Pulmonary Disease Reviews

Volume 4

Edited by

Roger C. Bone, M.D.

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Preface

The purpose of Pulmonary Disease Reviews is to provide access to the latest advances that impact on clinicians and academicians concerned with pulmonary disease and critical care medicine. Expanded sections on basic mechanisms of lung injury, exercise physiology, sleep, sepsis, and critical care medicine are displayed in this volume to illustrate recent trends. The individual chapter authors are without exception experts in the fields they review. Each is active in clinical or basic investigation of his or her subject. Their chore is to highlight the best, most provocative, or most quoted literature pertaining to their subject in the preceding year. They abstract the article, making certain that the original data are presented in enough depth to allow the reader to decide independently on the conclusions reached by the article author or chapter author. The chapter author then speculates on the clinical relevance and new research ideas that are raised by the reviewed papers. It is hoped that each chapter will serve as a "journal club" with an expert in the area being discussed conducting the session.

Pulmonary disease is a challenging and exciting, but demanding, subspecialty that requires the complete internist to provide optimal medical care. This volume attempts to make the difficult task of staying current a little easier.

Roger C. Bone, M.D.

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1
Oxygen Transfer

David R. Dantzker

INTRODUCTION

Mammals have evolved a remarkably efficient system for the transfer of oxygen from the environment to the cells that use it for oxidative metabolism. This system has built into it marked redundancy and a number of compensatory mechanisms that allow continued optimization of gas exchange in the face of environmental or internal stress. This chapter will look predominantly at studies which have explored these mechanisms.

Since the ventilation-perfusion ratio determines both the alveolar and end-capillary PO_2, the matching of ventilation and blood flow within the lungs is paramount to the maintenance of adequate gas exchange. Vasoconstriction in response to hypoxia is thought to be one conservative mechanism by which this is accomplished. As originally described by von Euler and Liljestrand in 1946, a decrease in alveolar PO_2 results in an increase in the vascular tone of the perfusing artery. This tends to redistribute blood away from hypoxic lung units, optimizing the ventilation-perfusion ratio. The mechanisms by which this fall in PO_2 is transduced are still unclear, as is the manner in which the vasoconstriction is accomplished. Proponents of both neural and humoral mediators have presented "proof" for each side, but the search for the mediator of hypoxic vasoconstriction goes on.

While it is generally agreed that the alveolar PO_2 is able to influence pulmonary vascular tone, some investigators have also suggested that the PO_2 in the mixed venous blood ($P_{\bar{v}}O_2$) may also play a role in determining pulmonary vascular resistance. Fishman has suggested that the overall tone of the pulmonary vascular bed may be set by the venous PO_2 while local "fine tuning" is accomplished in response to alveolar PO_2 (*Fishman A P: Hypoxia on the pulmonary circulation. Circ Res* 38: 221, 1976).

The first paper to be reviewed explores the ability of changes in $P_{\bar{v}}O_2$) to influence pulmonary vascular tone.

PULMONARY VASOCONSTRICTOR RESPONSES TO GRADED DECREASES IN PRECAPILLARY BLOOD PO_2 IN INTACT-CHEST CAT

A.L. Hyman, R.T. Higashida, E.W. Spannhake, and P.J. Kadowitz
(Departments of Surgery and Pharmacology, Tulane University School of Medicine, New Orleans, Louisiana)

J Appl Physiol: Respirat Environ Exercise Physiol 51(4):1009-1016, 1991.

The effects of graded changes in pulmonary lobar arterial blood PO_2 and ventilatory hypoxia were investigated in the intact-chest cat under conditions of controlled lobar blood flow. A reduction in precapillary PO_2 from systemic arterial levels to below 60 Torr increased lobar arterial pressure. Ventilation with 10% O_2 increased lobar arterial pressure, and responses to ventilatory hypoxia and precapillary hypoxemia were independent but additive (Figure 1). The magnitude of the pressor response to precapillary hypoxemia was similar in experiments in which the lung was autoperfused with right atrial blood or

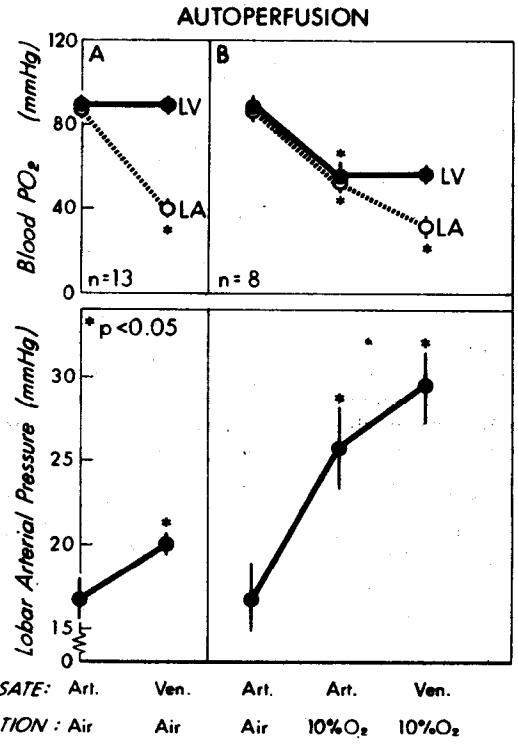

Figure 1. A:effects of switching the perfusate (infusate) from systemic arterial (Art) to right atrial blood (Ven) on lobar arterial pressure, lobar arterial, and lobar venous PO_2 while animal breathes air in autoperfusion experiments. B:effects of ventilation with 10% O_2 when lobe is perfused with systemic arterial blood, and when lobe is ventilated with 10% O_2 and is perfused with right atrial blood. n, No. of animals. (Courtesy of A.L. Hyman and the Journal of Applied Physiology.

cross-perfused with aortic blood from a doner cat breathing 10% O_2. During retrograde perfusion of the ventilated lung, a reduction in pulmonary venous PO_2 to 40 Torr did not affect inflow pressure. This data suggests that sensor sites upstream to the alveolar-capillary region in segments of lobar artery unexposed to alveolar gas sense a reduction in precapillary blood PO_2 and elicit a pulmonary vasoconstrictor response. The sensor site in the precapillary segment is independent of sensor in the alveolar-capillary exposed segment region, and the effects of stimulation of both sensors on the pulmonary vascular bed are additive. In addition, the present data indicate that sensors in the pulmonary veins do not sense a reduction in PO_2 in venous blood and elicit a vasoconstrictor response. These data suggest that the mixed venous blood PO_2 may exert an important regulatory role in controlling pulmonary arterial pressure and pulmonary vascular resistance in the cat under normal and pathological conditions.

COMMENTS

This paper clearly demonstrates that in the cat, changes in the PO_2 of the pulmonary arterial blood can lead to changes in pulmonary vascular resistance. The stepwise response of resistance to changes in the $P_{\bar{v}}O_2$ below a threshold level of 60 mmHg strongly suggests that this reflex may play a significant role in modulating pulmonary arterial tone over the whole physiological range.

Previous studies have reached similar conclusions, but many of these experiments were flawed by the lack of sufficient data. A major problem in experimental design is the control of changes in alveolar PO_2. It is well known that a change in the $P_{\bar{v}}O_2$ will alter both the alveolar and end-capillary PO_2 of each lung unit. The degree to which this effect is expressed will depend on the ventilation-perfusion ratio of each unit. Thus, one might argue that alterations in pulmonary vascular resistance seen after changing the $P_{\bar{v}}O_2$ result from its influence on alveolar PO_2 rather than from any direct effect. This is, in fact, the conclusion of another recent study by Benumof, Pirlo, Johanson, and Trusdale (J Appl Physiol: Respirat Environ Exercise Physiol 51:871-874, 1981).

However, this study demonstrates, at least for one animal species, that the effect of the $P_{\bar{v}}O_2$ is independent of its effect on the alveolar PO_2. This was shown in two ways. The relationship between pulmonary arterial tone and $P_{\bar{v}}O_2$ was seen when the animal breathed 100% O_2, and the effect still existed when the arterial blood from the test lobe remained at baseline values.

What are the clinical consequences of such a controlling mechanism? Since each lung unit is exposed to the same $P_{\bar{v}}O_2$, it may suggest that baseline pulmonary vascular tone is significantly dependent on the nonpulmonary events that control the $P_{\bar{v}}O_2$. These include cardiac output and the overall metabolic rate. At first thought, this might appear as poor planning, since the widened arterial-venous O_2 difference seen in a low cardiac output state would result in a greater right ventricular afterload. However, as the authors of this study point out, under certain circumstances this relationship might prove beneficial. In the case of high flow states such as in congenital heart disease where the

arterial-venous oxygen difference is narrowed, the high $P_{\bar{v}}O_2$, and thus lower PVR, would afford some protection to the right ventricle. In addition, in conditions during which peripheral oxygen needs increase, the elevated pulmonary vascular resistance induced by a low $P_{\bar{v}}O_2$ would lead to a more uniform blood flow distribution and thus more efficient gas exchange in the lung. The ability of $P_{\bar{v}}O_2$ to influence pulmonary vascular tone may also explain the well described relationship between cardiac output and percent shunt in the lungs of patients with pulmonary edema.

One of the problems in evaluating the efficiency of gas transfer in the lungs is the ability to determine the mechanism of any abnormality and to quantitate any changes which might occur. The next paper looks at some of the problems involved in this.

PULMONARY VENOUS ADMIXTURE DURING MECHANICAL VENTILATION WITH VARYING FIO_2 AND PEEP

G.C. Carlon, W.S. Howland, A.D. Turnbull, R.C. Kahn (Department of Critical Care, Memorial Sloan-Kettering Cancer Center, New York, New York)

Crit Care Med 8:616, 1980.

Many authors have indicated that high FIO_2 (0.75-1.0) ventilation may increase pulmonary venous admixture. Reabsorption atelectasis is supposedly responsible for this adverse effect. The authors attempted to determine if increasing PEEP during high FIO_2 ventilation could eliminate the detrimental influence of the latter. In 17 patients in respiratory failure, hemodynamic and respiratory variables were measured during ventilation with FIO_2 0.50, 0.75, and 1.0 and PEEP varying from -3 to +5 cm H_2O from baseline. Before exposure to FIO_2 0.75, addition of PEEP resulted in a decrease of $\dot{Q}_s/\dot{Q}_t$ from a mean of 26.6-21.9%. After exposure to FIO_2 0.75-1.0, $\dot{Q}_s/\dot{Q}_t$ remained at levels not different from baseline, even when PEEP 8 cm H_2O above baseline was added. The authors conclude that ventilation with high FIO_2 is not useful in determining $\dot{Q}_s/\dot{Q}_t$, and may prevent the improvement in pulmonary venous admixture associated with PEEP therapy.

COMMENTS

This study was designed to look again at the already overstudied question of oxygen-induced atelectasis. The major finding was the failure of the measured venous admixture to fall as the inspired oxygen tension was increased. This failure was interpreted by the authors as suggesting the presence of an increase in the shunt due to increasing FIO_2. That this may have happened in these patients cannot be disputed retrospectively; that the authors can conclude this from their data, however, can be.

The venous admixture, as estimated from the measurement of arterial and mixed venous O_2 content and the calculation of alveolar PO_2, provides an index of the degree of abnormal gas exchange within the lung. When the patient is breathing room air, this index is influenced by the presence of ventilation-perfusion inequality and diffusion impairment as well as by the presence of true right-to-left shunt. In addition, nonpulmonary factors may

influence this value through their effect on the mixed venous PO_2. These factors include alterations in cardiac output, hemoglobin concentration, and overall oxygen consumption. As the FIO_2 is increased, the contribution of all of these factors, with the exception of true shunt, will diminish. The rate at which these factors decrease their influence on the calculated venous admixture is quite variable and depends on the underlying pathophysiology. However, once the patient has breathed 100% oxygen for sufficient time to wash out all the remaining nitrogen, the calculation of venous admixture will be determined only by the level of true shunt. Thus, in patients in whom abnormalities other than shunt contribute to the observed hypoxemia, one would expect an alinear fall in the calculated venous admixture until it reaches the level of the true shunt. Conversely, in patients in whom shunt is the only mechanism of abnormal gas exchange, the measured venous admixture would be the same at any FIO_2 and thus remain unchanged as the FIO_2 was increased; unless, of course, the actual shunt changed.

*In 1960, Briscoe, et al (*J Appl Physiol *15:785, 1960) suggested that a situation might occur within the lungs of patients with chronic obstructive lung disease in which the ratio of ventilation to blood flow might fall so low that the rate of gas uptake from that lung unit might exceed the rate of gas replacement and the unit would gradually collapse. This theoretical concept was later re-explored (*Dantzker D R, Wagner P D, West J B: Instability of lung units with low $\dot{V}_A/\dot{Q}$ ratios during O_2 breathing. J Appl Physiol *38:816, 1975) and it was demonstrated that at any FIO_2 there was some critical ratio of ventilation to blood flow below which this phenomena would be expected. The higher the FIO_2, the higher this ratio becomes; thus, the more likely that such lung units would be present. An additional confounding factor is the problem of collateral ventilation, which has been clearly demonstrated to be very effective in human lungs. It would appear likely that as a lung unit reaches critical $\dot{V}_A/\dot{Q}$ ratios and begins to collapse, it may be able to increase its ventilation from surrounding lung units via collateral channels. This effect may be accentuated by pressures within this collapsing unit, which are probably magnified secondary to lung interdependency.*

*Many studies have been designed to test this hypothesis, but most have suffered, as does this one, from the necessity of using oxygen both as the analytical tool and as the variable being altered. Studies measuring shunt by non-oxygen techniques have demonstrated in certain patients, breathing 100% oxygen will lead to the development of shunt that was not present on room air (*Wagner P D, et al: Continuous distributions of ventilation-perfusion ratios in normal subjects breathing air and 100% O_2. J Clin Invest *54:54, 1974). However, in studies of patients with COPD and asthma, no increase in shunt was seen despite the presence of lung units with $\dot{V}_A/\dot{Q}$ ratios in the critical range (*Wagner P D, et al: Ventilation-perfusion inequality in chronic obstructive pulmonary disease. J Clin Invest *59:203, 1977;* Wagner P D, et al: Ventilation-perfusion inequality in asymptomatic asthma. Am Rev Respir Dis *118:511, 1978).*