Haldane and Eschenbacher transformation*

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Background and history

In 1986 I attended a congress, Methodische Fragen zur Indirekten Kalorimetrie in Austria, where the methods of indirect calorimetry measurements were discussed.[1] Of particular interest: why during cardiopulmonary exercise testing, measurements seem accurate with normal breathing, but are implausible with elevated FIO_2 concentrations.

The group reached these conclusions:

- When $FIO_2 < 40\%$, measurements seem accurate.
- With FIO_2 between 40% and 60%, a careful calibration is required to achieve results that are plausible, although not always.
- When FIO_2 is between 60% and 80%, most values are not plausible.
- For FIO_2 above 80%, all values are implausible.
- At FIO_2 of 100%, no calculation of VO_2 is possible.

Similar conclusions can be found in the *Handbook of Gas Exchange and Indirect Calorimetry* published by the Finnish company Datex.[2]

During this same period, in the late 1980s, one manufacturer of cardiopulmonary exercise testing even withdrew the system from the market due to similar concerns regarding results that were either implausible and/or not reproducible.

In 1987 Jaeger, the predecessor company to CareFusion, received similar complaints from customers in Italy and South Africa that the values delivered from our EOS-Sprint were implausible at elevated FIO_2 concentrations.

I carefully repeated the tests in our Hoechberg, Germany, location and got the same results as those reported from Italy and South Africa. I discovered that these inaccurate results seemed to be a general problem with the Haldane transformation. I set about to solve this problem by creating new formulas.

These new formulas delivered plausible results over the whole range, even at $FIO_2 = 100\%$.

Note: The inspired and expired volumes (VI, VE) are expressed in BTPS, while VO_2 and VCO_2 are expressed in STPB. For simplification of the formulas, the conversion factors are ignored in the following discussions. The change in the water vapor content between inspiration and expiration can be ignored as the analyzed gases are conditioned *(dried)* before analysis. Furthermore, $FICO_2$ *(normally ca. 0.03–0.05%)* is ignored as well.

* The term "Eschenbacher transformation" was coined by our Italian representative after verifying that the formula I developed was giving plausible values over the whole range of FIO_2, even at 100%.

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Haldane transformation (HT)[3]

Oxygen uptake (VO_2), carbon dioxide output (VCO_2) as well as nitrogen exchange (VN_2) are calculated as the difference between inspired and expired volumes. The following basic calculations are used:

$$VO_2 = FIO_2 \times VI - FEO_2 \times VE \quad (1)$$

$$VCO_2 = FECO_2 \times VE - FICO_2 \times VI \quad (2)$$

$$VN_2 = FIN_2 \times VI - FEN_2 \times VE \quad (3)$$

with:

FI: mean inspired gas fractions of O_2, CO_2 and N_2
FE: mean expired gas fractions of O_2, CO_2 and N_2
VI: inspired volume
VE: expired volume

During ergospirometry testing, traditionally only the expired volume is measured, while the inspired volume is calculated via the Haldane transformation. Haldane made the assumption that there is no nitrogen exchange:

$$VN_2 = 0 \quad (4)$$

With this assumption, equation (*3*) leads to:

$$VI = VE \times (FEN_2/FIN_2) \quad (5)$$

The low concentration gases in the air *(e.g., helium or argon)* act like nitrogen and can be neglected or added to the nitrogen content, so we get the following two equations:

$$FIN_2 + FIO_2 + FICO_2 = 1 \quad (6)$$

$$FEN_2 + FEO_2 + FECO_2 = 1 \quad (7)$$

or:

$$FIN_2 = 1 - FIO_2 - FICO_2 \quad (6a)$$

$$FEN_2 = 1 - FEO_2 - FECO_2 \quad (7a)$$

(*6a*), (*7a*) in (*5*) leads to the following result:

$$VI = VE \times (1 - FEO_2 - FECO_2)/(1 - FIO_2 - FICO_2) \quad (8)$$

(*8*) in (*1*) therefore gives:

$$VO_2 = VE \times kH \times FIO_2 - VE \times FEO_2 \quad (9)$$

with the Haldane correction factor:

$$kH = (1 - FEO_2 - FECO_2)/(1 - FIO_2 - FICO_2) \quad (10)$$

Discussion of the Haldane transformation

Under normal conditions we can expect for a constant workload, that below the ventilatory threshold 2 (VT2) the same oxygen uptake is needed as well as the same carbon dioxide is produced, independent of the inspired FIO_2.

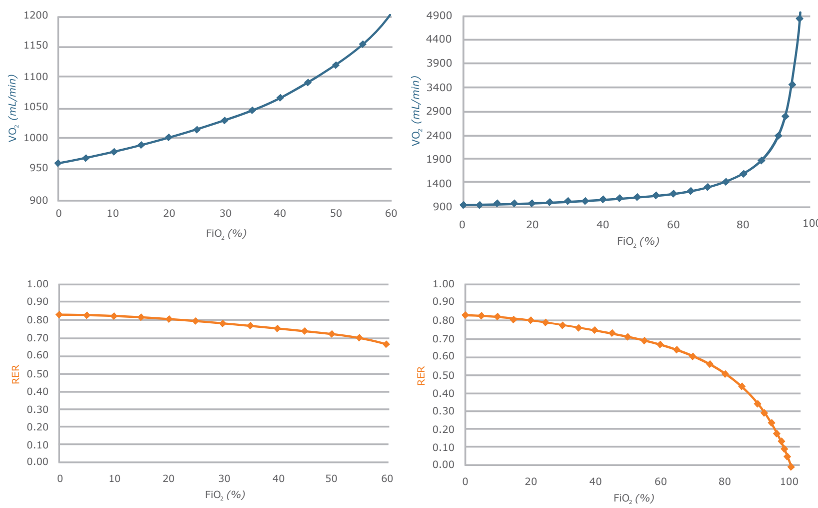
So the difference of the gas fractions should be constant:

$DFO_2 = FIO_2 - FEO_2$
respectively
$DFCO_2 = FECO_2$ *(with $FICO_2 = 0$)*

For example, at 40 W we will measure about:

$VE = 20$ L/min
$DFCO_2 = 4\%$
$DFO_2 = 4.8\%$

Using the Haldane transformation with these values and varying the inspiratory FIO_2 concentration, we will get the following results:



VO_2 and RER as a function of FIO_2 with the Haldane transformation for a typical 40 W exercise. Note the scalings.

Left side: VO_2 increases from ca. 1000 mL/min at 20% FIO_2 to around 1200mL/min at 60% FIO_2, while RER decreases from 0.80 down to < 0.70.

Right side: VO_2 increases to > 5000 mL/min at 97% FIO_2 and goes to infinity, while RER goes down to zero.

The following conclusions can be derived:

- With FIO_2 approaching 100% the calculated VO_2 goes to infinity, due to the Haldane transformation, which is obviously not valid. That also seems to be the reason why in *Principles of Exercise Testing and Interpretation,* all cases with oxygen breathing do not show any data for VO_2, RER and other depending parameters.[4]
- For FIO_2 going to 0% the oxygen uptake gives the same value as if VI = VE. This, however, is for example:

  $VO_2 = 960$ mL/min
  $VCO_2 = 800$ mL/min

  in contradiction to:

  $VI - VE = VO_2 - VCO_2 = 160$ mL/min or $VI \neq VE$
- Due to the HT, the VI *(and therefore also the inspiratory tidal volume VTin)* should increase dramatically with high FIO_2,

for example, above to VTin > 2 x VTex at 99.2% FIO_2. However, such differences could not be measured and would cause an enormous drift in the spirogram, which could not be observed as well.

- As the formula is neither valid for FIO_2 nearing 0%, nor for FIO_2 going to 100%, and measurements often show that the results are already questionable at FIO_2 of about 50% *(1000 mL/min at 20%,1125 mL/min and RER = 0.7 at 50%)* the question is: For which FIO_2 can the Haldane transformation be applied at all?
- Last but not least, many publications indicate that there is also a nitrogen exchange during the respiration *(both a retention, as well as a production, is possible, depending, for example, on the content of the last meal and measurement time after the last meal).*[5] This of course is in contradiction to the assumption (*4*) that $VN_2 = 0$.

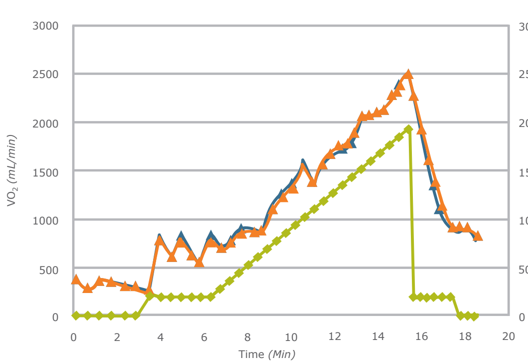
New considerations for Eschenbacher transformation (ET)

Both the implausible values at elevated oxygen breathing, as well as the fact that the Haldane transformation cannot be applied at 100% oxygen breathing, forced me to develop a new calculation that:

- Is not based on the assumption that $VN_2 = 0$
- Still takes into account that for RER not equal to 1, VI is different to VE
- Calculates plausible values also at elevated FIO_2
- Even allows to calculate VO_2 at FIO_2 = 100%

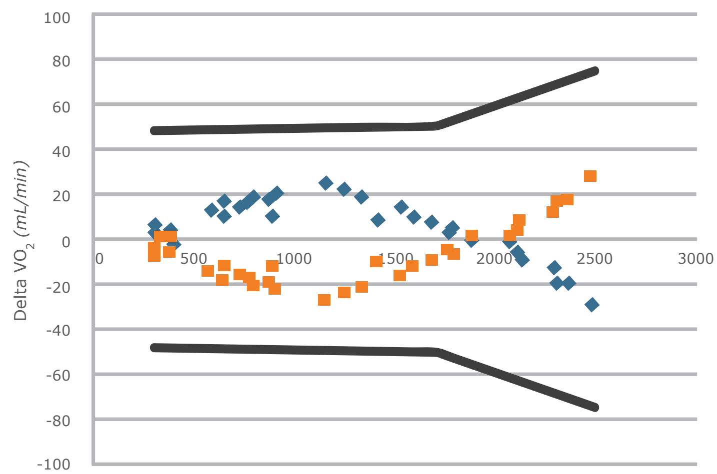
Measurements at normal room air

At normal ambient conditions *(FIO_2 = 20.93%)*, both calculations deliver the same values within the measurement accuracy.



VO_2 at normal conditions *(FIO_2 = 20.93%)*, evaluated with the HT *(blue)* and ET *(orange)*. No significant differences between both calculations can be observed.

Also the Bland-Altman comparison shows a good agreement.

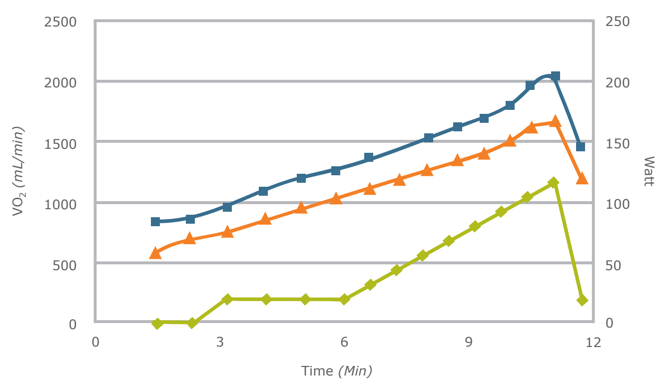


Bland-Altman comparison for VO_2 between the HT *(blue)* and ET *(orange)* at FIO_2 = 20.93%. RER = 1 is reached at ca. VO_2 = 2000 mL/min. While the HT VO_2 is a bit higher for RER < 1 and lower for RER > 1, the ET is a bit lower for RER < 1 and higher for RER > 1. Both calculations, however, are within the measurement accuracy *(solid lines).*

The VO_2 with the HT is a bit higher at RER < 1 and a bit lower at RER > 1, while the ET shows the opposite tendency. Therefore, RER will also show small differences between HT and ET, but both deviations are within the measurement accuracy.

Measurements at elevated FIO_2

More obvious are the differences at higher FIO_2 values for VO_2 and RER.



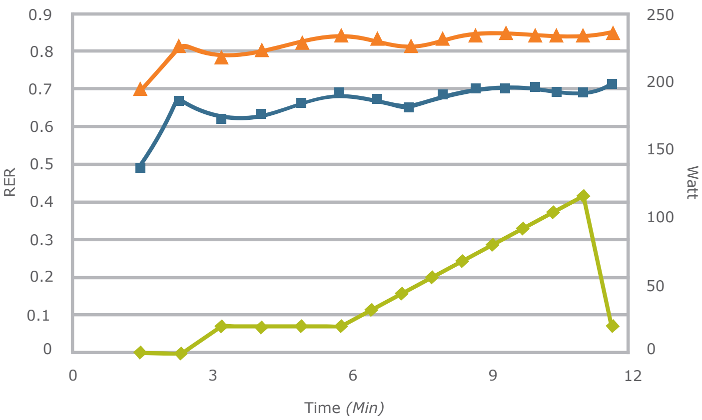
VO_2 measurement at ca. FIO_2 = 60%. While the HT *(blue)* seems to overestimate VO_2 *(e.g., 1790 mL/min at 90 W)*, the ET *(orange)* delivers more plausible values *(1505 mL/min at 90 W).*

According to Wasserman, we normally expect for VO_2:[4]

$$VO_2 = 5.8 \times BW + 151 + 10.3 \times W$$

which leads in a measurement above to a value of ca.1530 mL/min at 90 W *(BW = 79 kg)*. While the ET calculates a VO_2 value close to this expected value *(1505 mL/min)*, the HT seems to overestimate the VO_2 at 90 W by around 250 mL/min.

The difference between the ET and the HT is even more obvious when comparing the resulting RER.



RER measurement at ca. FIO_2 = 60%. Due to the overestimation of the VO_2 via the HT *(blue)*, the RER remains implausible below 0.70 almost over the whole measurement, while the ET delivers plausible RER values *(between ca. 0.80 and 0.85)*.

While the ET delivers plausible values for RER *(between ca. 0.80 and 0.85)*, the HT calculates RER values which are unrealistic. The RER with the HT remains below 0.70 for almost the entire measurement, although an RER below 0.70 *(= fat-burning)*—after the wash-in period—is physiologically impossible.

Measurements at 100% FIO_2 breathing

While the HT does not permit calculating VO_2 at all at 100% FIO_2, the ET delivers plausible values even at 100% oxygen breathing *(examples will be published soon as well)*.

Conclusion

The HT seems to be limited to FIO_2 values close to room air. Higher FIO_2 values will create significant deviations and HT cannot be used at 100% oxygen breathing.

In contrast, the ET delivers plausible values over the whole FIO_2 range, even at 100% oxygen breathing.

Due to this limitation, should the Haldane transformation be used at all—or is it time to skip it?

During my investigations I also had the following impression *(needs to be investigated in detail, even if it can be already explained by the HT assumption):* While in the case of nitrogen production, the HT calculation is already implausible at FIO_2 < 50%, it seems that in case of nitrogen retention, the HT seems to deliver more plausible values even at higher FIO_2.

A change between nitrogen retention and nitrogen production strongly depends on the last meal itself as well as on the time between the meal and the measurement.[5]

Therefore at least at higher FIO_2 the HT will lead to large fluctuations and nonreproducible results even with the same patient.

References

1 Kleinberger G, Eckart J. *Methodische Fragen zur indirekten Kalorimetrie.* Salzburg, Austria. 1986, Bd.-Hrsg. ISBN: 3886032388. **2** Handbook of Gas Exchange and Indirect Calorimetry. Datex. Finland, Doc No. 876710. **3** Consolazi CF, Johnson RE, Pecora LJ. *Physiological Measurements of Metabolic Functions in Man.* New York: McGraw-Hill; 1963. **4** Wasserman K, Hansen JE, Sue DY, et al. *Principles of Exercise Testing and Interpretation.* 5th ed. Lippincott Williams & Wilkins; 2012. ISBN-13: 978-1-60913-899-8. **5** Wilmore JH, Costill DL. Adequacy of the Haldane transformation in the computation of exercise VO2 in man. *J Appl Physiol.*1973;1-35.

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