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Hypoxic Pulmonary Vasoconstriction and Infusion of Sodium Nitroprusside

IN ALL MAMMALIAN SPECIES tested, alveolar hypoxia of *in-vivo* and *in-vitro* whole lung, unilateral lung, lobe, and lobule of lung causes pulmonary vasoconstriction. Similarly, *in-vitro* environmental hypoxia of small pulmonary vessels with intact perivascular tissue causes pulmonary vasconstriction.[1] Both of these phenomena are called hypoxic pulmonary vasconstriction (HPV). The mechanism of HPV is proposed to be either a direct action of alveolar hypoxia on pulmonary vasculature[2] or an alveolar hypoxia-induced release of a vasoactive substance.[3] Although the diversity of human experimental models has naturally been limited, there are three major lines of evidence that HPV also operates in human beings. First, life at high altitude or whole-lung respiration of low inspired oxygen concentrations increases pulmonary arterial pressure. This is true for newcomers, for the acclimatized, and for natives.[1] The vasoconstriction is considerable, and in normal people, breathing 10 per cent O_2 doubles pulmonary arterial pressure while pulmonary wedge pressure remains constant.[4] The increased pulmonary arterial pressure increases perfusion of the apices of the lung and results in gas exchange in a region of lung not normally utilized. Thus, during breathing of a low concentration of O_2, the Pa_{O_2} is greater and the alveolar–arterial oxygen tension difference and dead space-to-tidal volume ratio are less than would be expected or predicted on the basis of the normal distribution of ventilation and blood flow. Second, hypoxic ventilation (10 per cent O_2) or atelectasis of one lung generally causes a 30–40 per cent diversion of blood flow away from hypoxic to nonhypoxic lung. The strength of the vasoconstrictor response in man is sufficient to overcome significant vertical hydrostatic gradients.[5] This is of great importance in minimizing transpulmonary shunt during diseases of one lung, one-lung anesthesia, and inadvertent intubation of a mainstem bronchus. Third, in patients with chronic obstructive pulmonary disease,[7,11,12] asthma,[6,8,13] and mitral stenosis,[9,10] who do not have bronchospasm, administration of pulmonary vasodilator drugs such as isoproterenol,[6–9] nitroglycerin,[10,11] and aminophylline[12,13] causes decreases in Pa_{O_2}, pulmonary vascular resistance, and pulmonary arterial pressure and an increase in right-to-left transpulmonary shunt. The mechanism for these changes is thought to be release of pre-existing HPV. In accordance with the latter two lines of evidence (one-lung hypoxia, vasodilator drug effects on whole-lung disease), HPV is thought to divert blood flow away from hypoxic regions of the lung and thereby serve as an autoregulatory mechanism that favorably adjusts regional ventilation-to-perfusion ratios and thereby protects Pa_{O_2}.

In this issue of ANESTHESIOLOGY, two different experimental models and distributions of alveolar hypoxia are used to study the interaction of sodium nitroprusside (SNP) with HPV,[14,15] and in a past issue of ANESTHESIOLOGY yet a third model is described.[16] When the pulmonary lesion is caused by intravenous oleic acid and is therefore miliary, administration of SNP causes pulmonary arterial pressure (P_{pa}), pulmonary vascular resistance (PVR), and Pa_{O_2} to decrease slightly, while right-to-left transpulmonary shunt increases.[15] These findings are entirely compatible with SNP-induced relaxation of HPV. When the pulmonary lesion is caused by hypoxic ventilation[14] and atelectasis[16] of one lung, SNP administration increases blood flow to the hypoxic lung in the two models. These findings are in good agree-

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ment with previous similar models of pulmonary hypoxia and SNP infusion.[17,*]

The similarity of the data from the nitrogen-ventilated and atelectatic lung models suggests that the mechanism of decreased blood flow through nitrogen-ventilated lung is the same as that for atelectactic, namely HPV. There is additional evidence that this is the case.† When a lobe of the lung is made completely atelectatic, lobar blood flow decreases by 50 per cent. Reexpansion and ventilation of the previously atelectatic lobe with nitrogen, 95 per cent, and CO_2, 5 per cent, completely fail to restore any of the blood flow. This indicates that no passive mechanical forces are responsible for the decreased blood flow. Ventilation of the lobe with 100 per cent O_2 completely restores blood flow to preatelectatic control values. This indicates that HPV is primarily responsible for the decrease in blood flow through both nitrogen-ventilated and atelectatic lobes. The finding that SNP administration increases blood flow to the nitrogen-ventilated[14] and atelectatic[16] lobes equally also suggests that the mechanisms of decreased blood flow in atelectatic lung and nitrogen-ventilated lung are the same and occur by active vasoconstriction.

The relationship of the experimental models to human pulmonary disease deserves consideration. Oleic acid-induced injury is similar to, but probably not the same as, the lesion of the adult respiratory distress syndrome. The oleic acid-induced lesion reported by Colley *et al.*[15] caused only moderate increases in pulmonary vascular resistance and pulmonary arterial pressure. The oleic acid-induced increase in pulmonary vascular resistance could have been due to either thrombosis or HPV. The small effects of SNP imply that HPV was of minimal magnitude. The nitrogen-ventilated lung model of Hill *et al.*[14] did not have CO_2 added to the inspired gas mixture, and the hypoxic lung became relatively hypocapnic. The only circumstance during which human lung is both hypoxic and hypocapnic is at altitude. Additionally, since there were concomitant decreases in the CO_2 concentration in hypoxic lung, and since hypocapnia is a potent inhibitor of HPV, SNP effects on HPV may not have reached stability at the end of the allotted 10-min observation time.[18] In the absence of species differences, SNP effects in the previously described atelectatic lung model[16] can be extrapolated to human atelectatic lung more directly.

What has been the effect of SNP on gas exchange in human beings with pulmonary disease? Both decreased Pa_{O_2} with increased right-to-left shunting and decreased PVR have been reported to occur during SNP infusion in patients with congestive heart failure,[19,20] and low-output cardiac failure,[21] during cardiac, pulmonary, and otolaryngologic operations[22,23] and following vascular surgical procedures.[24] All of the subjects in these human studies could be presumed to have a hypoxic lung compartment by virtue of old age,[25] induction of general anesthesia,[26] pulmonary edema, retraction of the lung, or some combination of these elements. A SNP-induced increase in transpulmonary shunt and decreases in pulmonary vascular resistance and Pa_{O_2} are compatible with the hypothesis that SNP inhibited HPV.

The indications for SNP infusion are management of hypertensive crisis in awake and anesthetized patients, controlled hypotension during anesthesia, control of dissecting aneurysm, decrease in left ventricular afterload in patient with acute myocardial infarction and those with low-cardiac-output states, and management of ergot poisoning.[27] What effect on arterial oxygenation can we expect from SNP infusion in patients who have pulmonary disease? The answer depends on whether the disease is minimal, moderate or extensive. First, with the exception of a possible increase in alveolar deadspace ventilation, SNP infusion should have no effect on arterial oxygenation in patients with normal lungs. Second, the animal studies with the models of pulmonary disease discussed above collectively provide a reasonable simulation of certain forms of moderate human pulmonary disease and indicate that SNP infusion can inhibit HPV. The human experience with SNP is compatible with this concept, provided the patients have a hypoxic lung compartment. The clinical lesson from these findings is that arterial oxygenation must be carefully monitored when SNP is used in patients with possible moderate active vasoconstrictor pulmonary disease. Third, data from nitrogen-ventilated lobes indicate that progressively increased pulmonary vascular pressure progressively inhibits HPV.[28] Thus, it is not surprising to find that as the size of the hypoxic compartment increases, pulmonary arterial pressure increases and the amount of HPV does not increase.[29] These findings suggest that in patients with extensive pulmonary disease which is accompanied by pulmonary hypertension, there may be relatively little HPV autoregulation in the lung. Pulmonary hypertension and increased PVR have been found to be a universal feature of acute respiratory failure in man,[30] and the extent of pulmonary hypertension has correlated well with the severity of arterial hypoxemia.[31] Therefore, the answer to the question of SNP effects on arterial oxygenation in patients with extensive pul-

* Arkin DB, Wahrenbrock EA: Hypoxemia following nitroprusside administration: Effect on cardiac output and pulmonary autoregulation (abstr). American Society of Anesthesiologists Annual Meeting, 1975, pp 161–162.

† Benumof JL, Scanlon TS, Moyce PR, et al: Mechanism of blood flow reduction through atelactatic lung (abstr). American Society of Anesthesiologists Annual Meeting, 1977, pp 235–236.

monary disease is not certain, but, as indicated above, if there were little HPV, then SNP would have little effect on the distribution of pulmonary blood flow.

The studies published in this issue, along with the previous work, suggest several experiments that could usefully be performed. It would be interesting to examine SNP effects in an experimental model that had high pulmonary vascular pressures caused either by an extensive hypoxic lung compartment or by cardiac failure. It is possible that by lowering pulmonary vascular pressure, HPV might be unchanged or increased by SNP infusion. It would be important to determine the effects of nitroglycerin, pentolinium and trimethaphan infusions on HPV, in studies similar to those described in this issue. Last, in patients with pulmonary disease and in one-lung ventilation of patients and volunteers, studies of blood flow distribution and arterial oxygenation during vasodilator drug infusion would clearly be most direct. A precedent for such work has already been accomplished by administration of halothane during one-lung ventilation in human beings.[32]

JONATHAN L. BENUMOF, M.D.
Associate Professor of Anesthesia
Anesthesia Research Laboratory, T-001
University of California, San Diego
San Diego, California 92103

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