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Mechanism for Worsening Gas Exchange at Increased Cardiac Output: It's Time for an Occam's Razor

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Abstract

Previous investigators reported that gas exchange consistently worsened when cardiac output (Qt) was increased under normal and pathological conditions. The aim of the present paper is to offer an alternative explanation, besides the one previously proposed that was based on some attenuation of hypoxic pulmonary vasoconstriction. The new concept emphases the inherent heterogeneity of regional blood flow (Q), as well as the skewed relationship between ventilation perfusion ratio (V/Q) and arterial oxygen tension (PaO_2). Namely, PaO_2 is exquisitely sensitive to any change of V/Q ratio from 0 to 1, which is many times more than that from 1 to 100. As Qt is increased, the additional pulmonary flow is by no means uniformly distributed. Thus, either ventilation (V) remains stable or even becomes more variable, V/Q heterogeneity increases at increased Qt. The higher Q in most regions reduces their corresponding V/Q ratios from the previously normal value of about 0.8 to 1, precipitously into the hypoxic range towards true shunt (V/Q = 0) and increases the V/Q mismatch. In contrary, the simultaneously created higher V/Q units cannot mitigate these adverse changes because of the sigmoid shape of hemoglobin oxygen dissociation curve. By this mechanism, diseased lungs are more susceptible to hypoxemia when Qt is increased due to their pre-existing V/Q abnormalities.

Keywords: Heterogeneity of regional blood flow; Oxygen-carbon dioxide diagram; Shunt; Venous admixture; Ventilation perfusion mismatch

Introduction

Under normal condition, ventilation (V) and perfusion (Q) are well matched, with the V/Q ratio in most regions close to one [1]. Consequently, there is efficient transfer of oxygen from the alveoli to the pulmonary capillary blood, resulting in minimal venous admixture [2]. Because of this precise matching, it is often assumed incorrectly that either V or Q per se is homogenous.

In the studies of gas exchange, shunt fraction (Qs/Qt) was initially used to estimate the extent of venous admixture, using 100% inspired oxygen. But these results were vague, because they were premised on a basic 2-compartment model consists of only normal (V/Q = 1) and shunt (V/Q = 0) units. Consequently, in these early reports the varying impacts of miscellaneous low V/Q units (V/Q < 1) on arterial oxygenation were not well described [3.4], mainly due to the limitation in V/Q resolution at the time, rather than their de facto absence. The discovery of the multiple inert gas elimination technique (MIGET) eventually led to more sophisticated descriptions of V/Q compartments in the lung, but the solution was based on mathematical approximation and not on direct measurements [5,6]. Thus, quantification of low V/Q units could still be somewhat variable e.g. uni-modal vs multi-modal distributions [7,8], and their three dimensional locations were essentially unknown. More recently, the use of fluorescent microsphere (FMS) technique significantly improved the accuracy of V/Q mapping of lung regions and reliably provided anatomical information [9-11].

Previous investigators have shown that when cardiac output (Qt) was increased in normal as well as diseased lungs, gas exchange often deteriorates and venous admixture worsens [3,4]. This phenomenon has been extensively reported under both clinical and experimental conditions, such as pulmonary edema [7,12], chronic obstructive lung disease [13], pulmonary embolism [14,15] and adult respiratory distress syndrome [16] etc. These observations were also reproducible when Qt was increased by very different methods, i.e. opening the arterial-venous fistula [4,12], titrating pre-load [3,7], changing flow during arterial venous bypass [17], or using vasopressor [18]. Furthermore, during vigorous exercise at sea level even among healthy subjects, there was an inexplicable increase in alveolar to arterial oxygen tension difference (A-a DO2). However, it was not be abolished by inhaling 100% oxygen [19], thus ruling out simple explanations such as diffusion limitation.

Interestingly, these observations were actually contrary to what one might expect from the Fick's equation [1]. In other words, we may anticipate that when Qt is increased, the venous oxygen saturation (SvO2) will also increase. But this rise in SvO2 should justifiably improve the arterial oxygen saturation (SaO2) from the same lung, resulting in the theoretical but opposite conclusion that venous admixture would be reduced instead. Thus, a timely explanation is required to address this paradox.

Nevertheless, several attempts have been made to elucidate this apparent contradiction. One of the more prevalent ideas is that hypoxic pulmonary vasoconstriction (HPV) has been in some way attenuated [13]. Some suggested that this was possibly related to the higher SvO2 of the returning blood mediating at the pulmonary capillary levels [20,21]. However, such explanations remain questionable [22] because there was never any direct measurement of regional alveolar oxygen tension (PAO_2), or regional V and Q at such

refined level of resolution, to either refute or confirm the concept. Others attributed this phenomenon to the effect of some vasodilators such as nefedipine or niroprusside used to increase Qt in certain experimental conditions [13,23]. But these drugs specifically affected vascular tones and the conclusions could not be generalized.

The purpose of the present paper is to propose an alternative mechanism for this puzzling question. Premises will be first presented, followed by a cogent conclusion.

Premise #1: Regional Blood Flow Is Heterogeneous

Regional blood flow (Q) in the lung, even under normal condition, is heterogeneous, as it is simultaneously subject to many physiological and anatomical determinants.

The effect of gravity has been well described, in which the lung is divided into different zones in accordance to the relative magnitude of pulmonary arterial pressure (Pa), pulmonary venous pressure (Pv) and alveolar pressure (PA) [24,25]. However, within each zone, there are remarkable heterogeneities of Q despite the depiction of a simplified diagram [26]. At the same time, Q is determined by the radial gradient from the hila [27], degree of pulmonary edema [28], blood flow in the adjacent regions over time [29], posture [30], and collateral circulation [31], just to name a few. The inflated regional lung volume also affects the pulmonary vascular resistance and the relative distribution of flow in the alveolar vs extra-alveolar vessels [32,33]. Metabolic factors, such as PO2, PCO2, catacholamines, histamines, serotonin and endothelins etc. add further complexities [31], as they mediate differently the vascular tones of pulmonary arteriolar and venous vessels [34-36]. Finally, variations in regional hematocrit can also influence the regional blood flow pattern [37,38]. Under pathological conditions in which destruction of the pulmonary capillary bed occurs, e.g. emphysema or pulmonary fibrosis, heterogeneity of Q will be even more severe.

Generally speaking, the distribution of Q in the normal lung is bell shaped. In the MIGET data, the histogram of Q show how it distributes over the entire range of V/Q and its standard deviation (SD), quantified as Log SDQ, can be estimated using the inert gases retention data [5]. Log SDQ approximates the breadth of its main peak and correlates with the heterogeneity of Q. In patients with acute lung injury, this pattern may take different forms, including a widened central peak, a skewed profile or even a multi-modal shape [8,39]

Premise # 2: When Qt Increases, the Variance of Regional Q Increases with Adverse Consequences

Tsang et al showed that when Qt was increased, the mean and variance of regional Q were also increased [4], under control setting or various high and low pressure pulmonary edema conditions. Similar experimental results were found during resuscitation of acute pulmonary bead embolism when Qt was increased by nor-epinephrine, the mean and variance of Q were also consistently higher within each gravitational section in the lung [40]. Burnham et al reported that pulmonary perfusion heterogeneity was increased by sustained exercise in human [41]. In some other studies in which athletes underwent vigorous exercise at sea level, the subjects' Log SDQ, as well as A-aDO2, was significantly higher, as Qt was augmented to the highest level [19,42]. Despite these observations, these investigators could not offer plausible explanation to this apparent increase in venous admixture according to their MIGET data.

Conceptually, this increase in Q variance at higher Qt is analogous to what one may observe in the changing economy of a developing nation. While the average income for all citizens goes higher and a majority of them become richer to different extents, some gain even more than expected from the proportional change in gross domestic product (GDP), calculated from year to year. However, there is still a minority getting worse off. Similarly, when Qt is increased, the average Q goes up and most lung regions receive more flow, some more than the others.

As a result, it is reasonable to propose that when regional flow (Q) is higher at increased Qt, and when V remains in steady state, the corresponding V/Q in most regions will become mathematically lower and more heterogeneous, however slightly, because of the increased magnitude and variance of the denominator (Q).

Furthermore, even in the scenario in which both minute ventilation and cardiac output simultaneously increase, V/Q mismatch can still worsens, particularly in diseased lungs, as the two variables change independently, to different extents and in different regions. When both LogSDV and Log SDQ increase concomitantly, overall V/Q does not reflect regional V/Q changes. This will apply whether V and Q distributions are either uni-modal or multi-modal.

Possible exceptions to this include high level athletes during modest exercise or thoroughbred racehorses [43], because of their immense physiological reserve to preserve V/Q homogeneity. These are special cases that do not represent the general condition.

However, when V/Q heterogeneity increases, the creation of low V/Q units is much more consequential to hypoxemia than the creation of high V/Q units. Note that the latter cannot compensate for the deterioration in gas exchange caused by the former, because higher V/Q units are not only lower in number and carry a smaller weighing factor or flow (Q), but the dissolved amount of any additional oxygen in plasma from higher V/Q units is very limited, resulting in only minor impact on the determination of overall PaO_2 due to the shape of the hemoglobin oxygen dissociation curve.

Sporadic coordinated shifts of regional ventilation and perfusion are unlikely to be relevant in the present discussion [44]. The sheer numbers of simultaneous and varying changes of V and Q in the current context of higher Qt make them statistically improbable to be pertinent.

For some theoretical discussions on normal lung, see Appendix A.

Premise # 3: Regional Ventilation is Heterogeneous

Regional ventilation (V) is also heterogeneous. It is again subject to many determining factors, many of which are quite different from those related to Q [45]. Besides gravity [46] and pleural pressure [47], there are other unique mechanical considerations, i.e. regional airway resistance [48], compliance, specific tidal volume [49], respiratory rate or inspiratory flow [50]. Variations in diffusing capacity [51], or interactions between diffusion convection dependent inhomogeneity (DCDI) and convection dependent inhomogeneity (CDI) can also have separate impact on gas exchange [52]. The heterogeneity of V is usually less than that of Q.

The measurement of V heterogeneity can be performed by either MIGET or FMS method. The reported data in normal lung show that

the V distribution vs V/Q also has Gaussian characteristics, although not in strict mathematical terms. The V heterogeneity is estimated usually by LogSDV, using the excretion data from MIGET [5].

Premise # 4: The Curvilinear Relationship between V/Q and PaO_2 is Skewed

Figure 1 shows the curvilinear relationship between V/Q ratio and PaO_2 plotted in a linear scale. It is modified from a previous graph where the X-axis was presented in a log scale [24], which has the visual effect of compressing the curve horizontally. The points of V and A denotes the mixed venous and arterial points at V/Q = 0 and 1 respectively in a normal lung breathing room air. The points of X, Y, Z are more arbitrary, with their V/Q values marked at approximately 5, 10 and 100 respectively.

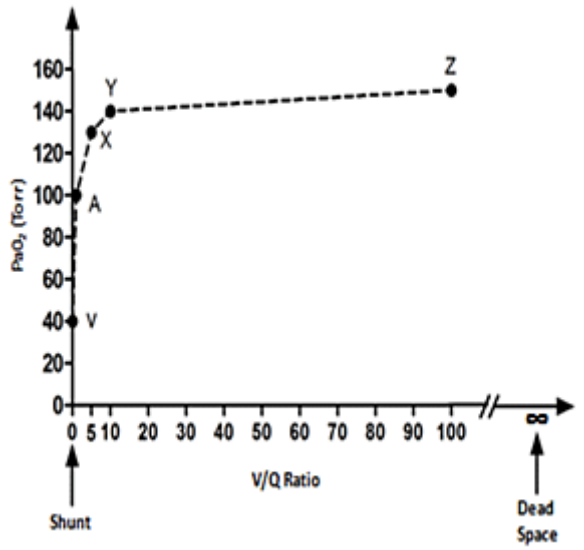

Figure 1: shows the skewed relationship between V/Q ratio and arterial oxygen tension (PaO_2). The slopes of the segments VA, AX, XY, YZ are very different (see text). Note that PaO_2 dramatically decreases as V/Q decreases in the narrow segment from 1 to 0, whereas it changes very little beyond V/Q > 10.

As it has also been shown in the O2-CO2 diagram [53], within the V/Q range of 0 to 1, PaO_2 is extraordinarily sensitive to any drop in V/Q. This is very different from that in the V/Q range from, say 10 to 100. In the narrow range of V/Q below 1, a roughly drawn line there gives a slope of about 60, or (100-40)/(1-0), whereas the same in the V/Q range from 10 to 100, it will be only about 0.11 or (150-140)/(100-10). Similarly, in the curvilinear segments of AX and XY, their approximate linear slopes are 6 and 2 respectively. This amazing sensitivity of PaO_2 to changes in V/Q at its lowest range hides the answer to the question posed in this paper.

PaO_2 generally increases when V/Q increases [53]. But there are intricacies in the details. Firstly, the vast majority of gas exchange units are located at V/Q ≈ 1, not 5 or 10, meaning that any increase in the denominator Q, there is no buffer to keep V/Q ≥ 1, away from the hypoxic range. Secondly, the disparate V/Q ranges in relation to PaO_2 mentioned above are not commonly recognized. Remarkably, it is in this particular low V/Q range (V/Q <1) that any decrease here can directly decrease PaO_2 and increase the measured venous admixture, whereas the same numerical V/Q drop in the higher range (V/Q >1) is much less consequential (Figure 1). Note that when Q is disproportionately high, e.g. 1 or 2 standard deviation higher than the mean, its impact on lowering the regional V/Q or the overall venous admixture will be almost hyperbolic.

If one maps out a physical distance from 0 to 100 units on a line, a segment from 0 to the first unit is short compared to its entirety and its length is not different from that between the 99th to 100th units. But on the V/Q scale, they are so critically different that the patient's life depends on it.

Proposed mechanism for increased venous admixture at higher cardiac output

Let's summarize the premises stated so far and derive our conclusion:

There are considerable heterogeneities of V and Q in the lung by themselves, each subject to their own anatomical and physiological factors.

Higher Qt increases the mean and variance of Q, resulting in the majority of lung regions receiving more Q and many gaining even more disproportionately.

Mathematically, higher Q results in lowering the V/Q ratio, especially in those previously well matched areas, where V/Q is precariously balanced at approximately 1. Physiologically, any small decrease of V/Q from 1 leads the PaO_2 to go down a very steep segment in the PaO_2-V/Q curve (Figure 1), resulting in notable worsening of gas exchange.

Any simultaneous increase in the variance of V and Q compounds the heterogeneity of their ratio (V/Q). However, the created lower V/Q units have more adverse impact on gas exchange due to their higher number post priori and the shape of the hemoglobin oxygen dissociation curve.

Therefore. if V is maintained in steady state or even becomes more heterogeneous, any concomitant increase in Qt results in more estimated venous admixture, particularly if more regions receive disproportionately higher Q.

Some investigators have tried to determine, in futility, whether there was more flow to the areas of low V/Q in order to explain the increased in venous admixture at higher Qt. Their presumed approach, though more intuitive, remained questionable. We should now consider a different paradigm, in that these V/Q units exist dynamically at different Qt, as they are created secondarily by high Q.

Past explanations remain unsatisfactory. As it was mentioned earlier, attenuation of hypoxic pulmonary vasoconstriction (HPV) was suggested as a potential mechanism for higher venous admixture at increased Qt, possibly due to the higher SvO2 in the blood reaching the micro-vascular levels in the lung. But it was not based on any direct experimental evidence [22,54]. Other investigators reported that HPV could readily be overcome by local vascular pressure and rendering it even less significant [23,55]. Tsang et al found that there was no preferential blood flow to edematous and presumably more hypoxic regions when Qt was increased [4]. Some proposed that diffusion barrier or rapid red blood cell transit time may become

relevant at higher regional Q but these speculations were later ruled out due to the very high affinity of oxygen to hemoglobin and the thin epithelial/endothelial layers [2].

Furthermore, oxygen is different from other insoluble inert gases, e.g. SF6, in which the content in blood correlates linearly with its tension according to Henry's Law. Their differences here, subtle or otherwise, might explain part of the discrepancies between the predicted and observed PaO_2 in some studies when Q was very high and regional V/Q became extremely low [19,42].

So, the author's new postulate is that for both normal and diseased lungs, the mechanism of lowering of the V/Q ratio by the increased denominator (Q) is equally applicable. Arithmetic is not an opinion. The only difference between normal and diseased lungs is their susceptibility to more hypoxemia at increased Qt, because the latter already has more heterogeneity in Q.

Conclusion

It is now proposed that when Q heterogeneity increases at higher Qt, many lower V/Q units (V/Q < 1) are subsequently created by the disproportionately higher Q. The key to its understanding is that V/Q and PaO_2 have a severely skewed curvilinear relationship, especially when V/Q is between 0 and 1. Any drop in regional V/Q causes increases in venous admixture. This physiological concept also has clinical relevance, particularly when hemodynamics and gas exchange are being manipulated and interpreted simultaneously by the bedside. The reader can decide whether it meets the test of Occam's Razor.

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Appendix A:

Assuming that the distribution of Q in a normal lung is represented by a theoretical distribution "A" before Qt is increased while distribution "B" represents the one after, (with their respective means being μA and μB and their respective standard deviations being σA and σB) and that both A and B distributions approximate Gaussian, the probabilities that any random sample (QB) from distribution B is larger than any random sample (QA) from distribution A, or P(QB > QA), can be calculated (Table 1) [56]. This is achieved by first converting the Gaussian distribution into the standard Gaussian Z, the one with mean of zero and standard deviation of one. It is followed by looking up an approximation from a standard normal table which is available in most probability and statistical books or on-line

Thus, if rμ = μB/μA and rσ = σB/σA are both larger than 1, P(QB > QA) is always larger than 0.5 or better than even chance (Table 1). Even if these distributions were not strictly Gaussian in mathematical terms but they remain in comparable pattern to each other, the overall conclusions that P(QB > QA) > 0.5 would still generally hold. In other words, it is reasonable to suggest that when Qt is increased and as the mean and variance of Q also increase concomitantly, the majority of lung regions will receive higher flow in the same lung

For example, when both the mean and standard deviation of "B" are 50% higher than "A",

[P(QB > QA)] is about 71%, i.e. much higher than even chance. Thus, in the determination of regional V/Q ratio, if V is constant and Q in the denominator is more likely to increase, V/Q in the majority of areas will become lower.

			rσ = σB/σA		
rμ = μB/μA	1.00	1.25	1.50	1.75	2.00
1.00	0.5000	0.5000	0.5000	0.5000	0.5000
1.25	0.6382	0.6226	0.6092	0.5980	0.5885
1.50	0.7602	0.7339	0.7105	0.6901	0.6726
1.75	0.8556	0.8256	0.7973	0.7716	0.7488
2.00	0.9214	0.8942	0.8664	0.8395	0.8145

Table 1: shows the hypothetical probability, [P(QB>QA)], that any sample in Distribution B is larger than any sample in Distribution A, if both A and B are Gaussian and the ratios of their means and standard deviation are rμ and rσ respectively.

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