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Functional morphometry for the estimation of the alveolar surface area in prematurely-born infants

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ABSTRACT

Conventionally, the alveolar surface area (S_A) has been measured by using post-mortem morphometry. Such studies have highlighted that S_A in prematurely-born infants is markedly smaller when compared to term-born infants as a result of postnatal impairment or arrest of alveolar development. We herein explore how, non-invasive measurements of the ventilation/perfusion ratio (V_A/Q) can be used to estimate S_A in prematurely-born surviving, convalescent infants. We also compare S_A in prematurely-born infants measured at term-corrected age, to term-born infants using previously published datasets of V_A/Q. Fick's first law of diffusion is employed for the conversion of V_A/Q measurements to S_A values after correcting for differences in pulmonary perfusion, thickness of the respiratory membrane and alveolar-arterial gradient. We report that S_A is fivefold smaller in prematurely-born compared to term-born infants. We conclude that non-invasive measurements of V_A/Q can be used for the functional estimation of S_A which could, in turn, be used as a future outcome measure in respiratory studies of prematurely-born infants.

1. Introduction

Premature birth is frequently followed by numerous acute and chronic respiratory complications owing mainly to the immaturity of the lungs and the detrimental effect of prolonged invasive mechanical ventilation. With recent advances in neonatal care, the great majority of premature infants survive to be discharged home even if they are born before 24 weeks of gestation which had been generally considered the borderline of viability (Glass et al., 2015; Younge et al., 2016). These infants develop a characteristic chronic lung disease called bronchopulmonary dysplasia (BPD) which is a consequence of the interplay of a number of interrelated pathological contributors (Jensen and Schmidt, 2014).

Morphologically, BPD is characterized by a simplification of the pulmonary architecture with fewer and larger alveolar spaces (Coalson, 2006). This translates to a reduced alveolar surface area (S_A) across which oxygen and carbon dioxide are exchanged and a decreased capacity for the diffusion of these vital gases. Some studies have used post-mortem material to morphometrically quantify this reduction in S_A in infants with fatal BPD: while a term-born infant without respiratory disease has an S_A of 4.7–8.3 m^2 (Zeltner et al., 1987), an extremely premature infant (born before 28 weeks of gestation) when measured at a term-corrected age (the age when the infant would have been born had it not been premature) might have a S_A as small as 0.6 m^2 (Margraf et al., 1991). Of note, using similar measuring methodology this area in adult lungs might range from 97 to 194 m^2 (Zeltner et al., 1987).

The reduced S_A might explain why prematurely-born infants may present later in life with profound exercise limitation as low-intensity everyday activities do not require the recruitment of all the available S_A but in conditions of increased cardiorespiratory demand, such as during moderate-high intensity aerobic exercise, the decreased S_A becomes a limiting factor (Malleske et al., 2017; Mitchell and Teague, 1998). Furthermore, these infants are at greater risk of respiratory failure after even minor pulmonary insults due to a limited pulmonary reserve (Thomas et al., 2000).

The clinical usefulness of anatomical studies is limited only to deceased infants that undergo a post-mortem examination and further morphometric analysis. An alternative method to estimate the S_A would be via functional measurements of the ventilation to perfusion (V_A/Q) ratio which can be performed on surviving infants, hence greatly expanding the statistical data sample and allowing better perception of the disease and its associations. The diffusion of gases across the

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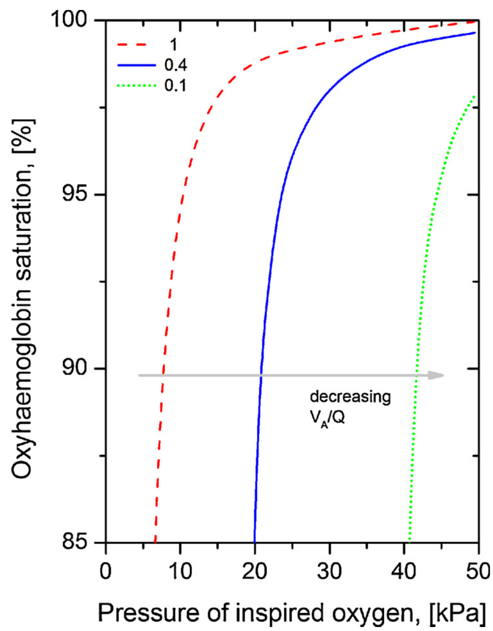

Fig. 1. The oxygen haemoglobin dissociation curve: proportion of haemoglobin saturation versus pressure of inspired oxygen. Decreasing V_A/Q shifts the curve to the right.

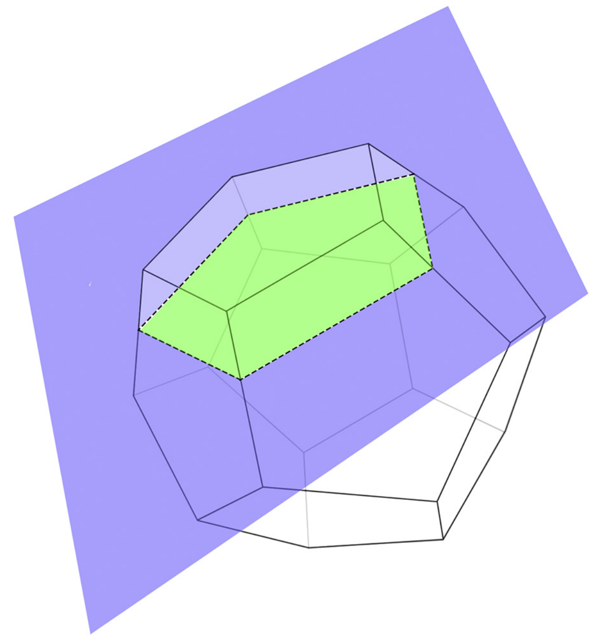

Fig. 2. A solid canonical dodecahedron with a planar intersection resulting in a shape of a pentagon.

respiratory membrane is described by Fick's first law of diffusion which dictates that the rate of ventilation is a function of the surface of the membrane (S_A), the thickness of the gas exchange membrane, the diffusion coefficient of the gas and the partial pressure difference of the gas between the two sides of the membrane (Hamid et al., 2005). Thus, knowledge of the V_A/Q could translate to a functional estimation of the S_A after accounting for differences in pulmonary perfusion, thickness of the respiratory membrane and differences in the partial pressure of the gas across the membrane.

Non-invasive assessment of the V_A/Q can be undertaken by recording paired measurements of fraction of inspired oxygen (F_IO_2) and the corresponding transcutaneous oxygen saturation (SpO_2): thus, a specific individual's oxyhemoglobin dissociation curve (ODC) can be constructed (Fig. 1).

The aim of this study is two-fold: to derive a method of calculation of S_A in prematurely-born infants using measurements of V_A/Q that have been non-invasively obtained and to compare the S_A in term healthy infants and prematurely-born infants studied at a term-corrected age.

2. Methods

2.1. Alveolar surface area in normal term infants

Zeltner et al. have shown that the alveolar surface area in normal term infants grows in close proportion to body mass as

$$S_A = 1.783W^{1.015} \quad (1)$$

where W is the body weight in kg and S_A is given in m^2 (Zeltner et al., 1987). For the purposes of this study we have assumed that the exponent of W in Eq. (1) can be approximated by unity. S_A can then be normalised to body weight expressed as S_A/W with units of m^2 per kg of body weight.

2.2. Difference in pulmonary perfusion

The difference in pulmonary perfusion between healthy term and prematurely-born infants measured at term was calculated from echocardiographic studies that used wave Doppler measurements of the left ventricular output in the absence of significant abnormal communications between the left and the right circulation (Sehgal et al., 2016).

2.3. Difference in the thickness of the respiratory membrane

In order to calculate the thickness of the gas exchange membrane, d, expected in Fick's law of diffusion and given that the intersection of a solid dodecahedron with a generic plane results in a pentagon (Fig. 2) we adopt the dodecahedral geometric model for the alveolus (Weibel, 1963). We further calculate the total volume of the lungs, the total surface area of the alveoli, the average septal volume of the lungs and from this the mean thickness of the septal membrane. Please refer to Appendix A for the mathematical model applied and the final equation used to calculate d.

Calculation of d for prematurely-born and term-born infants was made possible by introduction, in the ensuing equation of S_A, the volume of the two lungs and the total number of alveoli obtained from published morphometric studies (Margraf et al., 1991).

2.4. Difference in oxygen partial pressure differentials

The difference in the partial pressure of oxygen across the respiratory membrane was estimated by the alveolar-arterial gradient (AaG). The mean value of AaG for term infants measured at a mean (range) age of 5 (2–8) days was 17 (range 5–30) mmHg and for premature infants with a birth weight of 0,88–1,11 kg measured between 50 and 98 days of age was 32 (range 11–65) mmHg (Bourbon et al., 2005).

2.5. Noninvasive assessment of the ventilation to perfusion ratio

The degree by which any individual's curve is relatively shifted to the right compared to an ideal theoretical curve that represents a non-diseased state, can be used to calculate that individual's V_A/Q (Fig. 1) (Sapsford and Jones, 1995).

Paired measurements of F_IO_2 versus SpO_2 were used to construct an F_IO_2 versus SpO_2 curve. This curve has been used as a surrogate of the oxyhemoglobin dissociation curve and values of the ventilation/perfusion (V_A/Q) ratio have been reported (Dassios et al., 2017; Dassios