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*Editorials*

# Interplay of intrapulmonary and extrapulmonary factors on pulmonary gas exchange during weaning

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Traditionally every medical student is taught that the 4 causes of arterial hypoxemia are hypoventilation, increased (anatomical or physiologic) shunt, ventilation-perfusion ($\dot{V}_A/\dot{Q}$) mismatching and alveolar-endcapillary diffusion limitation for oxygen. Hypercapnia may be caused by hypoventilation and $\dot{V}_A/\dot{Q}$ inequalities. With hypoventilation hypercapnia will always be present, while with $\dot{V}_A/\dot{Q}$ abnormalities the increase in arterial $PCO_2$ may or may not be evident, depending upon the underlying ventilatory conditions. From a clinical standpoint, the latter two mechanisms together with shunt are the 3 most relevant intrapulmonary causes of abnormal respiratory (oxygen and carbon dioxide) blood gases, while diffusion limitation appears to be a small component of abnormal pulmonary gas exchange both in health and disease.

Although each of these mechanisms can produce abnormal respiratory blood gases, one of the most important contributions of the studies of pulmonary gas exchange over the last 2 decades [1] has been experimental evidence of the key role played by other factors (so-called, extrapulmonary) in determining the absolute levels of the arterial $PO_2$ and $PCO_2$. Besides the position of the oxyhemoglobin dissociation curve, the 4 most influential factors on $PaO_2$ are inspired $PO_2$, total ventilation, cardiac output and oxygen consumption (uptake). At present, there are numerous experimental and clinical settings showing that a reduction in inspired $PO_2$, total ventilation or in cardiac output, or an increase in oxygen uptake, may decrease $PaO_2$, other things being equal; and vice versa [1, 2]. Total ventilation is contemplated here as an extrapulmonary factor because it is the result of tidal volume times respiratory frequency set by extrapulmonary breathing control mechanisms. Alternatively, arterial $PCO_2$ may be determined by changes in $CO_2$ production (output), total ventilation, or in acid-base status.

In pulmonary medicine, however, abnormal $\dot{V}_A/\dot{Q}$ relationships is by far the most conspicuous of the pathophysiology of pulmonary gas exchange because it is present in all but one (caused by alveolar hypoventilation) of the most common pulmonary conditions. Accordingly, a realistic approach to knowledge (and hence to therapy) of the underlying pathogenetic mechanisms should require the capability to explore quantitatively and qualitatively ventilation and pulmonary blood flow within the lungs. Interestingly, although $\dot{V}_A/\dot{Q}$ mismatch was recognized as an important event at the beginning of our century, the pioneering studies focused on the respiratory gases started only approximately 50 years later from the work of Rahn and Fenn and that of Riley and associates. Subsequently, Fahri extended the kinetic analysis of inert gas exchange within the lungs and peripheral tissues reviewed formerly by Ketty, and showed how inert gases could be used to estimate quantitatively $\dot{V}_A/\dot{Q}$ relationships. The advent of computers dramatically improved the possibility to conduct numerical analysis of respiratory gas exchange. From this there were experimental and theoretical studies [3, 4] which viewed the lungs as an essentially continuous distribution of units of gas exchange having a wide range of $\dot{V}_A/\dot{Q}$ ratios. With all these conceptual and technologic considerations in mind, Wagner and associates in the early 1970s developed the so-called multiple inert gas elimination technique (MIGET) [5, 6] as a means of producing more information about an essentially continuous $\dot{V}_A/\dot{Q}$ distribution. Nowadays, the MIGET represents a major breakthrough in our understanding of the role of $\dot{V}_A/\dot{Q}$ mismatching in pulmonary disease without inflicting by itself perturbation to pulmonary circulation.

Although the MIGET is a technically demanding approach and requires considerable theoretical understanding for its proper interpretation and utilization, the principles governing inert gas elimination within the lung are relatively simple. These are essentially based on the concept that the uptake (or retention) ($Pc'/P\bar{v}$) or elimination (or excretion) ($PA/P\bar{v}$) of an inert gas in any homogenous area of the lung is given by the following equation,

$$Pc'/P\bar{v} = PA/P\bar{v} = \lambda/(\lambda + \dot{V}_A/\dot{Q})$$

where $Pc'$, $P\bar{v}$, and $PA$ correspond to endcapillary, mixed

venous and alveolar partial pressures, respectively, and $\lambda$ to the blood: gas partition coefficient or solubility. The MIGET is a formidable research tool which facilitates, firstly, the obtention of an estimate of the pattern of alveolar ventilation and pulmonary perfusion. Secondly, it permits the calculation of numerical variables which describe quantitative abnormalities. Thirdly, it infers the presence of the alveolar-endcapillary diffusion limitation for oxygen. Fourthly, it assists in the partitioning of the alveolar-arterial $PO_2$ difference into components due to shunt, $\dot{V}_A/\dot{Q}$ mismatching and diffusion limitation for oxygen. With the MIGET, finally, changes in $PaO_2$ can be apportioned into intrapulmonary and extrapulmonary determinants to facilitate our understanding of the physiological basis of these changes, especially critical when they operate simultaneously.

The investigation of Santak and coworkers assessing the influence of two different modes of assisted ventilation on pulmonary gas exchange during weaning in abdominal surgical patients published recently in an issue of this *Journal* [7] provides an elegant example of the importance of the interplay between intrapulmonary and extrapulmonary determinants of respiratory arterial blood gases on pulmonary gas exchange in the intensive care setting. They compared the influence of controlled mechanical ventilation (CMV) versus that of synchronized intermittent mandatory ventilation (SIMV) together with inspiratory pressure support (IPS) using conventional and inert gas exchange tools. The most striking finding was the significant mild increase in minute ventilation, essentially at the expenses of an increased respiratory rate, when patients were removed from CMV to the mode of SIMV plus IPS. Increased minute ventilation was associated with a dual effect on $\dot{V}_A/\dot{Q}$ ratio distributions. On the one hand, there was a mild improvement in $\dot{V}_A/\dot{Q}$ mismatching, as assessed by a significant increase in the mean $\dot{V}_A/\dot{Q}$ ratio for ventilation (the first moment of the distribution), e.g., the $\dot{V}_A/\dot{Q}$ distribution shifted to the right because of an increase in the overall $\dot{V}_A/\dot{Q}$ ratio, thus enhancing the efficiency of gas exchange per se. On the other, there was a significant increase in dead space which represents a further $\dot{V}_A/\dot{Q}$ worsening. Yet, $PaO_2$ and $PaCO_2$ remained unaltered between the 2 conditions investigated. Cardiac output and oxygen uptake (calculated through the Fick principle) did not change. It would have been also of interest, however, to compare the same mode of assisted ventilation (SIMV plus IPS) versus spontaneous ventilation during weaning to assess the potential influence of cardiac output on gas exchange. When patients are removed from mechanical ventilation, in addition to breathing pattern alterations the increase in cardiac output may play a key role in modulating pulmonary gas exchange [8, 9].

From the clinical viewpoint, $PaO_2$ remained unchanged because the beneficial effects on $PaO_2$ caused by increased minute ventilation (extrapulmonary factor) and the improvement in $\dot{V}_A/\dot{Q}$ mismatch (increased overall $\dot{V}_A/\dot{Q}$ ratio) (intrapulmonary factor) were likely offset by the simultaneous deleterious effect on $PaO_2$ due to the deterioration in $\dot{V}_A/\dot{Q}$ relationships (increased dead space) (intrapulmonary factor). Moreover, we hypothesize that oxygen consumption (extrapulmonary factor) could have increased likely during ISMV plus IPS, thus having an additional negative influence on $PaO_2$, as it has been shown previously in other studies during weaning from conventional mechanical ventilation [8, 10, 11]. The absence of an increased oxygen uptake is not, however, an unexpected finding in the study of Santak et al. [7], since it may be explained by the large variability of cardiac output measurements with the thermodilution technique, used to calculate oxygen consumption through the Fick principle [11]. Alternatively, it is conceivable that the increased minute ventilation (extrapulmonary factor) tending to reduce $PaCO_2$ during ISMV plus IPS and the increase in dead space (intrapulmonary factor) tending to increase $PaCO_2$ tend likely to balance, thus keeping actual $PaCO_2$ unaltered.

In summary, the study of the Düsseldorf's team shows a dual effect on $\dot{V}_A/\dot{Q}$ relationships (increases in overall $\dot{V}_A/\dot{Q}$ ratio and dead space) during the application of the mode of synchronized intermittent mandatory ventilation plus inspiratory pressure support compared to more conventional assisted ventilation. Furthermore, these $\dot{V}_A/\dot{Q}$ distribution changes could not be detected by conventional arterial blood gas measurements alone. This means that it is not only pattern of $\dot{V}_A/\dot{Q}$ mismatch per se, but its severity combined with extrapulmonary factors, namely total ventilation, cardiac output and/or oxygen uptake, that together conform with arterial $PO_2$ and $PCO_2$ in each individual in each clinical setting. These data, therefore, stress the importance of the interaction of intrapulmonary and extrapulmonary determinants in governing gas exchange. According to the results of this interplay, respiratory blood gas measurements may change in either direction, or simply remain unaltered. The important message for the clinician though is that arterial respiratory gases may be completely insensitive to adequately reflect the abnormalities that operate at the level of the different determinants of pulmonary gas exchange.

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