Innocor®

BREATH-BY-BREATH METHOD

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1 BREATH-BY-BREATH METHOD

1.1 SCOPE

The purpose of this document is to give an introduction to the Breath-by-Breath Method used in Innocor. This section applies to users of Innocor with only limited experience in gas exchange measurements.

For more detailed information about the Breath-by-Breath method, please contact Innovision A/S or simply look in medical article databases.

1.2 INTRODUCTION

The breath-by-breath method is the fastest responding of the non-invasive gas exchange methods for determination of the metabolic rate. Gas composition and respiratory flow are measured continuously at a high frequency.

The principle in the determination of the oxygen consumption and the carbon dioxide excretion is to estimate the difference between airway influx and efflux of oxygen and carbon dioxide during inspiration and expiration. This is done by integrating the product of oxygen or carbon dioxide concentration and flow in the respiratory gas over an interval, which covers a complete respiratory cycle.

The results can be corrected partly for changes in oxygen and carbon dioxide contents of the lungs by using equations based on the change in functional residual capacity (FRC) from one breath to the next (Beaver et al., 1981) and by assuming constant $F_{ET}o_2$ and $F_{ET}co_2$ from breath to breath. The change in FRC is determined from the nitrogen balance equation, which requires that the nitrogen flux across the alveolar membrane is practically zero.

The respiratory (expiratory) minute ventilation is estimated by simply integrating the flow over one whole expiration and dividing by the length of the breath. This is also the case for the alveolar ventilation except that the product of anatomical dead space and respiratory rate is subtracted. The anatomical dead space is determined from the capnogram (CO_2 curve) and the flow signal. The respiratory rate, the tidal volume and the time of inspiration are determined from the flow signal alone.

The end-tidal concentrations are determined as the minimum/maximum concentrations of oxygen/carbon dioxide at the end of expiration. The respiratory and expiratory quotients are found as the ratio between carbon dioxide excretion and oxygen consumption, and as the ratio between respiratory minute ventilation and oxygen consumption or carbon dioxide excretion, respectively.

This document will enable the reader to understand the cardiopulmonary parameters measured by Innocor and the way they are determined.

1.3 BREATH-BY-BREATH PARAMETERS

The Breath-by-Breath parameters measured by the Innocor are:

Primary parameters:

Symbol	Name	Description & Unit
Vo_2	Oxygen uptake	The amount of oxygen extracted from the inspired gas in a given time, [l/min @ STPD].
Vco_2	Carbon dioxide excretion	The amount of carbon dioxide exhaled from the body into the atmosphere in a given time, [l/min @ STPD].
V_E	Expiratory minute ventilation	The volume of air exhaled from the body in one minute, [l/min @ BTPS].

Secondary / derived parameters:

Symbol	Name	Description & Unit
Vo_2/kg	Oxygen uptake per kg	The amount of oxygen extracted from the inspired gas in a given time per kg body weight, [ml/min/kg @ STPD]
R	Respiratory gas exchange ratio	The ratio of the carbon dioxide excretion to the oxygen uptake.
V_A	Alveolar ventilation	The volume of air exhaled from the alveoli per minute, [l/min @ BTPS].
V_D	Anatomical dead space	The volume of the upper airways, trachea and bronchi. (Fowler dead space). [l @ BTPS].
V_T	Tidal volume	Volume of expired air during a breath, [l @ BTPS].
Resp.Freq.	Respiratory rate	Breathing frequency [/min].
Fo_2-et	End-tidal concentration of oxygen	The oxygen concentration in the expired gas at the end of the exhalation, [%].
Fco_2-et	End-tidal concentration of carbon dioxide	The carbon dioxide concentration in the expired gas at the end of the exhalation, [%].
V_E/Vo_2	Expiratory quotient / ventilatory equivalent for oxygen	The ratio of ventilation to oxygen uptake.
V_E/Vco_2	Expiratory quotient / ventilatory equivalent for carbon dioxide	The ratio of ventilation to carbon dioxide excretion.

The following parameters can be calculated after an incremental exercise test:

Symbol	Name	Description & Unit
AT	Anaerobic threshold	The exercise Vo_2 above which anaerobic production supplements aerobic production. Exercise above AT is reflected by an increase in lactate concentration. The AT is measured by the V-slope* method on the plot of Vco_2 against Vo_2.
RC	Respiratory compensation	The exercise Vo_2 above which the ventilation starts to increase more than the Vco_2 in order to compensate for the lactic acidosis. The RC is measured by the V-slope* method on the plot of V_E against Vco_2.
@Rest	Rest values	The values of the BBB parameters at rest – an average of the last minute before start of exercise.
@AT	Values at AT point	The values of the BBB parameters at the AT point – an average of the 30 seconds around the AT point.
@Max	Values at max exercise	The values of the BBB parameters at the max exercise level – found as 30 seconds average around the maximum of Vo_2.

** Beaver WL, Wassermann K, Whipp BJ (1986) "A new method for detecting anaerobic threshold by gas exchange" J Appl Physiol 60:2020-2027*

All the listed parameters will be explained in detail in the following.

1.4 BREATH-BY-BREATH EQUATIONS

In the following equations for the calculations of the Breath-by-Breath parameters the gas signals and flow signal are corrected for time delay. Refer to the figure below:

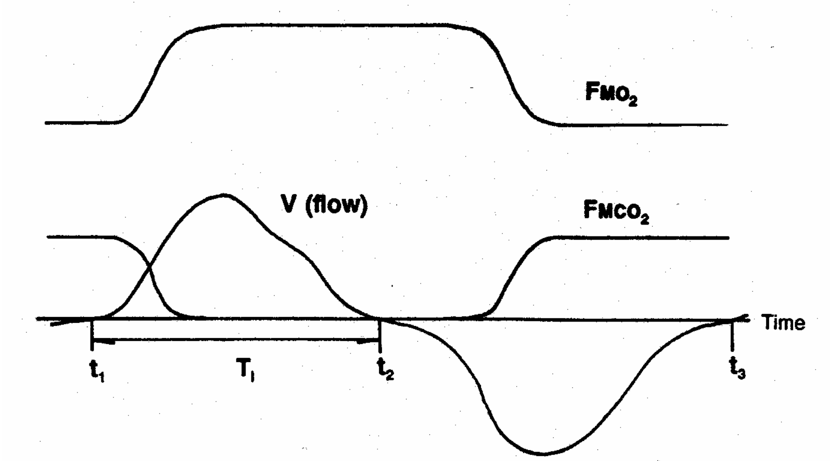

Figure 1.4-1 Illustration of a single breath O_2 and CO_2 concentrations and respiratory flow with definition of variables.

t_1 = start of an inspiration
t_2 = start of the following expiration
t_3 = start of the following inspiration
V = flow at mouthpiece (here defined to be positive for inspiration)
F_{MX} = fractional concentration of gas X (O_2, CO_2 or N_2) at mouthpiece
F_{AX} = fractional concentration of gas X (O_2, CO_2 or N_2) in alveolar space, determined as the average value $(F_{MX}(t_1)+F_{MX}(t_3))/2$
C_1 = conversion factor from ATP to STPD, see section 1.4.20
C_2 = conversion factor from BTPS to STPD, see section 1.4.20

The gas analyser in the Innocor can not measure nitrogen directly. The nitrogen (incl. argon) concentration is determined as the rest:

$$F_{M,N2} = 1 - F_{M,O2} - F_{M,CO2} - F_{M,N2O} - F_{M,SF6}$$

1.4.1 Oxygen uptake (Vo_2)

The oxygen uptake is the amount of oxygen extracted from the inspired gas in a given time, [l/min @ STPD]. The oxygen uptake is the difference between the oxygen volume inspired and expired. When corrected for the change in lung volume from breath to breath the equation is:

$$Vo_2 = \frac{1}{(t_3 - t_1)} \bullet \Bigg[\int_{t_1}^{t_2} V_{ATP}(\tau) \bullet C_1 \bullet F_{MO_2}(\tau) \bullet d\tau + \int_{t_2}^{t_3} V_{BTPS}(\tau) \bullet C_2 \bullet F_{MO_2}(\tau) \bullet d\tau - \frac{F_{AO_2}}{F_{AN_2}} \bullet [\int_{t_1}^{t_2} V_{ATP}(\tau) \bullet C_1 \bullet F_{MN_2}(\tau) \bullet d\tau + \int_{t_2}^{t_3} V_{BTPS}(\tau) \bullet C_2 \bullet F_{MN_2}(\tau) \bullet d\tau] \Bigg]$$

The oxygen uptake during rest is approximately 3.5 ml/min per kg or 250 ml/min for a 70 kg person. The oxygen uptake increases with exercise level, and during exercise on a bicycle ergometer Vo_2 can be estimated as:

Vo_2 = 5.8·weight+151+10.1*load [ml/min]

Example:

Weight = 70 kg
Load = 100 watt
Vo_2 = 5.8·70+151+10.1*100 ml/min = 1.567 l/min

1.4.2 Carbon dioxide excretion (Vco_2)

The carbon dioxide excretion is the amount of carbon dioxide exhaled from the body into the atmosphere in a given time, [l/min @ STPD]. The carbon dioxide excretion is the difference between the carbon dioxide volume expired and inspired. When corrected for the change in lung volume from breath to breath the equation is:

$$Vco_2 = \frac{-1}{(t_3 - t_1)} \bullet \Bigg[\int_{t_1}^{t_2} V_{ATP}(\tau) \bullet C_1 \bullet F_{MCO_2}(\tau) \bullet d\tau + \int_{t_2}^{t_3} V_{BTPS}(\tau) \bullet C_2 \bullet F_{MCO_2}(\tau) \bullet d\tau - \frac{F_{ACO_2}}{F_{AN_2}} \bullet [\int_{t_1}^{t_2} V_{ATP}(\tau) \bullet C_1 \bullet F_{MN_2}(\tau) \bullet d\tau + \int_{t_2}^{t_3} V_{BTPS}(\tau) \bullet C_2 \bullet F_{MN_2}(\tau) \bullet d\tau] \Bigg]$$

1.4.3 Expiratory minute ventilation (V_E)

The expiratory minute ventilation is the volume of air exhaled from the body in one minute, [l/min @ BTPS]. The expiratory minute ventilation is the integrated flow during expiration divided by the breath length.

$$V_E = -\frac{1}{t_3 - t_1} \bullet \int_{t_2}^{t_3} V_{BTPS}(\tau) \bullet d\tau$$

1.4.4 Oxygen uptake per kg (Vo_2/kg)

Oxygen uptake per kg is the amount of oxygen extracted from the inspired gas in a given time per kg body weight, [ml/min/kg @ STPD].

$Vo_2/kg = Vo_2 / weight \cdot 1000$

The Vo_2/kg at rest is approximately 3.5 ml/min/kg. The maximum Vo_2/kg during maximum exercise is a normalised parameter, which depends on the fitness of the subject.

1.4.5 Respiratory gas exchange ratio (R)

Respiratory gas exchange ratio is the ratio of the carbon dioxide excretion to the oxygen uptake.

$R = Vco_2 / Vo_2$

At rest and at steady state the R is in the range 0.7-1.0. During an exercise test the R increases – at the end above 1. During recovery the R increases further (<2).

1.4.6 Alveolar ventilation (V_A)

The alveolar ventilation is the volume of air exhaled from the alveoli per minute, [l/min @ BTPS]. The alveolar ventilation is the integrated flow during expiration subtracted the subject and instrument dead space divided by the breath length.

$$V_A = \frac{1}{t_3 - t_1} \bullet \left[\int_{t_2}^{t_3} -V_{BTPS}(\tau) \bullet d\tau - V_D - V_{total\ instrument\ dead\ space} \right]$$

An alternative calculation of V_A is:

$$V_A = V_E - Resp.Freq \bullet [V_D + V_{total\ instrument\ dead\ space}]$$

Example:

t_3-t_1 = 0.05 min (Resp.Freq = 20 /min)
$\int V \cdot d\tau$ = -1 litre
V_D = 0.150 litre
$V_{total\ instrument\ dead\ space}$ = 0.136 litre
V_E = 1/0.05·1 = 20.00 l/min
V_A = 1/0.05·(1-0.150-0.136) = 14.28 l/min

1.4.7 Anatomical dead space (V_D)

The anatomical dead space is the volume of the upper airways, trachea and bronchi. (Fowler dead space). [l @ BTPS].

The expirogram is normally divided into 3 phases: Phase I, where no CO_2 is present, phase II, where the CO_2 concentration rises rapidly during dead space wash-out, and phase III, identified by a slower and nearly linear increase in CO_2 concentration, which represents delayed alveolar concentration. To estimate the anatomical dead space, a regression line is determined for phase III, and the dead space is defined as the expired volume where two areas are equal. One area is bounded by the zero line, the vertical line at the dead space and the CO_2 curve, and the second area by the vertical line at the dead space, the alveolar regression line and the CO_2 curve. The volume found in this way is subtracted the instrument dead space (from the inlet to the mouth):

$V_D = V(To) - V_{\text{instrument dead space, flowmeter}}$

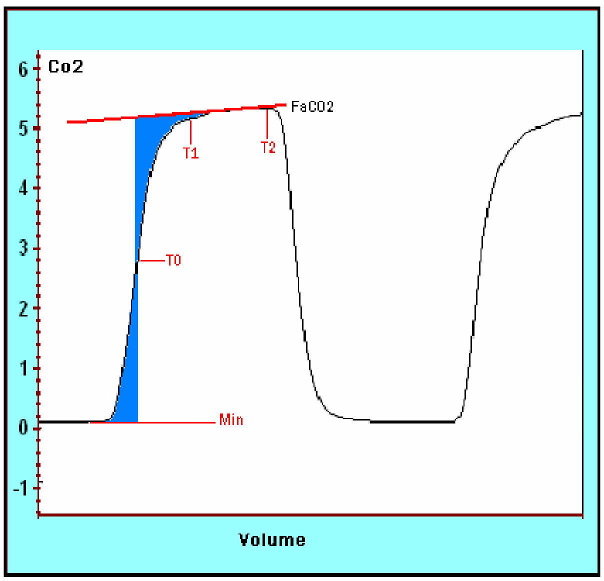

Figure 1.4.7-1 Illustration of an expirogram for the determination of the anatomical dead space.

The different dead spaces are defined in figure 1.4.7-2, and consist of

V_D	= Anatomical dead space.
$V_{\text{instrument dead space, flowmeter}}$	= gdFlowdeadspace, volume from mouth to inlet.
$V_{\text{instrument dead space, RVU}}$	= gdValvedeadspace, volume from inlet to ambient air port.
$V_{\text{total instrument dead space}}$	= $V_{\text{instrument dead space, flowmeter}} + V_{\text{instrument dead space, RVU}}$

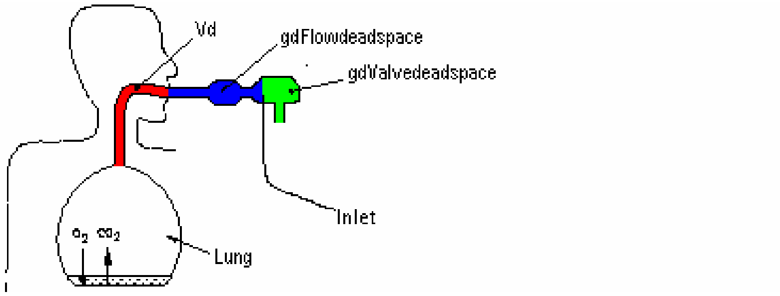

Figure 1.4.7-2 Illustration of the anatomical dead space and instrument dead spaces.

A standard configured Innocor has the following dead spaces:

$V_{\text{instrument dead space, flowmeter}}$	= 116 ml (172 ml with flexible tube)
$V_{\text{instrument dead space, RVU}}$	= 20 ml
$V_{\text{total instrument dead space}}$	= 136 ml (192 ml with flexible tube)

1.4.8 Tidal volume (V_T)

Tidal volume is the volume of air exhaled during a breath, [l @ BTPS].

$$V_T = -\int_{t_2}^{t_3} V_{BTPS}(\tau) \bullet d\tau$$

An alternative calculation of V_T is:

$$V_T = \frac{V_E}{Resp.Freq}$$

1.4.9 Respiratory rate (Resp.Freq.)

The respiratory rate is the breathing frequency [/min].

$$Resp.Freq = \frac{1}{t_3 - t_1}$$

1.4.10 End-tidal concentration of oxygen (Fo_2-et)

The end-tidal concentration of oxygen is the oxygen concentration in the expired gas at the end of the exhalation, [%]. The end-tidal concentration of oxygen is found as a 250 ms average at the same time as the end-tidal concentration of carbon dioxide, see below.

1.4.11 End-tidal concentration of carbon dioxide (Fco_2-et)

The end-tidal concentration of carbon dioxide is the carbon dioxide concentration in the expired gas at the end of the exhalation, [%]. The end-tidal concentration of carbon dioxide is found as the maximum value of a 250 ms moving averaging.

1.4.12 Expiratory quotient for oxygen (V_E/Vo_2)

The expiratory quotient / ventilatory equivalent for oxygen is the ratio of ventilation to oxygen uptake. The expiratory quotient is corrected for instrument dead space.

$V_E/Vo_2 = (V_E – Resp.Freq \cdot V_{\text{total instrument dead space}}) / Vo_2$

Normal values of V_E/Vo_2 at AT is in the range 20 – 33.

1.4.13 Expiratory quotient for carbon dioxide (V_E/Vco_2)

The expiratory quotient / ventilatory equivalent for carbon dioxide is the ratio of ventilation to carbon dioxide excretion. The expiratory quotient is corrected for instrument dead space.

$V_E/Vco_2 = (V_E - Resp.Freq \cdot V_{total\ instrument\ dead\ space}) / Vco_2$

Normal values of V_E/Vco_2 at AT is in the range 23 – 36.

1.4.14 Anaerobic threshold (AT)

The anaerobic threshold is the exercise Vo_2 above which anaerobic production supplements aerobic production. Exercise above AT is reflected by an increase in lactate concentration. The AT is measured by the V-slope* method on the plot of Vco_2 against Vo_2, see figure below.

** Beaver WL, Wassermann K, Whipp BJ (1986) "A new method for detecting anaerobic threshold by gas exchange" J Appl Physiol 60:2020-2027*

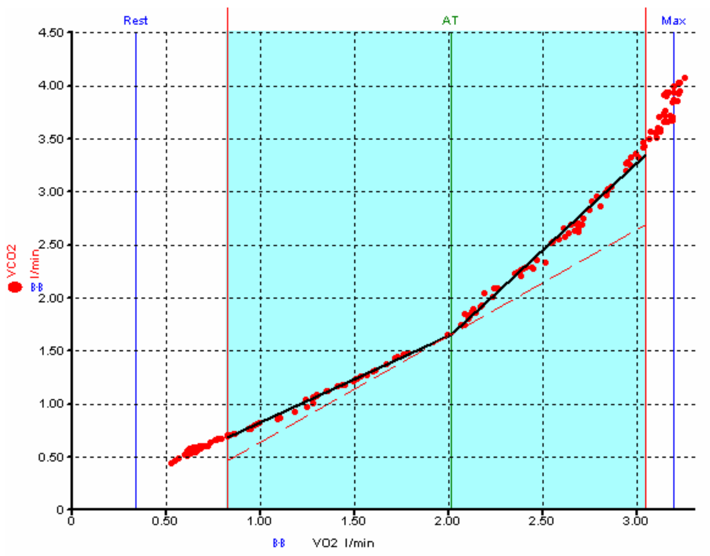

Figure 1.4.14-1 Illustration of the determination of the anaerobic threshold measured by the V-slope method.

Normal values of AT is 50 to 65% of maximum Vo_2.

1.4.15 Respiratory compensation (RC)

The respiratory compensation is the exercise Vco_2 above which the ventilation starts to increase more than the Vco_2 in order to compensate for the lactic acidosis. The RC is measured by the V-slope method on the plot of V_E against Vco_2.

1.4.16 Rest values

The rest values are the breath-by-breath parameters at rest – an average of the last minute before start of exercise (start exercise is defined as the time where a change from zero is found in the load, speed or slope. Start of unloaded pedalling is defined as start of exercise).

1.4.17 AT values

The AT values are the breath-by-breath parameters at the anaerobic threshold – an average of 30 seconds around the AT point.

1.4.18 Max values

The max values are the breath-by-breath parameters at the max exercise level – a 30 seconds average. The time is found as the 30 seconds time period where the average of the Vo_2 is highest.

1.4.19 Gas delay

In order to calculate breath-by-breath parameters the flow and gas must be aligned time wise. Flow is measured instantaneously whereas the gas signals are delayed due to gas transport from inlet tip to measurement cell. Due to the delay in the gas signals, the gas signals must be shifted back in time. The accuracy of this delay is important – an error of 25 ms at rest gives an error of approx. 5% in the Vo_2 and Vco_2 calculations!
The calculation of the delay is based on the respiratory flow and the fractional concentration of CO_2 / O_2 at the change from expiration to inspiration, where the fastest change in CO_2 concentration occurs. The time from a change in direction of the flow (to inspiration) to the corresponding change in CO_2 / O_2 concentration consists of two parts: The first part, which is flow dependent, is caused by the instrumental dead space from the breathing port to where the sample inlet is positioned (see figure1.4.7-2). The other part is the constant gas delay caused by the sample gas transit time and response time of the gas analyser. The delay between flow and gas signals is calculated from the time between the change in flow and the change in the CO_2 / O_2 signal, when this time is corrected for the time corresponding to the flushing of the instrumental dead space ($V_{instrument\ dead\ space,\ RVU}$ = 20 ml @ standard Innocor).

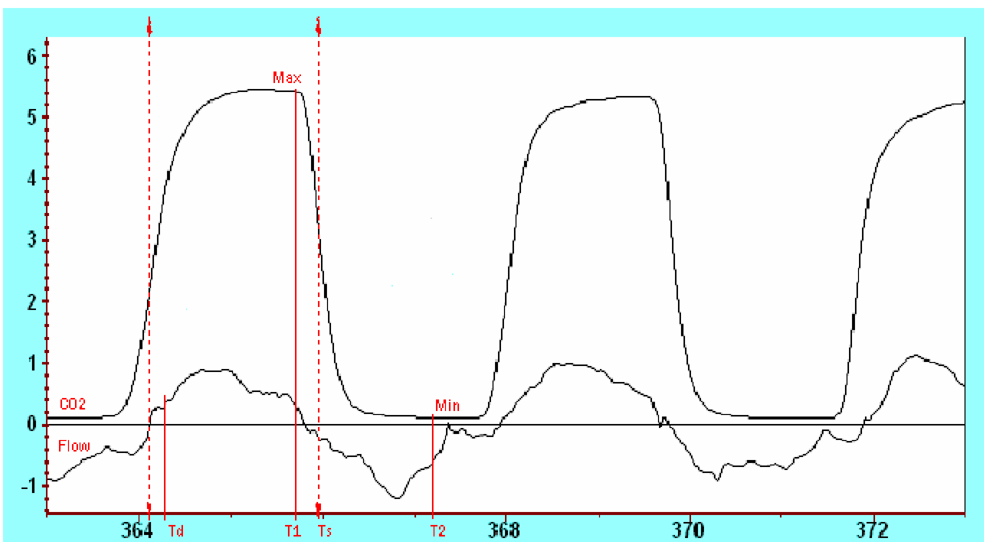

Figure 1.4.19-1 Illustration of the determination of the gas delay.
Td = time where dead space volume is inspired.
Ts = time where CO_2 is dropped ½ based on an equal area determination
Ts – Td = gas delay
Flow is positive during inspiration.

In the Innocor the gas delay can be determined prior to a test, where the operator shall make 10 special breaths: Slow expirations followed by a fast inspiration in order to minimise the time to washout the dead space.
The gas delay is also determined automatically during an exercise test, when the exercise level exceeds approx. 40-50% of max exercise level.
The delay determination is based on the last 10 gas delay calculations using averaging and removal of any extreme values.
Normal values for the gas delay on the Innocor is 1400 – 1700 ms.

1.4.20 Conversion between ATP, STPD and BTPS

The volume of a number of moles (n) of gas molecules depends on the thermodynamic temperature (T) and the ambient pressure (P). The following relationship holds for dry gas:

$$V = n \cdot R \cdot T / P$$

where R = gas constant, and T is expressed in Kelvin (T(K) = 273.2 + t(ºC)).
Air and expired gas are made up of gas molecules and water vapour. In a gas mixture saturated with water vapour and in contact with water (such as occurs in the lung) the number of water molecules in the gas phase varies with temperature and pressure. As the number of molecules is not constant, the above gas law should be applied to dry gas. This also holds outside the lung when gas saturated with water vapour is compressed or cools down.

BTPS: In respiratory physiology lung volumes and flows are standardised to barometric pressure at sea level, body temperature, saturated with water vapour: body temperature and pressure, saturated.

ATPS: Measured at ambient temperature, pressure, saturated with water vapour (e.g. expired gas, which has cooled down): ambient temperature and pressure, saturated.

ATP: Like ATPS, but not saturated with water vapour (e.g. room air).

ATPD: Like ATPS, but dry (e.g. from a gas bottle).

STPD: Oxygen consumption and carbon dioxide excretion are standardised to standard temperature (0 ºC), barometric pressure at sea level (101.3 kPa / 760 mmHg) and dry gas: standard temperature and pressure, dry.

Correction from ATP to STPD. Multiply the ATP-value by:

$$C_1 = \frac{273}{273 + t_a} \cdot \frac{P_B - \frac{RH}{100} \cdot P_{H2O}(t_a)}{760}$$

Correction from BTPS to STPD. Multiply the BTPS-value by:

$$C_2 = \frac{273}{273 + 37} \cdot \frac{P_B - 47}{760}$$

where

t_a = ambient temperature in °C
P_B = barometric pressure in mmHg
RH = relative humidity in %
$P_{H2O}(t_a)$ = saturated water vapour pressure in mmHg at temperature t_a, see table below

Temperature [°C]	Water vapour pressure [mmHg]
0	4.7
1	5.2
2	5.6
3	6.1
4	6.5
5	7.0
6	7.4
7	7.9
8	8.3
9	8.8
10	9.2
11	9.8
12	10.5
13	11.2
14	12.0

Temperature [°C]	Water vapour pressure [mmHg]
15	12.8
16	13.6
17	14.5
18	15.5
19	16.5
20	17.5
21	18.7
22	19.8
23	21.1
24	22.4
25	23.8
26	25.2
27	26.7
28	28.3
29	30.0

Temperature [°C]	Water vapour pressure [mmHg]
30	31.8
31	33.7
32	35.7
33	37.7
34	39.9
35	42.2
36	44.6
37	47.1
38	49.7
39	52.4
40	55.3