CORRESPONDENCE

Carbon monoxide transfer coefficient K_{CO} (TL/VA): a flawed index

To the Editor:

In their recent "Perspective", HUGHES and PRIDE [1] described the carbon monoxide (CO) transfer factor (TL_{CO}) as the product of two primary measurements: alveolar volume (VA) and CO transfer coefficient K_{CO} (TL/VA). VA is primary in that it has a physiological identity. However, FORSTER [2] has pointed out that in the context of the measurement of transfer factor, the volume is merely that of the gas exchanger; it has no more physiological significance than can be attached to the volume ($VA+V_{bag}$) that is used for the rebreathing method. FORSTER [2] also warned against interpreting K_{CO} as a separate index. Its status as a primary index would have been different if KROGH [3] had been right in her belief that TL was proportional to VA ; in this case, K_{CO} in healthy persons would have been constant. Unfortunately, she made few observations and many subsequent studies showed that she was wrong [2]. The refutation of her hypothesis destroyed the case for regarding K_{CO} as a primary physiological index. Instead, it is merely a stage in the measurement of the transfer factor for the lung as a whole. In this circumstance, the transfer factor per litre of lung volume is designated appropriately by the ratio TL/VA and not, as HUGHES and PRIDE [1] have claimed, by K_{CO} .

Since TL is not proportional to VA , the ratio TL/VA misrepresents the real relationship between the variables [4]. In some circumstances, the resulting distortion can contribute to diagnosis. For example, in emphysema, the transfer defect appears to be amplified as the ratio is depressed if the lung volume is increased. In the converse circumstance of a small lung volume due to a restrictive defect, the distortion can lead to a transfer defect being overlooked as the ratio may then be normal or increased. These facts are not disputed by HUGHES and PRIDE [1]; instead, they point out that anyone using the ratio should choose the appropriate model for its interpretation. This is fine for lung function specialists, but not for peripheral users. At every European Respiratory Society annual conference that I have attended, speakers have referred to standardizing transfer factor for lung volume by using the ratio. The high profile given by our Editor to the defence of K_{CO} of HUGHES and PRIDE [1] will help to ensure that the practice continues!

The "defence" elegantly demonstrates that the ratio can be rationally interpreted. This involves making allowances for the anatomical and physiological factors that contribute to TL and choosing between four alternative models of lung function. In addition, distortion due to the faulty arithmetic model is minimized by expressing longitudinal change as a ratio.

The schema of HUGHES and PRIDE [1] is of Byzantine complexity and is based on an index carbon monoxide transfer coefficient that is arithmetically flawed. Time will tell if it can provide more information than is contained in gas transfer factor for the lung and alveolar volume. Meanwhile, my colleagues and I have rightly been criticized for not qualifying the circumstances when it is appropriate to make an allowance for alveolar volume in patients based on that in healthy subjects. There are few data and a strong *prima facie* case for believing otherwise in some circumstances. However, HUGHES and PRIDE [1] give several examples of where it is appropriate to make such an adjustment and cite an instance where this turned out to be so, despite a reasonable expectation to the contrary [5]. It is our view that there will be others. This could be a fruitful field for further research. Meanwhile, any laboratory using carbon monoxide transfer coefficient should do so circumspectly. Gas transfer factor for the lung should also be reported and interpretation should take alveolar volume into account. There is no place for carbon monoxide transfer coefficient in respiratory surveys.

J.E. Cotes

Dept Physiological Sciences, Medical School, Newcastle-upon-Tyne, NE2 4HH, UK.

References

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From the authors:

We appreciate the major contribution that J.E. Cotes has made to the establishment of the single breath carbon monoxide (CO) transfer factor ($TL_{CO, sb}$) in

clinical physiology and epidemiology over the 40 yrs following the introduction of the current version of the method by OGILVIE *et al.* [1]. His letter re-iterates some of the arguments in his 1996 article [2], which was the stimulus for us to present a different "point of view" in our recent article [3]. Interested readers should consult the original papers for full details, but we can summarize how our point of view differs from that of J.E. Cotes, using the simple equation introduced by KROGH [4] to calculate $TL_{CO, sb}$ in 1915;

$$TL_{CO} = (kCO \times VA) / (PB) \quad (1)$$

where kCO is the rate constant for removal of CO from alveolar gas during the breath-holding period (expressed as min^{-1}), VA is the alveolar volume during breath-holding and PB is barometric pressure, corrected for water vapour pressure. Currently, the CO transfer coefficient (KCO) is used which is equivalent to kCO/PB .

KROGH [4] emphasized that KCO and VA could vary widely and independently, (for instance, showing a rise in KCO at a given VA during exercise) and all subsequent workers have agreed that, even at rest, KCO/VA is not a constant. J.E. Cotes argues that this observation "destroyed the case for regarding KCO as a primary physiological index". We do not understand the reason for this opinion. We would expect many, perhaps most, physiological indices to vary with lung volume and would not discard, to name a few, airways resistance (R_{aw}), maximum expiratory flow, pulmonary vascular resistance, respiratory muscle pressures and lung compliance, just because R_{aw} (*etc.*)/ VA ratios were not constant. Indeed, we believe that the variable relation between KCO and VA in different lung diseases [3] is the major reason for KCO providing much information not revealed by the value of TL_{CO} alone. Nor do we understand how, according to J.E. Cotes, KCO is "arithmetically flawed". But, should that be the case, we would expect $KCO \times VA$, *i.e.* $TL_{CO, sb}$, to share this flaw. All authors also agree that, in assessing the results of the single breath CO transfer test, two components of M. Krogh's three component equation [4] should be presented. J.E. Cotes states that KCO should not be reported in surveys, and emphasizes TL_{CO} and VA , which can be re-written as $(KCO \times VA)$ and VA . But of course, once two components are known, the third is always precisely defined, whether or not it is explicitly reported.

In our paper we used KCO rather than the arithmetically identical TL_{CO}/VA because TL_{CO}/VA gives the misleading impression of being a ratio (and is so described by J.E. Cotes seven times in his letter) when, because $TL_{CO}/VA = (KCO \times VA)/VA = KCO$, it is in fact the rate constant for CO uptake by the lung. Furthermore, use of TL_{CO}/VA suggests that TL_{CO} and VA are independent variables, which leads, not surprisingly, to the common misconception that TL_{CO}/VA standardizes TL_{CO} for lung volume. Some of this confusion would be reduced if TL_{CO}/VA , styled diffusing capacity (DL_{CO})/ VA in North America, was discarded in favour of KCO .

Because a reduction in carbon monoxide transfer factor (TL_{CO}) may result from a variety of combinations of changes in carbon monoxide transfer coefficient (KCO) and alveolar volume (VA) with differing pathophysiological implications, we believe these are best revealed by explicitly reporting the carbon monoxide transfer coefficient (KCO) and alveolar volume (VA).

J.M.B. Hughes, N.B. Pride

Division of Respiratory Medicine, Imperial College School of Medicine, Hammersmith Hospital Campus, Du Cane Road, London W12 0NN, UK.

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