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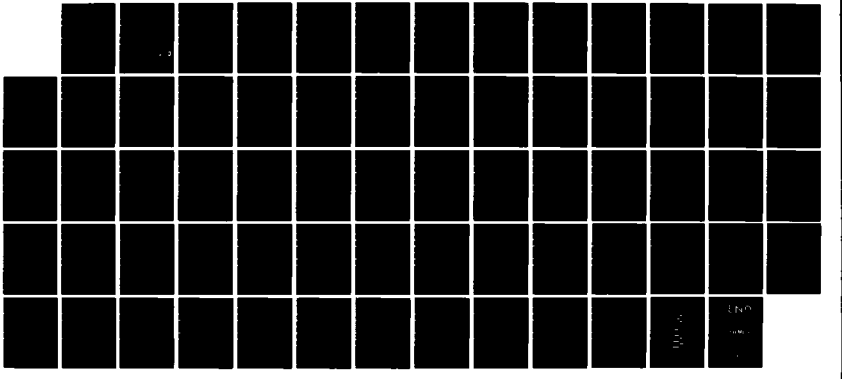

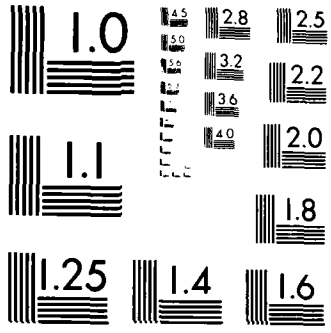

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EFFECTS OF CHRONIC HYPEROXIA ON THE CARDIOVASCULAR RESPONSES TO VASOACTIVE COMPOUNDS IN THE RABBIT

By JEFFREY C. SVENTEK

A thesis submitted to the

Graduate School-New Brunswick

Rutgers, The State University of New Jersey

in partial fulfillment of the requirements

for the degree of

Master of Science

Graduate Program in Physiology and Neurobiology

Written under the direction of

Professor Edward ~~J. Zam~~braski

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Effects of chronic hyperoxia on the cardiovascular responses to vasoactive compounds in the rabbit

by JEFFREY C. SVENTEK

Thesis Director: Professor Edward J. Zambraski

Hyperoxia has been shown to disrupt certain membrane bound enzyme systems within the pulmonary endothelium which are responsible for the metabolism of several endogenous vasoactive compounds. This study evaluated whether the potential disruption of the angiotensin converting enzyme (ACE) and the prostaglandin dehydrogenase/reductase (PGDH/R) enzyme, as a consequence of chronic hyperoxia, would alter the activation/deactivation of the angiotensins (I and II) or prostaglandins and thereby alter their peripheral cardiovascular actions. Two groups of conscious, chronically catheterized rabbits, one group exposed to ambient air and the other group exposed to >98% oxygen, were given bolus injections of angiotensin I, angiotensin II, prostaglandin E_2, sodium nitroprusside, and phenylephrine before and during extended exposure to air or oxygen. Basal mean arterial pressure decreased for both groups during the exposure. However, the normoxic and the hyperoxic basal mean arterial pressures were never significantly different from one another at any exposure point. Basal heart rate for the hyperoxic animals significantly increased during the exposure period while the basal heart rate for the normoxic group was unaltered. The hyperoxic animals demonstrated a significant

decrease in mean arterial pressure responsiveness to both angiotensin I and angiotensin II. The decrease in the angiotensin II response achieved significance prior to any significant changes in the angiotensin I response. The hyperoxic animals also demonstrated a significant increase in the vasodilatory responses to arterial prostaglandin E_2 throughout the entire oxygen exposure and a transient change in the mean arterial pressure response to sodium nitroprusside. Intravenous prostaglandin E_2 responses were unaltered with hyperoxia. Normoxic animals did not demonstrate any significant changes for any of the drugs tested. These data indicate that chronic hyperoxia induces changes in the ACE, and may alter systemic angiotensin II receptors. The ability of the PGDH/R enzyme to regulate the peripheral vasoactivity of intravenous prostaglandin E_2 was unaltered with hyperoxia.

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By JEFFREY C. SVENTEK

Captain, United States Air Force

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LIST OF ABBREVIATIONS

ACE----------Angiotensin Converting Enzyme

Ang I----------Angiotensin I

Ang II----------Angiotensin II

BPAP----------Benzoyl-Phenylalanyl-Alanyl-Proline

DPC----------Dipeptidyl Carboxypeptidase

GSH----------Reduced Glutathione

HR----------Heart Rate

i.a.----------Intra-arterial

i.v.----------Intravenous

MAP----------Mean Arterial Pressure

NADP+----------Nicotinamide Adenine Dinucleotide Phosphate

NP----------Sodium Nitroprusside

PE----------Phenylephrine

PGA_1----------Prostaglandin A_1

PGA_2----------Prostaglandin A_2

PGDH/R----------Prostaglandin Dehydrogenase/Reductase

PGE_1----------Prostaglandin E_1

PGE_2----------Prostaglandin E_2

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existed. Post hoc analysis of the analysis of variance was accomplished using the least significant difference. Normoxic versus hyperoxic group data were evaluated using a standard Student t test for independent samples. A difference was considered significant if $p<0.05$.

recorder during all injections. Arterial pressure was measured via the carotid arterial catheter using a Statham P23AA transducer. MAP was determined by electronically averaging pulsatile pressure. HR was determined from pulsatile arterial pressure.

At the end of each bolus injection series, animals were reexposed to either 100% or 21% oxygen. This protocol was continued until the oxygen exposure proved fatal to the experimental animals. Control animals were terminated by pentobarbital overdose after 88 hours of exposure. Following either hyperoxia induced death or termination by anesthesia overdose, lungs were excised and weighed for wet weight. To determine lung dry weight, lungs were homogenized and dried in an oven at 65°C for 2 weeks (42) and then weighed. Comparisons were made for dry weight versus wet weight as an indice of pulmonary edema.

All values in the text represent the mean $\pm$ SEM. Statistical analysis utilized an analysis of variance for repeated measures for 21 animals through 56 hours of exposure for the hyperoxic group and for 5 animals through 88 hours of exposure for the normoxic group. An analysis of variance for repeated measures was also utilized to analyze the data for the nine animals that survived through 72 hours of hyperoxia. A comparison of sample means for the nine surviving animals with the population means of the 21 experimental animals through 56 hours was made and no significant differences were obtained. Additionally, the mean for the nine surviving hyperoxic animals was compared with the mean of the 15 surviving animals at the 64 hour exposure time point and no significant differences

METHODS AND MATERIALS

Twenty six male and female rabbits, 2.5 - 4.6 kg in weight, were randomly divided into a control normoxic group (n=5) and an experimental hyperoxic group (n=21). Animals were maintained on standard rabbit chow and provided water ad libitum throughout the experiment. Polyethylene catheters were implanted in the right external jugular vein and the right carotid artery of anesthesized rabbits (pentobarbital, 30 mg/kg) under sterile surgical conditions.

The animals were allowed 24 hours to recover and then control MAP and HR measurements in response to select vasoactive compounds were made by administering bolus injections of: 0.3 µg Ang I (i.v.), 0.3 µg Ang II (i.v.), 0.2 µg PGE_2 (i.a.), 0.4 µg PGE_2 (i.v.), 100 µg NP (i.v.), and 100 µg PE (i.v.). These dosages resulted in changes in MAP ranging from -40 to +100 mmHg. MAP and HR were allowed to return to preinjection levels before the next drug was administered. A second control bolus injection series was administered to each animal 24 hours later.

Animals then were placed in a sealed exposure chamber. Experimental animals were exposed to 100% oxygen, whereas, control animals were exposed to ambient (21% oxygen) air. Oxygen percentage inside the chamber was continuously monitored by a rapid response oxygen analyzer and maintained at a minimum of 98% for the experimental animals and 20.9% for the control animals. Animals were removed from the chamber every 8 hours during the exposure and the bolus injection series was repeated.

MAP and HR were continuously recorded on a Grass direct writing

PGDH/R enzyme, through measured changes in MAP responses to intravenous bolus injections of PGE_2, and

(4) to indirectly assess any changes in systemic Ang II receptors, through measured changes in MAP responses to intravenous bolus injections of Ang II.

change in the systemic cardiovascular response to intravenous PGE_2 after 8 hours of 100% oxygen exposure (55). These data suggest that after 8 hours of hyperoxia the ability of the renin-angiotensin system and circulating alpha adrenergic stimuli to influence systemic vasoregulation was still intact. This suggests that the ACE and the PGDH/R enzyme are functioning normally in determining the systemic levels of these vasoactive compounds after 8 hours of oxygen exposure.

Because 8 hours of oxygen exposure showed an augmentation in the cardiovascular responses to the angiotensins rather than the expected reduction in response, the question was raised whether by extending the exposure time beyond 8 hours one could elicit different changes in cardiovascular responses? Therefore, a project which extended the hyperoxia exposure time course beyond 8 hours was completed. The hypothesis was that chronic hyperoxia affects the systemic cardiovascular responses to specific vasoactive compounds, whose systemic levels are controlled by enzymes located in the endothelium of the pulmonary vasculature.

The primary purposes of this experiment were:

(1) to evaluate the effects of chronic hyperoxia on the cardiovascular system's response to exogenously administered vasoactive compounds,

(2) to indirectly assess any changes in the activity of the ACE, through measured changes in MAP responses to intravenous bolus injections of Ang I,

(3) to indirectly assess any changes in the activity of the

any obvious morphological changes in pulmonary tissue occurred. Because these enzymes determine systemic levels of various endogenous vasoactive compounds, the question of what effects do reductions in the activities of these two enzymes have on the circulating levels of the vasoactive compounds they normally regulate? Harabin et. al., (24), demonstrated an increase in the concentration of Ang I in pulmonary venous blood in conscious dogs under hyperoxic conditions. The systemic levels of the vasoactive compound Ang II, which were not measured by Harabin et. al. (24), should also be significantly affected by the reduced activity of the ACE enzyme because the conversion of Ang I to Ang II occurs primarily in the pulmonary vascular bed (34). Additionally, it is also known that Ang II is not affected by passage through the pulmonary vasculature (28). Similar work evaluating the effects of hyperoxia on the PGDH/R enzyme are lacking. However, measured levels of prostaglandin metabolites in lung lymph effluent show decreased levels with hyperoxia, suggesting a decreased activity of the PGDH/R enzyme (42).

Pitt (46) has suggested that any alteration in the pharmacokinetic function of the lung ultimately results in changes in systemic vasoregulation. A recent <u>in vivo</u> experiment in anesthesized dogs showed no changes in the systemic vasoregulation associated with the arterial administration of sodium nitroprusside (NP), phenylephrine (PE), and PGE_2 after oxygen exposure (55). However, there was a significant increase in the response of the systemic vasculature to intravenous Ang I and Ang II without any

conditions (22). This enzyme is commonly called Angiotensin Converting Enzyme (ACE), but is more appropriately called dipeptidyl carboxypeptidase (DPC) due to its ability to catalyze both the conversion of Ang I to Ang II and inactivation of bradykinin.

Gillis and coworkers (14,22) demonstrated a reduction in the this enzyme's ability to remove an Ang I analog called BPAP under hyperoxic conditions. BPAP is a synthetic tripeptide labelled with tritium and the letters represent the constituents; benzoyl-phenylalanyl-alanyl-proline (14,22). Their work showed significant reductions in ACE activity within 16 hours of exposure to 98% oxygen under ambient sea level pressures, whereas morphological changes in these animals were not present until 30 hours after oxygen exposure (14,22). These experiments, in conscious chronically catheterized rabbits, represent one of the first in vivo studies evaluating the effects of high oxygen tensions on the activities of specific endothelial enzymes. Before this study, most research efforts involved exposing animals to high concentrations of oxygen, excising the lungs, and then evaluating the effects of the oxygen while perfusing the isolated tissue (32,53,56). Therefore, the efforts of Gillis et. al. (14,22) in their evaluation of hyperoxia on ACE along with the work of Newman et. al. (42) on the PGDH/R enzyme represent a new and needed direction in determining the in vivo effects of hyperoxia on the activities of specific pulmonary enzymes.

The data from these in vivo experiments and the previous results using the isolated lung suggested that high oxygen concentrations were deleteriously affecting the ACE and the PGDH/R enzyme before

toxicity. For example, McGiff et. al. (40) confirmed that PGE_1 and PGE_2 were removed by dog lung in vivo and further showed that PGA_1 and PGA_2 survived the passage through the lungs without change. Dusting et. al. (15) showed that prostacyclin passes through the pulmonary circulation unchanged. Thus, even within this closely related group of substances, the inactivation process can distinguish different endoperoxides. The enzyme system which possesses this unique ability has been identified as the prostaglandin dehydrogenase/reductase (PGDH/R) enzyme (45). This enzyme system has been shown to possess decreased activity under hyperoxic conditions of 36 to 48 hours in vitro (32,44,53,56). The exact mechanism associated with this decrease in activity is not known. However, Klein et. al. (32) suggested that four possible alternatives exist to explain this phenomenon: (1) nonhomogeneity of perfusion, (2) inhibition of transcellular transport processes, (3) loss of prostaglandin dehydrogenase activity, and (4) cofactor limitation due to decreased NADP+ (32). More recent work has shown that the effects of hyperoxia on the PGDH/R enzyme appears to be a direct action of oxygen on the enzyme, causing a reduction in dehydrogenase activity (42,56). Of particular interest is the work done by Newman et. al. (42) whose data in sheep suggest that the activity of this enzyme is reduced with hyperoxia (42).

Another enzyme, localized on the luminal surface of the pulmonary endothelium (8,50), which activates angiotensin I (Ang I) by converting it to the more vasoactive angiotensin II (Ang II) (43) and inactivates bradykinin (18) is also affected by hyperoxic

alveolar cells are the earliest sites of injury in pulmonary oxygen toxicity. As these cells become susceptible to the free oxygen radicals, the barrier that normally exists between the alveolar airspace and the vascular compartment deteriorates, allowing an influx of proteins and fluid from the circulation. This may lead to sequential lung damage as a result of the loss of integrity of the barrier between the alveolus and the capillary. At concentrations of 95-100% oxygen this damage is severe, resulting in a major loss of endothelium with accompanying edema and subsequent death of the animal (11).

Therefore, oxygen free radicals can cause membrane damage, genetic damage, and enzymic inactivation (13). The natural defense mechanisms discussed earlier (i.e., superoxide dismutase and catalase) are designed to cope with radicals produced at normal oxygen tensions. However, at increased oxygen concentrations natural defenses are overwhelmed, resulting in excess oxygen radical-related cell damage. When the rate of this damage exceeds the rate of repair, cell and organism death can result (13).

Recent work has centered around the association of hyperoxia with the known enzymic inactivation effects on enzyme systems bound in the endothelial membrane structure of the pulmonary vasculature (22,32,42,53,56). Because enzymes in the pulmonary endothelium possess the ability to change the biological activity of a variety of substances presented to it by the circulation (2,46,51,52), much in vitro work has been undertaken to evaluate if specific enzymes are involved in the etiology and progression of pulmonary oxygen

essential for the development of pulmonary oxygen toxicity (48). Therefore, the role of PMN recruitment in the etiology and progression of pulmonary oxygen is unknown.

In addition to the superoxide dismutase and catalase enzymes which quench oxygen radicals, various other compounds can also act as antioxidants. Of primary importance is reduced glutathione (GSH), which is a preferential substrate for many oxidizing agents, thus sparing protein sulfhydryl groups from oxidation (33). GSH is also a substrate for glutathione peroxidase which converts hydrogen peroxide or lipid peroxides to water or non-toxic lipid hydroxides (19). The oxidized glutathione is reduced by glutathione reductase which uses NADPH generated in the hexose monophosphate shunt as the reducing agent (13). Other cellular compounds that can act as antioxidants and radical quenchers include ascorbic acid (vitamin C), cysteine and alpha tocopherol (vitamin E) (13,47).

In summary, the chain of events leading to hyperoxia-induced death can best be summarized as shown in figure 1. The relative importance of the two different pathways in figure 1 may depend on oxygen concentration, and subject species or age. It is likely that both internal and PMN-generated oxygen radicals contribute to the ultimate death of the animal.

The types of damage caused by oxygen radicals include lipid peroxidation, oxidation of protein sulfhydryls and oxidation of nucleic acids (5,21). Crapo et. al. (11) demonstrated that the endothelial cells of the pulmonary vessels and the epithelial Type I

of superoxide radicals and hydrogen peroxide. It is not known whether it is possible to quench the free hydroxyl radicals due to their very high reactivity with almost any biological compound (13,47). However, in vitro work has shown that this radical form can be scavenged by mannitol, benzoate and vitamin E (47).

Recently, another highly reactive oxygen free radical was discovered (47). This radical, referred to as singlet excited oxygen, is a result of the chemical interaction between superoxide anions and hydroxyl radicals (47). The contribution of this radical to the development of pulmonary oxygen toxicity is not known (47).

Polymorphonuclear (PMN) leukocytes may play a primary role in the generation of oxygen radicals and therefore may be a significant factor in the resulting lung damage and death (13). The influx of PMN into the lung endothelial and epithelial cells is due to the production and release of PMN chemotactic factors by lung macrophages responding to the hyperoxia induced increase in free oxygen radicals already present in the cell (20,25). PMN recruitment acts as a positive feedback system for the generation of oxygen radicals and actually increases the already adverse conditions within the pulmonary cells. Therefore, it is paramount that the cells are able to quench the radicals as efficiently as possible. More recent evidence has raised questions concerning the role of PMN recruitment in the progression of pulmonary oxygen toxicity (48). These authors state that their data do not exlcude the possibility that PMN may aggravate the lung damage caused by hyperoxia (48). However, their work demonstrated that PMN are not

generated by active phagocytes as part of their bactericidal function (1).

Superoxide anions are catalytically scavenged and converted to molecular oxygen by the enzyme superoxide dismutase (13). This enzyme is found in all aerobic cells of the body and acts to react superoxide anions with one another to form molecular oxygen and hydrogen peroxide (21). Hydrogen peroxide, like the superoxide anion, is short lived and can also damage cells and microorganisms. Hydrogen peroxide is also released by active phagocytes when they scavenge bacteria (16). In the presence of iron, superoxide anion and hydrogen peroxide can react to form the hydroxyl radical (38). The hydroxyl radical is very reactive and does not move far from its site of generation without reacting with some biological molecule (39). Hydrogen peroxide is much less reactive and is therefore able to diffuse through solutions and/or membranes to induce damage at short distances from its site of generation (13).

Hydrogen peroxide is detoxified by the enzyme catalase to form water and molecular oxygen (39). The catalase reaction together with the actions of superoxide dismutase act in concert to protect the cell and the organism against the toxic actions of oxygen free radicals. As long as these enzymes maintain their functions, the hydroxyl radical will not form (13). However, in the presence of high concentrations of free radicals, these protective enzymes seem to last only for approximately 24 hours, after which pulmonary damage becomes evident (47). Once these antioxidant enzyme systems are lost, free hydroxyl radicals will form due to the accumulation

(10,12,13,22,26,42,47,53). Bean has classified the pathological responses of the pulmonary system to high concentrations of oxygen into two phases: the initial or acute phase and the subsequent or proliferative phase (3). This distinction is based on the chronological occurrence of the various symptoms observed. For example, the earliest symptoms classified under the initial phase include: edema, hemorrhage, swelling of the lung tissue, destruction of capillary endothelial cells, and destruction of the Type I alveolar epithelial cells (10). As the oxygen toxicity progresses, symptoms such as interstitial fibrosis, proliferation of fibroblasts, and proliferation of Type II alveolar epithelial cells occur (10). These conditions all occur during the subsequent phase of pulmonary oxygen toxicity and are considered an attempt by the body to repair itself (10).

Many theories as to the etiology of pulmonary oxygen toxicity have been proposed. No single theory fully explains the mechanism(s) of the toxicity problem. Recent data suggest the possibility of action on the pulmonary tissue by oxygen free radicals (12,13,42,53). Numerous biological oxidations (27) and autooxidations can convert molecular oxygen to the oxygen free radical, superoxide anion (17). This reaction involves the reduction of molecular oxygen by one electron, forming the highly reactive and short lived superoxide anion. The autooxidations of mitochondrial respiratory chain constituents (hydroquinones and flavins) and several other enzymatic reactions may also liberate superoxide anions (13,47). Additionally, superoxide radicals are

INTRODUCTION

Oxygen, since its discovery by Priestly in 1774 (9), has been recognized as the most important gas for sustaining life and as such has been the object of intense investigation. In 1775, the deleterious effects produced by high concentrations of oxygen were reported by Lavoisier, and Paul Bert in 1877 observed that all organisms were susceptible to the damaging effects of high concentrations of hyperbaric oxygen (58). The first clinical evidence of oxygen toxicity appeared in the 1940's when high concentrations of inspired oxygen were associated with damage to the eyes of newborn infants (35).

Oxygen toxicity may be manifested either through the pulmonary system or the central nervous system (10). Central nervous system oxygen toxicity will normally only occur at high oxygen concentrations applied at pressures greater than three atmospheres (e.g., breathing 100% oxygen at 66 feet below sea level). Hyperbaric oxygen toxicity progresses rapidly and symptoms are sudden and very severe (10). Common symptoms associated with central nervous system oxygen toxicity include facial twitching and convulsions. These effects can be fatal to the animal if not quickly corrected (10).

Pulmonary oxygen toxicity is observed clinically more frequently than central nervous system oxygen toxicity because it may occur under ambient conditions (i.e., one atmosphere of pressure). When 100% oxygen is delivered under normobaric conditions for a duration of 24 hours, damage to the pulmonary system occurs

RESULTS

The hyperoxic group had a mean body weight that was significantly greater than the normoxic group's mean body weight (Table I). Due to this difference, all measurements involving tissue weight were normalized for body weight (Table I). Lung wet weights and lung dry weights were not different for the two groups (Table I). However, when the lung dry/wet weight ratios for the two groups were compared, a significant difference existed (Table I). Because the lung dry weight for both groups were equal (Table I), the difference in the dry/wet weight ratio was due to a difference in wet weight (Table I).

Basal MAP and HR values for each control day and each 8 hour time point during the exposure to either ambient air or oxygen were compared for within group and between group differences. Table II shows that the basal MAP and HR values varied by no more than 15% on the two control days. MAP for the hyperoxic group was significantly lower on control day 2 when compared with the MAP on control day 1 (Table II). This difference was attributed to two animals whose basal MAP dropped 23 mmHg each from control day 1 to control day 2. However, there were no differences between the normoxic group values and the hyperoxic group's MAP values on either day (Table II). Basal HR demonstrated no differences within the groups or between the groups on either day (Table II). Therefore, the values for MAP and HR for each animal on control day 1 and control day 2 were averaged with the group mean MAP and HR values listed in the column titled "Basal Values" (Table II). These are the values that all

exposure MAP and HR values were compared with for statistical analysis. No differences existed between the groups for the MAP and HR "Basal Values" (Table II). These "Basal Values" represent the 100% of control for MAP and HR displayed in figure 2.

MAP decreased for both the normoxic and the hyperoxic animals during the 72 hour exposures (Table III). The normoxic group demonstrated a significantly lower basal MAP at 16 hours (not shown in Table III) and maintained a lowered MAP throughout the remainder of the exposure (Table III). The hyperoxic group did not show a decreased MAP until 40 hours and then maintained the significantly lower MAP throughout the remainder of the exposure (Table III). However, at no time were the MAP values different between the two groups (Table III). Due to the high degree of variability in individual MAP, the values for each animal were converted to percent of control. These data (fig. 2) show results similar to the original data in Table III. Both groups displayed decreased MAP during the 72 hours of exposure to ambient air or oxygen.

HR values, which were not different between the normoxic and hyperoxic groups for the basal condition, showed a rapid and significant increase for the hyperoxic group while the normoxic animals' HR remained the same throughout the exposure protocol (Table III). After only 8 hours of oxygen exposure, the hyperoxic animal's HR was significantly higher than the group's control value (Table III). In addition, the hyperoxic group HR was also different from the normoxic group's HR at 8 hours (Table III). The hyperoxic group maintained this significantly elevated HR throughout the 72

hour oxygen exposure (Table III). Figure 2 displays basal HR as a percent of control for both the normoxic group and the hyperoxic group. The normoxic HR was not different from the control value of 205 bts/min (100% of control) at any time during the ambient air exposure (fig 2). The hyperoxic HR increased by 14.7% ($p<0.05$) over the control after only 8 hours and maintained this increased HR throughout the remainder of the exposure, achieving a maximum of 126.6% ($p<0.05$) of the control after 40 hours of hyperoxia (fig 2). The hyperoxic group's HR was significantly higher than the normoxic HR at 16,24,56, and 72 hours (fig 2).

Table IV outlines the maximal MAP responses to the vasoactive compounds tested on each of the two control days. There were no significant differences for any of the vasoactive compounds on control day 1 or control day 2 (Table IV). The basal Ang I responses for the hyperoxic group were significantly lower than the normoxic group (Table IV). For all other compounds there were no significant differences for either within or between group comparisons (Table IV).

The responses to exogenous vasoactive compounds at each of the 8 hour time points during the 72 hour exposure were evaluated for differences from the control value within the same group. Differences between the normoxic and hyperoxic groups at the same time point were also evaluated. Figure 3 displays the maximal changes in MAP in response to the vasoconstrictors Ang I, Ang II, and PE. This figure only shows data through the 72 hour exposure point. Three rabbits survived through 80 hours and two rabbits were

still alive at 88 hours (Table VII). MAP responses for all vasoactive compounds at each 8 hour time point are provided in Tables V, VI, and VII.

MAP responses to Ang I were unaltered for the normoxic animals over the 72 hour period (fig 3). The hyperoxic group response to Ang I was significantly lower than the group's control response after 32 hours, where the MAP response was only 83.4% of control (fig 3). The MAP response recovered over the next 16 hours demonstrating responses at the 40 and 48 hour points that were not different from control (fig 3). The MAP response to Ang I for the hyperoxic animals decreased significantly after 56, 64, and 72 hours, reaching a level of only 46.9% of the control value at 72 hours (fig 3). The hyperoxic group MAP response was different from the normoxic group response at 32, 56, and 72 hours (fig 3). The animals that survived beyond 72 hours of oxygen exposure maintained the decreased MAP response to Ang I while the normoxic group maintained its MAP responses at levels not significantly different from the control (Table VII).

The MAP response to exogenous Ang II for the normoxic group was unaltered throughout the 72 hour exposure (fig 3). The normoxic group's MAP responses to Ang II after 80 and 88 hours were also unchanged from the normoxic control value of 26.1 mmHg (Table VII). The hyperoxic group maintained its ability to respond to Ang II only until 16 hours of hyperoxia (fig 3). After 16 hours, the hyperoxic animals' MAP response to Ang II was significantly lower than the group's control response of 28.3 mmHg by 18% (fig 3). The hyperoxic

group maintained the lower MAP response to Ang II through 72 hours, achieving a maximum of 55.3% of control ($p<0.05$) at 72 hours (fig 3). The animals surviving at 80 and 88 hours also demonstrated a reduced MAP response to Ang II (Table VII). Between group comparisons, normoxic versus hyperoxic, showed that significant differences existed at all time points except for 8 and 32 hours (fig 3).

Maximal changes in MAP to bolus administration of PE was unaltered for both the normoxic and hyperoxic groups throughout the 72 hour exposures (fig 3).

The vasodilatory response to arterial administration of PGE_2 was unchanged for the normoxic group over 72 hours (fig 4). However, the MAP response to arterial PGE_2 in the hyperoxic group was significantly greater than the control response of -8.5 mmHg at all time points except at 32 and 64 hours (fig 4). The maximum vasodilatory response of -13.2 mmHg occurred for the nine animals at 72 hours (Table VII). This represented a MAP response of 154.4% ($p<0.05$) of the control response (fig 4). However, the animals surviving beyond 72 hours of oxygen exposure did not maintain the significantly increased MAP response to arterial PGE_2 (Table VII). At no point during the exposure were the responses for the normoxic and hyperoxic groups significantly different from one another (fig 4).

Intravenous PGE_2 acted as a vasoconstrictor transiently increasing MAP (Table V). The normoxic group MAP response to PGE_2 (i.v.) was unaltered throughout the exposure except at 32 hours (fig

4). At 32 hours, the normoxic group MAP response was increased by 139% over the control response of 5.2 mmHg ($p<0.05$) (fig 4). The MAP responses for the normoxic group were not significantly different from the control responses for the remainder of the 72 hour exposure (fig 4) nor at 80 and 88 hours (Table VII). The hyperoxic group MAP response to intravenous PGE_2 was unaltered until 72 hours (fig 4). The MAP response at 72 hours represented a decrease of 46% from the control response of 5.8 mmHg ($p<0.05$) (fig 4). This significant drop in MAP response was due to two animals which demonstrated vasodilatory responses rather than pressor responses to intravenous PGE_2. The MAP response to PGE_2 (i.v.) for the animals surviving beyond 72 hours returned to levels comparable to the control response (Table VII). The MAP response for the hyperoxic group was significantly lower than the normoxic group after 48 and 72 hours (fig 4).

NP exhibited a potent vasodilatory response throughout 72 hours for the normoxic animals without any significant changes in their response from the control response of -25.0 mmHg (fig 4). The normoxic group MAP response to NP was unaltered at 80 and 88 hours (Table VII). The hyperoxic group MAP response to NP was unaltered through 32 hours (fig 4). However, after 40 hours the vasodilatory response to NP was -25.5 mmHg (Table VI) which represented a MAP response of 145% of control ($p<0.05$) (fig 4). This elevated response to NP was maintained at 48 and 56 hours (fig 4) and then returned to nonsignificant response levels at 64 and 72 hours (fig 4). The animals surviving after 80 and 88 hours of hyperoxia

demonstrated elevated MAP responses to NP (Table VII). The only exposure time point to demonstrate a statistically significant difference between the normoxic and hyperoxic MAP response to NP was after 16 hours (fig 4).

Figure 5 displays the data for MAP responses to the drugs tested as a percent of control for the hyperoxic group at 8, 24, 40, 56, 64, and 72 hours. The upward bars represent the MAP responses of the hyperoxic group to the vasoconstrictors Ang I, Ang II, PE, and intravenous PGE_2 (fig 5). The downward deflecting bars represent the MAP responses to the vasodilatory compounds arterial PGE_2 and NP (fig 5).

After 8 hours of hyperoxia, the only significant change in MAP reponse was for arterial PGE_2 which was 60% higher than the control response (fig 5). By 24 hours, in addition to the PGE_2 (i.a.) response which was still significantly elevated, the Ang II MAP response was significantly lower than the control response (fig 5). It is interesting to note that even though the decrease in Ang I response after 24 hours of hyperoxia was similar to the reduction in Ang II response (84% vs 82%), the Ang I response was not different from the Ang I control response (fig 5).

Forty hours of hyperoxia significantly elevated the arterial PGE_2 MAP response and significantly decreased the Ang II response (fig 5). Additionally, after 40 hours, a greater vasodilatory response to NP occurred in the hyperoxic group (fig 5). At this point in the oxygen exposure, the Ang II response was reduced to 69.3% of the control response ($p<0.05$) while the Ang I response was

91.3% of its control ($p>0.05$) (fig 5).

After 56 hours of oxygen exposure, MAP responses to PGE_2 (i.a.), Ang II, Ang I and NP were significantly different from their control MAP responses (fig 5). The Ang I MAP response was only 80.7% of its control response ($p<0.05$) (fig 5). The Ang II response was only 73.3% of its control response ($p<0.05$) (fig 5).

At 64 hours of hyperoxia, the 15 animals still alive demonstrated significantly different MAP responses to Ang I and Ang II while the MAP responses to arterial PGE_2 and NP were similar to control responses (fig 5). The Ang I MAP response was 71.5% of its control ($p<0.05$) while the Ang II MAP response was 63.7% of its control ($p<0.05$) (fig 5).

After 72 hours of hyperoxia, MAP responses to arterial PGE_2, intravenous PGE_2, Ang I, and Ang II were all significantly different from their respective control MAP responses (fig 5). The vasodilatory response to arterial PGE_2 was greater by 85.9% ($p<0.05$) (fig 5). The vasoconstrictor response to intravenous PGE_2 was decreased to a level of 54% of its control MAP response ($p<0.05$) (fig 5). Ang I and Ang II MAP responses remained significantly lower with the Ang I response representing 46.9% of the Ang I MAP control response and the Ang II MAP response representing 55.3% of its control MAP response.

DISCUSSION

The ability of the pulmonary vasculature to influence systemic levels of several vasoactive compounds is now well recognized and represents what is commonly referred to as the lung's pharmacokinetic function (2,14,46,49,51,52). The present study attempted to indirectly assess changes in this pharmacokinetic function in response to chronic hyperoxia by measuring changes in the systemic MAP responses to specific vasoactive compounds. In vitro (32,56) and in vivo (14,22,24,42) work have indicated that high oxygen tensions reduce the activities of specific membrane bound enzymes of the pulmonary vasculature which are responsible for the activation or deactivation of endogenous compounds that possess known vasoactive properties. Specifically, the ability of the ACE to proteolytically convert Ang I to Ang II has been shown to be reduced under conditions of hyperoxia (14,22,24). Additionally, Schatte et. al. (53) provided evidence for a reduction in the dehydrogenase activity of the PGDH/R enzyme responsible for inactivating circulating prostaglandins.

The significant decrease in basal MAP was a function of the surgery required for the experiment. Both groups displayed the same initial drop in basal MAP followed by maintenance of the lower MAP over the remainder of the exposure period. These data suggest that the reduced basal MAP was not due to hyperoxia. Rather, the drop in MAP was probably due to the chronic catheters implanted in the jugular vein and carotid artery. Dobuler et. al. (14) found the same response in chronically catheterized conscious rabbits. To avoid

this problem in future work, animals should be allowed 48 hours for recovery purposes followed by two days of control readings so that the basal MAP will have adequate time to recover from the anesthesia and adjust to the indwelling catheters.

Even though the normoxic and hyperoxic basal MAP decreased significantly during the exposure, the ability of the vasculature to respond to the compounds tested remained intact. This fact was substantiated by the normoxic group's ability to maintain responses that were not significantly different from their respective controls for all drugs tested (figs 3 and 4).

The basal HR change seen in the hyperoxic animals appears to be a direct result of oxygen exposure. This was also observed in conscious dogs *exposed* to oxygen for 96 hours (24). Therefore, oxygen has a chronotropic effect on the heart in both dogs and rabbits in vivo.

Data for lung weights provided evidence of pulmonary edema in the hyperoxic lungs but not in the lungs of the normoxic animals. This is consistent with the known pathology of pulmonary oxygen toxicity (10,13). Autopsies of all animals indicated that the hyperoxic animals died as a result of inadequate gas exchange which was complicated by the presence of interstitial fluids. This was determined by the significant differences obtained in the lung dry/wet weight ratio (Table I).

Previous work from our laboratory failed to provide any evidence for inactivation of these specific enzyme systems with an acute period of hyperoxia and in fact provided good evidence that

these enzyme systems maintained their pharmacokinetic function in the face of 8 hours of hyperoxia (55). The Ang I and Ang II data from the present study demonstrated a reduced ability of the systemic vasculature to respond to these pressor agents after as little as 16 hours of oxygen exposure. In contrast to the acute study (55), the potentiation of Ang I and Ang II MAP response following 8 hours of hyperoxia was not observed. Major differences between these two studies could account for this phenomenon.

The acute study utilized anesthesized dogs while the present study evaluated conscious rabbits. Interspecies differences in response to oxygen exposure with regard to life expectancy and pathology are well documented (10,12). Additionally, it has been suggested that the enzymic inactivation response may also be species dependent (24). Therefore, the MAP response differences after 8 hours of oxygen exposure may simply be a species dependent phenomenon.

Another very important factor which could explain the differences in Ang I and Ang II MAP responses after 8 hours of hyperoxia was the use of anesthesia in the acute study. Anesthesia has been shown to confound the changes observed in the pulmonary tissue responses to hyperoxia and actually acts to protect the lung (4). More recently, it was proposed that the use of anesthesia may also alter the pulmonary enzyme response to hyperoxia (24). The data from the present study suggests that the use of anesthesia in the acute study (55) protected the animal from the effects of hyperoxia. This indicates that <u>in vivo</u> studies must utilize

conscious animals to avoid masking of the hyperoxic effects. Therefore, the use of two different animal species, combined with the use of anesthesia in the acute study (55) versus conscious animals in the present study, may explain the observed differences in MAP responses to Ang I and Ang II after 8 hours of oxygen exposure.

Data for exposures beyond 8 hours showed that changes in systemic MAP responses to intravenous Ang I occurred after 32 hours of hyperoxia, recovered briefly, and then decreased to significantly lower levels after 56 hours (fig 3). The significant reduction in the systemic MAP response to Ang I in the hyperoxic animals and not in the normoxic group suggests that the high oxygen tensions reduced the activity of ACE. This is consistent with recent work in conscious dogs which showed an increased systemic concentration of Ang I following 72 hours of hyperoxia (24). However, the systemic MAP response to intravenous Ang II decreased significantly prior to the MAP response changes for Ang I. Because the Ang II MAP response decreased prior to the decrease in Ang I MAP response, it was not possible to ascertain whether the Ang I MAP response changes were a result of enzyme inactivation or was due to a reduced ability of the systemic vasculature to respond to Ang II.

The systemic pressor response to Ang II is mediated by peripheral Ang II receptors (36) which are thought to induce an accumulation of intracellular cGMP resulting in vasoconstriction (7). However, recent investigations of the possible second messengers for Ang II suggest that other cyclic nucleotides,

calcium, and potassium may also be involved in the transduction of the signal from the receptors to the vascular smooth muscle (49). The significant decrease in the MAP response to Ang II due to hyperoxia could be the result of: (1) changes in receptor activity, (2) changes in receptor number, (3) modulation of Ang II pressor activity by other compounds, (4) saturation of available receptors due to increased endogenous Ang II levels, or (5) reduced ability of vascular smooth muscle to respond to the Ang II stimulus.

The decreased MAP response to Ang II was present even though there were no changes in pressor response to the alpha adrenergic agonist PE (fig 3). This suggests that the vascular smooth muscle was capable of responding to constrictor agents at all times during the oxygen exposure. The intact PE response rules out the possibility that reduced MAP response to Ang II was due to a reduced ability of the vascular smooth muscle to respond to Ang II. Therefore, the decreased pressor response to Ang II is probably limited to a problem in the transduction of the Ang II message through the receptor to the vascular smooth muscle.

The ability of oxygen to oxidize sulfhydryl groups is well recognized and is considered one of the primary mechanisms by which enzyme inactivation occurs (12,13,26,47). Receptors, being of proteinaceous design, might also be affected by hyperoxic conditions. For example, if the exposed regions of the Ang II receptor protein on the luminal surface possess large amounts of exposed sulfhydryl groups, high oxygen tensions in the blood and plasma may induce oxidation of these groups and formation of

disulfide bonds. The disulfide bonds may therefore change the conformation of the receptor making it inaccessible to Ang II. Additionally, if the sulfhydryl groups are active in the binding of Ang II at the active site, oxidation of only a few sulfhydryl groups might drastically reduce the affinity of the receptor. Because Ang II receptors have not been purified from any source, it is not possible to verify these hypotheses.

Ang II receptors have been demonstrated to down regulate when exposed to high levels of Ang II for an extended period of time (54,57). Harabin et. al. (24) calculated that systemic levels of Ang II increase by as much as 50% with chronic hyperoxia. Therefore, a possible increase in systemic concentration of Ang II could have caused an internalization or desensitization of Ang II receptors which would have then resulted in the reduced responsiveness to Ang II. A limitation to this hypothesis is that systemic levels of Ang II have not been measured during chronic exposure to oxygen.

If systemic Ang II concentration does increase with hyperoxia, then another possible explanation for the reduced MAP response to this pressor agent could be the result of increased systemic levels of potent vasodilators attenuating the response. Ang II is known to increase the release of prostacyclin from the lung and other tissues (23), which has the capacity to attenuate Ang II vasoconstriction (30). Therefore, an increased release of prostacyclin from the lungs, due to higher circulating levels of Ang II, would actually attenuate the pressor response of Ang II. This hypothesis is not

TABLE 5 Maximal changes in mean arterial pressure (MAP) in response to all compounds tested at 8, 16, 24 and 32 hours for normoxic (NOR) and hyperoxic (O_2) rabbits

	DURATION OF EXPOSURE (HRS)									
	Basal Values		8		16		24		32	
Compound	NOR (n=5)	O_2 (n=21)	NOR (n=5)	O_2 (n=21)	NOR (n=5)	O_2 (n=21)	NOR (n=5)	O_2 (n=21)	NOR (n=5)	O_2 (n=21)
Ang I	23.1±3.0	17.9±1.0†	26.0±4.4	17.5±1.4†	25.6±3.6	15.3±1.3†	25.4±4.5	14.6±1.3*†	26.8±4.0	14.7±1.3*†
Ang II	28.3±2.8	26.1±1.3	33.0±3.0	26.0±2.1	32.4±4.8	22.0±2.2*†	31.4±3.2	22.3±2.2*	31.6±4.2	20.6±1.8*†
PE	51.6±2.5	45.3±2.9	52.2±4.4	42.8±3.0	46.2±6.2	41.6±3.1	54.4±4.8	41.2±3.7	52.8±5.4	40.5±3.1
PGE_2 (i.a.)	-9.3±1.2	-8.5±0.9	-12.4±2.1	-12.8±1.7*	-10.8±2.2	-12.0±1.2*	-11.8±2.2	-10.9±1.3	-14.4±4.1	-10.0±1.8
PGF_2 (i.v.)	5.2±0.8	5.8±0.5	7.8±1.6	7.4±1.1	7.6±1.9	6.8±1.1	7.8±2.2	6.6±1.0	11.0±3.0	6.6±0.7†
NP	-25.0±4.1	-20.3±1.2	-24.2±3.8	-21.7±1.6	-17.2±4.0*	-20.8±1.6	-23.8±5.9	-20.5±1.3	-33.6±7.4*	-23.1±2.4

*Values represent mean ± S.E.M.
*P<0.05 vs basal value within same group
†P<0.05 normoxic vs hyperoxic at same time point

TABLE 4 Maximal changes in mean arterial pressure (MAP) in response to all compounds tested at each control period for normoxic (NOR) and hyperoxic (O_2) rabbits

Compound	Control Day 1		Control Day 2		Basal Values	
	NOR (n=5)	O_2 (n=21)	NOR (n=5)	O_2 (n=21)	NOR (n=5)	O_2 (n=21)
Ang I	21.7±2.7	17.1±1.1	24.6±3.3	18.6±1.2	23.1±3.0	17.9±1.0†
Ang II	27.9±2.7	25.3±1.4	28.7±3.1	27.0±1.7	28.3±2.8	26.1±1.3
PE	54.8±2.8	46.4±3.6	48.4±2.9	44.6±2.7	51.6±2.5	45.3±2.9
PGE_2 (i.a.)	-9.6±1.5	-8.9±1.3	-8.9±1.2	-8.1±0.8	-9.3±1.2	-8.5±0.9
PGE_2 (i.v.)	5.7±0.8	6.0±0.6	4.7±1.1	5.6±0.7	5.2±0.8	5.8±0.5
NP	-26.0±4.1	-21.4±1.6	-23.9±4.2	-19.2±1.2	-25.0±4.1	-20.3±1.2

Values represent mean ± S.E.M.
†P<0.05 normoxic vs hyperoxic at same time point

TABLE 1 Mean arterial pressure (MAP) and heart rate (HR) values for basal conditions and at 8–72 hours for normoxic (NOR) and hyperoxic (O_2) rabbits

	Basal Values		DURATION OF EXPOSURE (HRS)									
			8		24		40		56		72	
	NOR (n=5)	O_2 (n=21)	NOR (n=5)	O_2 (n=21)	NOR (n=5)	O_2 (n=21)	NOR (n=5)	O_2 (n=21)	NOR (n=5)	O_2 (n=21)	NOR (n=5)	O_2 (n=21)
MAP (mmHg)	72.1± 2.6	78.7+ 4.0	68.8+ 4.0	74.9± 3.2	62.0± 2.4*	73.5+ 4.8	62.8± 0.8*	74.6± 5.2	62.0± 2.2*	64.1± 5.4*	63.2± 2.9*	66.3+ 4.8
HR (bts/min)	205± 19	229+ 7	207± 19	255± 8*+	207± 23	271± 9*+	217± 22	286± 7*+	206± 27	279± 4*+	216± 24	266+ 8*+

Values represent mean ± S.E.M.
*P<0.05 vs basal value within same group
+P<0.05 normoxic vs hyperoxic at same time point

TABLE 2 Reproducibility of control mean arterial pressure (MAP) and heart rate (HR) values for normoxic (NOR) and hyperoxic (O_2) rabbits

	CONTROL DAY 1		CONTROL DAY 2		BASAL VALUES	
	NOR (n=5)	O_2 (n=21)	NOR (n=5)	O_2 (n=21)	NOR (n=5)	O_2 (n=21)
MAP (mmHg)	69.8±3.2	89.1±3.8	72.4±3.0	75.5±4.3*	72.1±2.6	78.7±4.0
HR (bts/min)	206±12	232±7	204±26	227±8	205±19	229±7

Values represent mean ± S.E.M.
*P<0.05 Control Day 1 vs. Control Day 2 within same group
Basal values = Mean of Control Day 1 and Control Day 2

TABLE 1 Body and lung weights for hyperoxic and normoxic rabbits

	Hyperoxic (n=21)	Normoxic (n=5)
Body Weight (kg)	3.6±0.1	2.7±0.1*
Lung Wet Weight (gm lung/kg BW)	7.6±0.4	6.2±0.7
Lung Dry Weight (gm lung/kg BW)	1.2±0.1	1.2±0.1
Lung Dry/Wet Weight	0.16±0.01	0.20±0.02*

*Values represent mean ± SEM
*P<0.05

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(1) The ability of the cardiovascular system to respond to PE, NP, PGE_2 (i.a.), and PGE_2 (i.v.) remains intact with chronic oxygen exposure.

(2) Chronic hyperoxia caused a reduced systemic MAP response to both Ang I and Ang II, providing indirect evidence for ACE disruption and/or systemic Ang II receptor degradation.

(3) Chronic oxygen exposure did not significantly alter the systemic MAP response to the alpha adrenergic agonist PE, indicating that the ability of the vascular smooth muscle to respond to alpha adrenergic stimuli remains intact with chronic hyperoxia.

(4) Chronic hyperoxia did not affect the vasoactivity of intravenous PGE_2, indicating that the ability of the PGDH/R enzyme to metabolize this endoperoxide remains intact.

The present study opens a new direction for research in the area of pulmonary oxygen toxicity. Future efforts along the same investigative lines as this study should combine the measured changes in systemic MAP response with appropriate arterial-venous measurements of the vasoactive compounds being tested. Additionally, evidence now exists that hyperoxic conditions have adverse effects on systemic Ang II receptors.

to draw any definitive conclusions. Therefore, the PGE_2 data from this study suggests that PGE_2 does not influence systemic MAP under normoxic or hyperoxic conditions. Rather, it serves to influence blood pressure and flow locally (41). Additionally, the systemic PGE_2 responses are not affected by chronic hyperoxia.

The significant differences observed in the MAP responses to NP suggest an increased intracellular accumulation of cGMP in response to the same amount of injected NP. The vasodilatory action of NP is mediated through the compound's release of nitric oxide which penetrates the cell membrane (29). Intracellularly, the nitric oxide causes an accumulation of cGMP which acts to induce a relaxation of the vascular smooth muscle (29). Therefore, the increased vasodilatory response observed at 40, 48, and 56 hours of oxygen exposure suggest that the intracellular cGMP levels in response to the same NP stimulus were increased. Another possible explanation for this phenomenon again might be associated with an increase in smooth muscle tone in select vascular beds which would display a greater vasodilatory response. In contrast to the increased vasodilatory response observed for arterial PGE_2, the changes observed for NP occurred much later in the oxygen exposure (8 versus 40 hours) and were not maintained beyond 56 hours of hyperoxia (fig 4). Therefore. it appears that the increased vasodilatory response to NP was due to an intracellular change in cGMP response.

The results of this study demonstrated several important findings.

response may be secondary to the changes observed for the Ang II MAP response. In order to further elucidate the effects of hyperoxia on ACE activity, a repeat of this experiment is necessary with proper measurements of arterial-venous Ang I and Ang II concentrations to verify the activity of this enzyme and correlate it with the observed systemic cardiovascular response changes.

Data for arterial and intravenous PGE_2 suggest that the vasoactivity of this compound remains intact under chronic hyperoxic conditions (fig 4). The increased vasodilatory response for arterial PGE_2, which occurred after only 8 hours of oxygen exposure, may have been due to an increase in peripheral vascular resistance in select vascular beds. This phenomenon has been demonstrated (55). Increased smooth muscle tone would allow for a greater vascular response in those beds with greater resistance. This would then result in a larger decrease in MAP response for arterial PGE_2.

No changes were observed in the PGE_2 (i.v.) MAP response until 72 hours (fig 4). The two animals that demonstrated a vasodilatory rather than a vasoconstrictor response were responsible for the significant decrease at 72 hours. These two animals provided evidence that hyperoxia may be responsible for the change in the MAP response. Three days of hyperoxia causes approximately 50% of the pulmonary endothelium to be destroyed (31). The loss of endothelium and the concomitant loss of PGDH/R with the endothelial cells would allow intravenous PGE_2 to transit the lungs without being metabolized causing systemic vasodilation. Because this phenomenon was only observed in 2 of the 9 animals at 72 hours, it is difficult

without precedent. It has been demonstrated previously that prostaglandins do in fact attenuate the normal physiological responses of many hormones that act through a membrane bound receptor linked to the accumulation of intracellular cyclic nucleotides (6).

A final hypothesis for the reduced MAP response to Ang II involves the possible saturation of Ang II receptors. Again, assuming that systemic Ang II levels are elevated during chronic hyperoxia, many of the Ang II receptors would be occupied and there would be fewer receptors available to respond to the injected Ang II. This exact condition exists in animals where extracellular volume is decreased through salt depletion (6). Under these conditions, an increased MAP did not occur due to a reduction in plasma volume and a decreased responsiveness in the arteriolar smooth muscle (6). Hyperoxia does not cause any major hemodynamic changes *in vivo* until just prior to death (24,37). Therefore, saturation of Ang II receptors cannot account for the decreased Ang II MAP response.

The ability to indirectly assess decreases in the ACE enzyme activity through measured changes in Ang I MAP responses are complicated by the earlier changes in Ang II MAP responses. It is important to note that even though the reduction in the Ang I MAP response did not achieve statistical significance until the 32 hour oxygen exposure point, the change in response, expressed as a percent of control, closely paralleled the changes in Ang II MAP responses (fig 5). This suggests that the observed changes in Ang I

TABLE 6 Maximal changes in mean arterial pressure (MAP) in response to all compounds at 40, 48 and 56 hours for normoxic (NOR) and hyperoxic (0_2) rabbits

Compound	Basal Values NOR (n=5)	Basal Values 0_2 (n=21)	DURATION OF EXPOSURE (HRS) 0 NOR (n=5)	0 0_2 (n=21)	48 NOR (n=5)	48 0_2 (n=21)	56 NOR (n=5)	56 0_2 (n=21)
Ang I	23.1±3.0	17.9±1.0†	24.2±4.7	15.7±1.4†	25.0±6.2	15.5±1.6†	27.8±5.5	13.4±1.3*†
Ang II	28.3±2.8	26.1±1.3	34.6±4.2*	18.3±1.8*†	28.8±4.0	21.0±1.7*	29.0±3.1	18.7±1.7*†
PE	51.6±2.5	45.3±2.9	46.6±5.9	38.7±3.0*	48.4±4.4	38.7±3.0*	47.6±5.2*	36.4±2.1*
PGE_2 (i.a.)	-9.3±1.2	-8.5±0.9	-12.2±4.6	-10.7±1.5	-9.6±2.9	-12.4±1.0*	-7.8±2.1	-12.1±1.3*
PGE_2 (i.v.)	5.2±0.8	5.8±0.5	12.8±8.5	7.4±1.5	9.0±2.1	4.6±1.0	6.8±1.2	4.5±1.0
NP	-25.0±4.1	-20.3±1.2	-23.8±5.2	-25.5±2.4*	-22.0±5.3	-24.3±2.0	-17.0±2.5	-27.1±2.6*

Values represent mean ± S.E.M.
*P<0.05 vs basal value within same group
†P<0.05 normoxic vs hyperoxic at same time point

TABLE 7 Maximal changes in mean arterial pressure (MAP) in response to all compounds tested at 64, 72, 80 and 88 hours for normoxic (NOR) and hyperoxic (O_2) rabbits

COMPOUND	Basal Values		DURATION OF EXPOSURE (HRS)							
			64		72		80		88	
	NOR (n=5)	O_2 (n=21)	NOR (n=5)	O_2 (n=21)	NOR (n=5)	O_2 (n=21)	NOR (n=5)	O_2 (n=21)	NOR (n=5)	O_2 (n=21)
Ang I	23.1±3.0	17.9±1.0†	22.4±2.5	11.6±1.9*†	23.4±3.5	7.6±1.9*†	21.2±3.2	10.3±5.8	19.8±3.2	8.0±8.0
Ang II	28.3±2.8	26.1±1.3	30.4±2.3	16.7±2.7*†	28.8±3.9	13.1±2.4*†	26.6±2.7	15.7±9.9	24.8±2.6	12.0±12.0
PE	51.6±2.5	45.3±2.9	49.2±4.8	34.0±3.5†	49.6±7.9	34.9±4.0	49.2±5.9	26.7±6.6	45.0±6.3	25.0±9.0
PGE_2 (i.a.)	-9.3±1.2	-8.5±0.9	-11.2±3.3	-10.4±2.3	-12.4±1.6	-13.2±3.2	-11.0±3.3	-8.0±2.3	-14.6±2.8	-9.0±3.0
PGE_2 (i.v.)	5.2±0.8	5.8±0.5	8.0±0.8	3.8±1.5	8.8±0.8	2.6±1.6†	7.8±1.4	4.7±3.7	8.6±1.6	4.0±4.1
NP	-25.0±4.1	-20.3±1.2	-20.8±2.6	-24.3±2.8	-22.8±3.0	-21.2±3.1	-21.4±3.3	-26.0±5.8	-21.4±4.1	-24.0±14.0

* Values represent mean ± S.E.M.
* P<0.05 vs basal value within same group
† P<0.05 normoxic vs hypoxic at same time point

Figure 1. Proposed sequence of events leading to hyperoxia induced death. (Modified from Deneke and Fanburg, 1982).

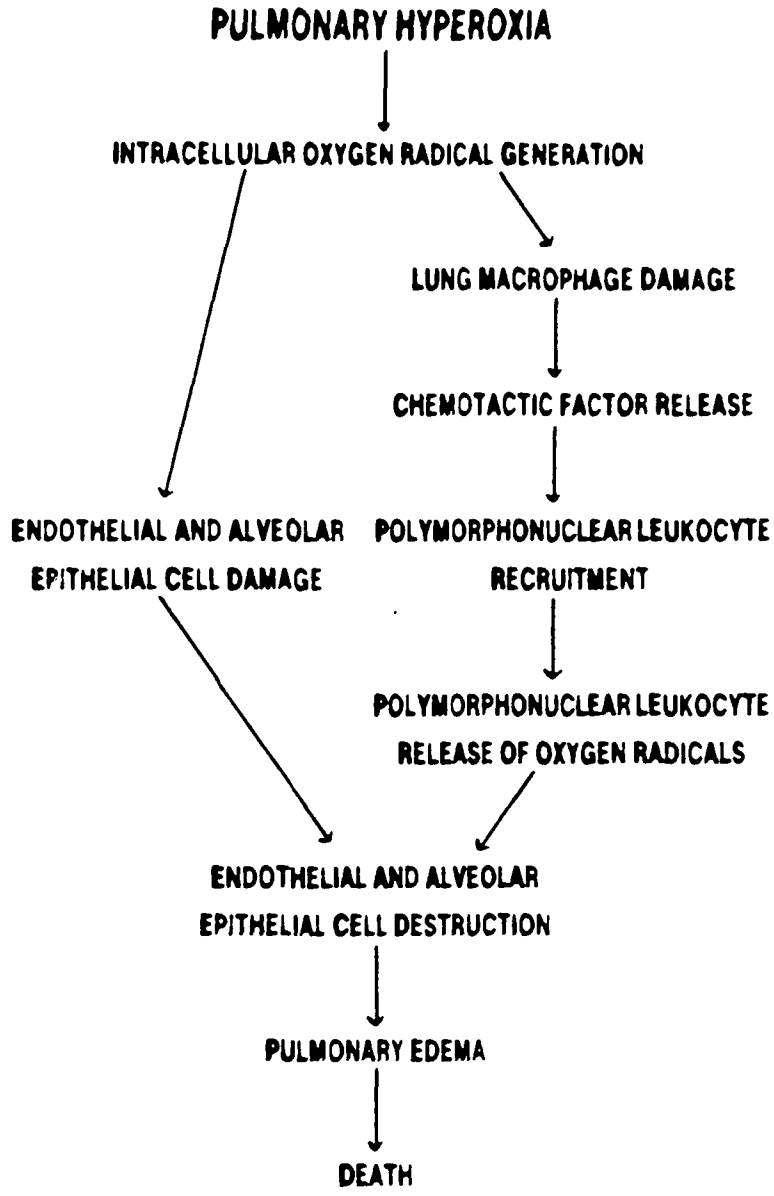

PULMONARY HYPEROXIA
INTRACELLULAR OXYGEN RADICAL GENERATION
LUNG MACROPHAGE DAMAGE
CHEMOTACTIC FACTOR RELEASE
ENDOTHELIAL AND ALVEOLAR EPITHELIAL CELL DAMAGE
POLYMORPHONUCLEAR LEUKOCYTE RECRUITMENT
POLYMORPHONUCLEAR LEUKOCYTE RELEASE OF OXYGEN RADICALS
ENDOTHELIAL AND ALVEOLAR EPITHELIAL CELL DESTRUCTION
PULMONARY EDEMA
DEATH

Figure 2. Basal mean arterial pressure and heart rate at the control and each 8 hour exposure time point for normoxic and hyperoxic rabbits.
Values represent mean ± SEM.
* $P<0.05$ versus pre-normoxic/hyperoxic value within same group.
† $P<0.05$ normoxic versus hyperoxic at same time point.

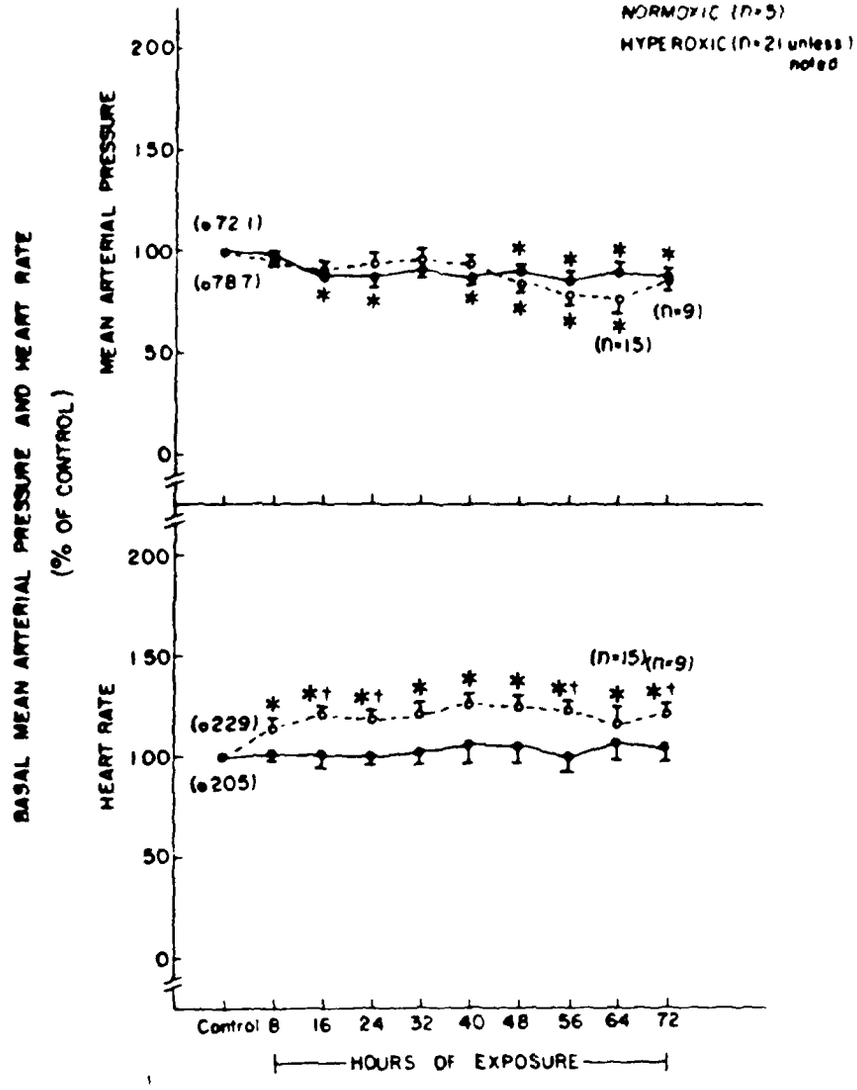

NORMOXIC (n=5)
HYPEROXIC (n=21 unless noted
BASAL MEAN ARTERIAL PRESSURE AND HEART RATE
(% OF CONTROL)
MEAN ARTERIAL PRESSURE
HEART RATE
200
150
100
50
0
(o72 1)
(o78 7)
(n=9)
(n=15)
(n=15)(n=9)
(o229)
(o205)
Control 8 16 24 32 40 48 56 64 72
HOURS OF EXPOSURE

Figure 3. Maximal changes in mean arterial pressure (MAP) in response to angiotensin I (Ang I), angiotensin II (Ang II), and phenylephrine (PE) at the control and each 8 hour exposure time point for normoxic and hyperoxic rabbits.
Values are mean ± SEM.
* $P<0.05$ versus pre-normoxic/hyperoxic value within same group.
† $P<0.05$ normoxic versus hyperoxic at same time point.

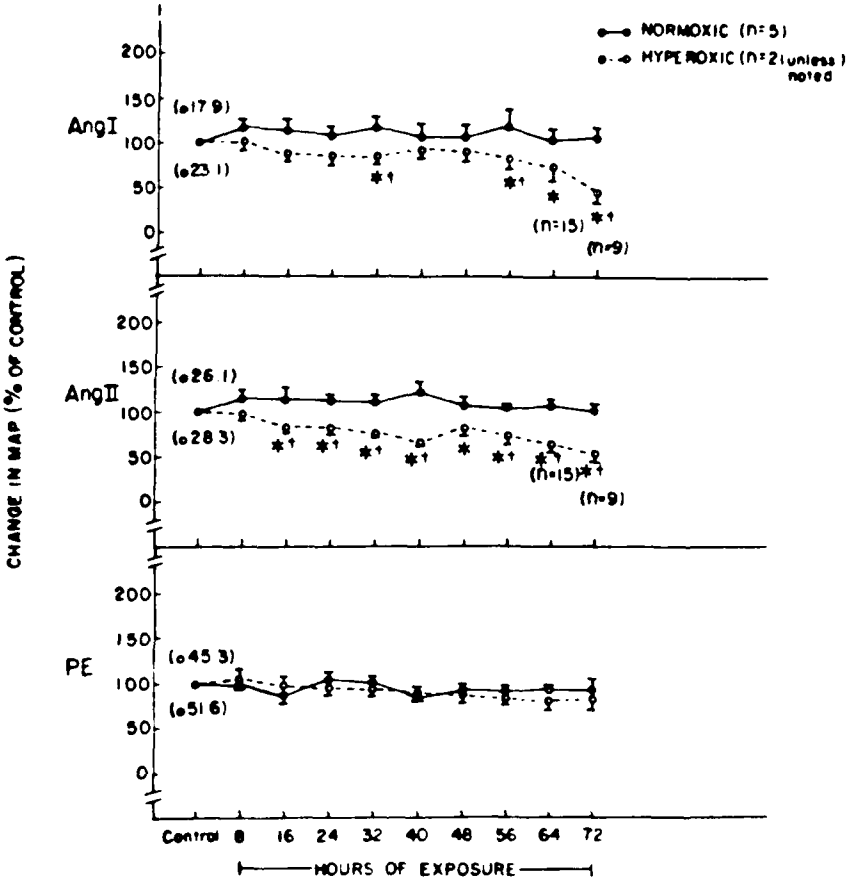

NORMOXIC (n=5)
HYPEROXIC (n=21 unless noted
CHANGE IN MAP (% OF CONTROL)
AngI
(e17.9)
(e23.1)
(n=15)
(n=9)
AngII
(e26.1)
(e28.3)
(n=15)
(n=9)
PE
(e45.3)
(e51.6)
200
150
100
50
0
Control
8
16
24
32
40
48
56
64
72
HOURS OF EXPOSURE

Figure 4. Maximal changes in mean arterial pressure (MAP) in response to arterial prostaglandin E_2 (PGE_2 i.a.), intravenous prostaglandin E_2 (PGE_2 i.v.), and sodium nitroprusside (NP) at the control and each 8 hour exposure time point for normoxic and hyperoxic rabbits.
Values represent mean ± SEM
* $P<0.05$ versus pre-normoxic/hyperoxic value within same group.
+ $P<0.05$ normoxic versus hyperoxic at same time point.

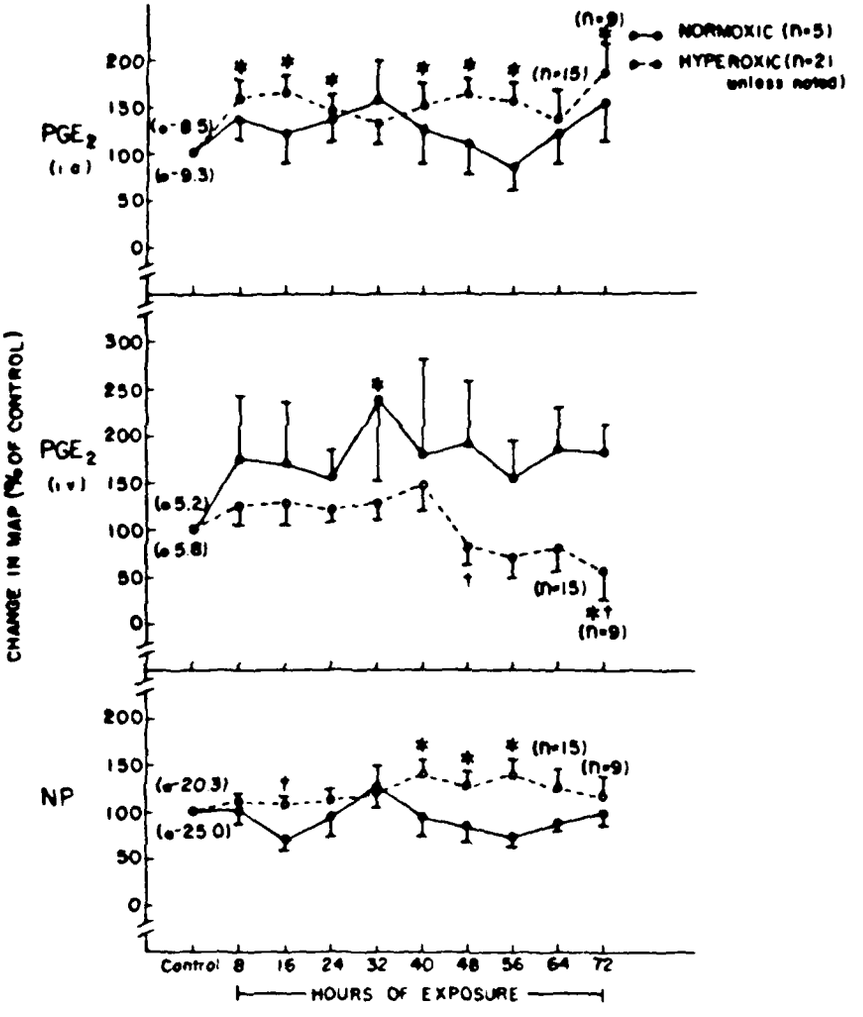
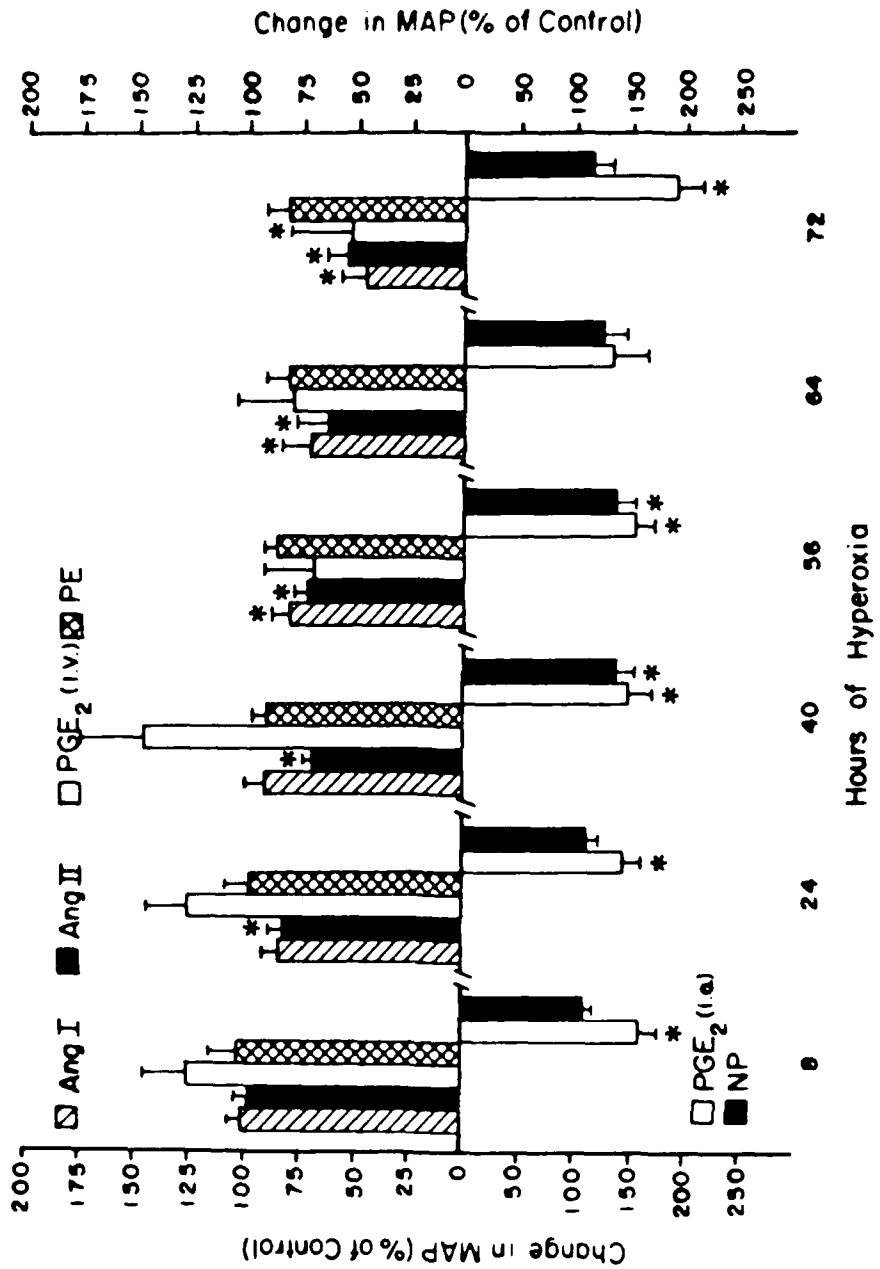

NORMOXIC (n=5)
HYPEROXIC (n=21 unless noted)
PGE2 (i.a)
PGE2 (i.v)
NP
CHANGE IN MAP (% OF CONTROL)
(n=9)
(n=15)
(a-8.5)
(a-9.3)
(a-5.2)
(a-5.8)
(a-20.3)
(a-25.0)
Control 8 16 24 32 40 48 56 64 72
HOURS OF EXPOSURE

Figure 5. Maximal changes in mean arterial pressure (MAP) for all vasoactive compounds tested at the 8, 24, 40, 56, 64 and 72 hour oxygen exposure time points for hyperoxic rabbits. (N=21 through 56 hours; N=15 at 64 hours; N=9 at 72 hours).
Values represent mean ± SEM.
* $P<0.05$ versus pre-hyperoxic value.


Change in MAP (% of Control)
200 175 150 125 100 75 50 25 0 50 100 150 200 250
Ang I
Ang II
PGE2 (i.v.)
PE
PGE2 (i.a.)
NP
8
24
40
56
64
72
Hours of Hyperoxia
Change in MAP (% of Control)

END

FILMED

8-85

DTIC