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REVIEW ARTICLE

Analysis of V/Q-matching—a safety "biomarker" in pulmonary drug development?

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Abstract

Ventilation (V′)/perfusion (Q′) mismatch (VQM) is the single most important reason for gas-exchange abnormalities in pulmonary diseases. Pharmacological approaches can further aggravated VQM and its assessment is important to avoid hypoxemia. A theoretical framework for VQM, its relevance in clinical trials, and a stepwise evaluation approach is outlined. This assessment should entail stratification of patients- and mechanisms-at-risk for VQM. Also, its boundary conditions (e.g. cardiac output, perfusion pressure, hemoglobin concentration, changes in ventilation) need to be taken into consideration. Ultimately, VQM assessment requires invasive approaches. VQM evaluation is an important safety "biomarker" to avoid negative study outcome due to gas-exchange abnormalities.

Keywords: Gas exchange, ventilation/perfusion mismatch, safety biomarker, hypoxemia

Introduction

In order to supply the organism with sufficient oxygen in the lung, the degree of pulmonary perfusion (Q′) is matched to the respective level of ventilation (V′; Tunnicliffe and Shah, 2008). This takes place on a sublobar level and has been known since 1960s when physiologists studied the relation of oxygen (O_2) uptake and carbon dioxide (CO_2) removal under different conditions (West, 1996). Ideally, blood is distributed to areas of the lung that receive adequate ventilation and is "shunted" away from diseased lung tissue where ventilation is impaired (West, 1995). Hereby the hypoxic pulmonary vasoconstriction (HPV), which can be found in pulmonary arteriolar smooth muscle cells (PASMC), is central in the regulation of blood flow (Figure 1, ②). The PASMC not only function as effectors by constriction but also have the ability to sense (alveolar) oxygen (Figures 1, ② and ③; Weissmann et al., 2001, 2006; Weir and Olschewski, 2006). It appears that certain ion channels are gated depending on the partial pressure of O_2; for example, Ca-triggered and voltage-dependent potassium channels (K_{Ca}, K_V) affect the contraction of PASMC in a dose-dependent fashion (Weir and Olschewski, 2006; Weissmann et al., 2006). The HPV is already active during the intrauterine phase since it helps to raise the pulmonary vascular resistance (PVR) and to redirect venous blood flow in fetuses through the Foramen ovale to the left atrium without reaching the pulmonary circulation (Weissmann et al., 2001, 2006; Weir and Olschewski, 2006).

The HPV, which appears to be prudent for optimal matching of pulmonary blood supply with local ventilation, can be affected by disease states as well as therapeutic interventions with the consequence of V/Q-mismatch (VQM). This gas-exchange impairment leads to a decrease in arterial oxygen partial pressure (paO_2), arterial oxygen saturation of hemoglobin (SaO_2; hypoxemia) with decreased tissue O_2 delivery. In patients with pneumonia, acute respiratory distress syndrome (ARDS), chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD), VQM is most relevant for the respective degree of impaired gas exchange and resulting hypoxemia (Figure 2; Wagner et al., 1974, 1977; West, 1995, 1996; Preston, 2007; Tunnicliffe and Shah, 2008; Blanco et al., 2010; Cornet et al., 2010).These lung diseases have in common that in certain regions of the lung Q′ will be higher compared with V′ (V′/Q′ < 1) because

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the HPV is impaired (e.g. through the presence of inflammatory cytokines; Ware and Matthay, 2000; Tunnicliffe and Shah, 2008). The other extreme of the spectrum of different "V/Q-ratios" is depicted in Figure 2: ventilation is unaffected and blood flow is reduced (V′ > Q′; e.g. in pulmonary embolism or chronic thromboembolic pulmonary hypertension (CTEPH) with resulting dead space ventilation; Elliott, 1992; Dartevelle et al., 2004; Lang and Klepetko, 2008).

For the purpose of this review, the later situation of dead space ventilation (V′ > Q′), which is less prone to lead to progressive hypoxemia, will not be considered. On the other side, VQM with V′ < Q′ and resulting hypoxemia has to be further distinguished from true right to

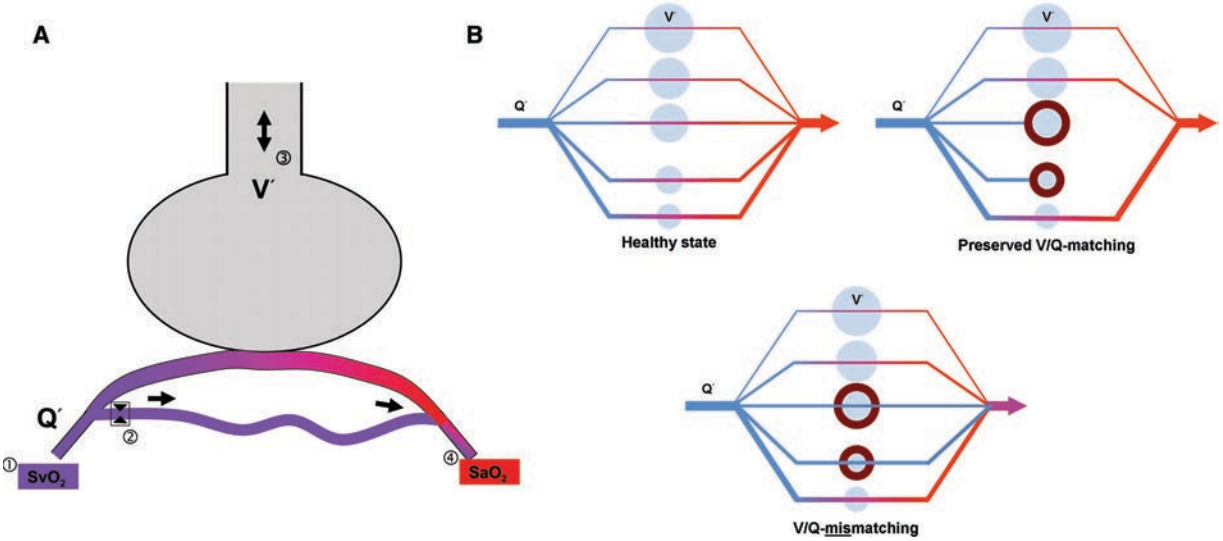

Figure 1. (A) Simplified diagram showing factors that might impact on pulmonary gas exchange. SvO_2: Central venous oxygen saturation of hemoglobin as a marker for cardiac output and perfusion pressure (①); Q′: local pulmonary blood flow; SaO_2: arterial oxygen saturation of hemoglobin as the end result of the different factors (④) involved in pulmonary gas exchange; V′: local pulmonary ventilation (not shown are factors that can influence V′ (e.g. broncho-obstruction, fluid accumulation in the depicted alveolus, etc.; ③); ②: symbol to represent hypoxic vasoconstriction (HPV). (B) Schematic depiction of three different situation reflecting the overall pulmonary matching of blood flow (Q′) and V′.

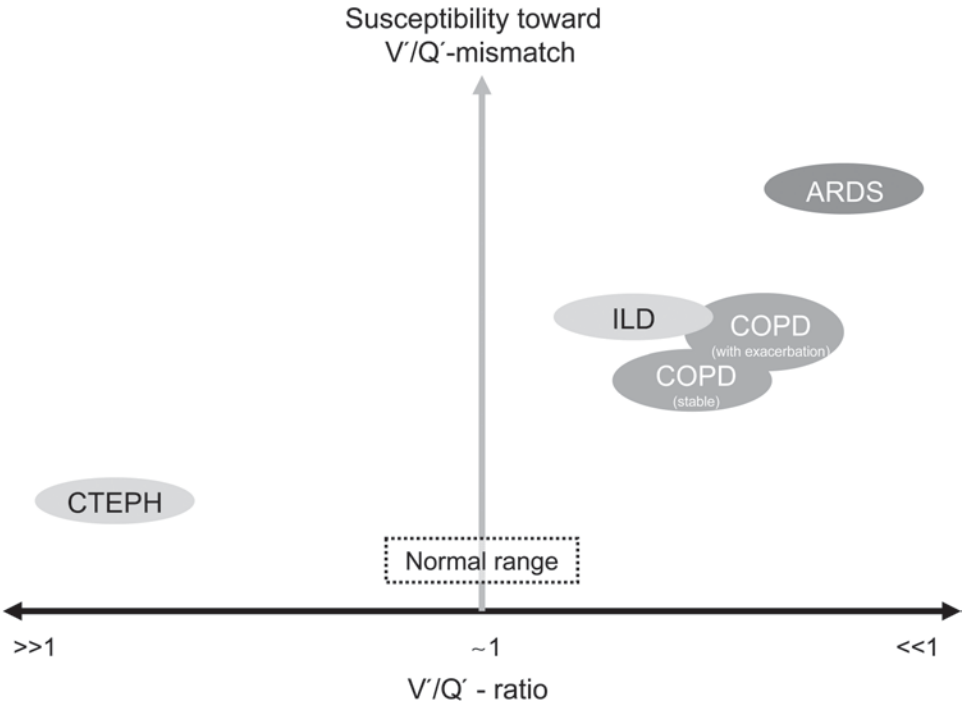

Figure 2. Diagram depicting different examples of disease entities that show varying degrees of V′/Q′-ratios (or V′/Q′-abnormalities) and susceptibility toward further V′/Q′-mismatch, for example, after treatment with vasodilators. ARDS: Acute respiratory distress syndrome; COPD: chronic obstructive pulmonary disease; CTEPH: chronic thromboembolic pulmonary hypertension; ILD: interstitial lung disease.

left shunt of blood caused by an anatomical connection [e.g. in patients with an atrial septal defect (ASD)]: here, deoxygenated venous blood will pass to the left side causing hypoxemia when the pressure in the right atrium exceeds the pressure on the left side. On clinical grounds, hypoxemia due to V/Q-mismatch can be distinguished from true shunt by increasing the inspired oxygen fraction, which will only affect hypoxemia in V/Q-mismatch. This does not hold true for severe forms of V/Q-mismatch (e.g. in ARDS) where arterial oxygen levels can remain low despite mechanical ventilation with 100% inspired oxygen (Wagner et al., 1974, 1977; West, 1995).

In this review, the implications of V/Q-mismatch are outlined especially for secondary forms of pulmonary hypertension where the underlying (lung) disease can make patients prone to an increased level of hypoxemia when his or her pulmonary ventilation and blood flow relation is altered, for example, due to the application of vasoactive drugs. Here, the assessment of V/Q-mismatch can serve as a safety "biomarker," which helps to tailor "V/Q-mismatch-prone" treatment (Table 1) in respect to the pharmacological mechanism and doses applied.

Measurement of V/Q-mismatch

General aspects

As stated above the outcome of VQM is admixture of venous blood to oxygenated blood leading to a decrease in paO_2 (Figure 1, ④), the arterial saturation of hemoglobin with oxygen (SaO_2), and thereby the arterial oxygen content (CaO_2) that reaches the left-sided circulation. Therefore, V/Q-mismatch can impair oxygen delivery to vital organs. One could assume that just measuring SaO_2 (e.g. with a pulse oxymeter) could be all that is necessary to assess V′/Q′-matching. Here, it has to be kept in mind that a change in SaO_2 can be caused by multiple effects in different compartments involved in gas exchange (including airflow and blood flow distribution; Figure 1): that is, besides VQM changes in the amount of oxygen that reaches the alveolar/capillary interface (hyper- or hypoventilation or due to changes in ventilators settings when mechanical ventilation is applied), modifications of the alveolar/capillary interface itself (e.g. a change in the alveolar water content when pulmonary edema evolves or improves) or alterations that affect the post-alveolar (capillary) side, for example, a change of the central venous oxygen saturation of hemoglobin (SvO_2) due to an alteration in cardiac output, in peripheral oxygen consumption, in the hemoglobin concentration, or in the hemoglobin–oxygen binding characteristics, a modification of the barrier that oxygen has to pass to get from the inspired air to the blood (e.g. a change in the alveolar water content when pulmonary edema evolves or improves; Figures 1, ①–④; West, 1995; Tunnicliffe and Shah, 2008) can affect SaO_2. Furthermore, changes in ventilation (e.g. in patients with ARDS who undergo changes of their ventilatory settings (e.g. increase in PEEP) or acute bronchial obstruction in asthma) can affect SaO_2 (West, 1995, 1996) and therefore need to be taken into consideration when approaching the subject "V/Q-mismatch" from a broader perspective.

In order to determine which factors are (mainly) responsible for a change in SaO_2, it is important to separate the different aspects outlined above. The same holds true in disease conditions in which the application of a pharmacological intervention can affect several factors: for example, in ARDS hypoxemia is a disease-defining condition. According to Figure 1, the degree of hypoxemia in ARDS depends on the alveolar/capillary interface (e.g. fluid accumulation and edema in the alveolus), SvO_2 (e.g. decreased cardiac output due to septic cardiomyopathy), and/or V′/Q′-matching. Especially when therapeutic interventions are aimed at the pulmonary vasculature and its increased resistance leading to pulmonary hypertension, which is prevalent in >90% of patients with ARDS, V/Q-matching can be affected (Figure 1B).

In general, pulmonary hypertension is divided into primary forms (PAH) where no changes in lung tissue is observed and the secondary forms of pulmonary hypertension, for example, with an underlying primary disease of the lung (non-pulmonary arterial hypertension-pulmonary hypertension (NPAHPH); Hoeper et al., 2009). To fully understand the effects of an intervention aimed to improve PVR and potential consequences on gas exchange, a clear understanding of the factors involved (Figure 1) is needed. In analogy to the ARDS example in most hypoxemic conditions where lung disease is prevalent (i.e. NPAHPH forms with underlying lung disease, e.g. COPD, ILD; Ryu et al., 2007; Behr and Ryu, 2008; Barberá and Blanco, 2009), a similar reasoning applies.

Table 1. Pharmacological approaches that can affect V/Q-mismatch.

Increase of V/Q-mismatch (e.g. vasodilators)
Iloprost i.v. (Walmrath et al., 1997)
Calcium channel blockers (Barberá and Blanco, 2009)
Salbutamol i.v. (Ballester et al., 1989)
High fraction of inhaled oxygen (Dantzker and Bower, 1981; Ballester et al., 1989)
Inhaled salbutamol in patients with COPD and exacerbation (Polverino et al., 2007)
Isoproterenol (Dantzker and Bower, 1981)
Nitroprusside (Dantzker and Bower, 1981)
Inhaled fenoterol high dose (Viegas et al., 1996)
Aminophylline i.v. (Barberá et al., 1992)
Sildenafil p.o. (Cornet et al., 2010; Blanco et al., 2010)
Decrease of V/Q-mismatch (e.g. inhaled approach, vasoconstrictors)
Inhaled prostaglandin PGI_2 (Walmrath et al., 1997)
Inhaled prostaglandin PGE_2 (Walmrath et al., 1997)
Inhaled NO (Walmrath et al., 1997)
Inhaled salbutamol (Ballester et al., 1989)
Almitine (Agustí and Rodriguez-Roisin, 1993)
Neutral in respect to V/Q-mismatch
Aminophylline i.v. (Montserrat et al., 1995)

Methodology to assess V/Q-mismatch

Indirect methods

For the physician taking care of a patient (e.g. with ARDS in the ICU), the concept of V′/Q′-mismatch is at the same time a real world problem which he needs to address in order to avoid effects of devastating hypoxemia and a pathophysiological phenomenon that is technically difficult to asses since access to all variables shown in Figure 1 is rarely possible. Most often the assumption is made that hypoxemia due to "V/Q-mismatch" (and contrary to other factors stated above) is responsive to supplementation of the inspired air with oxygen (Tunnicliffe and Shah, 2008).

In general, the more sophisticated technical modalities that allow determination of V/Q-mismatch can be divided into indirect methods whereby the measurement of different variables (e.g. concentration of inhaled oxygen in relation to its concentration in the bloodstream; see also approach stated above) the V/Q-relation is inferred upon. As tracer gases, oxygen, carbon dioxide, or nitrogen can serve (Hope et al., 1995; de Gray et al., 1997). The most advanced method to determine V/Q-ratios is the multiple inert gas elimination technique (MIGET; Wagner et al., 1974), which employs six tracer gases with different blood solubility. A saline solution equilibrated with the tracer gases is infused and arterial and alveolar gas concentrations are measured. Taking the different blood solubility coefficients of the tracer gases into account, a distribution curve can be calculated for pulmonary blood flow and alveolar ventilation. Due to its technical and labor demands, the MIGET method is only performed in a few centers worldwide and rarely clinically used.

Direct methods

Direct imaging methods using radiolabeled blood components and gases have for the first time shown that even under normal conditions pulmonary blood flow and ventilation are not evenly distributed nor perfectly matched (West, 1962, 1995). Newer imagine approaches utilize positron emission tomography (PET) technology (Musch and Venegas, 2005), electrical impedance tomography (EIT; Truebel et al., 2010), single-photon emission-computed tomography (SPECT; Bajc et al., 2010), or dual energy-computed tomography (DECT; Thieme et al., 2010) to assess V/Q-ratios in relation to different disease conditions. In general, these direct methods are based on the concept to use different "contrast agents" to assess ventilation and perfusion. For example, in his study with DECT, Thieme et al. (2010) applied xenon as a marker to look at gas exchange and an iodine-labeled contrast reagent to assess blood flow.

Furthermore, computed tomography (CT)- and magnetic resonance imaging (MRI)-based methods have been employed by several groups to assess V/Q-matching without employing scintigraphic technology (Reinartz et al., 2004; Bauman et al., 2009).

In summary, imaging-focused methods offer the potential advantage to display locoregional aspects of V/Q-matching but might fail to detect diffuse alterations of V/Q-matching, for example, due to their limited spatial resolution. These techniques have been largely used to look at changes caused by pulmonary embolism and its consequences and might due to their demanding technical necessities be less well-suited for pharmaceutical studies.

Relevance of V/Q-mismatch as a safety biomarker

V/Q-mismatch in the context "secondary" PH and lung disease

In the studies by Barberá et al. (1996), Stolz et al. (2008), and Blanco et al. (2010), vasodilating agents were applied to treat secondary pulmonary hypertension in patients with COPD (PH-COPD). These three studies give examples of impaired V/Q-matching after a therapeutic intervention was employed. Similar findings could be observed in ARDS (Cornet et al., 2010), in ILD (Augusti, 1994), and especially with different vasoactive interventions (Barberá and Blanco, 2009). The degree of VQM and its relation is not equal in all conditions: for example, while being prominent in ARDS (Wagner et al., 1974) and COPD (Augusti, 1994), in ILD; on the other hand, it was less clear and vasodilator effects on VQM in ILD are less prevalent (Günther et al., 2007).

In summary, the observation that vasodilation in lung diseases and secondary PH (NPAHPH) can cause V′/Q′-mismatch although quite prevalent (Barberá and Blanco, 2009) is complex and depends on several variables (e.g. specific lung disease and disease state, resting vs. active patient, absence vs. presence of exacerbations, the specific vasodilator used). It therefore appears to be necessary to monitor patients at risk for V′/Q′-mismatch when potentially V′/Q′-mismatch inducing treatment options are applied.

Monitoring for V′/Q′-mismatch

As pointed out above despite its relevance for oxygen delivery to the organism the measurement of V′/Q′-mismatch is not trivial and the current gold standard method MIGET (Wagner et al., 1974, 1977), which has provided a better understanding of the V′/Q′-physiology, is only used in a few centers worldwide and certainly could not serve as a biomarker in large clinical trials.

To address this dilemma, it is necessary to first of all define the compounds or mechanism at risk to induce or aggravate V/Q-mismatch. Here, clearly drugs with a potential to vasodilate and/or bronchodilate are "V′/Q′-mismatch-prone" (Barberá and Blanco, 2009), whereas for example an anti-inflammatory mechanism of action is less likely to impair gas exchange. Second, the population-at-risk needs to be defined: As shown in

Figure 2, patients with PAH are less likely to have V′/Q′-abnormalities and therefore the likelihood of having an aggravation of their hypoxia due to V′/Q′-mismatch is low. On the other side in ARDS the V′/Q′-mismatch induced hypoxia, which is to some degree unresponsive to supplementation of oxygen, is central in the pathophysiology of the disease and thus these patients are at higher risk for further deterioration of their V′/Q′-mismatch. Last but not least, a V′/Q′-mismatch inducing intervention might have other effects that mitigate or oppose negative effects on gas exchange, for example, bronchodilation (Khoukaz and Gross, 1999) and thereby improve ventilation or decreased oxygen consumption and thereby increase in SvO_2 (Figure 1, ①) in the long run, that is, acute effects of an intervention could differ from chronic changes and also should be taken into consideration.

Discussion

When planning an interventional study in patients with lung diseases and secondary forms of pulmonary hypertension, it seems obvious that an initial risk assessment should evaluate if the study population is at risk for V′/Q′-mismatch (e.g. ARDS >> PAH) and if the mechanism to be applied is V′/Q′-mismatch prone (e.g. vasodilators >> anti-inflammatory mechanism; Table 1; Agustí and Rodriguez-Roisin, 1993). Here, especially mechanisms that lower vascular tone need to be scrutinized since their V′/Q′-mismatch potential has been demonstrated in several studies (Table 1; Agustí and Rodriguez-Roisin, 1993). Afterward the intervention-related effects on gas exchange need to be monitored, that is, a safety "biomarker" used to screen for gas-exchange abnormalities is needed. Due to the technical difficulties with the direct and indirect assessment of VQM (e.g. MIGET is only feasible in small Phase IIa studies; Blanco et al., 2010), a pragmatic approach is required for larger clinical trials. Since a detrimental effect of V/Q-mismatch is hypoxemia (④ in Figure 1), the noninvasive assessment of SaO_2 or paO_2 and thereby the oxygenation status of the arterial blood seems to be the obvious "biomarker." The caveat to be kept in mind is the fact that a drop in SaO_2 (and thereby of oxygen delivery to all organs) might be caused by different mechanisms: for example, a drop in SvO_2 (① in Figure 1) caused by an increase in capillary oxygen extraction seen with a reduction in cardiac output, perfusion pressure, or both can cause a drop in SaO_2 (and paO_2) without changes in V′/Q′-matching. Along the same line can a change in hemoglobin content and thereby oxygen-carrying capacity change the oxygen extraction and thereby affect SvO_2. In addition, an alteration in ventilation might affect gas exchange and cause changes in SaO_2 unrelated to V′/Q′-matching (③ in Figure 1). Furthermore, changing baseline conditions [COPD (stable) vs. COPD (exacerbation)] or resting condition versus activity can alter physiology and thereby cause changes in SaO_2 unrelated to VQM.

Therefore, the approach to evaluate the oxygenation status of arterial blood (e.g. by SaO_2 or paO_2 measurement) as a safety "biomarker" to screen for V′/Q′-mismatch has to take its limitations into account. The risk to misjudge oxygenation changes can be decreased by assessing the boundary conditions at the same time: for example, cardiac output and perfusion pressure (both of which can be measured noninvasively) or ventilation changes can all be monitored and if stable increase the probability of oxygenation changes being caused by V′/Q′-changes. Since both, the risk assessment and the outlined practical approach combining assessment of oxygenation status and its boundary conditions are imperfect (e.g. sensitivity and specificity <100%; Agustí and Barberà, 1994) in patients at high risk, the measurement of V/Q-matching using more invasive approaches like MIGET might be needed as the ultimate safety "biomarker."

Declaration of interest

At the time of manuscript submission, all authors were fulltime employees of Bayer HealthCare in Germany.

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