Brief history of quantification of the lung gas exchange

In this short article, I will try to introduce very briefly a century-long effort for quantifying gas exchange in the human lung. Three non-scientific keywords - *Seven Devils*, *Holy Grail* and *Screw-up* – were adopted to illustrate rather casually important historical events at the interval of 50 years.

The Seven Devils

At the beginning of the last century, there existed a controversy about the gas exchange mechanism in the lung: is this *passive* or *active* process? i.e., can the exchange be achieved solely by passive diffusion or with an additional active, energy-consuming, mechanism? Christian Bohr, a distinguished respiratory physiologist of the day (and the father of Niels Bohr), was a major proponent of the active secretion theory which states the lung secretes O_2 like a gland [1]. But, it was opposed by one of his students, August Krogh. Using a series of experiments, Krogh revealed that Bohr's measurements were unreliable. Then, he finally refuted Bohr's secretion theory with the seven papers, called the *Seven Little Devils* published in a single year 1910, by showing that the passive diffusion alone is sufficient for the exchange [2]. Ten years later, Krogh was awarded the Nobel Prize in Medicine and Physiology.

In the middle of the debate, August Krogh and his wife, Marie Krogh, developed a method for measuring the **lung diffusing capacity** using inhaled carbon monoxide, which becomes nowadays an essential part of routine lung function tests as the only non-invasive measurement of gas exchange efficiency [3]. The lung diffusing capacity, DL, is actually a *conductance* for gas diffusion. For CO, it is written as:

$$DL_{CO} = V_{CO} / (PA_{CO}-Pc_{CO})$$

where V_{CO} is the volume of captured CO, PA_{CO} and Pc_{CO} are the CO pressure of the alveolar air and the capillary blood, respectively. Despite its poisoning (In fact, the Kroghs used themselves as experimental subjects), CO was chosen because inhaling very small amount makes the last term Pc_{CO} negligible, which is virtually impossible to measure for O_2.

Holy Grail

The infrared CO meter invented during World War II made the DL_{CO} measurement quicker and more practical [3]. DL_{CO} was found to be related to the alveolar O_2 pressure, P_{O2}. More precisely, $1/DL_{CO}$ (the resistance to CO transfer since DL_{CO} is a conductance) was found to be linearly proportional to PO_2 because O_2 competes with CO to get the same binding sites of hemoglobin. Collecting these discoveries, two physiologists, F.J.W. Roughton and R.E. Foster, devised in 1957 the famous Roughton-Forster (RF) equation:

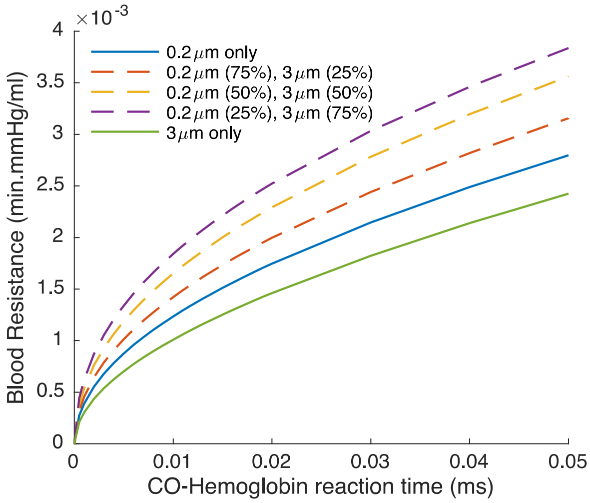
$$1/DL_{CO} = 1/D_M + 1/De$$

It separates, with electrical analogy, the total resistance into two components: the PO_2 independent membrane resistance, $1/D_M$, and the PO_2 dependent blood resistance, 1/De.

Studying interdisciplinary subjects, I have had chances to discuss with several physiologists and clinicians. I often heard during discussion that they used the term Holy Grail which was unfamiliar to me at first. Repeated experiences from different situations taught me that it refers to a specific objective, *separation of causes*:

Signals from human body such as DL_{CO} is related to many factors with complex, sometimes hidden, relations. The RF equation sought to separate the membrane and the blood contributions to DL_{CO}. Since its proposition, this equation has been used and taught as a **gold standard** in interpreting the CO capture.

<u>Screw-up</u>

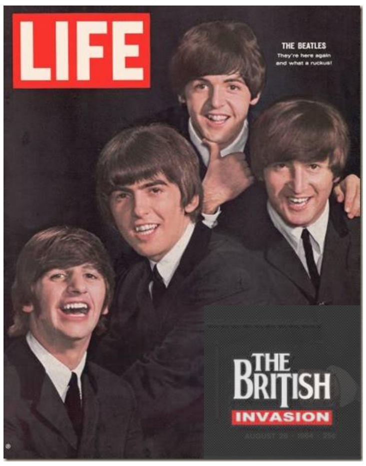


RF Blood resistance for different membrane configurations. Two membrane thickness, 0.2 μm and 3 μm, were arbitrarily chosen. Any combination of them results in different blood resistance while it was supposed to remain the same value.

From the viewpoint of physicist, the CO capture is essentially a diffusion-reaction problem. Bernard Sapoval and I began to investigate this problem by simply solving general equations: the diffusion equation for the membrane-plasma space and the diffusion-reaction equation for the red blood cell. It revealed serious flaws in the RF equation [4]. Among them, it was found that the two components of the RF equation are **not** independent. As seen in the left figure, the blood resistance 1/De varies with the membrane thickness that determines $1/D_M$. Meaning that, the RF equation has a *fundamental* defect.

At the last European Respiratory Society (ERS) meeting where we presented our finding, we met a physiologist, one of the two chairs of the joint task force of ERS and American Thoracic Society setting guidelines for diffusing capacity measurements. This was his greeting to us, "*Hi guys, screwing up my entire career!*"

While he was frank, we have indirectly experienced their frustrations from the referee reports that we received about our manuscripts. In fact, each publication came after a long history of struggle against endless remarks based on the RF equation. And we have already proposed a new and physically-robust equation for the DL_{CO} separation [5]. Yet, it appears that a few more devils are still required to fully substitute the half a century old frame (We have only two published and one under review while Krogh needed seven). But, if we finally make it, some day in the future one might recall this period as a period of French (physicist) Invasion to the Respiratory Physiology…



≪The British Invasion≫

References

[1] West (2004) *Am J Respir Crit Care Med* 169: 897–902.
[2] Gjedde (2010) *Adv Physiol Educ* 34: 174-85.
[3] Hughes, Borland (2015) *Thorax* 70: 391-4.
[4] Kang, Grebenkov, Guénard, Katz, Sapoval (2017) *Respir Physiol Neurobiol* in print.
[5] Kang, Sapoval (2016) *Respir Physiol Neurobiol* 225:48-59.

Min-Yeong Kang