Ventilation-Perfusion Matching during Exercise*

Peter D. Wagner, M.D.

In normal subjects, exercise widens the alveolar-arterial P0₂ difference ([A-a]O₂) despite a more uniform topographic distribution of ventilation-perfusion (VA/Q) ratios. While part of the increase in [A-a]O₂ (especially during heavy exercise) is due to diffusion limitation, a considerable amount is caused by an increase in VA/Q mismatch as detected by the multiple inert gas elimination technique. Why this occurs is unknown, but circumstantial evidence suggests it may be related to interstitial pulmonary edema rather than to factors dependent on ventilation, airway gas mixing, airway muscle tone, or pulmonary vascular tone. In patients with lung disease, the gas exchange consequences of exercise are variable. Thus, arterial P0₂ may increase, remain the same, or fall. In general, patients with advanced chronic obstructive pulmonary disease (COPD) or interstitial fibrosis who exercise show a fall in P0₂. This is usually not due to worsening VA/Q relationships but mostly to the well-known fall in mixed venous P0₂, which itself results from a relatively smaller increase in cardiac output than V0₂. However, in interstitial fibrosis (but not COPD), there is good evidence that a part of the fall in P0₂ on exercise is caused by alveolar-capillary diffusion limitation of O₂ transport; in COPD (but not interstitial fibrosis), a frequent additional contributing factor to the hypoxemia of exercise is an inadequate ventilatory response, such that minute ventilation does not rise as much as does CO₂ production or O₂ uptake, causing arterial POC0₂ to increase and P0₂ to fall.

Pulmonary gas exchange during exercise has long been a subject of interest, both to physiologists concerned with normal lungs and to clinicians who must deal with patients with lung disease. There are, in general, substantial changes in gas exchange efficiency, even in normal subjects, when exercise is compared with rest, and to this day, we are still unsure of the fundamental mechanisms underlying these perturbations. This article will present the evidence for these changes and speculate on possible mechanisms. Most of the emphasis is on normal subjects in whom conditions both at sea level and at high altitude will be discussed, but effects of exercise on gas exchange in adult patients with common chronic lung diseases will also be addressed.

**Potential Effects of Exercise on VA/Q Inequality**

Before presenting data on this topic, it seems reasonable to ask how exercise might alter gas exchange in general and VA/Q relationships in particular, with the discussion confined to normal subjects.

**Airway-Related Effects**

With the large increase in tidal volume, exercise may improve ventilation in lung regions operating at, near, and especially below, their closing volume, should such regions exist. However, this might be offset by the rapid extraction of O₂ out of alveolar gas in such regions whose end-expiratory volume is reduced yet whose blood flow is high. The low ratio of gas volume to blood flow would accentuate the rate of fall of alveolar P0₂ in such areas and have the tendency to reduce arterial P0₂.

The increase in respiratory rate and gas flow rates could **per se** alter ventilation distribution. Under such conditions, resistance and even inertial factors become relatively more important and elastic properties become somewhat less important in determining distribution. This could theoretically lead to reduced ventilation of regions already poorly ventilated at rest and better ventilation of already well-ventilated areas.

Due to changes in airway temperature and humidity caused by the hyperpnea of exercise, broncomotor tone and also airway secretions could be enhanced and lead to heterogeneity of ventilation distribution. In some subjects, this could progress to a stage in which the label of exercise-induced asthma is applied.

Yet another potential factor might be related to the clearly increased rate of transcapillary fluid flux in the lungs during exercise. If fluid accumulated in the interstitial parenchyma, local lung compliance might fall and reduce local ventilation. If fluid accumulated around the smaller conducting airways, relative airways obstruction might develop and further worsen ventilatory inhomogeneity.

Because conducting airway dead space is a far smaller fraction of tidal volume during exercise than at rest, the beneficial effect of the conducting airways on gas mixing would be less in evidence, and gas exchange efficiency could be reduced.

Finally, there might be insufficient time for gas mixing between the inhaled and resident alveolar gas each breath, which could also lead to effectively increased heterogeneity.

**Circulation-Related Effects**

This rise in pulmonary artery pressure seen during heavy exercise* is fairly substantial, and this may well lead to a more uniform topographic perfusion distribution, as has been found. Depending on the transmission of such pressures to the pulmonary microcirculation, however, there might be concurrently increased transcapillary fluid flux, which could lead to temporary interstitial edema if fluid clearance does not keep pace with transcapillary flux. If this caused regional perivascular fluid accumulation, inhomogeneity of blood flow could be accentuated. Especially at high altitude,* but even at sea level, pulmonary vascular tone may not be uniform throughout the lungs, further allowing the possibility of heterogeneity.

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so that alveolar-end capillary PO₂ differences develop. This would constitute diffusion limitation.

Finally, any small shunts normally present, but insignificant at rest, may have a greater effect on PO₂ during exercise.

This is not necessarily because the fractional perfusion of the shunt increases, but because the venous blood perfusing the shunt generally has a considerably reduced PO₂ compared with values at rest.

Thus, there is a large array of potential phenomena that could alter VA/Q relationships during exercise. The result is likely to be an extremely complex interaction among several processes and the result could well be improved, unchanged, or deteriorated VA/Q relationships. Some of the above factors border on the pathologic (interstitial edema, bronchial tone alterations), while others are passive consequences of a given lung structure.

OVERALL GAS EXCHANGE DURING EXERCISE IN NORMAL SUBJECTS

The alveolar-arterial PO₂ difference progressively increases with exercise⁷ (Fig 1A), reaching values of 20 to 30 mm Hg during (near) maximal exercise in average subjects, and even greater values (up to 40 mm Hg or more) in some elite athletes.⁸ At the same time, PO₂ in the mixed venous blood dramatically falls because the relative increase in VO₂ is considerably greater than that of cardiac output (Table 1), and mixed venous PCO₂ rises equally remarkably (Table 1).

Arterial PO₂ generally remains unchanged until extremely high exercise levels are undertaken, at which time it falls sometimes considerably⁹ as shown in Figure 1B. Arterial PCO₂ levels are also relatively stable until the appearance of high blood lactate levels produces acidosis, even more ventilation, and thus a fall in PCO₂ levels (Fig 1C).

Three factors contribute numerically to the increase in P(A-a)O₂: a fall in PaO₂, a fall in PaCO₂, and a rise in the respiratory exchange ratio. In other words, it is useful to point out that P(A-a)O₂ can be elevated even without a fall in PaO₂ if PaCO₂ falls and/or respiratory exchange ratio rises. The increase in P(A-a)O₂ implies gas exchange inefficiency has developed.

Table 1—Typical Changes from Rest to Near Maximal Exercise in Normal Subjects at Sea Level

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value at Rest</th>
<th>Value during Exercise</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minute ventilation, L/min</td>
<td>7.2</td>
<td>126</td>
<td>17.5</td>
</tr>
<tr>
<td>Tidal volume, ml</td>
<td>450</td>
<td>3,150</td>
<td>7.0</td>
</tr>
<tr>
<td>Respiratory rate, min⁻¹</td>
<td>12</td>
<td>40</td>
<td>3.3</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>6</td>
<td>25</td>
<td>4.2</td>
</tr>
<tr>
<td>Heart rate, min⁻¹</td>
<td>72</td>
<td>190</td>
<td>2.6</td>
</tr>
<tr>
<td>Stroke volume, ml</td>
<td>53</td>
<td>132</td>
<td>1.6</td>
</tr>
<tr>
<td>Overall VA/Q</td>
<td>0.9</td>
<td>4.8</td>
<td>5.3</td>
</tr>
<tr>
<td>Arterial PO₂, mm Hg</td>
<td>93</td>
<td>90</td>
<td>0.97</td>
</tr>
<tr>
<td>Arterial PCO₂, mm Hg</td>
<td>40</td>
<td>34</td>
<td>0.85</td>
</tr>
<tr>
<td>Mixed venous PO₂, mm Hg</td>
<td>40</td>
<td>20</td>
<td>0.5</td>
</tr>
<tr>
<td>Mixed venous PCO₂, mm Hg</td>
<td>45</td>
<td>70</td>
<td>1.6</td>
</tr>
<tr>
<td>P(A-a)O₂, mm Hg</td>
<td>9</td>
<td>28</td>
<td>3.1</td>
</tr>
<tr>
<td>V̇E/ VR, %</td>
<td>27</td>
<td>18</td>
<td>0.7</td>
</tr>
<tr>
<td>V̇O₂, ml/min</td>
<td>300</td>
<td>3,600</td>
<td>12.0</td>
</tr>
<tr>
<td>V̇CO₂, ml/min</td>
<td>240</td>
<td>4,000</td>
<td>16.7</td>
</tr>
<tr>
<td>r</td>
<td>0.8</td>
<td>1.11</td>
<td>1.4</td>
</tr>
</tbody>
</table>

Intrinsic structural inhomogeneity of the pulmonary circulation could produce greater flow heterogeneity at high perfusion rates in exercise, much as gas flow in the airways, as discussed above.

As end-expiratory volume falls with increasing exercise loads, pulmonary vascular resistance may rise (in dependent areas in particular, whose regional lung volume is less) and alter perfusion distribution.

Transit time of red blood cells may be sufficiently reduced...
Table 2—Computations Made with Published Computer Algorithm

<table>
<thead>
<tr>
<th>Stage</th>
<th>Action</th>
<th>$\dot{V}_{A}$</th>
<th>$Q_{T}$</th>
<th>LogSD$_{O_2}$</th>
<th>P(A-a)$_{O_2}$</th>
<th>P(A-a)$_{O_2}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rest</td>
<td>5.4</td>
<td>6.0</td>
<td>0.4</td>
<td>40</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>Increased</td>
<td>120</td>
<td>25</td>
<td>0.4</td>
<td>40</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>Decreased</td>
<td>120</td>
<td>25</td>
<td>0.4</td>
<td>20</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>Increased</td>
<td>120</td>
<td>25</td>
<td>0.6</td>
<td>20</td>
<td>16</td>
</tr>
</tbody>
</table>

Physiologic Basis of the Increased P(A-a)$_{O_2}$ of Exercise

Classic teaching ascribes an increased P(A-a)$_{O_2}$ to one or more of the following: ventilation-perfusion inequality, shunt, and diffusion limitation of alveolar-capillary $O_2$ transport. Somewhat more recently, it has been demonstrated that the overall ratio of ventilation to cardiac output can modify the numeric value of the P(A-a)$_{O_2}$, and clearly can the value of mixed venous $P_O_2$ (thus, as $P_O_2$ is reduced, P(A-a)$_{O_2}$ will increase for a fixed amount of $VA/Q$ mismatch). While the role of the latter modifiers cannot be quantified experimentally since their independent effect cannot be separated from any other changes induced by exercise, their importance can be estimated by computation, and this is now briefly considered.

Table 2 shows such computations made with a published computer algorithm. A sequence of 4 stages is examined, commencing with resting values typical of a normal subject. Thus, alveolar ventilation ($V_a$) is 5.4 L/min, cardiac output ($Q_T$) is 6.0 L/min, the amount of $V_{A}/Q$ inequality is small (LogSD$_{O_2}$ = 0.4), and mixed venous $P_{O_2}$ (PvO$_2$) is normal. The computed P(A-a)$_{O_2}$ is 9 mm Hg. The next stage reflects purely an increase in alveolar ventilation and cardiac output to values typical of heavy exercise, without change in LogSD$_{O_2}$ or PvO$_2$. Because overall $V_{A}/Q_T$ has increased so much from rest, P(A-a)$_{O_2}$ is smaller at 2 mm Hg, but when PvO$_2$ is allowed to fall to realistic levels, P(A-a)$_{O_2}$ is again increased (to 6 mm Hg). Finally, the additional effects of increased $V_{A}/Q$ mismatch (see below) further raise P(A-a)$_{O_2}$ to 16 mm Hg in this hypothetical example. The beneficial effect on P(A-a)$_{O_2}$ of increased $V_{A}/Q_T$ ratio is based on moving all $V_{A}/Q$ units in the lung higher onto the flatter part of the $O_2$ Hb dissociation curve; the opposite effect of a reduction in PvO$_2$ is explained by the converse.

Ventilation-Perfusion Inequality

Topographic $V_{A}/Q$ relationships appear to become more uniform, at least during moderate exercise up to $V_{O_2}$ levels of 1 to 2 L/min. Recall that this happens even as the P(A-a)$_{O_2}$ is increasing. The reduction in topographic inequality is consistent with a more uniform blood flow distribution due to the higher pulmonary artery pressures (compared with rest). These changes fit conventional theory and seem to be beyond dispute. They cannot, however, explain the seemingly paradoxical increase in P(A-a)$_{O_2}$.

Based on data obtained with the multiple inert gas elimination technique, it is clear that exercise can worsen $V_{A}/Q$ relationships. As shown by several studies, the $V_{A}/Q$ dispersion is found to increase, especially at very heavy exercise levels. (At light to moderate levels [<60% $V_{O_2,max}$], significant changes are often not evident.) In fact, although P(A-a)$_{O_2}$ uniformly increases with exercise intensity in essentially all subjects, $V_{A}/Q$ inequality is not seen to increase in nearly so many. As we reported, it required a relatively large number of subjects to show significant effects of exercise on $V_{A}/Q$ dispersion, and even then, many individuals appear not to develop more inequality on exercise.

Figure 2 shows an important ancillary observation in the same subjects: a greater tendency to develop mismatch on exercise in acute hypoxia. This is acutely reversed by hyperoxia at the same exercise load. In pointing out the effects of hypoxia in increasing $V_{A}/Q$ mismatch, it is also worth noting that in a different study, which also revealed greater $V_{A}/Q$ inequality on exercise, no spirometric abnormalities could be demonstrated, comparing data immedi-

Figure 2. Variable but statistically significant increase in $V_{A}/Q$ mismatch with sea level exercise. On average, from this study, the degree of $V_{A}/Q$ inequality as expressed by LogSD$_{O_2}$ increased by about 0.2 from rest to close to 4 L/min $V_{O_2}$. Each point represents an individual subject, and it should be noted that there is great variability in the tendency to develop increased $V_{A}/Q$ mismatch with exercise (data from Wagner et al).

Figure 3. Increased tendency to develop $V_{A}/Q$ mismatch on exercise in hypoxia. These data indicate a greater slope to the relationship between $V_{A}/Q$ mismatch (LogSD$_{O_2}$) and exercise level ($V_{O_2}$) as barometric pressure is reduced in a chamber where subjects breathe room air. As discussed in the text, these results suggest involvement of the pulmonary circulation in the genesis of the increased $V_{A}/Q$ mismatch of exercise (data from Wagner et al).
ately before and after exercise. Although this observation does not fully exclude airway-related causes of increased inequality, the combination of hypoxic aggravation and lack of spirometric changes seem to point to the circulation as the origin of the increased VA/Q mismatch, and in fact, an excellent relationship was found between pulmonary artery pressure and VA/Q dispersion.

It should be stressed that the importance of increased VA/Q mismatch during exercise is not in its effect on arterial oxygenation but on what it may be signifying about pulmonary function under extreme conditions. Thus, as was pointed out, the magnitude of increase in dispersion is relatively slight: logSDs increasing from 0.4 to 0.6 from rest to almost 4 L/min V̇O₂. This modest increase falls far short of explaining the much more dramatic increases in P(A-a)O₂ shown in Figure 1A, although it is noted that elite athletes with P(F-a)O₂ values 40 to 50 mm Hg have not yet had their VA/Q relationships analyzed by means of the multiple inert gas elimination technique, which remains the only way to determine VA/Q distribution in these circumstances. We estimated that no more than about 10 to 15 mm Hg of the total P(A-a)O₂ could be accounted for on the basis of VA/Q inequality at heavy exercise, leaving at least half of the P(A-a)O₂ to be explained by other mechanisms. It should also be noted that the VA/Q pattern remains normal in contour in that the normal unimodal appearance is preserved and only a modest widening of this single mode of lung units occurs. Except under exceptional circumstances, one does not observe the development of lung regions of grossly abnormal, extreme VA/Q ratio.

Tentative Explanations for the Development of VA/Q Inequality on Exercise

Any hypothesis advanced should account for the aggravation of mismatch by hypoxia and the lack of spirometric changes seen after exercise.

Perhaps the most attractive hypothesis is the temporary accumulation of interstitial fluid in the lungs causing altered distribution of ventilation and blood flow. As mentioned above, there is clearly increased transcapillary fluid flux, as expected from hydrostatic vascular pressure increases in both pulmonary artery and veins (the latter estimated from wedge pressures). This would likely be aggravated by hypoxia where pressures are even higher due to vasoconstriction, and are not inconsistent with preserved spirometry. There is some evidence of low-grade edema developing during exercise. It comes from studies of ventilatory patterns, as well as from studies of postexercise lung volumes. However, all of these data and approaches only imply a role for edema; unfortunately, there is no method available to detect directly small increases of extravascular water content from rest to exercise.

A competing hypothesis is intrinsically uneven vascular impedance accentuating inequality at high flow rates, and again it is easy to imagine that this could be aggravated by further (uneven) hypoxic vasoconstriction at high altitude. In fact, this hypothesis is but a step away from the most popular theory of high-altitude pulmonary edema, and it becomes tempting to speculate that what is seen in normal subjects at sea level during exercise and is accentuated in hypoxia is, in fact, the early stage of a continuum that ends in fulminant edema, as sometimes seen in (exercising) subjects at high altitude. The corollary of this idea has not been tested yet: Do those subjects who develop high-altitude pulmonary edema also develop more VA/Q mismatch breathing air at sea level during exercise? They certainly have a greater hypoxic vascular response.

When we turn to airway-related phenomena, the possibilities are both numerous (see above) and very difficult to pin down experimentally. While spirometry performed immediately after exercise clearly excludes gross airway caliber-related causes, it just as clearly does not exclude more subtle peripheral possibilities such as discussed earlier. Experimental physiology appears not to possess the tools at this time to resolve these issues under these extremely challenging study conditions.

Although it remains tempting to search for phenomena that arise from deterioration in structure or function, other possibilities remain unexplored. The idea that the reduced dead space/tidal volume ratio of exercise unmasks inequality actually present at rest but not measured because of mixing in the dead space has not been excluded. In fact, in anesthetized dogs, it was recently shown that, indeed, this simple "non-pathological" mechanism might account for up to half of the apparent increase in VA/Q dispersion seen in human exercise. This remains to be confirmed in human subjects.

A final hypothesis to account for the P(A-a)O₂ in terms of a form of VA/Q heterogeneity is that of insufficient time for mixing of inspired and alveolar gas, so-called gas phase diffusive limitation. This would produce interference to gas exchange that might be interpreted as increased VA/Q dispersion. Although this is possible, to our knowledge, there are no convincing data to support a quantitatively significant role in exercise. A necessary part of this hypothesis would be that high-molecular-weight gases would be interfered with more than those of low molecular weight. This has not actually been observed to any significant extent, and if it is a factor, it would seem to be a minor one.

In summary, VA/Q mismatch increases with exercise but the effects are not great. There is much intersubject variability and no clear-cut mechanism has been demonstrated to date. The probable mechanisms at this point revolve around circulatory rather than ventilatory abnormalities, and may well reflect temporary interstitial fluid accumulation in the lung.

Shunt

Shunts in normal subjects are probably of minor significance in the genesis of the large P(A-a)O₂ values during exercise. Direct right-to-left intrapulmonary and intracardiac shunts would certainly be detected by the multiple inert gas elimination technique with considerable sensitivity. They are simply not observed, and shunts are generally 0 or at most 0.5 to 1% of the cardiac output in the great majority of normal subjects.

Extrapulmonary shunts deserve more discussion. Most physiologists believe in the existence of small bronchial and/or thebesian vein shunts in normal humans. Particularly with the low thebesian vein PO₂, these shunts could contribute to the increased P(A-a)O₂. The multiple inert gas technique, by directly assessing intrapulmonary shunt and VA/Q inequality, can determine that fraction of the P(A-a)O₂ accounted for by these latter 2
factors. However, the inert gases are not affected by either extrapulmonary shunt or alveolar-capillary diffusion limitation, and thus any residual part of the P(A-a)O2 not explained by intrapulmonary shunt or V/Q mismatch is presumed due to extrapulmonary shunt and/or diffusion limitation.

During air breathing, this unexplained portion of the P(A-a)O2 is difficult to divide between these 2 factors, but during hypoxia (eg, at high altitude), one may make the reasonable argument that because the size of the extrapulmonary shunt would have to be 10% to 20% of the cardiac output to explain measured data, the far more probable cause of the 'unexplained' part of the P(A-a)O2 is diffusion limitation. The arguments, however, are based on logic and no experimental tools appear available to differentiate them rigorously.

If we put these uncertainties aside, at or near VO2max the major portion of the P(A-a)O2 even at sea level, but especially at high altitude, is due to diffusion limitation (± extrapulmonary shunt) and not to V/Q mismatch. As pointed out by Lilienthal et al so long ago, hypoxia brings out the importance of diffusion limitation while it simultaneously reduces the effect of V/Q mismatch as factors determining the P(A-a)O2. Recent studies with modern techniques have reinforced these old concepts strongly.

**Diffusion Limitation**

It is hard not to discuss this aspect of pulmonary gas exchange when conceptually and methodologically, it is so closely interwoven with V/Q inequality and shunt. Under extreme exercise loads, alveolar-capillary O2 transport appears greatly diffusion-limited. In fact, it appears to be the dominant factor in generation of the high P(A-a)O2 values during very heavy exercise at sea level, and even more important at high altitude. This is not because O2 diffusing capacity is unexpectedly low but rather because despite high estimates of diffusing capacity, the red blood cell transit time is simply insufficient to permit diffusive equilibration of end capillary blood with alveolar gas. The better the athlete, the more this appears to be the case.

**GAS EXCHANGE IN LUNG DISEASE**

This section will discuss the effects of exercise on gas exchange in 3 common pulmonary disease states: chronic obstructive lung disease (COPD), diffuse interstitial lung disease (DIF), and asthma.

Exercise testing with arterial blood sampling has become a common practice in evaluating patients with a variety of diseases, especially obstructive and restrictive conditions. In part, all that is asked of such studies is whether exercise-induced hypoxemia develops to the point that supplemental O2 is indicated. However, additional questions arise from changes in PaO2 produced by exercise, in particular, regarding possible alterations in V/Q relationships or the development of alveolar-capillary diffusion limitation. The ensuing section addresses by disease category what is known about the effects of exercise on gas exchange in chronic lung diseases. For the most part, data have come from patients with advanced disease. Although this accentuates the characteristic abnormalities in gas exchange, at the same time, it precludes much exercise and thus the effect of only modest work loads can be studied. Typically, such patients can mount a VO2 of only 3 to 4 times resting or less than about 1 L/min.

**Chronic Obstructive Lung Disease**

Clinical experience shows that patients with advanced COPD can exhibit almost any pattern of arterial blood gas change from resting values: arterial PO2 may rise, fall, or stay unchanged; arterial PCO2 similarly may rise, fall, or remain constant. It is worth first discussing potential explanations and then examining available data to determine which are applicable. Perhaps most fundamentally, if alveolar ventilation does not rise relatively as much as VO2 and V/Q, then arterial PO2 must fall and Pco2 must rise, all other factors remaining unchanged. Second, even in normal subjects, mixed venous PO2 falls progressively with increasing exercise because the relative increase in VO2 exceeds that of cardiac output. In patients with COPD, mixed venous PO2 is usually reduced even at rest, and may well fall substantially with even modest exercise. This occurs because of 1 or more factors interfering with cardiac performance: there may be coexisting ischemic heart disease since most patients with COPD are older and are smokers; there may be pulmonary hypertension due to the structural abnormalities of COPD compounded by hypoxic vasoconstriction. Thus, the cardiac output response to exercise may be subnormal, such that mixed venous PO2 is very low. In the presence of V/Q inequality, this will independently depress arterial PO2, if other factors remain unchanged.

Third, exercise could lead to altered V/Q relationships. As with normal subjects, the potential factors are many (see above), and while some lead to V/Q improvement, some will produce deterioration. Finally, incomplete diffusive mixing of inspired and alveolar gas or incomplete diffusive equilibration between alveolar gas and capillary blood could develop during exercise and depress arterial PO2 levels.

Because changes in P(A-a)O2, physiologic dead space, and venous admixture can be seen even when V/Q relationships remain unchanged, as total ventilation and/or blood flow increase, these indices are unreliable markers of changes in V/Q matching in patients with COPD.

The multiple inert gas elimination technique has been used in this category of patient on several occasions to sort out the relative importance of all of the above factors. What has been found and confirmed is that over the rather small range of increased VO2 attainable by patients with advanced disease, no changes in the degree or pattern of V/Q inequality appear to occur. This conclusion may or may not apply to patients with less advanced disease who could sustain higher exercise loads. Not only is the extent of V/Q mismatching unaffected, but there is no evidence that diffusive mixing or alveolar-capillary diffusion equilibration is incomplete. That diffusive gas mixing is sufficiently rapid not to compromise arterial PO2 is suggested by no preferential retention of high-molecular-weight gases when data are analyzed that have been obtained using the multiple inert gas technique. The same method also leads to predictions of arterial PO2 values (based on only the measured degree of V/Q mismatch) that statistically are not different from measured arterial PO2 values. This agreement leaves no room, therefore, for alveolar-capillary diffusion limitation as a factor altering arterial PO2.
Consequently, current evidence suggests that at least in the average patient with advanced disease, blood gas changes on exercise are explained by different relative increases among VO₂, VCO₂, alveolar ventilation, and cardiac output. Thus, increases in PaCO₂ generally reflect inadequate increases in ventilation and corresponding decreases in PaO₂ will occur. The fall in mixed venous PO₂ discussed above will further compromise alveolar PO₂. However, it must be emphasized that these conclusions apply to the general case; in specific patients, it is entirely possible that any or all of the mechanisms discussed above could lead to altered gas exchange.

In closing this section, a word about the carbon monoxide diffusing capacity (Dco) may be useful. This overall gas exchange parameter is frequently reduced in patients with COPD but it must be remembered that part of the reason for this is inequality of ventilation. When it is also realized that in the normal lung there is a considerable excess of mean red blood cell contact time available for gas exchange, it should not come as a surprise to find that even if Dco is reduced, diffusion limitation of O₂ exchange has not been demonstrated in patients with COPD.

**Interstitial Fibrosis (DIF)**

In this class of diseases characterized by varied causes but final common pathologic finding, most of the general comments about gas exchange during exercise made for patients with COPD also apply. At least the potential determinants of altered gas exchange are the same, even though the basic V̇A/Q maldistribution pattern of the 2 classes of abnormality may be different. Consequently, this discussion requires no repetition.

What is found in DIF is that exercise almost always leads to a reduction in PaO₂ with generally little change in the already lower than normal arterial PCO₂. Some CO₂ retention may occur in very advanced cases, or in the not infrequent setting of combined DIF and COPD. As with COPD, patients studied to date in order to analyze the determinants of exercise-induced hypoxemia have had mostly advanced disease, again precluding VO₂ values more than about 1 L/min during exercise. In such patients, as those with COPD, no change in the pattern or extent of V̇A/Q mismatch from resting values is found. The often considerable hypoxemia is due to a combination of 2 factors: the often precipitous fall in mixed venous PO₂ caused by inadequate cardiovascular responses to exercise, and the development or accentuation of alveolar-capillary PO₂ differences due to incomplete diffusive equilibration across the blood gas barrier. Ventilatory responses are usually adequate so that despite severe dyspnea, arterial PCO₂ does not rise. It is worth noting that unlike the situation in patients with COPD, there seems to be a relationship between the degree of reduction in Dco and the amount of hypoxemia caused by diffusion limitation. Thus, the lower the Dco, the more this factor plays a role. It appears that Dco must be reduced to at least 60% of predicted for the lung as a whole before diffusion limitation detectably alters arterial PO₂, and that reductions of Dco to 20% to 30% of predicted produce considerable alveolar-arterial PO₂ differences.

Despite the development of diffusion limitation in patients with DIF undergoing exercise, by far the largest factor contributing to the total P(A-a)O₂ remains V̇A/Q inequality. Thus, about 85% of the exercise P(A-a)O₂ on average comes from this source, and only 15%, therefore, comes from diffusion limitation. For a typical patient whose P(A-a)O₂ during exercise may be 60 mm Hg, this implies that 50 mm Hg comes from V̇A/Q mismatch and 10 mm Hg comes from incomplete diffusive equilibration.

**Asthma**

Very little work has been done studying the gas exchange of patients with asthma during exercise. Young et al have examined patients with exercise-induced asthma before and after exercise using the multiple inert gas elimination technique. They found that despite only mild V̇A/Q inequality at rest, all of their subjects developed increased mismatch during the postexercise period. At rest, V̇A/Q dispersion (logSDV/Q as earlier defined) was 0.54, while 15 to 28 min after exercise sufficient to increase heart rate to about 160/min, logSDV/Q averaged 1.0, which is a considerable increase. By 28 to 38 min after exercise, logSDV/Q had returned to control levels (0.58 mean). In general, spirometric deterioration and subsequent recovery mirrored these observations, but it appears that V̇A/Q relationships normalized somewhat earlier than spirometric ones. Arterial PO₂ also reflected these changes, falling from 92 to 74 mm Hg and returning to 79 mm Hg over the same time.

Thus, unlike patients with advanced, stable COPD and DIF, hypoxemia after exercise in this form of asthma is explained by worsening V̇A/Q inequality, and other potential factors appear secondary. This different result is not unreasonable since exercise clearly leads to increased airways obstruction as occurred in the patients studied by Young et al.

**Overall Conclusions**

Exercise in both normal subjects and patients with lung disease may alter gas exchange relationships by more than accounted for simply by increased total ventilation, cardiac output, VO₂ and VCO₂. Thus, V̇A/Q mismatching and/or diffusion limitation may become more evident, depending on the setting as described above. In normal subjects, V̇A/Q inequality often develops but the reasons remain unclear. The principal explanation for the considerably increased P(A-a)O₂ appears to be alveolar-capillary diffusion limitation. In patients with lung disease, the effects of exercise are more numerous and variable, but both V̇A/Q mismatching and diffusion limitation may be important contributors to hypoxemia, depending on the pathologic condition.

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