TITLE: MODERATE HYPOXIA IMPAIRS ENDOTHELIUM-DEPENDENT RELAXATION OF RABBIT PULMONARY ARTERY

AUTHOR: R. A. Johns, M.D.

AFFILIATION: Department of Anesthesiology, University of Virginia School of Medicine, Charlottesville, Virginia

Introduction: The endothelium plays an important role in the metabolism and production of vasoactive substances affecting the pulmonary circulation. Recent evidence indicates that endothelium-derived relaxing factor (EDRF) is a mediator for the vasodilation produced by several agents which relax pulmonary vessels. This substance may also be important in the modulation of basal pulmonary vascular tone. It is possible that inhibition of EDRF by hypoxia could play a role in modulating the hypoxic pulmonary vasoconstrictor response. This study was designed to determine if the relaxation of pulmonary arteries by agents which release EDRF is impaired by hypoxia.

Methods: New Zealand White rabbits (5 lb) were anesthetized with ketamine and sacrificed by aortic exsanguination. The heart-lung block was removed and placed in Krebs' solution. Right and left first branches of the pulmonary artery were carefully dissected free of perihilar fat and adventitia, and cut into 2.5 mm rings. The rings were then hung in water-jacketed baths containing Krebs' buffer at 37°C, gassed with 95% air/5% CO_2 and connected to Grass FT-03 force transducers to measure isometric tension. Optimal resting tension was determined by preliminary length-tension experiments, and active tension was induced with an EC50 dose of phenylephrine. Hypoxia was produced by gassing the baths with a blend of 95% nitrogen/5% CO_2 and 95% air/5% CO_2. The PO_2 of the Krebs' solution in the tissue baths was determined with a Radiometer blood gas analyzer. Indomethacin (2.8×10^{-6} M) was present in the buffer throughout all experiments to eliminate relaxation responses due to prostacyclin. To eliminate the endothelium-independent relaxation responses due to the ATP metabolic product adenosine, experiments involving ATP were performed in the presence and absence of compound BW-A1443U (1×10^{-5} M), an adenosine receptor inhibitor.

Cumulative dose-dependent relaxation responses to the endothelium-dependent vasodilators methacholine ($1X10^{-8}$ to 10^{-5} M), the calcium ionophore A23187 ($3X10^{-9}$ to $3X10^{-7}$ M), and adenosine triphosphate (ATP; $1X10^{-7}$ to $3x10^{-5}$ M), as well as to the endothelium-independent dilators, sodium nitroprusside (SNP; $1x10^{-10}$ to $3x10^{-7}$ M) and isoproterenol ($1x10^{-10}$ to $1x10^{-7}$ M), were determined before, during, and after exposure to hypoxia (PO_2's of 136 ± 2, 42 ± 1, and 137 ± 2, respectively). Each ring served as its own control and data were discarded if relaxation responses following hypoxia were not within 10% of those prior to hypoxia. Significant differences ($p<0.05$) between responses in air vs hypoxia were determined by Student's paired t-test; data are expressed as mean ± SEM.

Results: Dose-dependent vasodilation by the endothelium-dependent vasodilators methacholine, A23187, and ATP was significantly impaired by hypoxia while that to the endothelium-independent dilators sodium nitroprusside and isoproterenol was not. Representative data for each of these agents at their maximum dilating dose are presented in Table 1. Complete dose-response data for the calcium ionophore A23187 is shown in Fig. 1 and for SNP in Fig. 2.

Conclusions: Moderate hypoxia impairs endothelium-dependent vasodilation of rabbit pulmonary arteries but does not affect the relaxation due to endothelium-independent dilators. If this same effect occurs at resistance vessels in vivo, it could be a significant component of the mechanism of the hypoxic pulmonary vasoconstrictor response.

TABLE 1: EFFECT OF HYPOXIA ON RELAXATION OF RABBIT PULMONARY ARTERY

DRUG	1st CYCLE (NORMOXIA)	2nd CYCLE (HYPOXIA)	3rd CYCLE (NORMOXIA)
METHACHOLINE, 10^{-6}M	54.4±6.3	19.4±11.4*	55.6±4.8
A23187, $3X10^{-7}$M	82.8±6.1	27.3±16.6*	71.8±3.1
ATP, $3X10^{-5}$M	95.0±5.0	69.8±9.0*	96.5±4.0
ATP, $3X10^{-5}$M + BW-A1433U	71.8±6.4	31.0±9.3*	70.0±6.5
SNP, $3X10^{-7}$M	97.8±1.1	96.1±1.60	97.7±1.1
ISOPROTERENOL, 10^{-7}M	82.8±1.9	85.7±3.00	85.6±2.4

Relaxations to endothelium-dependent agents (*italic*) were significantly impaired by hypoxia while those to endothelium-*in*dependent agents were not. Data expressed as mean percent relaxation ± SEM; *p<0.05; n=6-10.

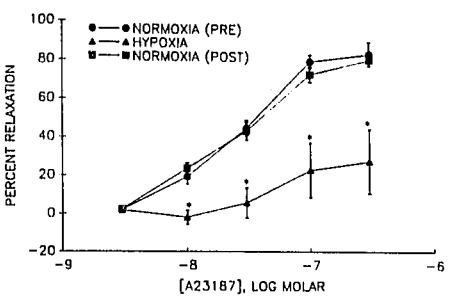

Fig. 1

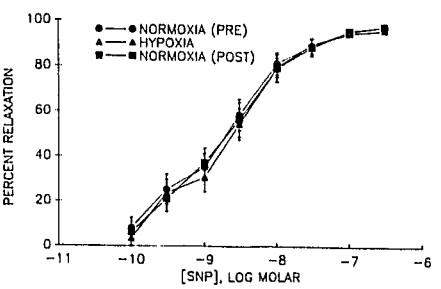

Fig. 2

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/69/3A/A858/641570/0000542-198809010-00858.pdf by guest on 03 April 2024