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## Another Point of View on Intermittent Hypoxia

IN 1946, Von Euler and Liljestrand<sup>1</sup> observed that ventilation with hypoxic gas mixtures induced pulmonary vasoconstriction. It was soon widely appreciated that hypoxic pulmonary vasoconstriction (HPV) could be a control mechanism for adjusting regional blood flow, serving to divert blood away from regions of alveolar hypoxia and thereby reducing the scatter of ventilation-perfusion ratios. In other words, HPV might be one of the very few active (as opposed to passive) intrapulmonary physiologic responses that reduce arterial hypoxemia.

Despite a considerable body of research that has accumulated in the subsequent thirty years, the importance of HPV in clinical practice remains a controversial topic. Some believe that HPV in the adult is just a physiologic curiosity or a vestigial remnant of a fetal property. Others, including this writer, believe that HPV may underly the signs and symptoms of a wide variety of pathophysiologic states from high-altitude pulmonary edema to hypoxemia during general anesthesia.<sup>2,3</sup>

A series of studies from the laboratory of Drs. E. Wahrenbrock and J. L. Benumof in San Diego have confirmed and extended the observations of earlier workers and provided overwhelming evidence of the

reproducibility and functional possibilities of HPV. Their studies together with those of Dr. M. K. Sykes in England and Dr. L. J. Bjertnaes in Norway have particularly warranted the serious attention of anesthesiologists,<sup>4-6</sup> for all are agreed that HPV is inhibited by many volatile anesthetic agents and by other drugs (e.g., nitroprusside) employed by anesthesiologists. The work carries the clear implications that arterial hypoxemia during anesthesia may often follow abolition of HPV. The same mechanism, namely HPV, is responsible for reducing blood flow through atelectatic regions of the lung.<sup>7</sup> Thus, patients or animals with substantial atelectasis or regional hypoxia show a deterioration of arterial oxygen tension when HPV is abolished pharmacologically.<sup>8</sup>

A rational therapeutic aim would be to improve arterial oxygenation by enhancing HPV. This is the subject of a paper by A. F. Pirlo, J. L. Benumof, and F. R. Trousdale in this issue of *ANESTHESIOLOGY*.<sup>9</sup> These authors have observed that diversion of blood flow from the hypoxic left lower lobe of the dog is enhanced following three or four preliminary brief exposures to hypoxia. Hypoxia was induced either by alternating oxygen with nitrogen or by inducing atelectasis repeatedly; and the results were essentially the same with either method. The authors conclude from these experiments that "in order to maximize

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HPV in the nonventilated lung during one lung ventilation (in anesthetized humans undergoing thoracic surgery), several repeated intermittent cycles of deflation-inflation to that lung should be performed during the initiation of one lung ventilation." Despite my conviction that HPV is of considerable clinical importance and my respect for this San Diego research group, I believe their extrapolation from the experimental model to clinical application is unjustified and perhaps incorrect. Of course it is just this type of controversy that makes research both exciting and delightful, for further experiments will certainly provide confirmation and if it follows the usual pattern, both views will turn out to be at best only partially correct. The purpose of this editorial is, therefore, to present another view of the data reported by Dr. Pirlo and his co-workers.

Every study exposes itself to two sources of critical discussion, the first is the study design and the second is the interpretation of the results in the context of present knowledge. With regard to study design of Pirlo *et al.*, their use of dogs is only a minor concern because there is ample evidence that the responses to HPV are very similar in many species including dogs and humans.<sup>2</sup> The Type I error inevitably associated with the use of repeated Student's *t* tests for statistical analysis of the data<sup>10</sup> is also not too damaging because the trend of the data is so clear that a more critical analysis would certainly not change the conclusion.

However, there are two major areas of uncertainty in the extrapolation from the dog model to the clinical patient, the first concerns the absence of an appropriate control group, and the second, the differences in the events preceding the experimental and clinical circumstances. Before it can be concluded that intermittent hypoxia is necessary to induce maximum vascular constriction, it is essential that control groups be examined to test the influence of time alone with either normoxia or hypoxia maintained constantly. There would seem to be no *a priori* reason to expect intermittency to be a requirement. The original report by Unger *et al.*<sup>11</sup> of potentiation of HPV with intermittent hypoxia was under a quite different constraint in this regard because those authors exposed the entire animal to hypoxia. Severe systemic hypoxemia not only dictated intermittency but also activated a variety of responses that influence HPV. The results were not so much a study of acute local vasoconstriction as one of whole body homeostasis during hypoxemia.

That omission of a control group may have led to misinterpretation is most convincingly emphasized by

the results reported by Miller and Hales.<sup>12</sup> The latter authors examined the responses of dogs when one or other lung was exposed to hypoxia. With intermittent exposures to hypoxia they observed immediate maximal responses in approximately half their animals and progressively increasing responses in the rest, but of greatest importance, in the present context, they found that time alone (*i.e.*, exposure to four hours of normoxia) had the same result as intermittent hypoxia. The studies demonstrated that neither intermittency nor even preliminary exposure to hypoxia was necessary to arrive at a maximum response, but only time and something about the animal itself.

Pirlo, Benumof, and Trousdale<sup>9</sup> offer some direct and indirect arguments to support their omission of a control group but their arguments are not very convincing. They cite a previous study,<sup>13</sup> in which hypoxia was maintained for one hour, as evidence that potentiation of HPV did not occur with time. However, the hypoxic decrease of left lower lobe blood flow of about 45 per cent was probably maximal at the start in these animals in which alveolar carbon dioxide tension was not controlled. Furthermore, when these same animals were again subjected to hypoxia but with constant alveolar carbon dioxide tension, blood flow to the left lower lobe immediately decreased by 60 per cent of the initial flow and remained constant thereafter. Therefore, in these very different circumstances the same results as those reported to occur with three or four intermittent exposures occurred with time and only one or two exposures.

One indirect argument advanced is that ". . . the left lower lobe is normally always normoxic; . . . and should not be expected to enhance the mechanisms necessary for the production of HPV."<sup>9</sup> The meaning of this sentence is not very clear, but there is much evidence to indicate that its premise is incorrect. Almost all investigators, including those employing the left lower lobe dog preparation, have noted that reducing the inspired oxygen concentration from 100 per cent to air-equivalent results in constriction. The lung by this view is normally in a state of slight but persistent HPV.

The second indirect argument concerns a belief that their indisputably large experience prevented organ damage during preparation. There is no evidence to support this belief and since the model requires thoracotomy, dissection of the main and left lower lobe pulmonary arteries to allow placement of flow probes as well as section and resuturing of the left lower lobe bronchus to enable that lobe to be separately ventilated, it would be optimistic to expect that

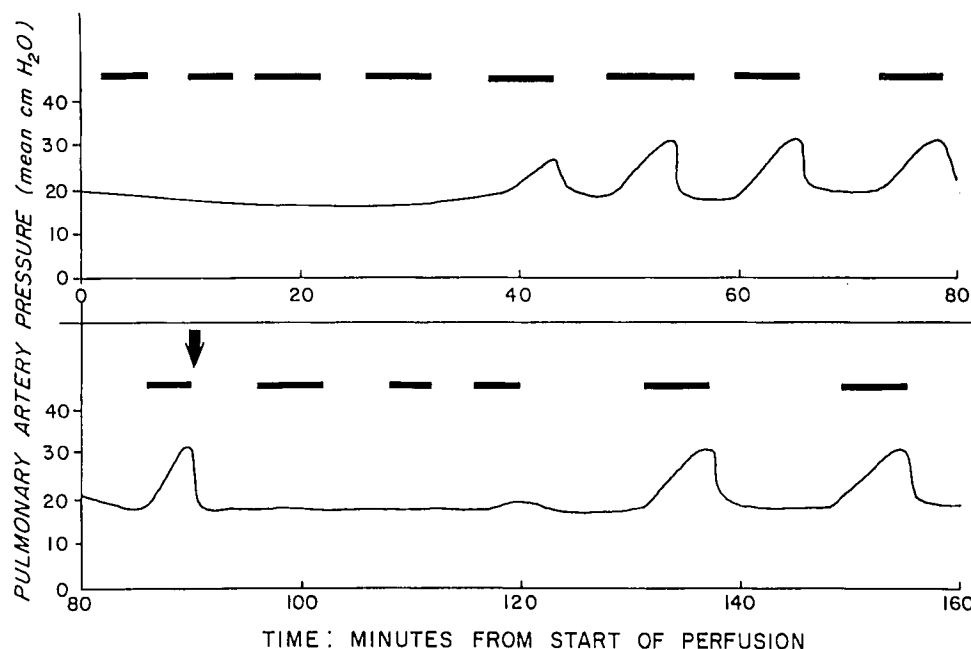


FIG. 1. Pulmonary pressure responses to hypoxia of a rat lung perfused *in vitro* with blood, beginning at time 0. The lung was ventilated and solid bars indicate the periods when a hypoxic gas mixture (3 per cent oxygen, 5 per cent carbon dioxide, balance nitrogen) was substituted for oxygen (95 per cent oxygen, 5 per cent carbon dioxide). The upper and lower panels are from a continuous recording. No pressure responses to hypoxia were observed for the first 40 min, then maximal responses were established. At the arrow on the lower panel, the lung was rapidly and forcefully collapsed by suction on the trachea; a delay of 40 min was again observed before hypoxic responses were reestablished.

temporary impairment of some functions could not occur. It is interesting to compare the results reported here with those repeatedly observed when HPV is tested on lungs perfused *in vitro*. In figure 1, the responsiveness of an *in vitro* rat lung preparation is seen to increase to a constant maximum after 40 min of intermittent exposures to hypoxia, and further the whole sequence is repeated after the same lung was subjected to a sudden forceful collapse. It seems as if many types of perturbation or trauma may abolish the HPV response but that it will return after 30 to 60 min independent of the gas exposure during the interval.

If this information is considered for the conditions of thoracic surgery in humans, several qualifications are in order. First, it seems quite likely that the initial response to hypoxia would be the maximum permitted by the disease state and drug exposure of the patient. But, it is also likely the procedures concomitant with surgery and deliberate collapse and retraction of a lung will partially or totally inhibit the HPV response. Whether three or four deliberate exposures to hypoxia would be of any benefit in terms of the final arterial oxygen tension remains unproven. In summary, I agree that the question is important but disagree in my conviction as to whether the paper by Pirlo, Benumof, and Trousdale provides the answer.

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