present data, 24) it is suggested that an increased formation of prostaglandins in the human umbilical artery at birth is a more likely cause of the closure of the vessel than an increase in $PO_2$.

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