statistical issues clearly in mind. Hence, I would like to emphasize that the possible confusion does not lie in failure to understand the complex statistics of signal-detection theory.

If its limitations are clearly understood, signal-detection theory can provide more overall information about analgesic drugs and techniques than that provided by less complex threshold studies. However, it has not yet been shown that this added information increases our ability to predict the clinical usefulness of analgesic drugs or techniques, or to predict the circumstances when a given drug will be effective. Indeed, the additional information, while interesting, may be misleading if it is directly employed in deciding which drugs or techniques have clinical merit, or even which drugs or techniques warrent further clinical evaluation.

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The Changing Arterial Oxygen Tension—Disease or Physician?

SINCE THE OXYGEN ELECTRODE became readily available to clinicians and research investigators two decades ago, there has been a tremendous increase in our knowledge of the variables influencing arterial oxygen tension (Pa_{O_2}). Nowhere is this truer than with pulmonary failure, including its management by techniques designed to maintain or restore lung volume.

It is probably not surprising, however, that we have focused disproportionately on factors influencing distribution of ventilation, rather than on the determinants of regional pulmonary blood flow. Decreases in lung volume are discernible clinically, roentgenographically, and by laboratory methods, and an associated increase in alveolar–arterial oxygen tension differences (AaD_{O_2}) is commonly observed. It is easy to conclude that an increase in lung volume, by one of the common clinical techniques such as positive end-expiratory pressure (PEEP) and the associated decrease in AaD_{O_2} are directly related. Similarly, in following the pulmonary course of a patient with pneumonia or congestive heart failure, we relate a decrease in AaD_{O_2} to an improvement in pulmonary status, primarily from a resolution of low-ventilation areas resulting from the disease process. In so doing, it is important to recognize that considerable changes in Pa_{O_2} values and AaD_{O_2} may occur independent of changes in lung volume or in pathologic status.

Changes in AaD_{O_2} secondary to techniques for positive-pressure distention of the lung may reflect the effect of airway pressure on pulmonary vascular resistance in ventilated regions. Kanarek demonstrated adverse redistribution of whole-lung pulmonary blood flow with PEEP and, in that instance, the magnitude of this adverse redistribution effect on Pa_{O_2} values exceeded any beneficial effect of positive pressure.[1] It is reasonable to assume that this trade-off occurs in all patients treated with PEEP and that the effect on AaD_{O_2} is the resultant of increasing ventilation to some low-ventilation/blood flow ($\dot{V}/\dot{Q}$) regions and increasing perfusion to others. In this issue, Benumof *et al.*[2] address this important problem using a dog model, and find considerable changes in distribution of pulmonary blood flow. Thus, one set of opposing factors acting during mechanical ventilation is defined.

Several other variables may also change Pa_{O_2} values significantly and to extents that vary under different clinical circumstances. For example, increasing the inspired oxygen concentration (FI_{O_2}) usually increases Pa_{O_2} when the ratio of shunt flow to cardiac output ($\dot{Q}_s/\dot{Q}_t$) is less than 50 per cent. This too, is an interaction between an increase in oxygen content in blood perfusing ventilated alveoli and a redistribution of pulmonary blood flow resulting from reversal of hypoxic pulmonary vasoconstriction (HPV). In lung that is sufficiently intact for HPV to occur, this interaction is important and may account for increases in $\dot{Q}_s/\dot{Q}_t$ of as much as 6 per cent.[3] In more severely diseased lung, $\dot{Q}_s/\dot{Q}_t$ may actually decrease as FI_{O_2} is increased.[4,5] This is probably due to the disease process preventing HPV. The increased FI_{O_2} overcomes the exaggerated diffusion and $\dot{V}/\dot{Q}$ barrier in this diseased lung. West has calculated that, whereas the contribution of low-$\dot{Q}_s/\dot{Q}_t$ can be overcome at low inspired oxygen levels in moderate disease, this threshold may be very high for lungs with extreme $\dot{V}/\dot{Q}$ scatter.[6]

Other factors influencing distribution of pulmonary blood flow, and therefore Pa_{O_2}, include cardiac output and left atrial pressure. As right-heart output increases, pulmonary vessels are recruited, probably by a combination of an unkinking mechanism and passive distention. Pulmonary vascular resistance decreases. There is no net change in pulmonary artery pressure over a wide range of flows. The recruited vessels are, at least in part, in low-volume regions of lung. Thus, in a variety of clinical circumstances, $\dot{Q}_s/\dot{Q}_t$ varies directly with cardiac output.[7,8] Fortunately, the decrease in Pa_{O_2} values that would otherwise result is opposed by an increase in central venous oxygen content ($C\bar{v}_{O_2}$) secondary to improved oxygen transport. It follows that the balance of this interaction should be quite different when cardiac output increases secondary to increased tissue demands, as opposed to increases due to more direct cardiac stimulation. The details of this distinction have yet to be reported.

The effect of left atrial pressure (LAP) is to oppose hypoxic pulmonary vasoconstriction. It has been demonstrated in man that the effect of oxygen in reversing HPV is inversely proportional to LAP,[3] the assumption being that at high intraluminal pressures HPV cannot occur and there is therefore no further effect from increasing FI_{O_2}. Benumof and his colleagues have detailed this relationship in dogs.[9] It is interesting that, in the management of patients with left-heart disease, one of the earliest effects of an increase in LAP may be a decrease in Pa_{O_2} values due to redistribution of pulmonary blood flow (*i.e.*, from reversal of HPV). Thus, a deterioration in Pa_{O_2} values could be anticipated at LAP levels not sufficient to cause increases in interstitial water from osmotic–hydrostatic pressure differences.

Finally, there is the effect on Pa_{O_2} values of shifts in the oxyhemoglobin-dissociation curve. For example, induced hypocarbia may produce clinically important decreases in Pa_{O_2} values when these values are at or below the shoulder of the dissociation curve.[10–12]

Thus, as an example, we examine a patient who has acute pulmonary failure with severely impaired pulmonary oxygen exchange and an increased AaD_{O_2}. He is given an increased inspired oxygen concentration and his lungs are mechanically ventilated with PEEP. As a consequence, his cardiac output decreases, as does his Pa_{CO_2}. An increase in Pa_{O_2} is observed. The tip of a physiologic iceberg is in fact the resultant of several effects. Underventilated lung is recruited and pulmonary blood flow adversely redistributed. Opposing that redistribution is the HPV, which is, in turn, opposed by LAP. The pulmonary blood flow distribution is beneficially influenced by the decrease in cardiac output, but this is offset by the associated decrease in $C\bar{v}_{O_2}$. The problem may be compounded when a patient receives pulmonary vasodilator drugs, such as anesthetic agents, sodium nitroprusside, aminophylline, or isopropyl norepinephrine.

As we examine this complex situation, it is noticable that the primary therapeutic change was to the ventilation component of the $\dot{V}/\dot{Q}$ interaction. All subsequent effects were on the perfusion "half." Quantitative prediction is tremendously difficult, since most of the interacting variables change nonlinearly in relation to each other. This nonlinearity is certainly true with respect to the influence of FI_{O_2} on Pa_{O_2}, at various levels of $\dot{V}/\dot{Q}$ scatter; the relationship between cardiac output and pulmonary vascular resistance; and in particular, factors dependent upon the oxyhemoglobin-dissociation curve. Fortunately, there is an important message for the clinician in that it is clear that this is another example of a situation in which it would be unwise to treat a patient on the basis of the laboratory data only. The many purely physiologic interactions that may occur, independent of change in pathologic status, should discourage the clinician from allocating cause to numerical effect in the absence of other clinical or physiologic information. It is possible to change the numbers widely with no real change in the disease as a result of manipulations of the ventilator, blood volume, or use of drugs. It is well to remember this as we allocate the label of therapeutic success to a particular numerical change.

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