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Oxygen therapy in hypoxaemic failure to subjects who breathe spontaneously: How can we improve oxygen supplementation?

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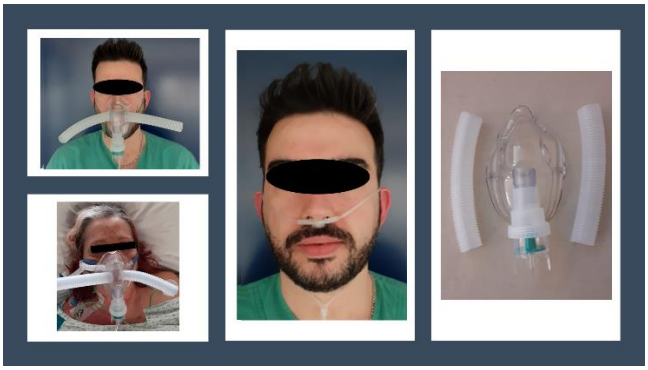

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« Et s'il était à refaire Je referais ce chemin »

Louis Aragon, la Diane française (1948)

Déclaration de conflits d'intérêts et de financement:

L'auteur déclare n'avoir aucun conflit d'intérêt réel ou potentiel en lien avec le contenu de cette thèse.

List of abbreviations (and units)

AA: Absorption Atelectasis
$AaDO_2$: Alveolar-arterial Oxygen Tension Difference
AHRF: Acute Hypoxaemic Respiratory Failure
ATP: Adenosine Triphosphate
ATPS: Ambient Temperature Pressure Satured
AVOID: Air Versus Oxygen in Myocardial Infarction
BK channels: Big Potassium Channels
BOOST-II: Benefits of Oxygen Saturation Targeting Study II
CaO_2: Oxygen arterial Contains
CGA: Compressed Gas Association
CO: Carbon Monoxide
COPD: Chronic Obstructive Pulmonary Disease
CV: Coefficient of Variation
Cx 40: Connexin 40
DTL: Dual Test Lung
DTM: Double Trunk Mask
EDRF: Endothelium-Derived Relaxing Factor
ET1: Endothelin1
FADH: Flavin Adenine Dinucleotide Reduced
FDO_2: Fraction Delivered in Oxygen
FiO_2: Fraction inspired in Oxygen
H_2O_2: Hydrogen Peroxide
HAO: High Affinity for Oxygen.
Hb: Haemoglobin concentration
HFNC: High Flow Nasal Canula
HH: Hypobaric Hypoxia
HIF: Hypoxic Induce Factor
HME: Heat Moisture Exchanger
HO-2: Haemoxygenase-2
HPV: Hypoxic Pulmonary Vasoconstriction
HVD: Hypoxaemic Ventilatory Decline
ICC: Intraclass Correlation Coefficient
ICU: Intensive Care Unit

IF: Inspiratory Flow (liter per second)
INP: Inspiratory Negative Pressure
IQR: Inter-Quartile Range
ISO: International Organization for Standardization
K_{ATP}: ATP-sensitive potassium channel
LAO: Low Affinity for Oxygen
LPM O_2: Oxygen flow (liter per minute)
MBAM: Modified Bland-Altman Method
MRC: Medical Research Council
MV: Mechanical Ventilation
NADH: Nicotinamide Adenine Dinucleotide Reduced
NC: Nasal Cannula
NIV: Non-Invasive Ventilation
NO: Nitric Oxide
NPO: Naso-Pharyngeal Oxygen
NRM: Non-Rebreathing Mask
NTS: Nucleus Tractus Solitarii or Nucleus of the solitary tract
OAH: Obesity-Associated Hypoventilation
OFR: Oxygen Flow Restrictor
OGC: Oxygen Gas Cylinder
OH: Hydroxyl Radicals
OM: Oxygen Mask
OMF: Oxygen Mass Flowmeter
OT: Oxygen Therapy
$PACO_2$: Alveolar Partial Pressure in CO_2 (mmHg)
PAO_2: Alveolar Pressure of Oxygen (mmHg)
PaO_2: Arterial Pressure of Oxygen (mmHg)
Patm: atmospheric Pressure (mmHg)
Pb: barometric Pressure (mmHg)
PCI: Percutaneous Coronary Intervention
PCV: Pulmonary Circulation Vasoconstriction
PeCO2 : Expiratory pressure in CO2
PiO_2: inspiratory Pressure of Oxygen (mmHg)
PNRM: Partial Non-Rebreathing Mask
POC: Portable Oxygen Concentrator
PRM: Partial Rebreathing Mask

PSIG: Pound-force per Square Inch Gauge

$PvapH_20$: Pressure of water vapor (mmHg)

Rf: Respiratory frequency (cycle per minute)

ROP: Retinopathy Of Prematurity

ROS: Reactive Oxygen Species

ROX index: Respiratory rate OXygenation index

RQ: Respiratory Quotient

RTN: Retro-Trapezoid Nucleus

SaO_2: Oxygen Saturation in arterial blood

SOFA: Sepsis-related Organ Failure Assessment

STEMI: ST Elevation Myocardial Infarction

SUPPORT: Pulse Oximetry Randomised Trial

Ti: inspiratory Time (second)

Te: expiratory Time (second)

TNRM: Total Non-Rebreathing Mask

TT: Thorpe Tube

Ttot: Total respiratory Time (in seconds)

V/Q: Ventilatory-Perfusion ratio

VCO_2: Cardon Dioxide production (Liter per min)

Vd: Dead space (Liter)

VE: Minute Ventilation (Liter per min)

VEGF: Vascular endothelial growth factor

VO_2: Oxygen uptake (Liter per min)

VRG: Ventral Respiratory Group

Vt: tidal Volume (Liter)

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Chapter 1: Objective of this thesis

Oxygen administration is probably one of the most used techniques in medical care. To be effective, oxygen must be administered adequately as this determines the effectiveness of the therapy. In this thesis, we analysed each stage of the O_2 supplementation which is likely to affect it. This thesis aimed to understand and improve the quality of the management of hypoxaemia patients supplemented with oxygen and ventilating spontaneously. The subject of this work concerns the administration of O_2, both in hospital and in ambulatory medicine. Before the beginning of this thesis, previous research on the administration of O_2 had highlighted the superiority of a mask of our design: The Double Trunk Mask. Our mask delivers high oxygen fractions that are superior to those provided by conventional oxygen masks. Research was carried out on patients hospitalised in the intensive care units and on a bench. During this period, research identified specificities in the supplementation of O_2. However, the question of the accuracy of the oxygen supplementation systems (hospital rotameters and oxygen cylinders), as well as the calculation of the value of the fraction delivered in oxygen (FDO_2), could not be thoroughly investigated. Also, the advent of high-throughput oxygenation systems has changed our approach to normobaric oxygen therapy. We investigated ways to optimise the supplementation of oxygen to spontaneously ventilating hypoxaemic patients. The introduction of this thesis includes notions on:

- Respiratory physiology about the transport of atmospheric oxygen to the cells
- Hypoxia and hypoxaemia
- Hyperoxia and hyperoxaemia
- Ventilatory and vascular adaptations during hypoxia and hypoxaemia
- Systems commonly used to administer oxygen in a clinical situation

This dissertation describes the following research work carried out:

Firstly, by deepening knowledge about the precision and accuracy of O_2 supplementation systems (rotameters, flowmeters) and the probable consequences on the risks of over or under oxygenating both adult and paediatric hypoxaemic patients.

Secondly, we conducted a bench study to verify the accuracy of a predictive formula of the FiO_2 of our design, as well as research on the clinical applications that use this formula.

Thirdly, we conducted two studies on the use of the Double Trunk Mask, on the one hand as an oxygen enricher in oxygenated patients using a high flow nasal cannula, and on the other hand in patients oxygenated by a nasal cannula with a low flow.

Chapter 2: Physiology of Oxygen

Oxygen is the most widespread chemical element (in mass) in the biosphere, air, water, and terrestrial rocks. Oxygen is the 8th element in the Mendeleev's table. In our cells, especially in the mitochondria, oxygen interacts with hydrogen. Due to its electronegativity, it can capture the electrons of the respiratory chain that come from the oxide reduction processes of $NADH_2$ or $FADH_2$ (1,2). This process allows the synthesis of ATP, the coenzyme that supplies energy to all active metabolic processes.

Oxygen is, therefore, indispensable to most living beings. To reach this goal, oxygen must be transported from the atmosphere inside the cells by “ventilation-circulation-respiration” coupling.

The purpose of “ventilation-circulation-respiration” coupling is to bring oxygen within the mitochondrial inner membrane (figure 1). Oxygen must undergo essential steps to reach the cells. If one of these steps is defective, oxygen will not reach the cells properly, which can lead to hypoxia (1).

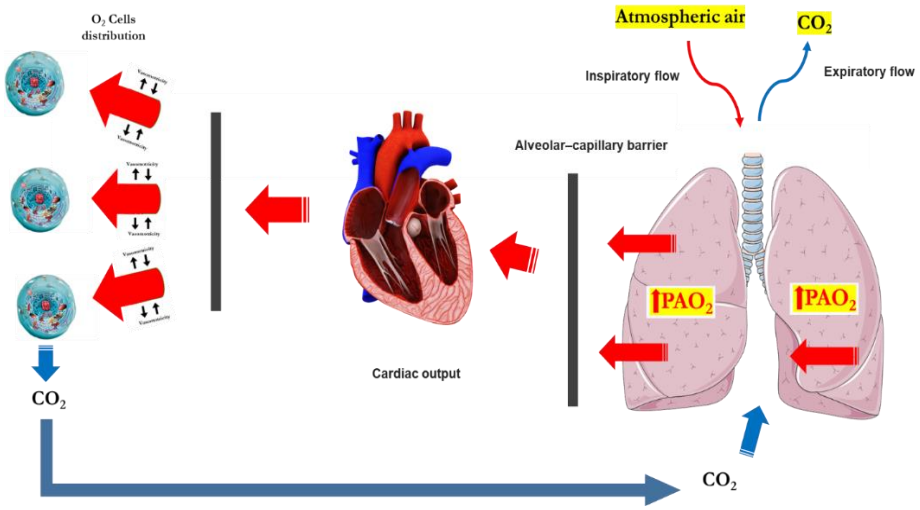


Figure 1: Schematic ventilatory-circulatory-respiration coupling

- Steps for oxygen to reach the cells (3):

a) Ventilation:

Human ventilation is a vital function to provide a bidirectional exchange of gases between the body and the atmosphere. Ventilation allows the regulation of both the $PACO_2$ ($PACO_2$: Alveolar pressure of carbon dioxide) and the PAO_2 (PAO_2: Alveolar pressure of oxygen). During this step, in standard conditions, because of Dalton's Law, the atmospheric pressure of oxygen will decrease from atmospheric air to the alveolar compartment. Indeed, when air penetrates airways, the atmospheric pressure of oxygen (PO_2) ~160 mmHg at the level sea) drops to ~150 mmHg (PiO_2: Inspiratory pressure of oxygen) due to the presence of H_2O vapour in the airways ($PvapH_2O$ ~47 mmHg at 37°C or an absolute humidity value of 44 mg/l, which represents a relative humidity of 100% at this temperature). Then, in the alveoli, the partial pressure will drop to 100 mmHg due to the presence of alveolar carbon dioxide ($PACO_2$: Alveolar partial pressure of carbon dioxide ~40 mmHg in healthy subjects) (figure 2). This difference (100 mmHg at rest and not 110 mmHg) is due to the inspiratory gas law. Indeed, the partial pressure of oxygen drop is 50 mmHg and not 40 mmHg because of the law of inspired gases which divides the partial pressure of CO_2 (40 mmHg) by the respiratory quotient (RQ = 0.8 at rest. See equation 1A).

Equation 1A: $$PAO_2 = PiO_2 - \left(\frac{PACO_2}{RQ}\right)$$

The $PACO_2$ value is dependent on the atmospheric and H_2O vapour pressures, as well as the inspiratory fraction in carbon dioxide and the ratio between carbon dioxide production (VCO_2) and alveolar ventilation (See equation 1B).

Equation 1B: $$PACO_2 = (Patm - Pvap\,H_2O) * \left(FiCO_2 + \left(\frac{VCO_2}{Va}\right)\right)$$

The PAO_2 value can also be expressed as the difference between PiO_2 and the product of atmospheric pressure and the ratio between oxygen uptake (VO_2) and alveolar ventilation (see equation 1C).

Equation 1C: $$PAO_2 = PiO_2 - \left(\frac{VO_2}{Va} * Pb\right)$$

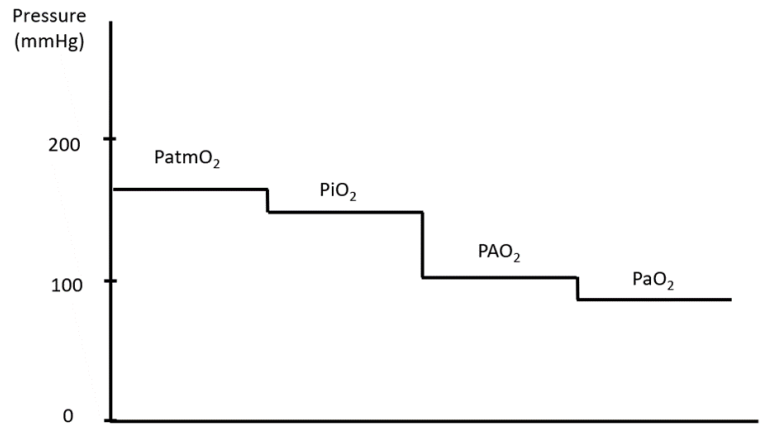


Figure 2: Oxygen pressure decrease from atmospheric to arterial content

Note: In this calculation, we have not considered the presence of other gases such as argon (inert gases) which exerts a pressure of 7 mmHg in the pulmonary alveolar.

In standard conditions (sea level in healthy subjects):

$FiCO_2$: Fractional inspired carbon dioxide (0.03%) = 0.0003

FiO_2: Fractional inspired oxygen (20.9%)

$PACO_2$: Alveolar pressure in Carbon Dioxide (±40 mmHg)

PAO_2: Alveolar pressure of oxygen (±100 mmHg)

PAO_2-PaO_2 differences = 5 to 10 mmHg

Patm: Atmospheric pressure (±760 mmHg)

PiO_2: Inspiratory pressure of oxygen (±150 mmHg)

PO_2: atmospheric pressure of oxygen (±160 mmHg)

$PvapH_2O$: Vapour pressure of H_2O (±47 mmHg)

RQ: Respiratory quotient (±0.8 at rest / 1 during endurance exercise)

Va : Alveolar ventilation = Rf X (Vt-Vd)

VCO_2: Carbon dioxide production (±0.200 L/min in adult at rest)

VO_2: Oxygen uptake (±250 mL/min - ±3.5 ml/kg/min in adult at rest)

b) Diffusion across the alveolar-capillary membrane:

Deoxygenated pulmonary blood becomes oxygenated in the pulmonary capillaries after diffusion across the alveolar-capillary barrier. This diffusion is dependent on the Fick's Law. This Law explains how a gas diffuses across a permeable membrane. Indeed, the diffusion phenomenon is determined by the surface area of the membrane, the partial pressure gradient of the gas across the membrane, and the thickness of the membrane (approximately 600 nm-2µm in healthy individuals) and by a diffusion coefficient of that gas for that membrane. At the sea level, the difference between the PAO_2 and the PVO_2 is roughly equal to 50 mmHg.

In healthy lungs, there is a slight mismatch between alveolar ventilation and pulmonary capillary perfusion (4). This V/Q mismatch and a small quantity of right-to-left shunt creates a slight difference between PAO_2 and PaO_2. Generally, PAO_2 is always higher than PaO_2 by at least 5–10 mmHg (in a healthy subject with physiologic ventilation and perfusion) (5). An increase of the alveolar-arterial oxygen tension difference above 10 mmHg indicates pulmonary disease as the cause of hypoxaemia. $AaDO_2$ (alveolar-arterial oxygen tension difference) is calculated by subtracting PaO_2 from PAO_2 (6). To calculate the intrapulmonary shunt, it is necessary to measure oxygen concentration in both arterial and mixed venous blood samples during oxygenation at 100% inspired oxygen. Interpretative guidelines for shunt calculation in critically ill patients with a pulmonary catheter suggest that a shunt less than 10% is clinically compatible (7).

c) Haemoglobin and oxygen dissociation curve:

Oxygen is carried in the blood both on haemoglobin (oxyhaemoglobin) and dissolved in plasma. Oxyhaemoglobin is the most important part of oxygen transport in arterial blood (~98%); the rest is dissolved oxygen (PaO_2) which represents ~2% of the arterial oxygen content. The equation to determine the oxygen arterial contain is:

$$CaO_2 = ([Hb] \text{ X } (1.31\text{-}1.39) \text{ X } SatO_2) + (0.003 \text{ X } PaO_2)$$

In clinical practice, we use the following equation:

$$CaO_2 = ([Hb] \text{ X } 1.31 \text{ X } SatO_2) + (0.003 \text{ X } PaO_2)$$

Haemoglobin has a maximum theoretical oxygen-carrying capacity from 1.31 to 1.39 ml O_2/gr Hb (Hüfner's constant), corresponding to a theoretical maximum oxygen capacity of 20.85 ml O_2/100 ml of arterial blood. However, direct measurement gives a capacity of 1.34 ml O_2/g Hb. Normal blood haemoglobin concentration is about 15 gr/dl (range 13.5–18.0 in healthy men and 11.5–16.0 in healthy women). However, in the blood, small abnormal

forms of haemoglobin exist (methaemoglobin and carboxyhaemoglobin), which reduce the oxygen-carrying capacity of haemoglobin. However, in clinical practice, this value seems to be closer to 1.31 ml O_2/gr Hb (8).

Note: Methaemoglobin is a haemoglobin which contains Fe^{+++} atoms instead of Fe^{++} atoms. Fe^{+++} atoms are not able to carry oxygen. Normally one to two percent of total haemoglobin is methaemoglobin.

Each haemoglobin molecule can carry four molecules of oxygen. When a molecule of oxygen binds to haemoglobin, the shape of it is altered, leading an overall change in the quaternary structure of haemoglobin. Subsequent oxygen molecules are then linked with higher affinity, which explains the form of the oxyhaemoglobin dissociation curve (9,10).Normal haemoglobin exists in two forms (11); either with a low affinity (LAO), or high affinity (HAO) for oxygen.

- LAO predominates in the tissues with high CO_2 tension, low pH environment, high temperature, or high level of 2,3-diphosphoglycerate (during anaemia) promoting oxygen release. This relationship between haemoglobin, carbon dioxide tension, high temperature, and pH is known as the **Bohr effect** (see below).

- HAO predominates in areas of low CO_2 tension, low temperatures, and high pH; this is known as the **Haldane effect** (see below).

d) Oxygen delivery:

Oxygen contained in the arterial blood is partially extracted. The oxygen extraction ratio in healthy individuals at rest is ~25% and can reach ~75% in extreme conditions.

Oxygen delivery (DO_2) is defined by the following equation:

Oxygen Delivery = Cardiac Output X Arterial oxygen content

$$DO_2 = CO \times CaO_2$$

$$DO_2 = (CO) \times (([Hb] \times 1.31 \times SatO_2) + (0.0031 \times PaO_2))$$

The oxygen delivery is ~1000 ml/min for an adult at rest with a cardiac output equal to 5L/min. Since only ~25% of the oxygen will be extracted, the oxygen uptake (VO_2) value is approximately equal to 250 ml/min (VO_2 ~3.5 ml/min/Kg) for a healthy adult at rest. It should be made clear, however, that this is an overall measure of oxygen delivery. Indeed, the oxygen flow is not constant throughout the body; instead, the microcirculation responds to altering tissue metabolic demands by varying the regional and local blood flow.

Therefore, modifications in cardiac output, arterial oxygen saturation, haemoglobin concentration or the respiratory chain affects oxygen delivery and consequently, cell function. This dysfunction can lead to **hypoxia** which leads to an increase in blood lactates(1,12).

e) Lung dead space physiology: (13,14)

In the lungs, dead space (DS) is the volume of ventilated air that does not participate in gas exchange. There are two types of DS:

Anatomical: the volume of air in the conducting zone of ventilation made up by the nose, trachea, and bronchi. In healthy adults, this volume is approximately equal to 150 ml (either 30% of Tidal volume or 2 mL/kg ideal body weight).

Physiologic: the addition of anatomical dead space and alveolar dead space (slight volume). In this case, alveolar dead space is defined as the volume of air in the respiratory zone that does not take part in gas exchange.

In physiology, alveolar ventilation is defined as the volume which reaches alveoli.

In a healthy subject, if we consider a $PaCO_2$ of ±40 mmHg and a $PeCO_2$ of ±28 mmHg, the VD/Vt is equal to 30%. In pathological situations, any modification of the VD/Vt ratio (COPD, lung inflation) will lead to a change in $PaCO_2$ value, which will impact the PaO_2 (equation 1D and 1E).

Equation 1D $$Patm = PAO_2 + PACO_2 + PN_2 + Pvap\ H_20$$

Equation 1E $$Ptot = \sim PaO_2 + PaCO_2 + PN_2$$

Chapter 3: Hypoxia-Hypoxaemia

a) Definition:

The words hypoxia and hypoxaemia are not synonymous (15).

-Hypoxia is a condition where the tissues do not receive adequate oxygen supply at the tissue level.

They are two types of hypoxia: Normobaric hypoxia and hypobaric hypoxia.

1) Normobaric hypoxia is defined as the failure of oxygenation at the tissue level at sea level. Hypoxia can lead to an increase in arterial blood lactate levels (>2 mmol/L) (16).

There are five types of normobaric hypoxia (Table 1) (3,15,17–19):

1) Stagnant hypoxia	Reduced cardiac output or reduced regional blood flow into and between organs (example: Impairment of venous return of blood, or trauma that induces shock, or any condition that reduces or prevents the circulation of the blood in any area of the body). For example: Raynaud Syndrome or Buerger disease, the application of a tourniquet to control bleeding, exposure to cold and some systemic infections with shock (20).
2) Hypoxaemic hypoxia	When arterial pressure of oxygen drops under low value (21,22).
3) Anaemic hypoxia (hyperaemic hypoxia)	During reduced haemoglobin or carbon monoxide poisoning (23).
4) Cytopathic hypoxia	Secondary to sepsis and inflammation. During sepsis, hypotension causes hypoxia in some organs despite high global oxygen delivery and mixed venous saturation. Mean pressure is an essential determinant of regional perfusion (24). Any cause of microcirculatory dysfunction will affect oxygen delivery during sepsis, when nitric oxide production is increased, leading to disorders of autoregulation along with the decreased vascular tone that manifests clinically as hypotension.
5) Histoxic hypoxia	Cyanide, narcotics, alcohol, formaldehyde, acetone, some anaesthetic agents. These agents can decrease cellular respiration (25).

Table 1: Types of Normobaric hypoxia

To this list, we can add hypoxia due to the artificial decrease in the inspired oxygen fraction (FiO_2 = ±16% or less) whereas the atmospheric pressure remains the same. Some athletes use this technique to try to enhance their sports performances. This technique is called: Intermit*tent Hypoxic Exposure (26,27).

2) Hypobaric Hypoxia (28,29): Hypobaric Hypoxia (HH) or altitude hypoxia is defined as a decrease of the partial pressure of oxygen in the pulmonary alveoli (PAO_2). HH is due to a decrease in atmospheric pressure at high altitudes (or stays in hypobaric chambers) (30). Generally, HH symptoms occur at altitudes of ≥2500 m in unacclimated individuals with a usual delay of 4–12 h after arrival at a new altitude (31). In general, HH symptoms are dyspnoea, loss of appetite, insomnia, headaches, nausea, and vomiting. In extreme situations, pulmonary or cerebral oedema can appear.

-Hypoxaemia is defined as a condition where the partial pressure of oxygen in the arterial blood (PaO_2) is below average (32).

The level of PaO_2 required to determine hypoxaemia is not clear. Different thresholds are used to define hypoxaemia. Some authors have defined hypoxaemia as a PaO_2 dropping below 80 mmHg (33,34) (SpO_2 ±94% (35) or ±75 mmHg (SpO_2 ±94%) or ±60 mmHg (SpO_2 ±90%) (36–40). In 2008, the British Thoracic Society recommend an SpO_2 target between 94% and 98% to avoid hypoxaemia (41). However, according to Beasley et al., oxygen should be titrated to a target SpO_2 range of 92–96% to avoid hypoxaemia (42). The exact low level of PaO_2 that is dangerous is unclear. In general, most patients are adequately oxygenated if their PaO_2 is above 60 mmHg (42,43). Finally, some authors define hypoxaemia as a decrease in the estimated $PaO_2/_{(estimate)}FiO_2$ (fractional inspired in oxygen) below a critical value (in general, 300 mmHg) (44). In this case, the degree of hypoxaemia can be classified as mild (PIF between 200 and 300 mmHg), moderate (PIF between 100 and 200 mmHg), or severe (PIF (PaO_2/FiO_2 ratio) < 100 mmHg) (45). Moreover, to define hypoxaemia, some authors used equations to determine the theoretical value of PaO_2 according to age:

$$PaO_2 = 105 - (\frac{age}{2}) \text{ (46)}$$

$$PaO_2 = 105 - \left(\frac{age}{3}\right) \text{ (47)}$$

$$PaO_2 = 7.6 * (10.4 - (0.035 * age) \text{ (48)}$$

Several theories exist about these equations and they sometimes contradict each other: for example, according to Guenard et al., PaO_2 decreases with age until age 70 years, and then stabilises (49), while Sorbini et al. state that the drop in PaO_2 after 70 years is about 0.43 mmHg per year (46), and Gothgen et al., reports that decreasing PaO_2 is independent of age (50).

b) Causes of hypoxaemia:

- Alterations in the quality of pulmonary ventilation (hypoventilation leading to increased $PACO_2$, decreasing PAO_2 and consequently PaO_2:

* Impaired central drive: Opioids, benzodiazepines, alcohol overdose, neurological and muscular weakness (51).

* Nerve supplying respiratory muscle: Guillain–Barre syndrome (52).

* Neuromuscular junction: Myasthenia gravis (53), Lambert–Eaton syndrome (54).

* Spinal cord level: Amyotrophic lateral sclerosis, cervical cord injury (55).

* Chest wall deformation: Kyphoscoliosis, thoracoplasty (56).

* Some cerebral haemorrhage (57).

- Lower PiO_2 (inspiratory pressure of oxygen):

As a decrease of FiO_2 (atmosphere rich in toxic gases such as: Fires, air pollution, normobaric hypoxic exposures, training in intermittent hypoxic exposure), or atmospheric pressure decreasing as in high altitude or stays in hypobaric chambers (58–60).

- Ventilatory/perfusion ratio (V/Q) mismatch (32,61):

* Low V/Q mismatch (62): Chronic obstructive pulmonary diseases, cystic fibrosis, interstitial lung diseases, pulmonary hypertension, asthma, bronchiectasis.

* V/Q near equal to zero: Pneumonia, atelectasis, intra-pulmonary shunt

* High V/Q mismatch (32): Pulmonary embolism. In this case, the high V/Q area receives less flow as blood is deflected to other areas. Consequently, the other areas receive greater blood flow, leading to the development of low V/Q and consequently hypoxaemia.

- Others: Effects of beta-2 agonists on ventilation/perfusion ratio. Beta-2 agonists can produce mild hypoxaemia by causing V/Q mismatch. A decrease in the V/Q ratio is due to the increased perfusion of poorly ventilated areas due to the salbutamol-induced release of hypoxic pulmonary vasoconstriction. In this case, the diversion of perfusion from well-ventilated areas creates areas with low V/Q ratios (61).

- Right to left shunt (62).

- Diffusion limitation (inflammation and fibrosis of the alveolocapillary membrane, low alveolar oxygen, and extremely short capillary transit time, pulmonary oedema, and advanced emphysema status) (32).Note: If oxygen is entirely absent, the condition is called **anoxia**.

c) Physio-pathologic effects of hypoxia-hypoxaemia:

When cells do not get enough oxygen, the production of ATP in cells decreases, and cellular functioning can be damaged (64). During acute hypoxia, the human body must adapt its metabolism to survive. Hypoxia leads to multiple physiological adaptations, which help to limit its harmful effects (65). These adaptations concern pulmonary ventilation on the one hand and both the pulmonary and peripheral circulation (blood flow and vasomotor activity) on the other hand (19), as well as vascular remodelling if hypoxia becomes chronic (66). Moreover, during chronic hypoxemia, erythropoietin is secreted by the peritubular cells of the kidney (but also in the spleen, liver, bone marrow, lung, and brain in small quantities). This glycoprotein hormone stimulates red blood cell production (erythropoiesis) in the bone marrow and increases the arterial content in oxygen(67).

(1) Ventilatory adaptation during hypoxaemia:

a) Generalities:

Changes in PaO_2 are detected by the peripherical chemoreceptors (carotid bodies and aortic bodies). The carotid bodies are a cluster of chemoreceptors cells located in the adventitia, near the bifurcation of the carotid artery (the carotid sinus is in this region) (figure 3A). The carotid bodies are composed of two types of cells: Glomus type I cells (peripheral chemoreceptors), and glomus type II cells (supportive cells) (figure 3B).

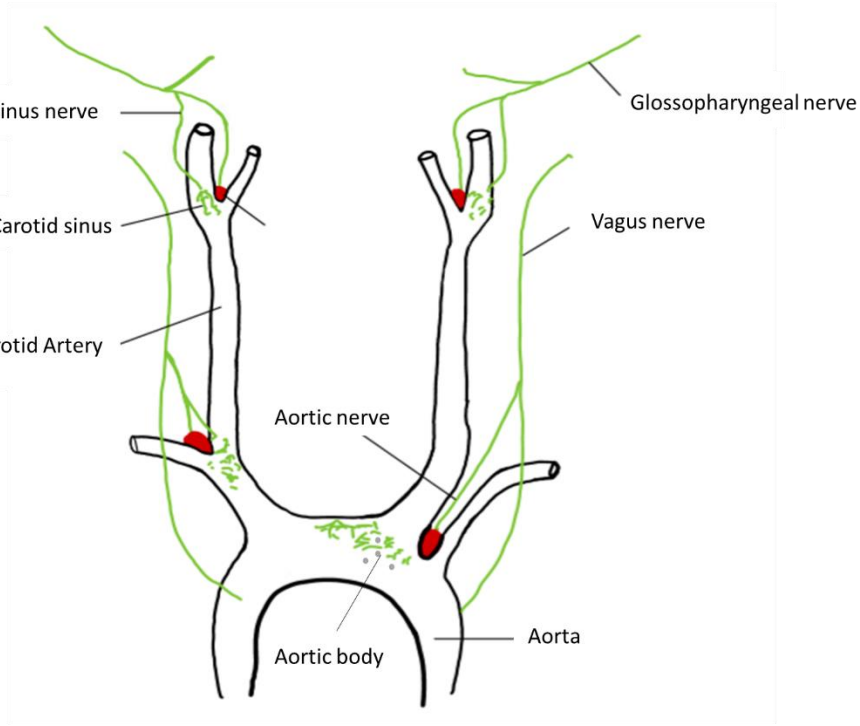


Figure 3A: Location of the carotid and aortic bodies

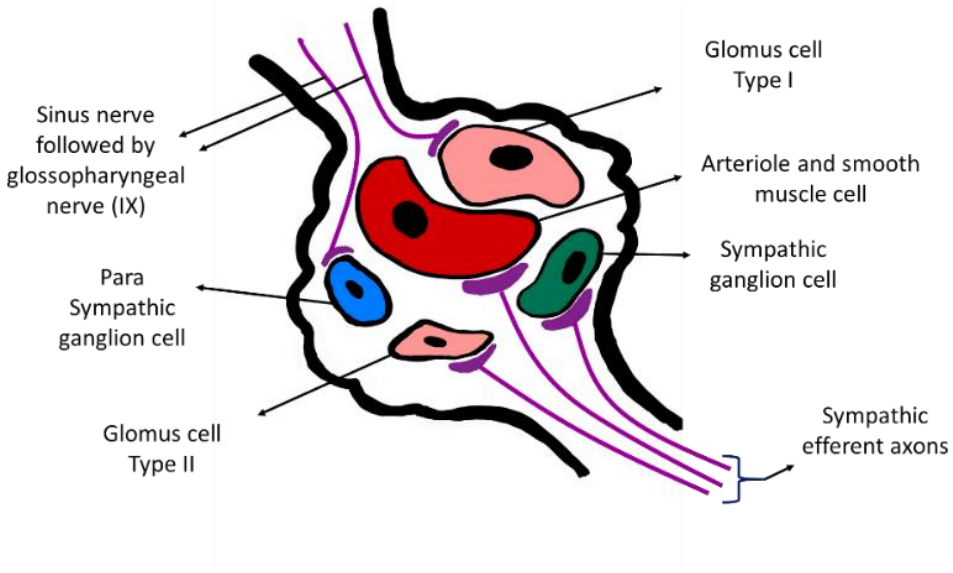


Figure 3B: Microscopic anatomy of the carotid body

When the body detects hypoxaemia, type I cells react by increasing pulmonary ventilation (which decreases $PACO_2$ and therefore immediately increases PAO_2 due to Dalton's law) by dopaminergic stimulation. This phenomenon is called acute hypoxic ventilatory response (AHVR). This response is a fundamental defence mechanism against hypoxaemia (68). In theory, this mechanism is triggered when PaO_2 levels go below ±60 mmHg (69). In this case, minute ventilation dramatically increases into the first minutes (70). After this period, minute ventilation starts to decline and reaches a plateau within ±20 minutes (figure 4). AHVR is time-dependent, and can be divided into two phases: The first phase (from 0 to 5 ± 3 min) of ventilation increases, followed by a second phase (from 5 to 20 min) of slow decline (71,72). Moreover, AHVR may be dependent on the pattern of previous hypoxic exposures and sustained CO_2 tensions (figure 5) (71,73,74). AHVR is initiated by the stimulation of type I glomus carotid bodies, neuroepithelial bodies present in the airway and, to a lesser degree, in the aortic cross, which are sensitive to arterial oxygen levels (75,76). In healthy subjects, the cardiovascular system coupling to this ventilatory function allows the supply of oxygen to the tissues.

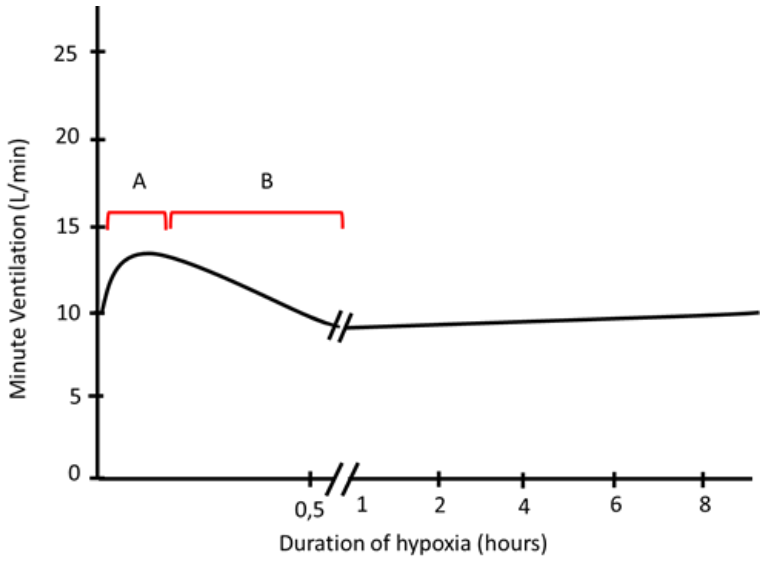


Figure 4: Minute ventilatory response during hypoxia. AHVR is divided into two phases: Phase A (from 0 to 5 ± 3min), where ventilation increases, followed by a second phase (from 5 to 20 min) of slow decline (Phase B)

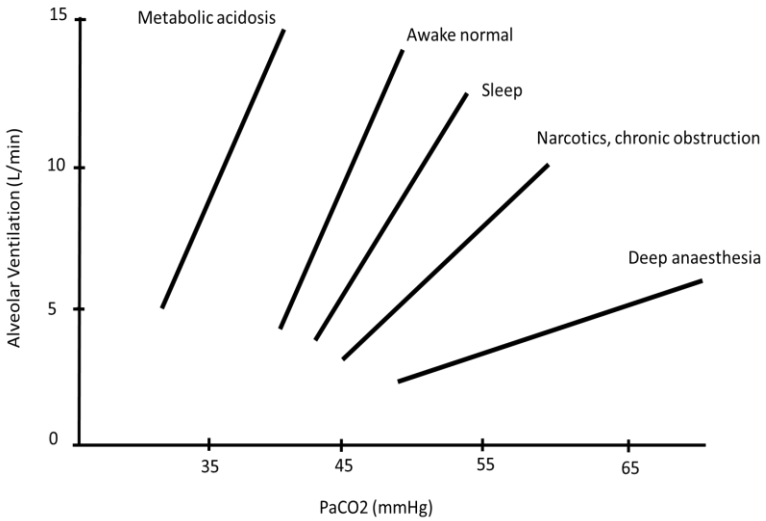


Figure 5A: The effects of sleep, narcotics, chronic pulmonary obstructive pulmonary disease, deep anaesthesia, and metabolic acidosis on the ventilatory response to carbon dioxide

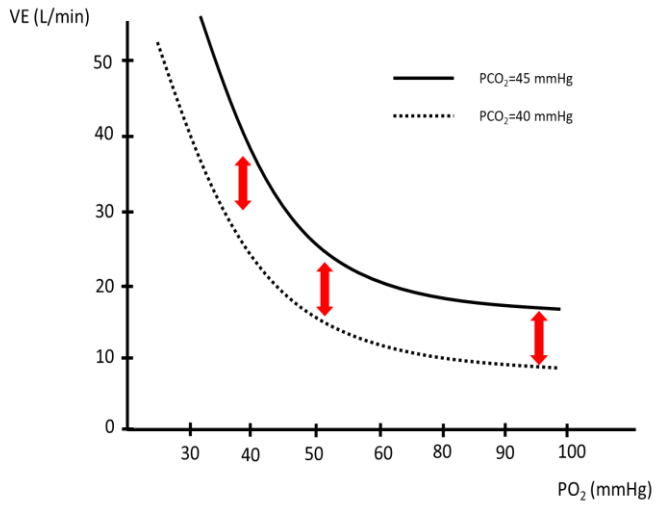


Figure 5B: Effect of $PaCO_2$ on ventilatory response to hypoxaemia

During hypoxaemia, transduction in the carotid body increases the production of transmitters from type I cells that activate afferent sensory channels. This production is dependent on voltage gated Ca^{2+} entry (membrane depolarisation). This response to hypoxaemia is initiated by the inhibition of specific O_2 sensitive K^+ channels (77,78). This depolarisation leads to stimulation of the carotid sinus nerve (29 mm in length ± and then the glossopharyngeal nerve (IX), which stimulate the cells in the nucleus of the mm) solitary tract (NTS) (79). The stimulation of NTS neurons generates a ventilatory response, expressed as increases in tidal volume and breathing frequency. At the same time, sympathetic and parasympathetic outflows increase cardiac output and vascular tone to maintain tissue PaO_2 enough to meet metabolic demands. Neurons in the NTS and contiguous medial medulla operate through multiple circuit pathways to regulate the tidal volume and respiratory frequency (by action of the phrenic nerve), as well as cardiac output and vascular tone (80).

The ventilatory response is impacted along with the inspiratory and then expiratory phase:

- Inspiratory drive: In the pre-Bötzinger complex of the ventral respiratory group (VRG), a cluster of pre-inspiratory “I-Driver” neurons excite motor neurons for the diaphragm, as well as the inspiratory muscles. These “I-Driver” neurons influence airway resistance in the tongue and oropharynx by stimulation of the hypoglossal nerve (cranial nerve XII) which acts on the genioglossus and geniohyoid muscles (76,81). For Lindsey et al. the inspiratory duration of I-Driver neurons can be shortened by carotid chemoreceptor stimulation. These observations have led to a model with parallel circuit mechanisms for tuning tidal volume and breathing frequency (figure 6A) (80,82).

- Expiratory drive: During hypoxia, active expiration is enhanced by the excitation of abdominal and intercostal expiratory muscles (transversus abdominis muscle, internal oblique muscle, external oblique muscle, and rectus abdominis muscle) (83). This activity is due to the excitation of both Bötzinger and adjacent retrotrapezoid nucleus/parafacial (RTN-parafacial) neurons. The parafacial-lateral tegmental field region is a site with complex neuronal interactions and where peripheral and central chemoreceptor influences converge; as noted above, it has been strongly implicated as a source of the expiratory drive (figure 6A and 6B) (84).

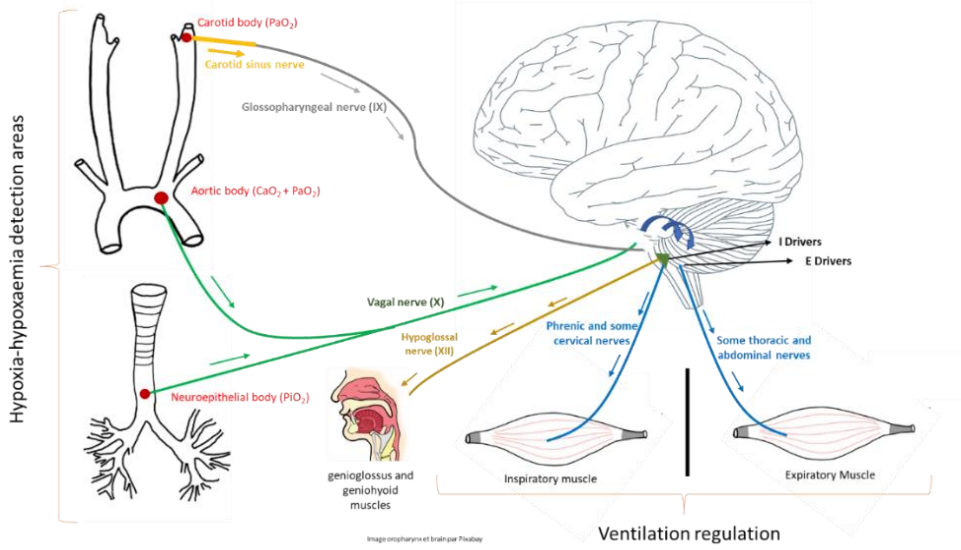


Figure 6A: Overview of structures implicated in ventilation regulation during hypoxia-hypoxaemia

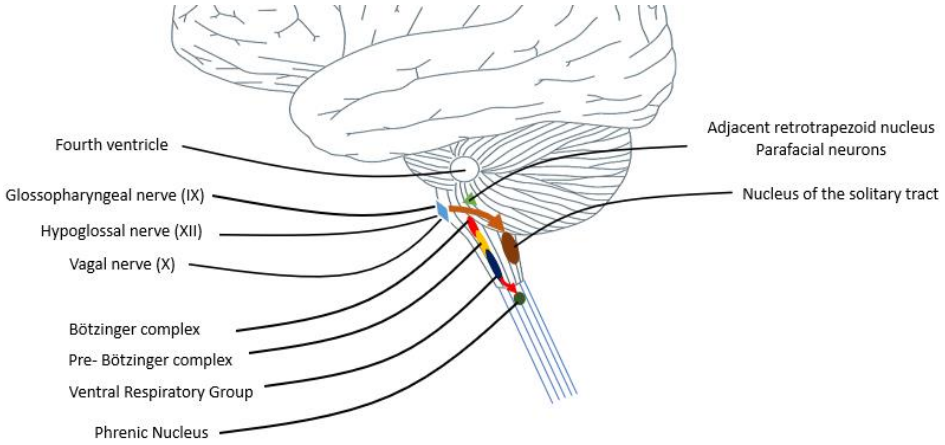


Figure 6B: Medulla oblongata organization for the ventilation control during hypoxia-hypoxaemia

The oxygen sensor implicated in hypoxaemia is haemoxygenase-2 (HO-2), which is a part of the BK channels complex of the carotid body's cells (BK channels). Indeed, in normal conditions, HO-2 reacts with oxygen to produce carbon monoxide (CO) as well as hydrogen

sulphide (H_2S) (78). In this last case, cystathionine gamma-lyase cleaves cystathionine into cysteine. Recent hypothesis highlights that hypoxaemia increases H_2S production in carotid bodies. This gas transmitter stimulates carotid bodies activities (85–87). Carbon Monoxide (CO) inhibits H_2S production by inactivation of cystathionine gamma-lyase. During hypoxaemia, HO-2 produces less CO, and consequently stimulates H_2S production, which blocks BK channels and therefore triggers a nervous signal which increases ventilation (figure 7) (77). In this case, the chemical reaction is:

$$Heme + O_2 \xrightarrow[\text{HO-2}]{} Biliverdin + Fe^{++} + CO$$

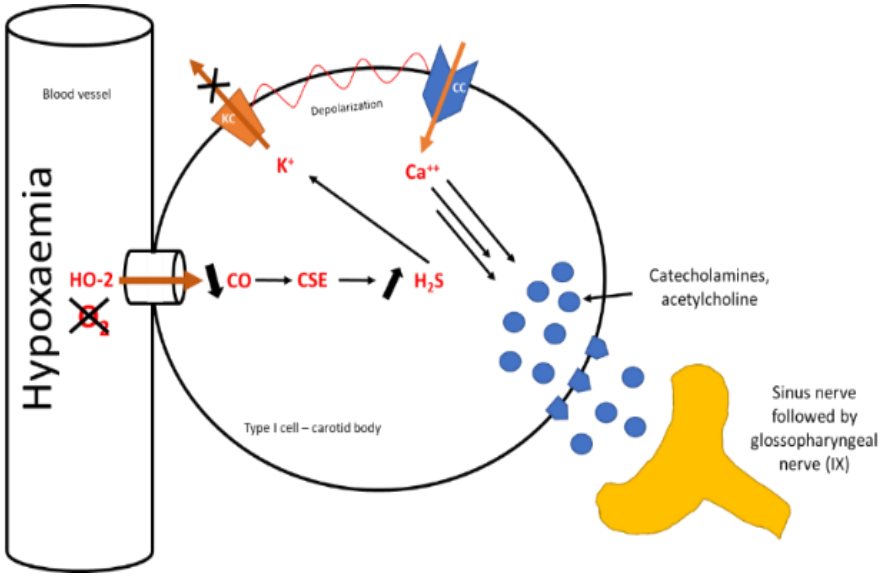


Figure 7: Heme oxygenase-2 (HO-2) signalling in hypoxic sensing by the carotid body (Type I cells). (CC) calcium channel; CO: carbon monoxide. H_2S: hydrogen sulfide; K +, (KC) potassium channel; CSE, cystathionine gamma-lyase

Note

About central oxygen sensing and gasping: Gasping is an abnormal ventilatory activity called "auto-resuscitative ventilation" phenomenon. Gasping probably occurs as a response to inadequate perfusion and/or hypoxia of the brain (88). This hypoxic ventilatory response is due to parallel actions on pre-Bötzinger complex I-Driver neurons (89). During this period, breathing is first enhanced and then depressed until apnoea or the cessation of breathing, followed by an auto-resuscitative gasping motor pattern. Gasping in patients in cardiac arrest (with ventricular fibrillation) is associated with successful resuscitation (90). Gasping ventilation increases intrathoracic, aortic and coronary perfusion pressures, which increase blood flow (88). The phrenic nerve is a mixed nerve (C3-C5 spinal nerve).

b) Structures involved in the regulation of ventilation:

Three groups of structures are involved in the regulation of ventilation: Central receptors, peripheral receptors, and effector muscles of the ventilatory response (76).

Central receptors:

They are located mainly in the brainstem (ventrolateral surface of medulla oblongata) close to the fourth ventricle (figure 6B) (91). These receptors detect changes in pH of cerebrospinal fluid. They are not in direct contact with arterial blood because the blood-brain barrier separates them from the fourth ventricle. Central receptors influence the regulation of $PaCO_2$. The bicarbonate ions and the H^+ protons do not go through the blood-brain barrier. However, CO_2 quickly diffuses from the blood to the cerebrospinal fluid. As a result, the pH of the cerebrospinal fluid will decrease, which will influence central receptors and modify the ventilatory pattern. Central receptors and peripheral receptors are sensitive to hypercapnia and pH changes, but central receptors are quantitatively more important than peripheral receptors. On the other hand, peripheral receptors respond more quickly than central receptors to hypercapnia. The ventilatory response during hypercapnia is increased in the case of hypoxaemia and decreased during sleep or anaesthesia (figure 5) (76). Ventilatory responses to hypoxia depend on the pattern and length of hypoxic exposure. Acute, prolonged, or intermittent hypoxic episodes can change ventilation. This change to ventilation can continue when hypoxic events cause its removal for seconds to years. However, the hypoxaemic ventilatory decline (HVD) is a decrease in ventilation that happens when hypoxaemia is sustained for 5 to 30 min in mammals. HVD occurs when hypoxaemia is maintained for at least 3 to 5 min in adult mammals and can continue for as long as eight weeks in humans during sustained hypoxaemia, for example during a stay at altitude (72,92).

Peripheral receptors:

There are two types of these receptors: chemoreceptors and mechanoreceptors (93).

- Chemoreceptors inform the central controllers of changes in PaO_2, pH, and, to a lesser extent, $PaCO_2$. There are two types of chemoreceptors: Carotid bodies and aortic bodies.

- Carotid bodies (carotid glomus or glomus carotidum) are the most important peripheral chemoreceptors. These are small clusters of receptors located in the adventitia, close to the bifurcation of the carotid artery. They are sensitive to a decrease in PaO_2, as well as to pH and PCO_2, but only secondarily. Other factors can stimulate carotid bodies, such as elevated temperature or hypoperfusion, which lead to an increase in minute ventilation, as often observed in clinical situations. This mechanism during hypoperfusion is probably due to stagnant hypoxia (94). The temperature amplifies the ventilatory response to both hypoxia and acidosis. Carotid bodies are also stimulated by nicotine and acetylcholine. The information is transmitted to the respiratory centres of the brainstem via fibres of the glossopharyngeal nerves (cranial nerve IX).

- Aortic bodies: These are located on the aortic arch and monitor oxygen concentrations closer to the heart. In contrast to carotid bodies, they are sensitive to drops in arterial oxygen content (CaO_2), as well as decreases in PaO_2 and pH. The information is transmitted to the respiratory centres of the brainstem via fibres of the pneumogastric nerve (Vagal nerve X).

- Carotid bodies are particularly stimulated when the PaO_2 drops below ±60 mmHg, which is the value from which the decrease in arterial oxygen content becomes linear on the dissociation curve of Hb. Both the carotid and aortic bodies increase sensory discharges during hypoxaemia (95). Concerning the response to hypoxaemia, carotid bodies are more sensitive to hypoxaemia then aortic chemoreceptors. When the arterial oxygen content decreases without a decrease in PaO_2 (CO poisoning, Hb drop, methaemoglobinaemia), carotid bodies do not detect this dramatic decrease in circulating oxygen, since the PaO_2 remains unchanged. Therefore, in this case, only the aortic corpuscles will transmit information to the respiratory centres, delaying the physiological alarm. The response time for carotid bodies is extremely short within the range of one to three seconds.

- Mechanoreceptors: They can be grouped into four general categories:

a) Epithelial receptors: Rapidly adapting discharge (polymodal receptors). These are composed of small-diameter myelinated fibres and are localised in the airway's epithelium, especially at the level of the carina of the bronchi. Their stimulation causes coughs, mucus secretion, polypnoea, and bronchospasm (96).

b) Stretch receptors: These are deep and slowly adapting, composed of large-diameter myelinated fibres. They respond to the stretching of the airway wall during bronchial distension (Hering Breuer reflex).

c) Musculotendinous receptors (muscle spindle and Golgi tendon organs).

d) J-receptors (pulmonary C-fibre receptors):

These are located within the alveolar walls, particularly in the capillaries of the lung. J-receptors are innervated by fibres of the Vagal nerve (X) (97). They respond during pulmonary oedema, pulmonary emboli, pneumonia, and congestive heart failure. In some cases, they may be stimulated by hyperinflation of the lung (98,99). The stimulation of J-receptors causes an increase in breathing rate and the sensation dyspnoea (96).

e) Specialized receptors:

These are stimulated for taste and swallowing. The stimulation of any group of receptors may cause changes in breathing, bronchoconstriction, airway mucus secretion, cardiovascular response, and laryngeal constriction.

To this list of mechanoreceptors, we can add two other systems which control ventilation:

- The limbic system: Emotions as well as voluntary cerebral cortex can influence ventilation.

- Effector muscles of the ventilatory response, such as respiratory muscles, work as an automatic feedback loop system.

Note: Cyon's nerve and Hering's nerve are the nerves that regulate cardiac activity (frequency and vascular pressure) during hypertension (baroreceptor reflex concept) (100).

Their receptors are located in the right atrium, the carotid sinus (and carotid body) and the aortic cross, and they detect vascular pressure variations. Nerve signals from the right atrium are delivered to the ventral surface of medulla by Cyon-Ludwig's aortic nerve (101). Nerve signals from the carotid sinus are routed to the ventral surface of the medulla by the carotid sinus Hering's nerve (a branch of the glossopharyngeal nerve) (102,103), whereas nerve signals from the aortic cross are routed to the ventral surface of medulla by the pneumogastric nerve (X).

(2) Pulmonary and peripheral circulation adaptation during hypoxaemia:

The vasomotricity of the systemic and pulmonary circulation are antagonistic (104). During hypoxaemia, the systemic circulation vasodilates, whereas the pulmonary circulation

vasoconstricts (PCV) (105). These processes are referred to in different ways: “Hypoxic vasodilation” (in the peripheral circulation) and “hypoxic vasoconstriction” (hypoxic pulmonary vasoconstriction: HPV), which is also called the Von Euler-Liljestrand mechanism (106). The goal of these processes is to shunt blood flow toward tissues that have a greater need for oxygen (systemic hypoxic vasodilatation) and away from poorly ventilated areas towards well-ventilated areas (figure 8) (19,107). HPV can substantially improve pulmonary gas exchange and improve arterial oxygenation during respiratory failure (108). Recently, a new hypothesis about transmitting alveolocapillary signals has been proposed. This hypothesis speculates that the ideal site for oxygen sensing might be at the alveolocapillary level rather than only at the capillary level. This alveolocapillary signal would lead to a subsequent retrograde propagation to upstream arterioles via connexin 40 (Cx40) endothelial gap junctions. The transformation of endothelial depolarisation into vasoconstriction involves endothelial voltage-dependent α1G subtype Ca^{2+} channels, cytosolic phospholipase A2, and epoxyeicosatrienoic acids (109–111). However, in condition’s pathophysiology, it is well established that major substances who acts in pulmonary vasomotricity are nitric oxide, prostacyclin (pulmonary vasodilators) and thromboxane, endothelin-1 (pulmonary vasoconstrictors) (112).

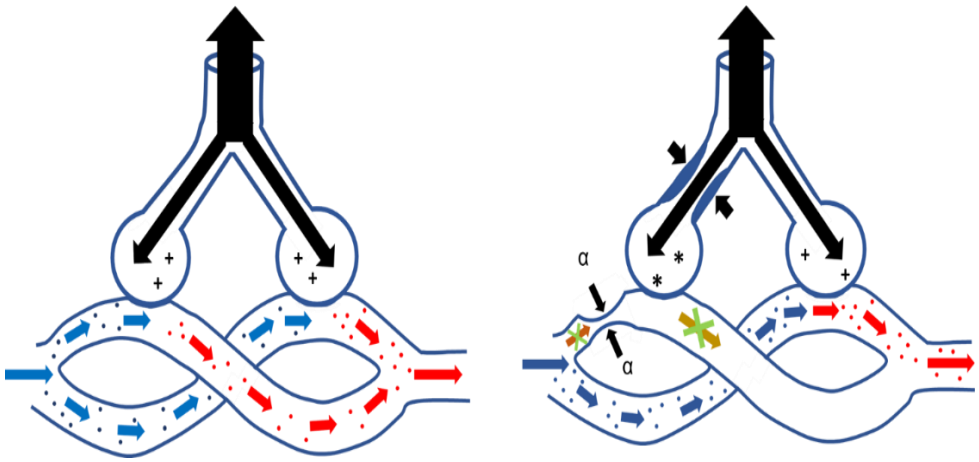


Figure 8: Von Euler-Liljestrand mechanism. When an alveolar area is poorly ventilated (**), the blood flow is shunt toward well-ventilated areas (+) thanks to vasoconstriction (α)

Note: Arrows and blue dots represent CO_2 in the blood. Arrows and red dots represent O_2 in the blood.

Pulmonary circulation:

Pulmonary circulation is a low-pressure system. Indeed, in healthy adults, the mean systolic and diastolic pressures in the pulmonary artery is about 19-10 mmHg (113). Because the blood flow only needs to reach the top of the lungs, the pressure required is lower; consequently, the walls of the pulmonary artery are thin (114). There is very little smooth muscle and relatively low resistance compared to the systemic circulation. Therefore, pulmonary artery walls are very distensible and compliant. The estimated pulmonary capillary diameters are around six micrometres (115).

The pulmonary circulatory flow is dependent on systemic blood, reaching it through the right heart as well as the afterload, which is determined by the aortic pressure and systemic vascular resistance (116). Moreover, the pulmonary circulation is also influenced by alveolar compression, gravity, body position, and lung volume (76). The pulmonary vasculature can be physiologically divided into extra- and intra-alveolar vessels (117). Their cross-sectional area varies depending on the lung volume, increasing in extra-alveolar vessels during expiration (a decrease in vascular resistance) and decreasing in intra-alveolar vessels (an increase in vascular resistance) (76). The pulmonary circulation vasomotricity (PCV) is also influenced by nitric oxide (NO) and endothelin-1 (ET-1), which are natural counterparts in vascular function (118). On the one hand, NO is a potent vasodilator, formerly known as endothelium-derived relaxing factor (EDRF) (119). On the other hand, ET-1 is the most potent of the endogenous vasoconstrictors (118).

Other factors such as angiotensin can increase the pulmonary artery tone, whereas acetylcholine have a relaxant effect on smooth muscle and can decrease the pulmonary artery tone (116,120,121). The PCV is further increased when the pulmonary vasculature is exposed to hypercapnia. The combined hypoxic and hypercapnic effects are additive on pulmonary vasoconstriction (122). This mechanism is due to the stimulation of chemoreceptor cells such as the as well as neuroepithelial bodies in the airways and the direct response of vascular smooth muscle cells to hypoxia (19). Carotid bodies contain neurotransmitters (mainly catecholamines and acetylcholine), whereas neuroepithelial bodies are neuronal cells in relation with the vagal nerve initiating information to the respiratory centres by the release of neuromodulators (i.e. serotonin) (123,124). Recently, studies have suggested that pulmonary artery smooth muscle cells constitute both the sensitive and transducer parts of the hypoxic signal as well as its contractile effector (116,125). This HPV response to hypoxia is further augmented during hypercapnia (116). However, if the HPV persists, this results in an increase in pulmonary resistance, which can induce pathological chronic pulmonary hypertension. Adrenergic and cholinergic nerve fibres seem to be involved in the HPV phenomenon. The adrenergic system contributes mainly to maintaining the initial resting tone needed for HPV (126).

The response of vascular smooth muscle cells can be explained as hypoxic pulmonary vasoconstriction (HPV), occurring within seconds of the onset of hypoxia. These cells, increase their intracellular Ca^{2+} concentration and contract (127), mainly through the activity of membrane K^+ channels. Hypoxia-induced K^+ influx in type I cells results in membrane depolarisation and consequently, in calcium influx (128). It should be noted that increasing cerebral blood flow by vasodilation is limited by hyperventilation, which causes cerebral vascular constriction (58). Peripheral vessels dilate, whereas the pulmonary vessels conduct blood to well-ventilated regions, thereby matching ventilation to perfusion. This response is intrinsic to pulmonary vasculature smooth muscle cells and is initiated by inhibition of one or several K^+ channels, which set the membrane potential (129–131). The resulting depolarisation activates voltage gated Ca^{2+} channels, which raises the cytosolic calcium levels and result in myocyte contraction. The K^+ channels are the effectors of hypoxic pulmonary vasoconstriction. However, their role is unclear in this phenomenon. It seems that mitochondria, through the production of R.O.S., could modulate the activity of some K^+ channels, as these channels tend to open when oxidized and close when reduced (figure 9 A and B) (19).

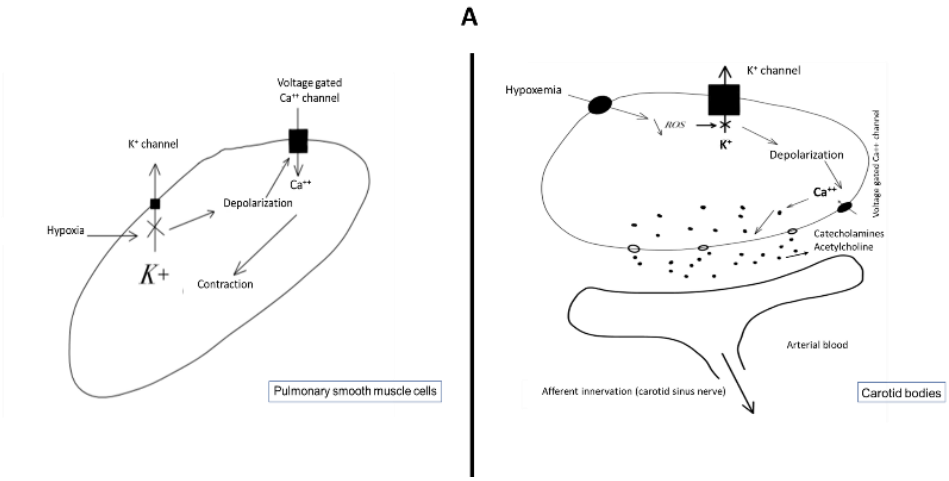


Figure 9A: Response of vascular smooth muscle cells to hypoxia in pulmonary smooth muscle cells and response of carotid bodies. In this case, afferent innervation is stimulated by secretion of acetylcholine or catecholamine.(19) Modified from Michiels

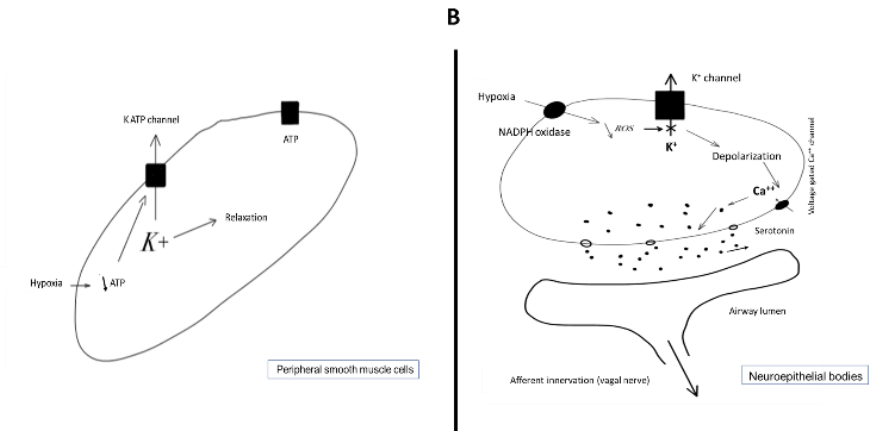


Figure 9B: Schematic representation of the response of vascular smooth muscle cells to hypoxia in peripheral smooth muscle cells Response of Neuroepithelial bodies. In this case, afferent innervation is stimulated by secretion of serotonin. (132) Modified from Michiels

Peripheral circulation:

Hypoxaemia leads to changes in blood flow in the coronary and brain circulation by vasodilation. The mechanism is triggered when the PaO_2 is below 70 mmHg (115). Different mechanisms are implicated:

Coronary flow: Adenosine plays a role in blood flow regulation through vasodilation. This molecule inhibits adenylate cyclase through G_i proteins, which limit myocardial expenditure during hypoxia (58).

Cerebral flow: Acute hypoxia leads to an increase in cerebral blood flow via the direct effects on vascular cells of cerebral arteries and arterioles (68). The hypoxia-induced drop in ATP levels opens KATP channels on smooth muscle cells, causing hyperpolarisation and vasodilation (133). Also, hypoxia rapidly increases the local production of nitric oxide and adenosine, further promoting vasodilation (119,134,135).

Note: Chronic hypoxaemia leads in hyperplasia of the glomus of type I cells. The type 2 cells appear to be a source of the increased number of glomus cells.(94) Hypoxia-inducible factor-1α (HIF-1α) is the master transcriptional regulator of cellular response to chronic hypoxia (136,137). HIF-1 induces the transcription of vascular endothelial growth factor (VEGF) that is involved in biological processes such as angiogenesis and erythropoiesis. These molecules promote and increase oxygen delivery to hypoxic regions. These processes increases the arterial content in oxygen (125,138–140).

Chapter 4: Hyperoxia-Hyperoxaemia

a) Generalities:

Hyperoxia is an increase in the alveolar pressure of oxygen (PAO_2) which is mainly dependent on FiO_2 value (141), whereas hyperoxaemia is defined as an increase in the arterial pressure of oxygen (PaO_2). To determine hyperoxia-hyperoxaemia, different thresholds are used to define them (Table 2).

Hyperoxia definition	
Anzueto et al. (142)	FiO_2 >0.95
Pilcher et al. (143)	FiO_2 = 1
Baleeiro et al. (144)	FiO_2 >0.95 (for days)
Zangl Q et al. (145)	FiO_2 >0.60
Davis et al. (145)	FiO_2 >0.95
Munoz et al. (146)	FiO_2 >0.80
Angelos et al. (147)	FiO_2 = 1
Goren et al. (148)	FiO_2 >80%
Angusamy et al. (149)	FiO_2 >85%
Cox et al. (150)	FiO_2 >90%
Warner et al. (151)	FiO_2 >85%
Jamieson et al. (152)	FiO_2 100%
Pryor et al. (153)	FiO_2 = 80%
Hyperoxaemia definition	
Bellomo et al. (154)	PaO_2 >300 mmHg
De Graaff A. et al. (155)	PaO_2 >120 mmHg
Damiani et al. (156)	PaO_2 >100 mmHg
Kilganon/Wang/Elmer et al. (157)	PaO_2 >300 mmHg
Quintard et al. (158)	PaO_2 >150 mmHg
Lloyd et al. (159)	PaO_2 >150 mmHg

Table 2: Author definitions of hyperoxia (by FiO_2 threshold) and hyperoxaemia (by PaO_2 or SpO_2 threshold)

In the early 19th century, Lorrain Smith (1862-1931) and Paul Bert (1833-1886) showed that oxygen at increased pressures was highly toxic for living matter (161,162). Clinical recognition of oxygen toxicity is relatively recent. Oxygen therapy has been liked to retrolental fibroplasia in premature infants also called: Retinopathy of prematurity (163). In the same period, Pratt et al. reported the first observation of hyperoxic acute lung injury in humans who receive high concentrations of oxygen (under normobaric conditions) for extended durations (164).

In the early 1970s, it was shown that breathing 50–100% oxygen (at standard atmospheric conditions) was potentially toxic to the lungs (165), but also the eyes, liver, heart, kidneys, blood, and endocrine system (166). It appears that pulmonary tissue is one of the tissues at the highest risk of damage from high-inspired oxygen concentrations (167). In this case, the damage caused to pulmonary tissue resembles the changes seen in acute respiratory distress syndrome (ARDS) and is strongly correlated to the concentration of oxygen (when the FiO_2 is above 0.50) and the duration of exposure (168).

A study of 3524 blood gas samples in oxygenated patients in a single hospital found that 41% of these samples exhibited hyperoxaemia (PaO_2 >120 mmHg) (35).

Excessive oxygen has detrimental effects because of oxidative stress and inflammation. In this case, this can lead to the formation of oxidizing free radicals: Reactive oxygen species (ROS), such as superoxide anions, hydrogen peroxide (H_2O_2), and hydroxyl radicals (OH) (figure 10 and 11). ROS can lead to cellular necrosis or apoptosis (152). ROS seems to play a role in the mechanism of reperfusion injury (127,169). The mitochondria is a primary intracellular source of ROS (170). In animals, prolonged hyperoxia causes histopathological changes like those seen in ARDS. The mechanisms by which hyperoxia causes lung injury remain incompletely understood (171).

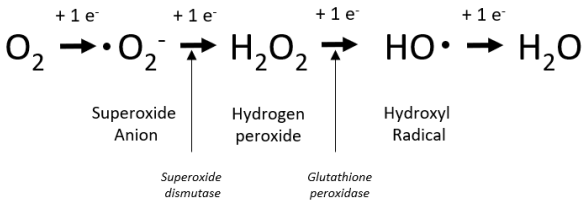


Figure 10: Steps in the formation of reactive oxygen species (ROS)

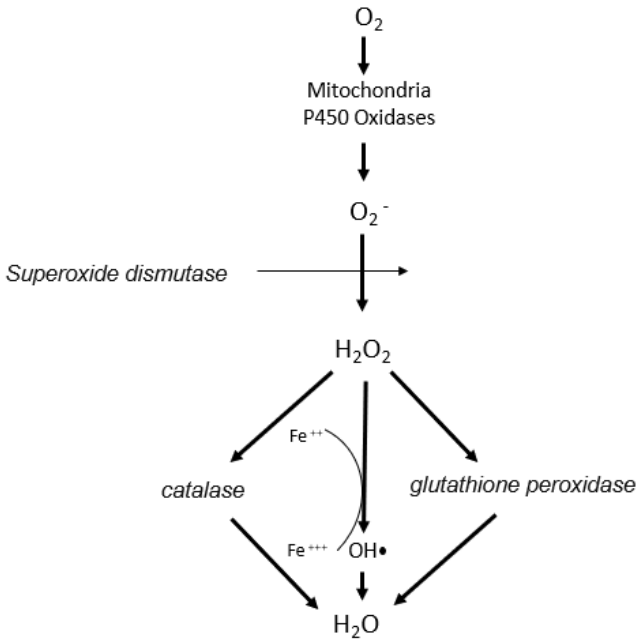


Figure 11: Steps in the formation of reactive oxygen species (ROS)

b) Pulmonary and vascular effects of high oxygenation:

- Pulmonary effects: Oxygen excess leads to pulmonary inflammation (172). In healthy volunteers, exposure to high oxygen concentrations for 6–25 hours provokes histological signs of tracheitis and alveolitis (173). A study has shown that hyperoxia causes significant bronchoconstriction, whereas hypoxia causes bronchodilatation in human airways (174). The use of oxygen may have unrecognised deleterious effects on the airway. Excessive treatment with oxygen in patients with COPD may enhance bronchoconstriction, Va/Q mismatch (by suppression of the hypoxic vasoconstriction effect), and could exacerbate CO_2 retention (174).

- Vascular and cardiac output effect: Hyperoxaemia decreases cardiac output by decreasing the heart rate and stroke volume (173). Under high O_2 concentrations, systemic vasoconstriction occurs, particularly in cerebral and coronary circulations. Data suggest that hyperoxaemia may redistribute cardiac output towards the hepato-splanchnic system and may shift energy metabolism towards preferential carbohydrate utilisation, thereby increasing mitochondrial respiratory efficiency (i.e., the ratio of ATP production to O_2 consumption) (173).

c) Potential harms effects of using high oxygenation during some pathologies:

- Acute myocardial infarction:

Oxygen therapy is still used in the management of patients with suspected acute myocardial infarction. However, supplemental O_2 breathing induces coronary vasoconstriction. Recent studies have examined the efficacy of supplemental oxygen in normoxaemic patients (175). These studies highlight the lack of benefit of routine oxygen therapy in patients with acute myocardial infarction with normal oxygen saturation levels (176).

European Resuscitation Council guidelines recommend an ''O_2 saturation of 94–98%, or 88–92% if the patient is at risk of hypercapnic respiratory failure" (177). Oxygen therapy does not reduce the risk of all-cause mortality, recurrent ischaemia or myocardial infarction, heart failure, or arrhythmias compared with no supplemental oxygen therapy for patients with acute myocardial infarction and normal oxygen saturation (178). In a meta-analysis, including eight RCTs with a total of 7998 participants (3982 and 4002 patients in O_2 and air groups, respectively), the authors concluded that supplemental O_2 therapy was not associated with important clinical benefits (179). The meta-analysis of Casso et al. shows that the routine use of oxygen therapy in patients with pulmonary congestion and SaO_2 <90% require oxygen therapy and SaO_2 monitoring to correct hypoxaemia and may require periodic blood-gas assessment (180). Another study has evaluated the effects of supplemental O_2 in patients with ST-elevation myocardial infarction (STEMI) accepted for acute percutaneous coronary intervention (PCI). The authors found no effect of high-flow oxygen compared with room air on the size of ischaemia before PCI, myocardial salvage, or the resulting infarct size (181). Recently two systematic reviews highlighted there is no evidence to uses oxygen therapy during acute myocardial infarction (182). Moreover, excessive O_2 levels may be harmful, resulting in greater infarct size and increased mortality (183). High arterial oxygenation is also associated with a large vascular response such as mean reductions in stroke volume and cardiac output, reduction in heart rate, increased peripheral vascular resistance, coronary artery vasoconstriction, and reduced coronary blood flow (184–187). The AVOID (Air Versus oxygen in Myocardial Infarction) study suggest that supplemental oxygen therapy in patients with ST- (STEMI) may be harmful to patients who are not hypoxaemic. This study highlights that high oxygen concentration increases myocardial injury, recurrent infarction, arrhythmias, and residual infarct size in non-hypoxaemic patients with myocardial infarction (175).

- Stroke:

Hyperoxaemia reduces cerebral blood flow (42). Clinical trial data evaluating the effects of different inspired oxygen levels are even more sparse in acute ischemic stroke (188). Oxygen therapy may be of benefit if administered within the first few hours of onset, but evidence also exists that it may result in increased harm (higher 1-year mortality) with continued administration (189). Oxygen therapy in stroke remains controversial. The clinical functions are improved transiently if high-flow oxygen therapy is started within 12 hours after the onset of ischemic stroke (190). Bravata et al. suggest that hypoxaemia may be underdiagnosed in routine practice. These authors find that only 47% of patients with hypoxaemia had every episode treated with oxygen, indicating this component of post-stroke care could be improved (69). Despite experimental evidence, hyperoxaemia seems deleterious in patients with stroke, those with ischemic brain injury (191).

- During resuscitation in cardiac arrest:

The benefit of supplemental oxygen during cardiopulmonary resuscitation remains uncertain (192). Some studies about oxygenation during cardiac arrest found that hyperoxaemia (PaO_2 >300 mmHg) is an independent predictor of poor outcome (193). However, others reported no association between blood oxygenation and neurological recovery and suggested ventilating cardiac arrest patients with 100% oxygen (194). In a systemic review and meta-analysis of animal studies, Pilcher et al. found that the administration of 100% oxygen therapy is associated with a worse neurological outcome than lower oxygen concentrations in animal models of cardiac arrest (143). There is evidence that hyperoxaemia leads to impairment in health status. The following issues must be clarified: What is the true PaO_2 threshold? Is it possible to administrate titrated oxygen therapy during cardiac reanimation? What is the time from which hyperoxaemia becomes toxic? Although the impact of high PaO_2 on survival needs to be further evaluated, in the absence of additional data, it still seems prudent to use 100% oxygen during cardiac, pulmonary resuscitation (193,195).

- Following cardiac arrest:

Kilgannon et al. highlight that among patients admitted to the ICU following resuscitation from cardiac arrest, arterial hyperoxaemia (PaO_2 >300 mmHg) was independently associated with increased in-hospital mortality compared with either hypoxaemia or normoxaemia (157). In a retrospective cohort study of more than 6,000 patients following resuscitation from cardiac arrest, hyperoxaemia (defined as a PaO_2 >300 mmHg) was associated with a significantly (OR: 1.8) worse outcome than both normoxaemia (60–300 mmHg) and hypoxaemia (< 60 mmHg - OR: 1.8) (157). In a retrospective analysis, Janz et al. found that higher levels of the maximum measured PaO_2 (254 mmHg; interquartile range,

172-363) is associated with increased in-hospital mortality and poor neurological status on hospital discharge (196). In a meta-analysis, hyperoxaemia (PaO_2 >300 mmHg) appears to be correlated with increased in-hospital mortality (197). Nevertheless, these results should be interpreted cautiously because of the high heterogeneity and a limited number of studies analysed. In a meta-analysis, Helmerhorst et al. conclude that arterial hyperoxaemia after cardiac arrest was associated with poor hospital outcome (198). However, considering the substantial heterogeneity of the included studies and the lack of a clinical definition, more evidence is needed to provide optimal oxygen targets to critical care physicians. For Elmer et al., severe hyperoxaemia (PaO_2 >300 mmHg) was independently associated with decreased survival to hospital discharge (199). Moderate (PaO_2: 101-299 mmHg) hyperoxaemia was not associated with decreased survival and was associated with improved organ function at 24 h (199). In the same way, Damiani et al. concluded in a meta-analysis that hyperoxaemia might be associated with increased mortality in patients resuscitated from cardiac arrest, but these results are limited by the high heterogeneity of the included studies (156). However, these results were contradicted in a multi-centric randomised prospective study concluding that hyperoxaemia had no independent association with mortality (200). Most of the studies converge towards the same results: Hyperoxaemia has a poor outcome after cardiac arrest. Unfortunately, several studies included in this meta-analysis are heterogeneous (154).

- Haemorrhagic shock:

During major haemorrhagic shock, cells oxygen delivery is impaired. Therefore, adequate oxygen administration is primordial to avoid detrimental of patient health status. Hyperoxaemia seems to alleviate the adverse effects of tissue hypoxia during haemorrhagic shock. However, excessive oxygenation may cause health deterioration: Infection and organ failure by oxidative injury. Xin Luo et al. analysed a novel oxygen administration strategy called hypoxaemic resuscitation, which is the gradual acclimatisation from hypoxaemia to normoxaemia (194). It was believed that strategy could reduce oxygen substrate for free radical production and oxidative stress (201).

- Neonatal resuscitation:

Since the 1950s, the practice of resuscitating neonates with 100% oxygen has been discontinued and replaced by room air for initial resuscitation (202). Studies have demonstrated that the use of 100% oxygen during the resuscitation of human neonates could increase mortality, myocardial injury and renal injury, and even be associated with a higher risk of childhood leukaemia and cancer (203,204). Furthermore, similarly to ischaemia-reperfusion injury, the use of 100% oxygen in the new-born following an asphyxiating perinatal event is thought to result in cerebral damage. Such is the evidence

base that resuscitation guidelines in neonates now advise that ventilatory support of term infants should start with air. For preterm infants, either air or a low concentration of oxygen (FiO_2 up to 30%) should be used initially. If oxygenation (ideally guided by oximetry) remains unacceptable despite effective ventilation, the use of oxygen supplementation should be considered (205–207).

- Retinopathy of prematurity (ROP):

The immature retinas of preterm neonates are sensible to hyperoxia that disrupt neurovascular growth, leading to retinopathy of prematurity (ROP) (208). Many risk factors can lead to ROP: High oxygen concentration is the most frequently identified risk factor in ROP (202). Hyperoxia leads to the suppression of vascular endothelial growth factor results in the arrest of retinal vascularisation. Afterwards, the increasingly metabolically active, yet poorly vascularised, retina becomes hypoxic, stimulating growth factor-induced vasoproliferation, which can cause retinal injury. A study has examined the effects of 89-94% SaO_2 versus 96-99% SaO_2 on ROP incidence, but the authors found no significant difference. The Surfactant, Positive Airway Pressure, Pulse Oximetry Randomised Trial (SUPPORT) and Benefits Of Oxygen Saturation Targeting Study II (BOOST-II) compared 85-89% SaO_2 vs 91-95% SaO_2 and found that lower oxygen levels were associated with increased mortality, but lower rates of ROP. Another study also compared 85-89% SaO_2 vs 91-95% SaO_2 but found no significant difference in either the rate of death or disability between the two groups (210–214).

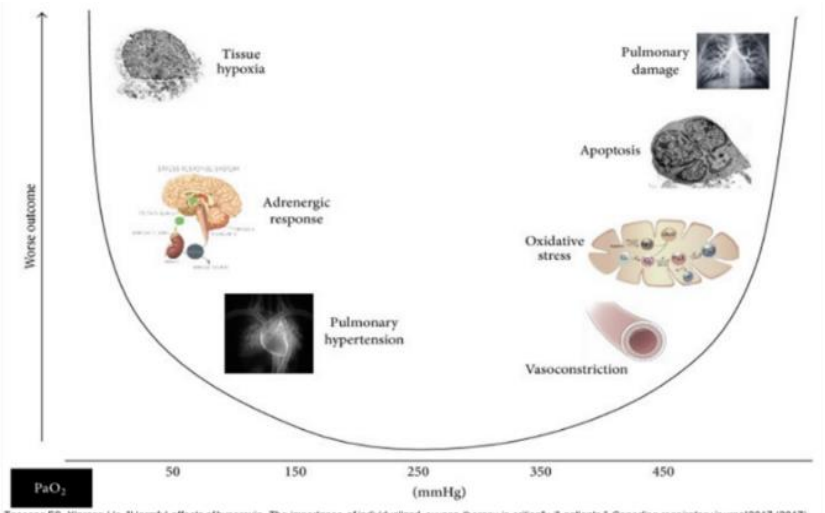
- Sepsis:

The use of hyperoxia in patients with sepsis is controversial (215). Hyperoxaemia stimulates ROS production and could worsen organ function in these patients (216). In a prospective pilot study, 83 sepsis patients admitted to the emergency department were treated with FiO_2 of 40% instead of 60-80%. The study authors found that 8% of the hyperoxic patients died in the hospital versus 6% with normoxia (217).

In an animal model of sepsis, Rodriguez et al. suggested that oxygen therapy greatly influences the progression and clinical manifestation of multiple system organ dysfunctions in experimental sepsis. They suggest that oxygen therapy should be carefully managed in septic patients to minimize their deleterious effects (218–221).

- Perioperative period:

For many clinicians, hyperoxia could reduce wound infection incidence during the intraoperative period (173). However, a meta-analysis with a high studies did not suggest that supplemental oxygen substantively reduces wound infection risk (figure 12) (222,223).



Vincent JL, Taccone FS, Xinrong He. "Harmful effects of hyperoxia. The importance of individualized oxygen therapy in critically ill patients." *Canadian respiratory journal* 2017 (2017).

Figure 12: Schematic showing U-shaped association of PaO_2 with outcome (220)

- Intensive Care Unit:

In 13 prospective randomized trials, Grensemann et al. did not find evidence indicating an advantage of oxygen supplementation in non-hypoxemic ICU patients. The only exception would be during carbon monoxide intoxication (224).

In 2018, Siemieniuk RAC et al. have published a working guideline to guide oxygen therapy in critical care. The authors' conclusions are as follows(225):

-High supplemental oxygen can increase mortality in hospital settings

-Many practitioners administer supplemental oxygen to patients regardless of their blood oxygen saturation

-During oxygen therapy, the peripheral capillary oxygen saturation (SpO_2) should be below or equal to 96% (strong recommendation)

-During acute myocardial infarction or stroke, oxygen therapy in patients with SpO_2 ≥90% should not be administered (strong recommendation)

-The authors report that “a target SpO_2 range of 90-94% seems reasonable for most patients and 88-92% for patients at risk of hypercapnic respiratory failure; use the minimum amount of oxygen necessary”

- Paraquat poisoning:

Oxygen is hazardous during paraquat poisoning (226). However, the range of oxygen concentrations over which this harmful interaction might occur has not been established.

- Antineoplastic agent bleomycin:

Oxygen potentiates the effect of bleomycin and may potentiate lung injury (ARDS) (227,228). In these cases, a lower oxygen saturation target range should be accepted (88% to 92%).

- Mendelson syndrome (aspiration pneumonia):

Oxygen may potentiate lung injury during aspiration of acids in animals. In humans with a Mendelson syndrome, the target saturation range should be 94–98%, but it would appear prudent to aim the lower half of the target range (19). Recently, Meeran Kunju et al. have proposed using oxygenation by HFNC to treat aspiration pneumonia as an alternative to non-invasive ventilation (229).

- Absorption atelectasis(AA):

During high FiO_2 supplementation, the lungs can be filled with oxygen (230). In this situation, oxygen diffuses quickly through the pulmonary venous blood. Consequently, there is not enough gas left in the alveoli to maintain patency, which promotes alveolar collapse, known as AA (230). According to Reber et al., AA occurs during 100% oxygen supplementation in healthy anaesthetised adults (231). However, according to Akca et al., AA does not appear to occur in patients ventilated with 80% oxygen or less (232).

- COPD and obesity-associated hypoventilation:

Oxygen therapy can cause worsening hypercapnia in patients with obesity-associated hypoventilation (OAH), like the response observed in COPD (see the chapter on hypercapnia).

d) Controversy:

In 2011, authors highlighted that transitory normobaric hyperoxia followed by a return to normoxia could lead to increasing hypoxia-inducible factor 1 (HIF-1), which increases erythropoietin concentration(233–235).

Chapter 5: Hypercapnia during oxygen therapy

Hypercapnia is defined when the $PaCO_2$ is above the normal range of 35-45 mmHg. A study of 918 patients who were not managed in intensive care units founds that 47% were hypercapnic at admission, with 20% having a pH below 7.35 and 9.4% a pH below 7.30 (236). Consequently, hypercapnia is frequent in acute care. However, some patients can develop oxygen-induced hypercapnia, such as COPD and obesity-associated hypoventilation (237). In this population, the patients the most susceptible to develop hypercapnia are those with the most severe hypoxaemia. The administration of high concentration oxygen could be associated with higher mortality in comparison with a more cautious approach of oxygen therapy (238–242). Three mechanisms can explain this phenomenon:

a) Hypoventilation:

Many health practitioners think that oxygen administration in patients with COPD could induce hypercapnia through the suppression of 'hypoxic drive' (“hypoxaemic drive”) (243). In reality, this is not the case: Firstly, high FiO_2 leads to a rapid decrease in minute ventilation (VE) with an elevation of $PaCO_2$ (243). Secondly, minute ventilation recovers from the initial decrease and is only marginally reduced in comparison with the baseline. Afterwards, $PaCO_2$ increases further despite the recovery of the minute ventilation. Therefore, the administration of high oxygen flow has a limited impact on minute ventilation and does not explain the total increase in $PaCO_2$ (figure 13) (244).

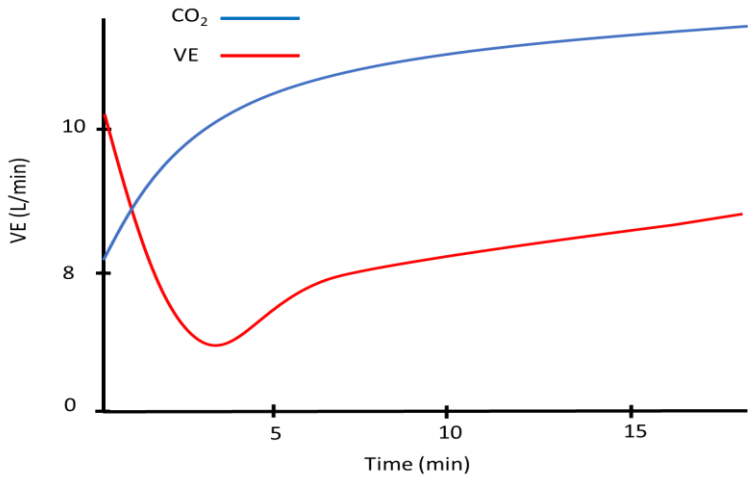


Figure 13: Effect of minute ventilation (VE) during oxygen-induced hypercapnia. During high oxygen administration, in the first instance, minute ventilation decreases in COPD with acute exacerbation. However, the oxygen-induced hypercapnia does not recover (245)

b) Ventilation-perfusion mismatching (Von Euler Liljestrand effect):

PAO_2 decrease leads to reduced alveolar perfusion because of the hypoxic pulmonary vasoconstriction mechanism (51). This PAO_2 decrease can be due to either a PiO_2 decrease or a $PACO_2$ increase. In this last case, because of Dalton's Law, alveolar hypoventilation leads to an increase in $PACO_2$ which decreases PAO_2. This PAO_2 decrease generates an alveolocapillary signal which lead to a propagation to upstream arterioles (109–111). Consequently, these upstream arterioles contract them and shunts blood flow away from poorly ventilated areas towards well-ventilated areas. This phenomenon allows the recovery of a normal perfusion ventilation ratio (VA/Q) (Von Euler Liljestrand effect) (246). In some patients (as COPD or obesity-associated hypoventilation syndrome), high oxygen levels artificially increase the PAO_2 in poorly ventilated alveolar spaces, which leads to less hypoxic pulmonary vasoconstriction. The arterial pulmonary blood (which contains CO_2 from cellular activity) is no longer diverted from poorly ventilated areas. Therefore, the CO_2 cannot be extracted from the blood due to a poorly ventilated alveolar space. This mechanism increase $PaCO_2$ level, and is called: Von Euler Liljestrand effect suppression (figure 14) (238,243).

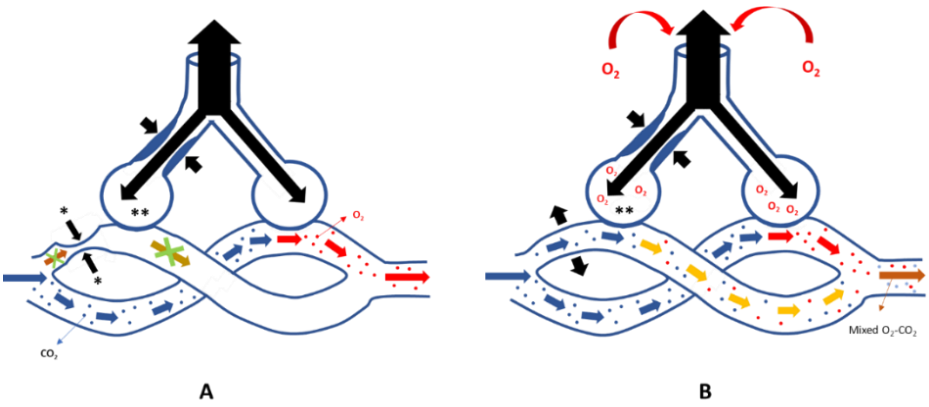


Figure 14: **A**: Von Euler Liljestrand phenomenon (localized pulmonary vasoconstriction *) when alveolar area is less ventilated as during bronchoconstriction (**). **B**: Von Euler Liljestrand effect suppression.

In some patients (COPD, obesity-associated hypoventilation), High oxygen therapy increases the PAO_2 in poorly ventilated alveolar spaces (**), which remove the hypoxic pulmonary vasoconstriction. The arterial pulmonary blood (which contains High CO_2 levels) is no longer diverted from poorly ventilated areas. Therefore, the CO_2 cannot be extracted from the blood due to a poorly ventilated alveolar space. This mechanism increases $PaCO_2$ level. Note: Arrows and blue dots represent CO_2 in the blood. Arrows and red dots represent O_2 in the blood.

c) Haldane effect:

Haemoglobin combines with CO_2 to form carbaminohaemoglobin (247). The Haldane Effect is the phenomenon where the binding of oxygen to haemoglobin promotes the release of carbon dioxide. The Haldane Effect is the inverse of the Bohr Effect, where oxygen and carbon dioxide compete for haemoglobin occupancy: Exchange facilitation between carbon dioxide for oxygen in the pulmonary and peripheral circulations (247). A shift to the right of the CO_2 dissociation curve will increase $PaCO_2$, which will generate an increase in minute ventilation, normalising $PaCO_2$. However, in patients with severe COPD, who are unable to increase minute ventilation correctly, the Haldane effect will increase $PaCO_2$. The Haldane effect explained approximately 25% of the total $PaCO_2$ increase due to O_2 administration (238). To determine the Bohr/Haldane effect, we can use the P50 method. The P50 is the oxygen tension at which haemoglobin is 50% saturated. The normal P50 is 26.7 mmHg. If the PaO_2 is less than this value, a rightward shift increases P50, and a leftward shift decreases P50 (248,249).

Chapter 6: Oxygen Therapy

Oxygen therapy is commonly delivered in both chronic and acute patient care. Its proper understanding, assessment, and administration are fundamental in respiratory care (250). In 2011, a survey study found that ±34% of ambulance journeys involve oxygen use and ±18% of hospital inpatients in the UK were being treated with oxygen at any given time (35).

Oxygen therapy can be administered in a number of situations (Table 3) (41,251).

Critical illnesses requiring high levels of supplemental oxygen	Cardiac arrest or resuscitation Shock, sepsis, major trauma, drowning, anaphylaxis, major haemorrhage, status epilepticus, major head injury Early tracheal intubation and ventilation if comatose Carbon monoxide poisoning (252) Pneumothorax that must not be exsufflated (253) For decompression illness (254–256) For cluster headache (257,258)
Illness requiring moderate levels of oxygen if the patient is hypoxaemic (41,251)	Acute hypoxaemia Acute asthma (259) Pneumonia (260) Lung cancer (261) Patients with pulmonary arterial hypertension (262,263)
Chronic illnesses requiring low oxygen levels (Long-term oxygen therapy) (264–269)	COPD with advanced lung disease Interstitial lung disease Long-term oxygen therapy is more benefits in COPD patients with severe resting hypoxaemia than COPD with moderate hypoxaemia (266)

Table 3: Several situations where oxygen therapy can be administered

Oxygen is both lifesaving and toxic. Inadequate tissue oxygenation or excessive oxygen administration can be detrimental (270). Its use must be carefully considered to avoid hypoxaemia but also hyperoxaemia (156,171,271,272). Severe hypoxaemia can lead to cellular hypoxia, organ dysfunction and death, while hyperoxaemia can impair health status (151).To avoid hyper or hypoxaemia, oxygen should be prescribed to achieve a target saturation of 94–98% for most acutely ill patients or 88–92% or patient-specific target range for those at risk of hypercapnic respiratory failure (35). However, hyperoxaemia is more frequent that hypoxaemia due to extensive uses of pulse oximetry that effectively detects hypoxaemia but cannot be used to detect hyperoxaemia (9). To deliver oxygen, several

systems are available: Oxygen Cylinders/Thorpe Tube/Oxygen Flow Restrictor (and portable oxygen concentrators)

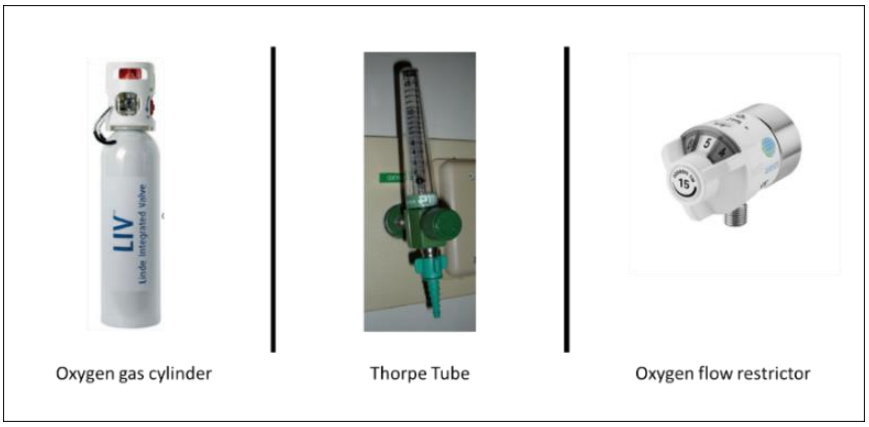


Figure 15. Oxygen Gas Cylinder, Thorpe Tube and Oxygen Flow Restrictor

a) Oxygen Gas Cylinder (OGC):

Oxygen gas cylinders are in steel or aluminium tanks containing the gas under high pressure (typically around 200 bar) (figure 15). Depending on their volume water (identified by the letter “B”), these oxygen cylinders, according to Boyle's Law, can release volumes from 200 to 10,000 litres at atmospheric pressure (5). The high pressure must be decreased to administer oxygen safely to a patient. To decrease this high pressure to an intermediate level (around 3 bar), oxygen cylinders are equipped with a pressure regulator. Two models of regulators exist:

- Pre-set single-stage regulators, using a single inlet valve

- Pre-set dual-stage regulators, using a series of valves.

Working at this intermediate pressure, a flow meter regulates the outflow using variable-flow orifice restrictors. This simple technique uses calibrated ports to deliver predetermined flow. In Europe, the accuracy of flow measurement devices for medical gases is governed by the ISO 15002 standards. According to these standards, the delivered flow should not deviate from the required flow by more than 0.5 L/min when the required flow is 5 L/min, and by more than 10% above this threshold. In North America, the standards required are set by the Compressed Gas Association (CGA). These standards specify an allowable error of 10% above or below the required flow (5,273).

b) Thorpe Tube (TT):

In hospitals, oxygen supply is mostly controlled by rotameters (Thorpe Tube − Oxygen Flowmeter = TT) (figure 15). The flow rates commonly delivered by these devices range from 0 to 15 l/min, but other ranges are available (from 0–1.5 L/min to 0–70 l/min). Several types of TT exist based on different physical approaches: Whether the pressure is compensated or not, or pre-calibrated orifices or electromagnetic valves. These devices are simple but fragile. Their operation becomes inaccurate when exposed to static electricity or a magnetic field, secondary to a mechanical shock or a lack of verticality, but also with changes in atmospheric pressure or room temperature (depending on the model) (274). In their study, Davidson et al. emphasised that when ICU patients are being transferred to other wards, the patient's SpO_2 is sometimes reduced even though the O_2 flow is not changed (275). According to these authors, the TT imprecision was a common cause of this altered SpO_2. In Europe and North America, the accuracy of flow measurement devices for connection to the wall outlet distribution systems of medical gases is also governed by the ISO 15002 standards and by CGA, respectively. A study has attempted to assess the accuracy of TT in actual conditions of use. A previous study showed that the inaccuracy of TT varies from 10% to 40% of the required flow (275).

c) Oxygen Flow Restrictor (OFR):

In recent years, a new generation of hospital regulators has appeared: Oxygen flow restrictors (OFR) (figure 15). The oxygen flow regulator helps to deliver in the exact litres per minute of oxygen. These devices use a series of calibrated opening in a disk that can be adjusted to deliver many flows (5). At a given inlet pressure, only so much flow can pass through a restricted orifice; a large orifice gives a high flow, a small orifice gives a low flow. Advantages of flow restrictor included low cost, reliability, gravity independence. Their disadvantage is that they are not backpressure compensated. Downstream resistances make flow less than expected because the meter is calibrated with the assumption that the only resistance is the internal orifice (276).

d) Portable Oxygen Concentrators (POC):

Portable oxygen concentrators were developed in the late 1970s. They are a continuous source of home oxygen without the use of heavy tanks and frequent deliveries (277). An oxygen concentrator captures the oxygen contained in the atmosphere (±21%) and converts it into concentrations of up to ±95% pure oxygen (5). Most POC's are composed by an air compressor, cylinders filled with zeolite pellets. POC's operate using pressure swing adsorption (PSA) method. In this case, the air is taken in, nitrogen is removed, and oxygen-enriched gas is released to the patient. POCs run on alternative current (wall outlet) or direct current (cigarette lighter) power (figure 16). Most POCs are equipped with batteries

which allow patients to leave home. Battery autonomy can vary from 2 to 6 hours. POCs are designed for patients with respiratory disorders such as COPD, but also in emergency medicine contexts such as mass casualty events or war zones (278).

Figure 16: Different POCs from easymedicalstore.com

Depending on the models, some POCs deliver oxygen according to three modes:

- Continuous flow: From 0.5 to 3 L/min for portable POCs and from 0.5 to 10 L/min for stationary POCs (277).

- Constant pulse volume of oxygen: In this case, the oxygen volume delivered is independent of respiratory rate. The volume of oxygen can vary from 11 to 96 mL (279).

- Fixed oxygen minute volume: With these devices, oxygen flow is programmed. The pulse volume delivered per breath is equal to the ratio between the programmed oxygen flow and the respiratory rate (RR). Paradoxically, with this system, during physical exercise, when the RR increases, the oxygen volume delivered decreases (278).

Note: Some POCs can complement home oxygen system by allowing patients to fill their high-pressure cylinders from a concentrator at home. The pump of the POC compresses oxygen into oxygen cylinders which give ambulatory patients greater independence and freedom.

Although these portable systems are efficient, adherence to ambulatory oxygen is generally quite low and it is difficult to identify the predictive factors of adherence to ambulatory oxygen (280).

Devices for oxygen administration:

a) Low flow systems:

Nasal cannula (NC)

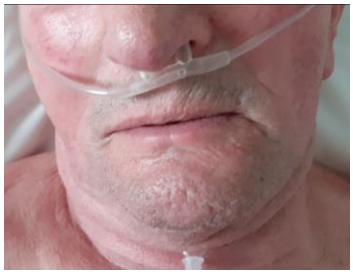


Figure 17: Nasal cannula

NC is used to deliver low and medium oxygen flow (0.5 to 6 L/min) (figure 17) (281). At a flow above 4L/min, some patients can feel discomfort and nasal dryness. Breathing with an open mouth produces the same inspired oxygen concentration or a higher concentration, especially when the respiratory rate is increased (282). No statistically significant difference was found in oxygen saturation levels achieved between the face mask and NC (283–285). In a randomised controlled trial of 60 hypoxaemic patients who compared a NC with a simple oxygen mask, the NC was reported to be more comfortable with fewer reports of dyspnoea and restlessness. Moreover, the NC was preferred for oxygen therapy by most patients. Although the efficiency of the two devices did not differ remarkably, the nasal cannula was the more comfortable and time-saving device for supplementation of oxygen therapy to hypoxaemic patients (286). The performance and variation of NC for medium oxygen flow are broadly similar to that of the face mask, both in laboratory experiments and in clinical practice (287,288). NCs are more likely to remain in position than face masks and maintain an adequate saturation in most patients (289).

Sometimes, the prongs of the NC slip on the face and can be found overlapping a nostril and the cheek. When the prongs of NC are not correctly placed in the nostrils, the FiO_2 decreases. To evaluate this situation, in a bench study, authors have concluded that the impact of FiO_2 was limited when the NC was overlapping a nostril and a cheek (290). The impact of minute ventilation increases on the FiO_2 values is essential (291). In adults at rest with normal inspiratory flow, for an oxygen flow rate of 1–6 L/min, a nasal cannula gives FiO_2 values ranging from approximately 24% to approximately 50% (35).

A survey study (n = 100) concluded that NC use could lead to pressure ulcers of the ear. The incidence of ear skin breakdown was 37%, with a range of 28–47% (292). A study highlighted

that NC has the benefit of higher compliance and comfort in patients, and cost savings for the institution (293).

In another study, the highest degree of comfort was found with the NC compared to face masks and oxygen catheters (294). However, since the delivered oxygen percentage is very inconsistent during respiratory distress, the NC is not recommended for acute severe hypoxaemia (5).

A NC at an oxygen flow of 1 to 3 L/min reversed hypoxaemia in 95% of stable patients with COPD (295).

Nasopharyngeal oxygen catheter:

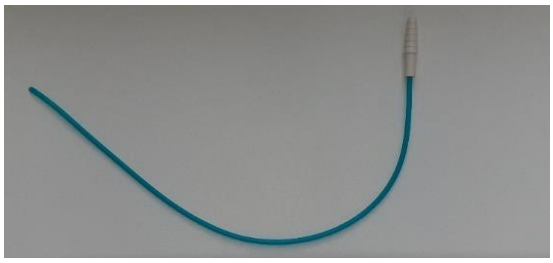


Figure 18: Nasopharyngeal oxygen catheter

Nasopharyngeal oxygen (NPO) therapy is an emerging alternative to conventional face mask oxygen administration (figure 18). NPOs are soft plastic catheters inserted into the patient's oropharynx (296). In a randomised cross-over design trial, in patients who received oxygen therapy through the Hudson facemask (Oxygen mask) and a nasal cannula (using a flow of 15L/min), the NPO resulted in a significantly higher expired end-tidal O_2-fraction ($FETO_2$) compared to the Hudson mask alone. During the nasal cannula period, the respiratory rate was significantly lower than during the face mask period. The end-tidal CO_2 pressure ($PETCO_2$) remained constant (297). Recent research in the adult ICU setting has shown the NPO route to be as effective as face mask oxygen administration in alleviating mild to moderate hypoxaemia and significantly more comfortable for patients (298). In a study that compared the performances of a medium concentration oxygen mask and a nasal catheter, by measuring the SpO_2 levels of 40 post-operative patients, no significant difference was found between the performances of these systems (299). In very few cases, the misplaced nasopharyngeal oxygen catheter caused secondary pneumo-orbitus and pneumocephalus (300).

Oxygen conserving device (Oxymizer): (301,302)

This device reduces the oxygen supply flow necessary to achieve adequate oxygen saturation (figure 19). In order to properly explain how this device works, we chose to literally transcribe the text of Moore-Gillon et al., in Thorax (301): “Within an outer plastic casing is a thin membrane that acts as a collapsible reservoir of about 18 ml capacity. The outer casing is vented to allow free expansion and collapse of the inner reservoir, from which soft nasal prongs arise. Gas flow from the oxygen source is at a steady rate. During expiration the reservoir fills with oxygen from the source. At the onset of inspiration, the reservoir empties, delivering this stored oxygen as a bolus. During the remainder of inspiration, after the reservoir (* figure 19) has collapsed, the device acts like a conventional cannula delivering oxygen at the set flow rate”.

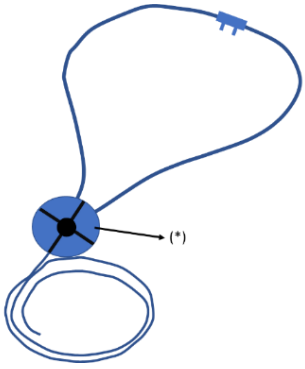


Figure 19: Oxymizer

Oxygen mask (OM): (figure 20)

Many different designs of OMs are available. In theory, a fraction of inspired oxygen from 40 to 60% can be achieved with oxygen flow rates from 6 to 10 L/min (35). According to Bateman et al., at low oxygen flow rates (<5 L/min), significant rebreathing could occur because exhaled air is not adequately flushed from the face mask (189). The authors recommended 5 L/min as the lowest oxygen flow rate to be used during oxygen therapy with an OM, to avoid rebreathing and excessive respiratory work (303); they concluded: “Consequently, this mask would not seem to be suitable for patients with hypercapnic respiratory failure” (286). According to Campkin et al., the carbon dioxide elimination through the Hudson mask is enhanced by increasing oxygen inflow and is inversely related to respiratory frequency (304). The use of a face mask is the most common method of oxygen administration in hospitals. However, Nolan et al. have shown that it must be

removed for many routine nursing tasks such as mouth care and the measurement of oral temperature. In some cases, the mask was not replaced correctly at the end of the procedure. During this study, the face mask remained off for several hours in some patients, and many had decreased oxygen saturation with mask displacement (289,305).

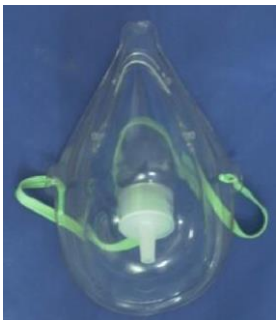


Figure 20: Oxygen mask

Wenoll System:

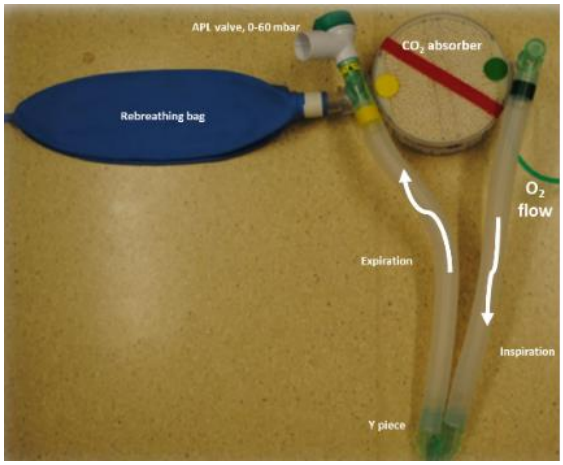


Figure 21: The Wenoll system

When the oxygen stock is limited (e.g., in critical situations such as war zones, disasters…), the administration of high FiO_2 for an extended period may become insufficient. To limit the O_2 volume required in spontaneous breathing or to give high oxygen concentrations during

mass casualty events, using the Wenoll system® (a rebreather with a closed circuit to recapture the exhaled O_2) can be an option (figure 21). This closed-circuit provides 100% FiO_2 for a low flow rate in patients at rest: The O_2 flow rate covers O_2 consumption (VO_2), and a soda-lime cartridge absorbs the CO_2 produced by the patient's metabolism (VCO_2). In this way, an O_2 flow rate of 1 to 2 L/ min with a usual O_2 cylinder or POC is generally sufficient to ensure an oxygen uptake (VO_2) of a patient ventilating at rest (306,307).

OxyMask:

The OxyMask is a face mask that uses a small “diffuser” to concentrate and direct oxygen flow toward the mouth and nose (figure 22). Moreover, the Oxymask has large openings which prevent CO_2 rebreathing. The authors hypothesised that this mask would enable more efficient oxygen administration than a Venturi mask in patients with chronic hypoxaemia. A study showed that the OxyMask delivers oxygen effectively. Oxyhaemoglobin saturation obtained with the OxyMask uses a lower oxygen flow rate than with the conventional Venturi mask, which demonstrates that it is a more efficient system (308,309). A retrospective study showed that OxyMask is a safe and less costly alternative to traditional oxygen administration devices (310).

Figure 22: The Oxymask

High-concentration reservoir mask (non-rebreathing mask: NRM):

NRM delivers an oxygen concentration of 60–80% or higher. It is useful for short-term treatment in critical illness, trauma patients, post-cardiac event, or respiratory arrest (189). However, recent clinical investigations have highlighted the potential for entrainment of room air to dilute air/oxygen mixtures delivered through non-rebreather facemasks (311).

Non-rebreather masks (NRM) are low-flow oxygen administration systems that provide oxygen at flow rates lower than the patient's inspiratory demands (figure 23).

Figure 23: Non-Rebreathing Mask

They are two types of NRM:

1) Partial Non-Rebreathing mask (PNRM): This mask is equipped with two valves, one located between the mask and the reservoir, which allows oxygen entry from the reservoir into the face mask. The second valve is localised on one hole of the mask (at the exhalation port) and prevents room air from entering the mask during inspiration, while allowing gas to escape during exhalation.

2) Total Non-Rebreathing Mask (TNRM): This mask is also called a "100% Mask"; it is equipped with three valves. It is the same as in the PNRM, except there is a third valve on the second hole of the mask.The PNRM is considered a less efficient oxygen administration device than the TNRM. This mask allows the administration of high-inspired O_2 concentration. However, there is a lack of evidence-based guidance on how to achieve this using currently available apparatus (312). High inspired oxygen concentrations can be delivered using three simple measures:

- Using a non-rebreathing mask with three valves
- Increasing the O_2 flow to 15 L/min
- Fitting the mask tight to the face

However, if the minute ventilation is too high (above 15L/min), the reservoir bag-mask can collapse, leading to suffocation (313–315). Moreover, clinical investigations have

highlighted the potential for entrainment of room air to dilute air/oxygen mixtures delivered through non-rebreather facemasks which decreases dramatically the FiO_2 (304).

b) High-flow oxygen administration systems:

1) Venturi mask:

The Venturi mask delivers an accurate oxygen concentration (FiO_2) but requires relatively high oxygen flow rates to achieve this. In a Venturi mask, 100% oxygen flows through tubing at a specified flow rate. The mask receives oxygen flow into a narrow tube called a "Venturi valve". By passing through this tube, the flow velocity is increased, and the pressure consequently decreases (Bernoulli effect). In the Venturi valve, there is also a side orifice which aspirates room air due to the depression caused by the Bernoulli effect, diluting the flow of 100% oxygen (316,317) and allowing FiO_2 to be administered with high accuracy and reliability. It can provide oxygenation and prevent carbon dioxide retention using oxygen mixed with air. Therefore, the oxygen flow is mixed with the room air at a constant and predictable rate.

These masks provided fixed oxygen concentrations of 0.24/0.28/0.31/0.35/0.40/0.60 determined by the width of the Venturi valve (316).

Figure 24: The Venturi mask

With this mask (figure 24), the total flow delivered to the patient can vary from 35 to 45 l/min. If the patient's peak inspiratory flow exceeds this total flow, the FIo2 inspired decrease because of ambient air entrainment into the mask. Patients with a respiratory rate >30 breaths/min often have an inspiratory flow rate above the minimum flow rate specified on the mask manufacturer (35). The accuracy of oxygen administration can be reduced if the mask is not accurately placed on the patient's face (318).

2) High-Flow Nasal Cannula:

High-Flow Nasal Cannula (HFNC) oxygen therapy is a technique delivering a high flow of heated and humidified oxygen to hypoxaemic subjects (figure 25). HFNC uses an air-oxygen blender to deliver high oxygen flows. HFNC allows a fractional inspired oxygen concentration (FiO_2) from 21% to 100% and generates a gas flow from 10 to 60 L/min. Compared to low-flow oxygen therapy, HFNC allows inspired oxygen concentration to be better controlled. However, the FiO_2 delivered by HFNC remains dependent on the flow rate, to the size of the nasal cannula and whether the patient's mouth is open or not (319–321). Moreover, the inspiratory flow seems to influence the FiO_2. In the case of respiratory distress, the inspiratory flow can exceed 100 L/min, causing a shift in the inspiratory demand and causing a significant dilution of the oxygen with the air in the room (44,282,322–325). A recent randomised controlled trial comparing the efficiency of HNFC, NIV (non-invasive ventilation) and traditional oxygen therapy demonstrated a decrease in the intubation rate and mortality in non-intubated acute hypoxaemic respiratory failure subjects (AHRF) in subjects who have a PaO_2/FiO_2 ratio ≤200 mmHg (326).

Figure 25: High Flow Nasal cannula (or HFNC)

c) Automatic O2 flow adjustments (Free O2):

Free O_2 is an automatic oxygen titration device that adjusts the oxygen flow rates administered to spontaneously breathing patients (Figure 26). The aim of the device is to maintain SpO_2 in a predefined target set by physicians in regard of patient pulse oximetry. The system limits hyperoxia and hypoxemia and to automatically wean them from oxygen. During rehabilitation in patients who have need high oxygen flows during exercise. Free O_2 maintains higher SpO_2 levels during exercise in comparison to manual O_2 titration. Automatic titration of oxygen flow improves exercise tolerance and increases walking distance (327–329)

Figure 26: Free O_2 device

Chapter 7: Thesis aims and publications

The general objective of this work was to determine the factors influencing oxygen administration during oxygen therapy and propose solutions to improve oxygen administration.

The specific aims of the individual studies were:

Aim of study I

To evaluate the accuracy of flow meters attached to oxygen gas cylinders (OGC with a flow meter) which are ready to be used.

Aim of study II

To evaluate the accuracy and precision of ready-to-use oxygen flow restrictors and compare our results with other studies.

Aim of study III

To validate a new FDO_2 prediction formula for tracheostomised or intubated patients with spontaneous breathing, which takes into account the inspiratory flow and compares it to other formulas

Aim of study IV

To evaluate the effect of the Double Trunk Mask on PaO_2 and $PaCO_2$ in hypoxaemic subjects treated with **high** flow nasal cannula.

Aim of study V

To evaluate the effect of the Double Trunk Mask on PaO_2 and $PaCO_2$ in hypoxaemic subjects treated with **low** flow nasal cannula.

Aim of study VI

We made a critique of the article by Roca et al. (330) and proposed several solutions about this study.

a) Study I: Accuracy of oxygen Flow Delivered by Compressed-Gas Cylinders in Hospital and Pre-hospital Emergency Care.

Duprez F, Michotte JB, Cuvelier G, Legrand A, Mashayekhi S, Reychler G.

Respir Care. 2018 Mar;63(3):332-338

I. Introduction

Oxygen therapy (OT) is widely used both in hospital and pre-hospital care (35,241,331).

In 2008, a study showed that 15 to 17% of patients hospitalised in the United Kingdom received oxygen at some point compared to 34% of patients who had been transported by ambulance (331).

In these situations, OT was delivered with a wall-mounted Thorpe Tube (TT) or oxygen gas cylinders (OGCs). TT is used in hospitals to deliver an oxygen flow. A driving pressure is applied to the inlet of the TT, and a float indicator rises in the tapered tube until the required flow is read (5). OGCs are in steel or aluminium tanks and contain the gas under high pressure; therefore, the high pressure must be decreased to administer oxygen safely to a patient. To decrease this pressure to an intermediate level (from 2,900 to 44 PSIG), OGCs are equipped with pressure regulators. Two models of regulators exist: pre-set single stage regulators (single stage) using a single inlet valve, and pre-set dual stage regulators (dual stage), which use a series of valves. Working at this intermediate pressure, a flow meter regulates the outflow using variable flow orifice restrictors. This simple technique uses calibrated ports to deliver pre-determined flow (5).

In Europe, the accuracy of flow measurement devices for medical gases is governed by the ISO 15002 standards (6). According to this standard, the delivered flow should not deviate from the required flow by more than 0.5 L/min when the required flow is below 5 L/min, and by more than 10% above this threshold. In North America, the required standards set by the CGA (Compressed Gas Association) are applied. These standards specify an allowable error of 10% above or below the required flow (5).

In North America, the gas pressure in OGC is usually expressed in PSIG (pound-force per square inch gauge), while the unit used in Europe is the Bar (Kgf/cm^2) (5).

OGCs and TTs are routinely used successively, for example during intra-hospital or pre-hospital transfers. It is, therefore, essential to know whether these systems deliver similar levels of oxygen flow to maintain the same level of oxygenation.

In 2013, a study highlighted the fact that several thousand deaths could be avoided each year in the U.K. with controlled oxygen use (3). The accuracy of oxygen flow is, therefore, a key element. Recent studies have examined the accuracy of TTs in clinical situations (274,275). They observed that the required flow was different from the delivered flow using TTs. This difference can lead to an over- or under-oxygenation of patients and can be deleterious in various disease conditions, such as chronic obstructive pulmonary disease, ischaemic disorders, and premature infants. However, few data exist regarding OGCs with a flow meter. This study aimed to evaluate the accuracy of flow meters attached to OGCs (OGCs with a flow meter) which are ready to be used.

II. Methods

Delivered flows by flow meters were evaluated on successive OGCs ready for use, selected from two hospital emergency departments, two ambulance services, and a firefighting brigade, in the Walloon region of Belgium, from March to May 2016. The OGC analysed were from the stock available on the days that the measures were taken.

Measurements:

- Gas pressure:

Before performing the flow measurements, the residual pressure of each OGC was checked by direct reading on the manometer. Any gas pressure in OGC higher than 1,450 PSIG was considered to be high pressure, and pressure from 0 to 1,450 PSIG was considered to be low pressure.

- Flow meter in OGCs:

The accuracy of OGC flow meters was analysed with a calibrated thermal mass flow meter (RED Y COMPACT™ GCM - 0 to 20 L/min - VÖGTLIN Instrument – Switzerland; accuracy: 1% of the full scale or ± 0.2 L/min). Flow measurement with the thermal mass flow meter RED Y is independent of the temperature and atmospheric pressure. In each OGC, different flows were evaluated in a random order (2, 4, 6, 9, and 12 L/min). Randomisation rate values were chosen with the random function of an Excel spreadsheet. The delivered flow was quantified after 5 seconds at a steady state. Measurements were performed at each flow, were measured twice, and then the mean value was recorded. Flows from 2 to 4 L/min and 6 to 12 L/min were considered as low and high flow, respectively.

Analysis:

Flows were expressed in standard units (L/min) and as a percentage of required flow (% required flow). For each flow, the minimum value, maximum value, range between both values and interquartile range (IQR) were calculated.

Mean values are expressed with their standard deviation for parametric data and median values with IQRs for non-parametric data. To evaluate the variability of OGC flow meters, a coefficient of variation (CV) was calculated.

Single and dual-stage groups were compared using an ANOVA test followed by a Holm Sidak method for parametric data. A Kruskal Wallis test followed by Dunn's method or Mann Whitney test was used for non-parametric comparisons.

To check the precision of measurements for the calibrated thermal mass flow meter, a Friedman test was performed to analyse three random oxygen flow measurements (1.5, 6, 9, 12 L/min) carried out during the phase of the precision experiment (10 dual stages at maximal pressure). The intraclass correlation coefficients (ICC) were calculated to verify the repeatability of three successive measurements of oxygen flows. ICC values greater than 0.75 were considered to reflect excellent repeatability.

An error analysis for each measurement was performed by calculating the difference between the delivered and required flow divided by the required flow.

III. Results

148 OGC were analysed (single and dual stage). Their provenance was (Table 1):

Ambulance service	n=36
Emergency department	n=88
Fire brigade	n=24
	n=148

Table 1: Source of compressed-gas cylinders

The distribution of OGC was: 53% (n=78) with a Single Stage (MESSER™) and 47% (n=70) with a Dual Stage (AIR LIQUIDE™).

Gas pressure:

The residual pressure for both OGC ranged from 73 to 2,900 PSIG. The median (25th and 75th percentile) residual pressure of single-stage was 1,885 (1,033-2,900) PSIG and 2,176 (1,087-2,900) PSIG for dual-stage (p=0.864).

For single-stage, 26 OGC (33%) were found to be pressurised at low pressure and 52 OGC (67%) at high pressure, for the dual-stage, 27 OGC (39%) were pressurised at low pressure and 43 OGC (61%) at high pressure (Table 2).

Type	Single Stage MESSER™	Dual Stage AIR LIQUIDE™
Number	n=78 (53%)	n=70 (47%)
Water volume	2 Liters: n=74 10 Liters: n=4	2 Liters: n=14 5 Liters: n=56
Median residual pressure (psig)	1,885 (1,033-2,900)	2,175 (1,087-2,900)
Low pressure (0 to 1,450 psig)	n=26 (33%)	n=27 (39%)
High pressure (1,451 to 2,900 psig)	n=52 (67%)	n=43 (61%)

Table 2. Compressed gas cylinder distribution between single and dual stage. Median values were expressed within the 25^{th} and 75^{th} percentile

Flow:

For all OGCs, the dispersion of the median value extended from 100 to 109% of the required flow for a single stage, and from 95 to 97% for the dual stage. Mainly for the single stage, the median value, range, and IQR decrease with increasing required flow (Table 3). Significant IQR differences ($p<0.05$) were observed between single and dual stage (Table 3). However, the gap between single and dual stage decreases with the increase in required flow value. The median value of delivered flow was equal to or higher than the required flow for the single stage and below the required flow for the dual stage (Fig. 1 and Table 3).

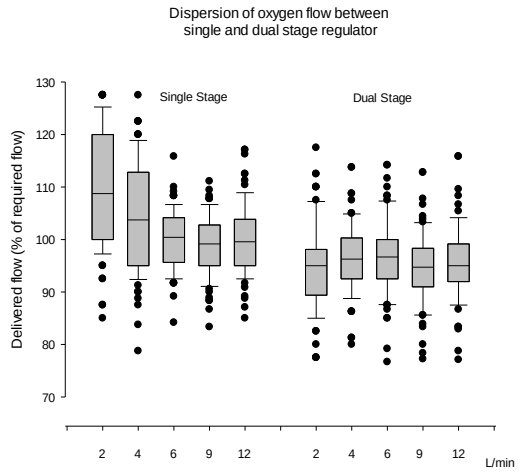


Figure 1: Accuracy of the delivered flow in the function of required flow. Delivered flows were expressed as a percentage of required oxygen flow. Values obtained using 78 single stages, and 70 dual stages for oxygen flow from 2 to 12 L/min. The boxes illustrate the 25th and 75th percentiles; whiskers correspond to the 5th and 95th percentiles; dots are outliers. For a single stage, but not for the dual-stage, median value differences were observed between low and high residual pressure. Indeed, with a single stage, at the same flow, the median values decreased when the OGCs were pressurised at low residual pressure (Fig. 2)

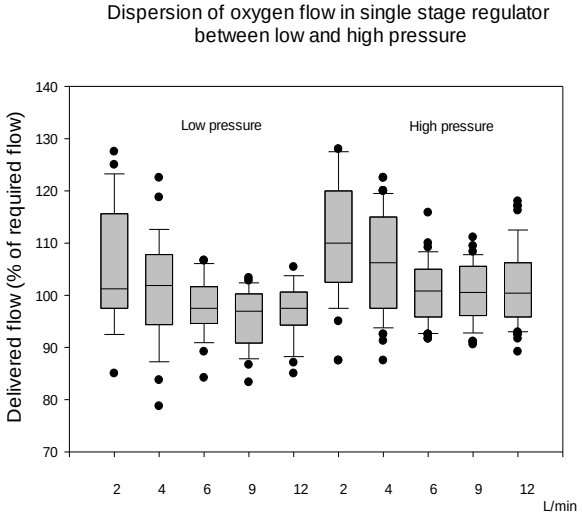


Figure 2: Dispersion of the delivered flow differences for 78 single-stage OGC between low pressure (ranged from 290 to 1,378 PSIG. n=26) and high pressure (ranged from 1,450 to 2,900 PSIG. n=52). $P<0.05$ for all groups using the Friedman Test.

Required O_2 flow	Single Stage					Dual Stage				
(L/min)	2	4	6	9	12	2	4	6	9	12
Max	128%	128%	116%	111%	117%	118%	114%	114%	113%	116%
P75	120%	113%	104%	103%	104%	98%	100%	100%	98%	99%
Median	109%	104%	100%	100%	100%	95%	96%	97%	95%	95%
P25	100%	95%	96%	95%	95%	89%	93%	93%	81%	92%
Min	85%	79%	84%	83%	85%	78%	80%	77%	77%	77%
IQR	20%	18%	9%	8%	9%	9%	8%	8%	7%	7%
Range	43%	49%	32%	28%	32%	40%	34%	38%	36%	39%

Table 3. Distribution of delivered oxygen flows expressed as a percentage of the difference between the required and delivered oxygen flow between single and dual stage

Variability of the measurements:

No statistical difference (p=0.608) was found with regards to the CV between the single and dual stage (Table 4). The Intraclass Correlation Coefficient ranged from 0.97 to 0.99 and reflected an excellent reproducibility of measurements for the thermal mass flow meter (Table 5). The error of measurement decreases when the flow increases, particularly for the single stage (Table 6).

Mean of delivered flows and coefficient of variation (CV) comparison between single and dual stage

Flow (L/min) (REQUIRED FLOW)	Single Stage Mean (+/-SD) in L/min	Dual Stage	Single Stage CV	Dual Stage
2	2.2 (+/-0.2)	1.9 (+/-0.2)	0.11	0.09
4	4.2 (+/-0.4)	3.9 (+/-0.3)	0.10	0.07
6	6.0 (+/-0.3)	5.8 (+/-0.4)	0.06	0.07
9	8.9 (+/-0.5)	8.5 (+/-0.6)	0.06	0.07
12	12.0 (+/-0.8)	11.5 (+/-0.9)	0.07	0.07
	p<0.05 *		p=0.608 **	

* ANOVA followed by Holm Sidak / **Student's t-test

Table 4. Mean of delivered flows and coefficient of variation (CV) comparison between single and dual stages * ANOVA followed by Holm Sidak / **Student's t-test

		Flow analyzer*		
Required flow (L/min)	Measurement	Median	25^{th}	75^{th}
1.5	1	1.3	1.2	1.5
	2	1.3	1.2	1.5
	3	1.3	1.3	1.5
6	1	5.8	5.5	6.1
	2	5.8	5.5	6.2
	3	5.9	5.6	6.2
9	1	8.4	8.1	8.6
	2	8.4	8.2	8.6
	3	8.4	8.2	8.8
12	1	11.1	10.7	12.2
	2	11.1	10.7	12.2
	3	11.1	10.7	12.3

Table 5. Repeatability of three measurements of required O_2 Flow of 1.5, 6, 9, 12 L/min of 10 OGC at full Pressure. Measurements were made using RED Y, VOGTLYN™ Using Friedman Test

	Single Stage				
Expected O_2 LPM	2	4	6	9	12
Mean O_2 observed	2.19	4.19	6	9	11.99
Percent error	9.6%	4.6%	0%	0%	-0.1%
	Dual Stage				
Expected O_2 LPM	2	4	6	9	12
Mean O_2 observed	1.89	3.85	5.79	8.52	11.46
Percent error	-5.5%	-3.6%	-3.5%	-5.4%	-4.5%

Table 6. Error analysis for each flow between single and dual stage. Percent error (PE) is calculated by the following formula: PE = 100 X (Observed flow – Expected flow)/Expected flow

IV. Discussion

This study evaluated the accuracy of oxygen flow delivered by OGC flow meters. Two brands of OGCs used were evaluated. Excellent accuracy of delivered oxygen flow for the two types of OGC analysed was found. Slight differences in the flow between the two brands were observed. While the differences between single and dual-stage regulators are measurable, the difference is unlikely to be clinically significant. On average, the single-stage tended to deliver flow above the required flow (mainly at low flow) while the dual-stage delivered a flow below the required flow. The dispersion of the measurements was slightly higher with a single-stage than the dual-stage. Independent of the pressure regulator system, delivered flows were, in general, close to the required flow. The error analysis shows that the percent error value decreases when the required flow value increases. This systematic error decreases with increasing flow, mainly for the single stage.

A similar study performed on a more significant number of TT in hospitals (n=476) showed median values of oxygen flow ranging from 91 to 110% of the required flow (274). The dispersion of the measurements is higher with TTs than with OGC flow meters. With the single stage, but not the dual-stage, median values of oxygen flow were lower with low gas pressure than with high gas pressure. This means that a decrease in pressure for the single stage has an impact on the delivered flow by decreasing this value. This difference can be explained because, with a dual stage, there is automatic compensation for any drop in the

supply pressure, which allows the delivered flow to be kept constant. Moreover, the dual-stage controls gas pressures have greater accuracy than a single-stage because, with this device, the pressure is gradually reduced through multi stage regulators (5). Finally, the dual stage produces flows that are more constant than those from a single stage. Taking these issues into consideration, the dual stage has less variability than a single stage. The results of the present study are consistent with two previous papers (274,275). These papers analysed the accuracy of the flow of Thorpe Tubes in a hospital. The conclusion of these studies was that the TTs tested showed poor accuracy.

On the other hand, the present results reveal that OGC has less variability of flow than TT. This means that the accuracy of OGC flow meters is better than that of TTs. Furthermore, the CV in the study by Davidson et al. (91 Thorpe Tubes analysed) was equal to 0.6 (±0.5) and 0.11 (±0.01) for the study by Duprez et al. (476 Thorpe Tubes analysed). In the current study, the CV is equal to 0.08 (±0.02) for the single stage and 0.07 (±0.01) for the dual stage.

These differences of variability between OGC flow meters and TT could be due to the RED Y COMPACT™ (accuracy ±1% for oxygen flow ranged of 0.5 to 20 L/min), which is a very accurate measuring instrument, while Davidson et al. used a Timeter RT-200™ (accuracy ±4% for oxygen flow range to 0.5 to 10 L/min). Furthermore, the flow meter of TT becomes inaccurate when exposed to static electricity or a magnetic field, secondary to a mechanical shock or a lack of verticality, and also to changes in atmospheric pressure or room temperature (5,332,333). These factors can lead to reading mistakes, which explains why the accuracy of OGC flow meters is higher than those of TTs.

However, in 1996, Henderson et al. studied the accuracy of oxygen flow through a nasal cannula in the operating room (332). They concluded that TT or OGC flow meters allow accurately delivered oxygen flows. On the other hand, oxygen flows from the Y-piece of a circle system were found to be lower than TT and OGC flow meters, especially when the adjustable pressure limiting (APL) valve was open. Despite this, patients who are oxygenated successively with different systems (OGC with a flow meter vs. TT) are unlikely to have a stable level of oxygenation, probably because the accuracy of the oxygen flow of these devices is different.

However, oxygen is rarely titrated in pre-hospital care once hypoxaemia has been reversed (334). Also, on arrival at the hospital, the oxygenation device is changed and could induce an over- or under-oxygenation if SpO_2 (or blood gas analysis) is not followed after this modification. As such, hyperoxia is a common finding upon hospital arrival in patients who received oxygen in pre-hospital care, and is, in fact, just as common as hypoxaemia (334). It must be emphasised that the situation described above could happen during intra-hospital transfers with the alternate use of TTs and OGCs with flow meters.

Recent guidelines recommend using pulse oximetry more frequently to avoid hyperoxia (334). This should encourage the staff of emergency departments to be cautious, and therefore to use pulse oximetry to determine the oxygen flow, rather than the previous flow after the patient's arrival. They should also consider the difference in oxygen supply (and the modification of ventilatory patterns) as a cause of the perturbation, before envisaging a change in the patient's health status.

Limitations:

This study evaluated the accuracy of a lot of OGC flow meters. Nonetheless, there are weaknesses in this study as only two types of OGC flow meters were studied, because, in Belgium, they were the only two that were readily available. Furthermore, during measurements, the ambient temperature was not taken into account, which could be a source of bias. Furthermore, the date on which each OGC flow meter was checked was not known, because, in Belgium, the law only requires OGC flow meters to be checked every five years.

V. Conclusion

This study shows that oxygen flow delivered by gas cylinders is accurate. Residual pressure influences the accuracy of oxygen flow, particularly with a single stage at low flow. OGCs with flow meters have lower variability than the wall mounted TTs used in hospitals. Any change in oxygenation system (TT vs. OGC with a flow meter or between different OGC flow meters) is a risky operation. Using SpO_2 more frequently should limit the probability of under- or over-oxygenation.

b) Study II: Accuracy of Oxygen Flow Delivered By Oxygen Flow Restrictors.

Accuracy of oxygen Flow Delivered by Oxygen Flow Restrictors.

Submitted to Clinical and Monitoring journal July 2019

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INTRODUCTION

oxygen therapy is commonly used in both acute and chronic care (335). Oxygen gas flowmeters (OGFs) are used to regulate the oxygen flow. In hospitals, oxygen flow is often delivered through a wall-mounted Thorpe tube (TT)(5). In recent years, a new generation of OGFs has appeared: The oxygen flow restrictor (OFR). These devices use a series of calibrated openings in a disk that can be adjusted to deliver many flows (5). At a given inlet pressure, only so much flow can pass through a restricted orifice. A large orifice produces a high flow, and a small orifice generates a low flow. These devices have a reputation for delivering more accurate oxygen flow rates compared to classical OGFs.

Recently, studies have examined the accuracy of oxygen flowmeters (273–275). These studies concluded there is large variability in delivery flow among the measurements from different OGFs. This variation could lead to over- or under-oxygenation, a phenomenon that can be potentially deleterious (336,337). To our knowledge, few studies have examined the accuracy of OFRs. This study aimed to evaluate the accuracy and precision of the ready-to-use Debson TM2™ OGF with flow restrictors and compare it with the accuracy of TTs.

METHODS

Delivered flows were evaluated on different ready-to-use OGFs: TT and OFR. OGFs were studied in units for adults where oxygen is frequently delivered (intensive care, emergency unit, respiratory unit, cardiology and surgery). The evaluated OGFs were those used routinely in these services and allocated to the next patient who required oxygen therapy. Only the OGF devices available on site on these days were analysed. Each analysed OFR was identified either by location on site or serial number to avoid repeating the same measurement on the same device twice.

Measurements:

Before performing the flow measurements, the inlet pressure was checked by direct reading on the manometer upon entry to the hospital unit.

Flows are expressed in absolute value and in standard units (L/min). The accuracy of each OGF was analysed with a calibrated thermal oxygen mass flowmeter (OMF; RED Y COMPACT™ GCM - 0 to 20 L/min - VÖGTLIN Instruments, Switzerland; accuracy 1% of full scale or ± 0.2 L/min). Flow measurements with the OMF were independent of temperature and atmospheric pressure. For both OGF types, different flows (2, 4, 6, 9 or 12 L/min) were evaluated in a random order (using the random function of an Excel spreadsheet). The delivered flow was quantified after 5 sec at a steady state. The measurements were performed twice at each flow, and the mean value was recorded. TT data are based on the calculations and plots available in studies published 2014 (274). To avoid parallax error, the oxygen flow reading for TTs was done by strictly horizontal sight.

Statistical analysis: Statistical analyses were performed with Sigma Stat™ (version 12.0, Systat Software Inc., London, UK) and Statistical Analysis System (version 9.4, SAS Institute, United States). Mean values are expressed with their standard deviation (SD) for parametric data and median values with interquartile ranges for non-parametric data.

We used a modified Bland-Altman method (MBAM) to assess the agreement between the required and actual oxygen flows (338,339). We used this method to avoid an overly optimistic reflection of the bias (and thus accuracy) of the OGFs. Indeed, we considered the OMF to be the accurate "gold standard" value. Thus, bias and accuracy were calculated relative to this standard gold standard and not to the average value: (OFR + OMF)/2.

We calculated the bias between the differences and estimated the agreement interval of the differences of the required oxygen flow compared to the actual oxygen flow (± 1.96 times the SD of the differences). To assess the relationship between bias and the magnitude of measurements, we performed a linear regression study. To quantify the goodness of linear regression, we calculated a coefficient of determination (R^2). An intraclass correlation coefficient (test-retest reliability), according to the method described by Shrout and Fleiss (10), was calculated to verify the repeatability of three random measurements of oxygen flows (2, 4, 6, 9 or 12 L/min) of six OFRs, which was performed during the precision experiment phase. An intraclass correlation coefficient greater than 0.75 was considered to reflect excellent repeatability of measurements.

RESULTS

Four hundred seventy-six TTs were analysed in eight general Belgian and French hospitals (Floval™, Caudalimeter™, DKD™, Drager™, Heyer™, Puritan Bennet™, RTM1™, RTM2™, RTM3™, Timeter™ and Taema™ ([0 – 15 L/min]). Ninety-six Debson TM2™ ([0 – 15 L/min]; Technologie Médicale, Noisy-le-Sec, France] OFRs were analysed in two general Belgian and French hospitals (Table 1).

	Thorpe Tube	France (n=205)	Belgium (n=367)	TOTAL
Air Liquide	Floval rotameter 0-15 France	4	3	7
Caudalimeter™	Ferno, UNIBODY Thorpe Tube 0-15, Wilmington, USA	-	47	47
DKD™	OHIO 7700 - 1260 - 931 England	7	0	7
Drager™	TT 0-15, Drägerwerk, Lübeck, Deutchland	-	4	4
Heyer™	660-0100 HEYER Medical AG, Bad Ems, Deutschland	-	10	10
Puritan bennet™	SLA - Slim Line Aluminum Body FME 901 Indian Creek Parkway USA	-	12	12
RTM1™, RTM2™, RTM3™	Technologie médicale, Noisy La Sec, France	74	246	320
Timeter™	Chemetron 32.15002 O3T Allied Healthcare Products USA	-	26	26
Taema™	oxygen flowmeter 0-15 LPM HW050803 Belgium	43	-	43
		128	348	**476**
	Oxygen Flow Restrictor			
Debson TM2	Technologie Médicale - Noisy Le Sec France	77	19	**96**
		General		**572**

Table 1: Brand distribution of the analysed oxygen gas flowmeters (Thorpe tubes and oxygen flow restrictors) from 10 Belgian and French hospitals

Inlet pressure:

For TTs, the maximum, median and minimum inlet pressures were 6.3, 5.4 and 4 Bar, respectively. For the OFRs, the maximum, median and minimum inlet pressures were 6.9, 6 and 4 Bar, respectively.

The flow of the flowmeters:

The intraclass correlation coefficient was equal to 0.999. This value reflected the excellent reliability of the measurements performed by OMF. Linear regression analysis showed an R^2 of 0.94 for TTs and 0.98 for OFRs (figure 1). For TTs, the bias value was -0.24 L/min (±0.88), and the limits of agreement were -1.97 to 1.48 L/min. For OFRs, the bias value was -0.30 L/min (±0.54), and the limits of agreement were -1.36 to 0.77 L/min (Table 2). At 2 and 4 L/min, TT values scattered out of the limits of agreement. At the same flow, OFR values remained within the limits of agreement. At 6 L/min and above, the number of values that were out of the limits of agreement increased approximately linearly for TTs and OFRs. However, the dispersion of the measurements was more prominent for the TTs compared to the OFRs (figure 2).

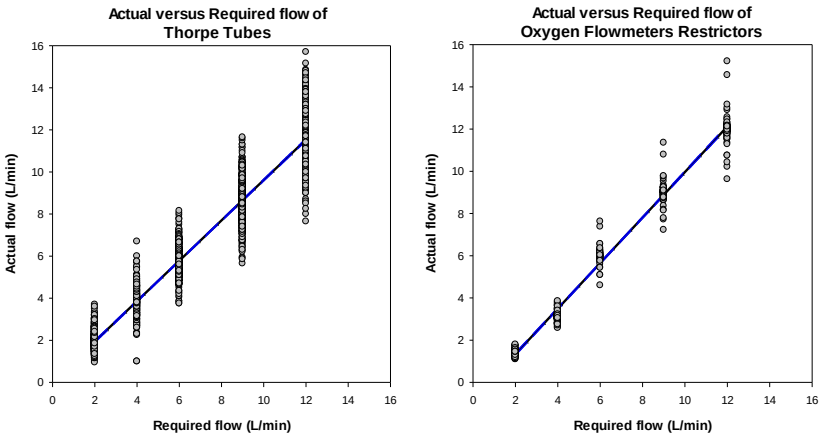

Figure 1: Linear regression analysis and scatter plot distribution between required flow and the actual flow of Thorpe tubes (n = 476) and oxygen flow restrictors (n = 96) at 2, 4, 6, 9 or 12 L/min oxygen flow rates

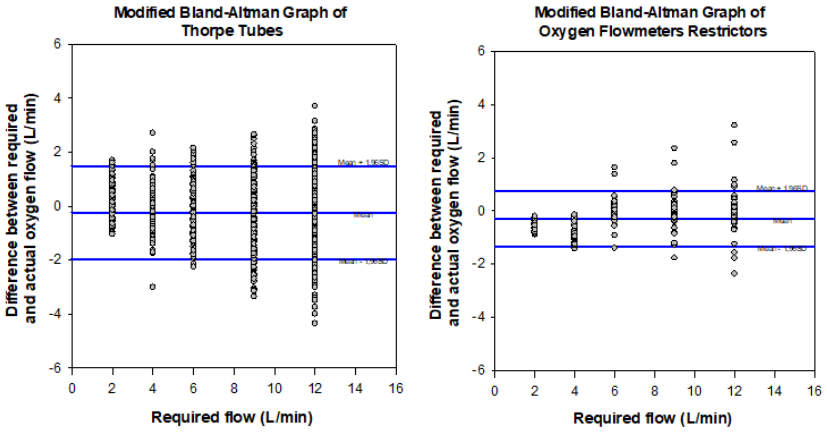

Figure 2: Modified Bland Altman analysis of the agreement between required flow and the actual flow for Thorpe tubes (n = 476) and oxygen flow restrictors (n = 96) at 2, 4, 6, 9 or 12 L/min oxygen flow

	Thorpe Tubes (n = 476)	Oxygen Flow Restrictors (n = 96)
Bias	-0.24	-0.30
Standard Deviation	±0.88	±0.54
Limits of agreement	-1.97 to 1.48	-1.36 to 0.77
Bias CI 95%	-0.28 to -0.21	-0.35 to -0.25
Lower Limit of Agreement CI	-2.03 to -1.90	-1.45 to -1.28
Upper Limit of Agreement CI	1.42 to 1.54	0.68 to 0.85

Table 2: Bias, standard deviation, limits of agreement and confidence interval (CI) for bias and lower and upper limit of agreement for Thorpe tubes and oxygen flow restrictors at 2, 4, 6, 9 or 12 L/min oxygen flow. Values are presented as L/min

DISCUSSION

This study evaluated the accuracy and precision of two OGF types, namely TTs and OFRs, using a calibrated thermal OMF. The linear regression analysis showed a strong association between the required and actual oxygen flow. The intraclass coefficient correlation demonstrated the excellent reliability of measurements performed by the OMF. The bias was slightly under the required flow for TTs and OFRs, but there were differences between the apparatuses. These data indicated accuracy variations in oxygen flow between the TTs and OFRs. Variances in the SD of the bias between TTs and OFRs showed that flow variability was higher for TTs compared to OFRs. These differences were observed at both low and high flow. At 2 and 4 L/min, TTs demonstrated a limited accuracy because some values scattered out of the limits of agreement. At the same flows, OFRs showed better accuracy because the values remained within the limits of agreement. From 6 L/ min and higher, the number of values that were out of the limits of agreement increased approximately linearly for TTs and OFRs. However, the dispersion of the measurements was more prominent for TTs compared to OFRS.

In 2012, Davidson et al. analyzed TTs from a tertiary hospital using a calibrated flow analyzer (275). The authors concluded that there was large variability among the measurements, mainly at low flow (1 and 3 L/min). Moreover, above 5 L/min, the actual flow was well above the required flow. Our study confirms these previous results and highlights that OFRs have better accuracy than TTs at low flow. Thereby, patients who are oxygenated successively with different OGFs are unlikely to have a stable oxygenation level because the accuracy of these devices is different.

TTs are fragile devices. Their accuracy can be altered when exposed to static electricity or a magnetic field, secondary to a mechanical shock or a lack of verticality. Additionally, wear

over time and changes in atmospheric pressure or room temperature (depending on the model) can alter performance. Mechanically, OFRs are much simpler compared to TTs. In theory, the holes through which the oxygen flows guarantee the sustainability of the flow accuracy. However, they accuracy is dependent on the inlet pressure. This factor may explain the accuracy differences between the two systems. Whatever the utilized system, there is always some inaccuracy in oxygen flow delivery. At high flow, the inaccuracy is higher both TTs and OFRs compared to low flow. In this case, practitioners who use prediction formulae to determining FiO_2 could over- or underestimate the health status of their patients (340,341). On the one hand, in paediatric care, the inaccuracies at low flow can lead to over or under oxygenation. Indeed, in this case, low flow variability may have a major impact on the FiO_2 of babies due to their low inspiratory flow (341–344). On the other hand, some patients with chronic obstructive pulmonary disorder (COPD) or obesity-associated hypoventilation can develop a hypercapnic decompensation with respiratory acidosis when an excessive oxygen flow is delivered (345). In this case, low oxygen flow inaccuracies can also affect these patients. At low flow, TTs show more variability compared to OFRs, and thus the risk of developing hypercapnia concomitant with oxygen therapy is more probable with TTs than OFRs.

To avoid over or under oxygenation, it is necessary to check the peripheral oxygen saturation (SpO_2), or blood gas analysis, as soon as a new or another OGF is used. Recent guidelines recommend a SpO_2 target of 88 to 92% in COPD patients, pending the blood gas results are adjusted to 94 to 98% if the $PaCO_2$ is normal (251,346).

Limitations: There are weaknesses in this study, as only one OFR brand was studied. In Belgium and France, this device is relatively new, as it has been on the market for less than 10 years. This factor explains why we found only one OFR brand available for our study. Further studies should be examined different OFR brands and also consider time effect on flow accuracy to confirm these results.

Conclusion: This study showed that oxygen flows delivered by OFRs were more accurate than TTs. Moreover, below 6 L/min, the OFR data were in the limits of the agreement. Above 4 L/min, some data began to fall outside the limits of agreement, and the trend increased with the elevation in flow. However, this variability was lower than the oxygen flow delivered by TTs. Changing oxygenation systems is risky and can lead to under- or over-oxygenation, particularly at high flow but also at low flow in paediatric patients. After any OGF change, SpO_2 measurements should be performed more frequently to ensure the level of oxygenation is always appropriate.

c) Study III: A New Formula for Predicting the Fraction of Delivered oxygen During Low-Flow oxygen Therapy

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Duprez F, Mashayekhi S, Cuvelier G, Legrand A, Reychler G.

A New Formula for Predicting the Fraction of Delivered Oxygen During Low-Flow Oxygen Therapy

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I. Introduction:

When trying to wean the patient off mechanical ventilation, spontaneous breathing trials assess the patient's ability to breathe while receiving no ventilator support. In general, these patients receive oxygen to avoid hypoxaemia. During this period, the fractional delivered oxygen (FDO_2) must be maintained within strict limits to avoid arterial oxygen variations. However, as reported by several studies, the FDO_2 varies according to the oxygen flow and/or the patient's respiratory pattern (respiratory frequency, tidal volume, etc.) (325,347,348). This raises the question about FDO_2 prediction in intubated or tracheotomised oxygenated patients who breathe spontaneously with a heat moisture exchanger (HME). In recent years, FDO_2 validated formulas have been promoted (349). However, they only take into account the administered O_2 flow and are only applicable in resting adult patients who breathe spontaneously and oxygenated through a nasal cannula, transtracheal catheters, tracheostomy, or endotracheal tube (349–351). Moreover, these formulas do not take into account the influence of the inspiratory flow (IF) on the variability of FDO_2 when the patient receives oxygen at low flow (35,277,352–360). We hypothesise that the IF has a major impact on the FDO_2 value during oxygen therapy at low flow and that these formulas are not accurate in clinical situations. This study aimed to validate a new FDO_2 prediction formula for tracheostomised or intubated patients with spontaneous breathing, which takes into account the IF and compares it to other formulas.

II. Material and methods

Part 1: The following FDO_2 prediction formula was developed (FDO_2 calculated - see online supplement) and compared to the FDO_2 measured in a bench study (FDO_2 measured).

$$FDO2 = 0.21 + (x) * LPM\ O2$$

$x = \frac{1}{(4*VE)}$ for Ti/Ttot = 0.33

$x = \frac{1}{(2.5*VE)}$ for Ti/Ttot = 0.50

LPM O_2: Oxygen flow (L/min)

VE : Minute ventilation (L/min)

Ti: Inspiratory time (sec)

Ttot: Total inspiratory and expiratory time (sec)

III. Model and settings

Spontaneous breathing was generated under ATPS conditions with a mechanical test lung (Dual Test Lung - Michigan Instruments, Inc. Grand Rapids Model 5600i) including two independent artificial lungs. With a special lung coupling clip, one lung was used to drive the second to achieve spontaneous breathing simulation. The settings of the artificial lung were resistance: ± 5 cm H_2O/L/sec and compliance: 0.06 L/cm H_2O. The first lung was driven by a mechanical ventilator Servo-i® set to volume control mode (continuous flow without auto-flow, time pause and inspiratory rise time at 0%, peep of 0 cm H_2O, the trigger was set at – 10 cm H_20 to avoid self-triggering). O_2 flow from a wall-mounted Thorpe Tube (Air Liquide™ RTM3; 0 to 15 L/min) was delivered through a HME Filter (Tracheolife® I Filter HME Kendall- Covidien – 353U19004 – Dead space volume: 16 mL). The HME filter was directly fixed to a flow sensor. The flow sensor was directly connected to the entry of the lung port inlet of the second DTL lung (See figure 1). An O_2 analyser port was located on the top plate of the second artificial lung. The three parameters were modified as follows:

O_2 flow (2, 3, 4, 5, 6 L/min)
Minute ventilation (VE) (5, 10, 15, 20 L/min)
Ti/Ttot (0.33 and 0.50)
Note: With these VE and Ti/Ttot IF values range from 10 to 60 L/min (Table 1)

	Inspiratory flow value for VE and Ti/Ttot			
VE (L/min)	5	10	15	20
Ti/Ttot = .33	15 L/min	30 L/min	45 L/min	60 L/min
Ti/Ttot = .50	10 L/min	20 L/min	30 L/min	40 L/min

Table1: IF values as regards to VE and Ti/Ttot values

Variables: The main measured variable was FDO_2 (expressed as the volumetric percentage of O_2 in the steady-state dual test lung).

FDO_2 was measured with a Datex Ohmeda™ O_2 Monitor (Model 5120, United States) calibrated with air room (21%) then at 30%, 35% and 50% with certified O_2 gas (Sensor type: Galvanic fuel cell reference 0237-2034-700; Accuracy: ± 2% of full Scale; Response time: 9 seconds; Measuring Range: 0-100%). FDO_2 was measured as the mean of 15 breaths after a stabilisation period of at least one minute.

O_2 flow was measured continuously with a Thermal O_2 Mass Flow Meter (Red Y Vögtlin™ Instruments GmbH, Switzerland: Accuracy ± 1.5% of full scale; Repeatability ± 0.1% of full scale).

VE and Ti/Ttot were measured with a data acquisition system IX-214 (Iworx®, United States) which included an SP-304 flow sensor and data-acquisition hardware connected to a Software Labscribe 3™ (Iworx®, United States). The flow sensor was calibrated using a 1-liter calibration syringe (Hans Rudolph 5540 ™ – United States) and ambient air. During this step, the gap between the required value and read value was a maximum of ± 30 mL. All measurements were made in triplicate.

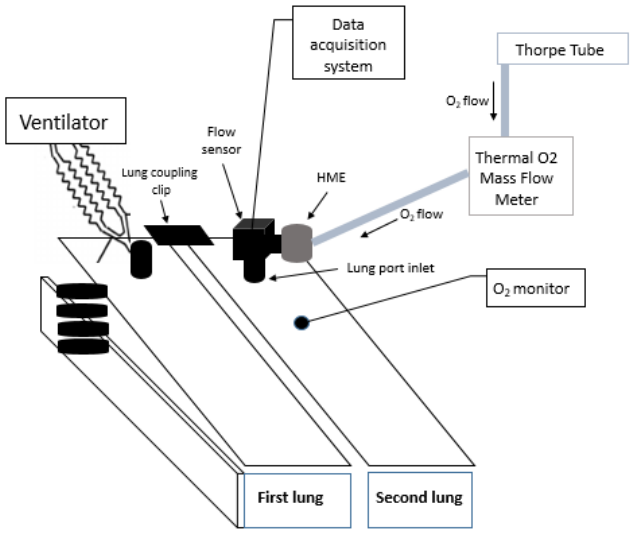

Figure 1: Bench test (Dual Test Lung)

The calculated FDO_2 values were compared to the FDO_2 values obtained through:

- Two previously validated formulas (PVF):

Shapiro formula:

$$FDO2 = 0.20 + (0.04 * LPM\ O2)$$

Vincent formula:

$$FDO2 = 0.21 + (0.03 * LPM\ O2)$$

Statistical Analysis: Data were analysed with the Sigma plot software (Version 12.0 Systat Software Inc., UK). Mean values are expressed with the standard deviation. The agreement between FDO_2 calculated by the mathematical model and the FDO_2 measured during the bench test measurements was expressed as proposed by Bland and Altman (338). As such, the bias and the limits of agreement are reported for each Ti/Ttot (95% CI for the difference between measurements). An Intra Class Correlation Coefficient (ICC) was calculated to measure the relation between FDO_2 calculated, and FDO_2 measured for each Ti/Ttot. To analyse the variability between the FDO_2 calculated with our formula and the measured FDO_2, a coefficient of variation was calculated for each Ti/Ttot. Finally, an agreement between FDO_2 calculated using the prediction formulas (Shapiro and Vincent) and the FDO_2 measured during the bench test measurements was calculated.

III. Results

In this bench study, when the O_2 flow and/or Ti/Ttot increases, the FDO_2 increases. When the VE increases, the FDO_2 decreases (figure 2).

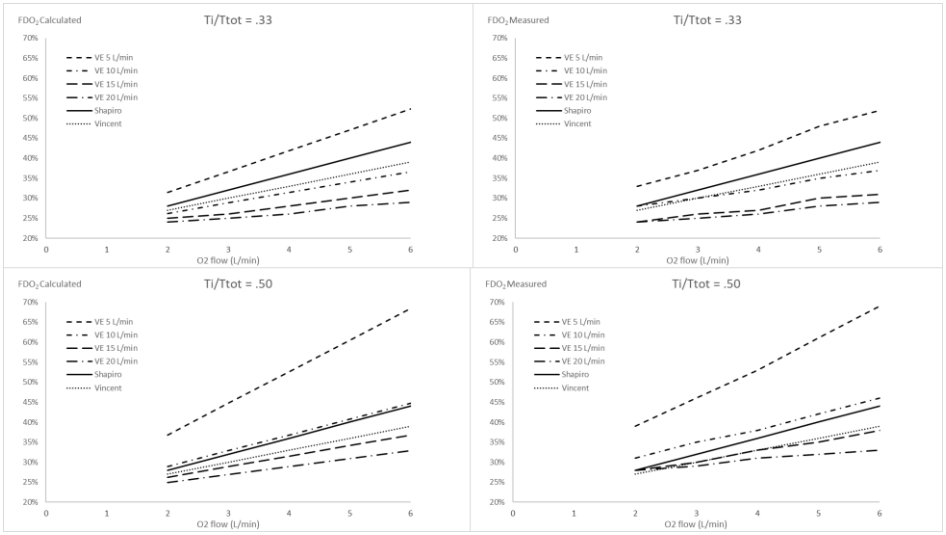

Figure 2: Graphic values of the calculated FDO_2 and the measured FDO_2 for O_2 flow ranging from 2 to 6 L/min, Minute Ventilation from 5 to 20 L/min for Ti/Ttot = 0.33 and Ti/Ttot = 0.50 and between the FDO_2 obtained with the Shapiro and Vincent formulas. IF values range from 10 to 60 L/min

Part 1

The results of the Bland Altman method between FDO_2 calculated using our mathematical model and the measured FDO_2 show that the bias value is 1.49% ± 0.84%, and the limits of agreement range from -0.17% to 3.14% (see figure 3). The ICC results were 0.991 for Ti/Ttot=0.33 and 0.994 for Ti/Ttot=0.50, and the coefficient of variation was 2.1% for Ti/Ttot=0.33 and 1.3% for Ti/Ttot =0 .50.

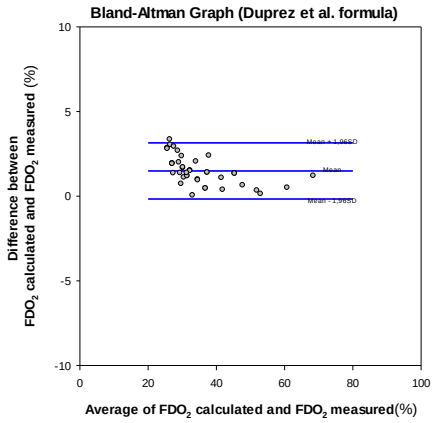

Figure 3: Bland-Altman graph comparing the FDO_2 calculated with our formula and the FDO_2 measured on the bench for an O_2 flow of 2 to 6 L/min, a Minute Ventilation ranging from 5 to 20 L/min) and a Ti/Ttot of 0.33 and 0.50. IF values range from 10 to 60 L/min

Part 2

The results of the Bland Altman method for the FDO_2 calculated by Shapiro and the FDO_2 measured on the bench shows that the bias value is 0.075% ± 8.66% and the limits of agreement range from -16.89% to 17.04%. For the Vincent formula, the bias value is 3.08% ± 8.56% and the limits of agreement range from -13.69% to 19.84% (see figure 4).

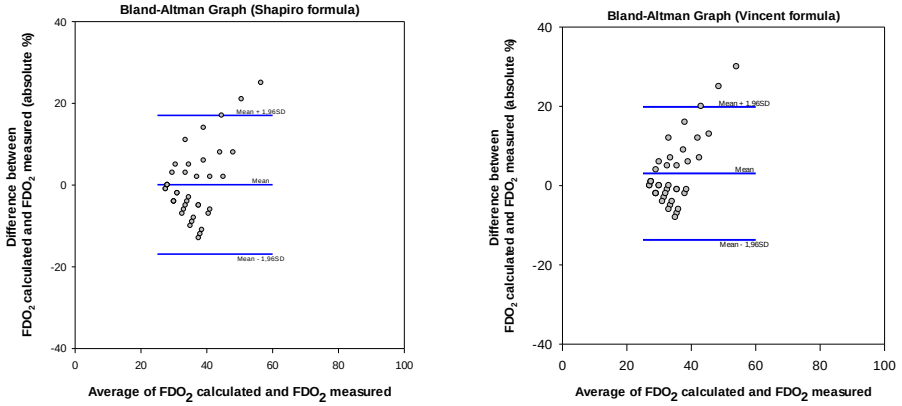

Figure 4: Bland-Altman graph comparing the FDO_2 calculated with the Shapiro formula and the measured FDO_2, and that calculated with the Vincent formula and the measured FDO_2, for an O_2 flow ranging from 2 to 6 L/min, Minute Ventilation ranging from 5 to 20 L/min) and a Ti/Ttot of 0.33 and 0.50. IF values range from 10 to 60 L/min

IV. Discussion

During O_2 administration through a Heat Moisture Exchanger in tracheostomised patients who breathed spontaneously, slight absolute differences were found between the FDO_2 calculated with our formula and the FDO_2 measured on the bench. The bias (with its limits of agreement), the ICC and the coefficient of variation were low between the measured and the calculated FDO_2, which shows the suitable validity of our prediction formula. However, when the FDO_2 increased, this bias varied, in an inversely proportional manner, probably due to the turbulence during high oxygen flow (361).

Bias between the calculated FDO_2 and the measured FDO_2 of both prediction formulas (Shapiro and Vincent) are small and show slight differences (Bias: Shapiro 0.075% ± 8.66% and Vincent 3.08% ± 8.56%). However, the standard deviation of these biases and the limits of agreement were more extensive compared to the values obtained with our formula.

According to our calculations, both prediction formulas are well suited for a healthy adult patient breathing at rest (VE= ± 8 L/min and a Ti/Ttot = 0.33). This means that these formulas are less suitable when the minute ventilation values differ from this threshold. Therefore, the Shapiro and the Vincent formulas should be used cautiously. Indeed, not considering these facts could lead to an over- or underestimation of oxygenation. The IF value is equal to the ratio between the minute volume and the inspiratory time-total time ratio:

$$\left(Inspiratory\ flow = \frac{(Rf * Vt)}{\frac{Ti}{Ttot}} \right)$$

According to our formula, the FDO_2 is roughly equal to the ratio between O_2 flow and IF. Therefore, in adult patients, as the IF value is much higher than the oxygen flow value, the impact of IF on FDO_2 is higher. However, in small patients, it is the opposite: The oxygen flow is higher than the IF. In this case, small variations of O_2 flow will have a major impact on FDO_2 (see figure 2). According to our research, this variation appears in several studies (1,11,19,22,23). Thus, when taking into consideration two VE values, the gap between both FDO_2 values increases when the oxygen flow increases (see figure 2). Consequently, during oxygen therapy, if the ventilatory pattern is not constant, the FDO_2 will not be constant either. When the O_2 flow is constant:

If the IF increases, then the FDO_2 will decrease. For example, under conditions of stress, hyperthermia, agitation, metabolic acidosis, pain, or exercise (i.e., COPD rehabilitation) (362,363). Similar observations were found by Couser et al. with patients oxygenated through a transtracheal catheter. These authors observed that a decrease in IF increased PaO_2 (355).

If the IF decreases, then the FDO_2 will increase. For example, under certain conditions of sedative medication and/or drug abuse, as well as in a reassuring and relaxing atmosphere, or when patients are in a deep sleep and are receiving O_2 by the low flow (354,357,364).

If the IF is small, then the FDO_2 value will be high, even with low oxygen flow (for example, during oxygen therapy in preterm infants).

These situations should encourage caution when IF varies during oxygenation at low flow because this can lead to a risk of over- or under-oxygenation. Indeed, if hypoxaemia (or hyperoxaemia) is only due to ventilatory pattern variations, it is sufficient to modify the oxygen flow to adjust the value of arterial pressure in oxygen. Other considerations should be considered regarding the dead space of HME. Indeed, during spontaneous ventilation with HME, the mixture with expired air could affect the oxygen fraction of inspired air. However, the dead space value of these devices generally varies from 9 to 29 mL (365): Firstly, the dead space of HME used in this study is equal to 16 mL, and secondly, a tracheostomy tube reduces the upper airway anatomical dead space by up to 150mL, or 50%. In these cases, the CO_2 contained in the anatomic dead space is lower than in normal physiological ventilation. Therefore, the impact on the FDO_2 decrease would be limited. Thirdly, during oxygenation with an oxygen administration device, in the expiratory phase, the continuous oxygen flow washout reduces the dead space, which limits the impact of CO_2 rebreathing (366).

The clinical utility of knowing the formula is that it could be helpful for the therapist to be aware of the initial set up for oxygen therapy for specific situations. For example, for small patients (or lower minute ventilation), low oxygen flow can deliver high FiO_2, for tall people (or high IF), high oxygen flow delivers less FiO_2 than with average IF, and during high oxygen flow in adults, any variation of IF will change the FiO_2 drastically.

The aim of this bench study was to validate a new formula to predict FDO_2 during oxygenation through an HME. The VE value and analysed oxygen flow ranged from 5 to 20 L/min (table 1) and from 2 to 6 L/min, respectively. However, we draw attention to the risk of under humidification of inspired gas during high oxygen flow through HME in patients who can breathe spontaneously (365).

Study limitations:

The present study had some limitations. In practice, using our prediction formula is difficult because patient exact IF value is unknown and oxygen flow meters have low accuracy (28,29,30).

Moreover, in this study, the IF used was continuous (rectangular form). However, the human IF wave is not continuous (waveform). As such, determining the exact value of FDO_2 is difficult in clinical situations. Also, our model has limitations because it does not reproduce anatomical dead space. Finally, the HME used is Tracheolife I®. Other systems exist with different dead space, which could affect results.

V. Conclusions

During supplemental oxygenation at low flow in patients who breathe spontaneously, the fractional delivered oxygen is influenced by the O_2 flow and the IF. According to our observations, the IF has a substantial impact on the FDO_2, and could therefore lead to over- or under-oxygenation if we are not careful. FDO_2 comparisons between the prediction formulas typically used by clinicians and FDO_2 measured on the bench show higher differences. Caution should be exercised when using these formulas for predicting FDO_2. Indeed, during the calculation of the PaO_2/FiO_2 ratio with the Shapiro or Vincent formulas, there is a high risk of overestimating the FiO_2, especially if the patient's inspiratory rate is high. This paper proposes a new prediction formula which takes into account oxygen flow and IF values. Our prediction formula shows good accuracy when predicting FDO_2 during supplemental oxygenation at low flow through a Heat Moisture Exchanger.

Mathematical reasoning:

During the inspiratory time (Ti), the respiratory muscles produce an intra-thoracic negative pressure and generate an airflow which falls into the airway and produces a tidal volume (Vt).

During O_2 administration at low flow, this volume, which penetrates in the upper airway in one breath, is composed of different volume gases:

a) O_2 volume due to inhaled oxygen flow (O_2f) during the inspiratory time: $(O2f * Ti)$

b) Air volume (containing principally N_2 and O_2) which equals the Vt amount minus O_2 volume due to oxygen flow during Ti. Note: Volume (a) + volume (b) = Vt value

As the O_2 volume in the air volume of (b) is equal to: $\big((Vt - (O2f * Ti) * 0.21)\big)$, we can write:

Tot insp O_2 bb = $(O2f * Ti)$ + $\big((Vt - (O2f * Ti) * 0.21)\big)$
Tot insp O_2 bb = Total inspired oxygen by breath (mL)
O_2 f : ML/sec
Ti : Sec
Vt: Litres

When redistributing, the formula becomes:

$$Tot\ insp\ O2\ bb = (O2f * Ti) + (0.21 * Vt) - (0.21 * (O2f * Ti)$$

As FDO_2, is equal to the ratio between the total inspired amount of O_2 and the total volume inspired, which enters the upper airway:

$$FDO2 = \frac{Tot\ insp\ O2\ bb}{Total\ volume\ inspired}$$

Then:

$$FDO2 = \frac{\big((O2f * Ti) + (0.21 * Vt)\big) - (O2f * Ti * 0.21)}{Vt}$$

When developed, the equation becomes:

$$FDO2 = \frac{(1 - 0.21) * (O2f * Ti) + 0.21 * Vt}{Vt}$$

Then: $FDO2 = 0.21 + 0.79 * \frac{O2f * Ti}{Vt}$

However, in this last equation, (O_2f) is expressed in mL/s which poses problems when using the ratio $\frac{Ti}{Vt}$ in calculating the FDO_2. To transform (O_2f) expressed in mL/sec into L/min, and the $\frac{Ti}{Vt}$ into a product of minute ventilation multiplied by $\frac{Ti}{Ttot}$, we need to use the following transformation:

$$\frac{O2f * Ti}{Vt} * \left(\frac{1}{Rf} * 60 * \frac{1}{Ttot}\right) = \frac{O2}{VE} * (\frac{Ti}{Ttot})$$

Rf: Respiratory frequency in cycles per minute
Vt: Tidal volume in litres
Ttot: Total respiratory time in seconds
O_2: Oxygen flow but expressed in L/min
VE: Minute ventilation in L/min and finally:

$$FDO2 = 0.21 + 0.79 * \left(\frac{O2}{VE}\right) * (\frac{Ti}{Ttot})$$

Provided that:

a) $(\frac{O2}{VE}) * (\frac{Ti}{Ttot}) \geq 0 \; and \; \leq 1$

b) O_2 purity = 100%

For Ti/Ttot = 0.33, if we consider that 0.79X0.33 was roughly equal to 0.25:

$$FDO2 = 0.21 + .25 * \left(\frac{O2}{VE}\right)$$

$$FDO2 = 0.21 + (\left(\frac{0.25}{VE}\right) * LPM\ O2)$$

$$FDO2 = 0.21 + \left(\left(\frac{1}{VE * 4}\right) * LPM\ O2\right)$$

For Ti/Ttot = 0.5, if we consider that 0.79X0.5 was roughly equal to 0.395:

$$FDO2 = 0.21 + .395 * \left(\frac{O2}{VE}\right)$$

$$FDO2 = 0.21 + (\left(\frac{0.395}{VE}\right) * LPM\ O2)$$

$$FDO2 = 0.21 + \left(\left(\frac{1}{VE * 2.5}\right) * LPM\ O2\right)$$

$$FDO2 = 0.21 + \left(\frac{1}{VE * 4}\right) * LMPO2$$

For Ti/Ttot = 0.33

$$FDO2 = 0.21 + \left(\frac{1}{VE * 2.5}\right) * LMPO2$$

For Ti/Ttot = 0.50

d) Study IV: The double-trunk mask improves oxygenation during high-flow nasal cannula therapy for acute hypoxaemic respiratory failure

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Adapted from:

Duprez F, Bruyneel A, Machayekhi S, Bouckaert Y, Brimioulle S, Cuvelier G, Reychler G.

The Double Trunk Mask Improves Oxygenation During High-Flow Nasal Cannula. Respir Care. 2019 Aug;64(8):908-914. doi: 10.4187/respcare.06520.

I. Introduction

High-flow nasal cannula (HFNC) oxygen therapy is a technique delivering a high flow of heated and humidified gas to hypoxaemic subjects. HFNC uses an air-oxygen blender to deliver high gas flows. HFNC allows a fractional inspired oxygen concentration (FiO_2) from 21% to 100% and generates a gas flow from 10 to 60 L/min (367,368). Compared to low-flow oxygen therapy, HFNC allows inspired oxygen concentration to be better controlled (353,363). However, the FiO_2 delivered by HFNC remains depending on the amount of flow, to the size of the nasal cannula and to whether or not the patient's mouth is open (365,369–371). In the case of respiratory distress, the inspiratory flow can exceed 100 L/min, causing a dilution of the administered oxygen by room air (370,372–374).

The Double Trunk Mask (DTM) is a device aimed to increase the FiO_2 in adult subjects who receive oxygen by a nasal cannula. The mask was developed by Hnatiuk et al. and modified by Duprez et al (70,374,375). The DTM is composed of a regular aerosol mask with two lateral holes. Corrugated tubing (15 cm length - ISO22) is inserted into each lateral hole. The dead space of the mask is 210 mL, and the volume of the trunks is 120 mL. The DTM is used in subjects who are already receiving O_2 through a nasal cannula (figure 1). The role of the tubing is to collect oxygen coming from the nasal cannula during expiration. During the next inspiration, the subject inhales the oxygenated gas mixture from the tubing instead of room air. The mask has been shown to increase PaO_2 without increasing $PaCO_2$ (376).

We hypothesise that, in subjects who receive oxygen by HFNC, the addition of the DTM would prevent the dilution of inspired gas by room air, due to high inspiratory flow and/or to the openness of the mouth, and thereby increase the FiO_2 and therefore the PaO_2. The primary outcome of our study was the effect of the DTM on PaO_2 in hypoxaemic subjects treated with HFNC. The secondary outcomes were $PaCO_2$ changes and subject comfort.

Figure 1: Subject receiving classical HFNC with Double Trunk Mask (DTM). The DTM is composed of a standard aerosol mask (nebulizer and mouthpiece) with 22 mm of diameter lateral holes. Here, 15 cm of corrugated tubing was inserted to each side of the mask. The DTM is just applied to the face of the subjects breathing spontaneously without obstruction airways. Note: Subjects already receive O_2 through a nasal cannula. Nasal cannula is positioned according to the manufacturer's recommendations. 1: Trunk – 2: Nasal Cannula of HFNC – 3: Nebuliser of aerosol – 4: Aerosol mask

II. Methods

This is a prospective multi-centric crossover pilot study with evaluation by an independent evaluator. The ethics review board of the Erasmus Hospital and Epicura-Tivoli Hospital approved the study protocol. Written informed consent was obtained from all participants before inclusion (NERB034008). The study was registered with ClinicalTrials.gov (NCT03319602).

We included 15 non-intubated adult subjects with acute hypoxaemic respiratory failure (AHFR) admitted to the intensive care unit (ICU) of the Epicura Hospital, Hornu, Belgium, and Tivoli University Hospital, La Louvière, Belgium, from October 2017 to March 2018.

Criteria for inclusion were: Hypoxaemia (PaO_2/FIO_2 < 300 mmHg), new or worsening respiratory symptoms (e.g. dyspnoea, shortness of breath, etc.), use of accessory respiratory muscles, respiratory rate above or equal to 30 breaths per min, presence of an arterial catheter, and absence of plan to change the ventilatory conditions over the next 2

hours (e.g. use of non-invasive or invasive mechanical ventilation). Subjects were included only in periods when the investigators were present in the ICU. The level of severity of hypoxaemia was assessed as follows: Mild (PaO_2/FiO_2 between 200 and 300 mmHg), moderate (PaO_2/FiO_2 between 100 and 200 mmHg), and severe (PaO_2/FiO_2 below 100 mmHg). The exclusion criteria were: COPD, pulmonary fibrosis, obesity-associated hypoventilation, respiratory acidosis, cardiogenic pulmonary oedema, systolic arterial pressure below 60 mmHg or treatment by epinephrine above to 0.1 µg/kg/min, altered consciousness (score 12 or less on the Glasgow Coma Scale) and acute confusion. A CONSORT flow diagram representing participant enrolment, allocation, and analysis throughout the study is presented in figure 2.

Data collection

At enrolment, the following variables were collected: Age, weight, height, arterial pressure (systolic/diastolic/mean), heart rate, respiratory rate, arterial blood gases, Sepsis-related Organ Failure Assessment (SOFA) score on day of study, Medical Research Council (MRC) dyspnoea 5-point Likert scale, subject comfort using a numeric scale, and the Glasgow Coma Scale. The aetiology of AHRF and the presence of bilateral pulmonary infiltrates on a chest X-ray were reported by a physician.

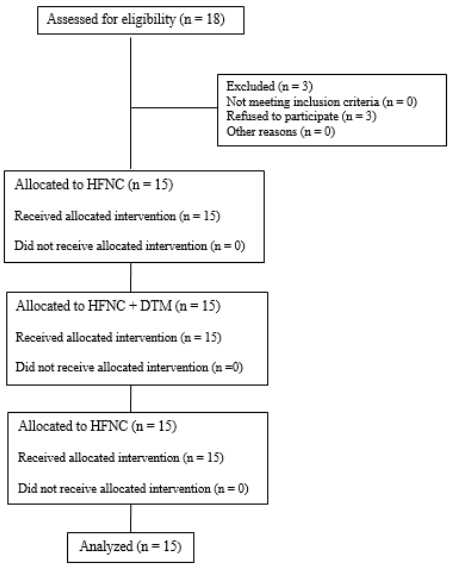


Figure 2: CONSORT flow diagram representing participant enrolment, allocation, and analysis throughout the study

An AIRVO™ 2 generated the HFNC (Fisher and Paykel Healthcare, Auckland New Zealand) connected to a standard nasal prong (Optiflow™ nasal cannula for MR850 AIRVO Auckland New Zealand). The AIRVO™ 2 can deliver air flows from 10 to 60 L/min. A calibrated ultrasonic oxygen analyser measured the gas outlet of the system. AIRVO TM 2 was connected to an RTM3 oxygen Thorpe Tube (Air Liquide™ – Paris – France - O_2 flow from 0 to 60 L/min - Ref: 11.05.121.17) connected to a wall oxygen supply. DTM consists of an aerosol mask (Dahlhausen, Köln, Germany - ref: 01.000.01.120 (CE0123) and two corrugated tubes (Dahlaussen, Köln, Germany- ref: 13.801.01.016 (CE123) with a 22mm diameter (ISO22), shortened to 15 cm (figure 1).

Study protocol

Subjects were placed in a semi-recumbent position, in a quiet environment, and oxygenated with Optiflow™ nasal cannula. The FiO_2 and airflow rate were adjusted to obtain a peripheral SpO_2 above or equal to 90%. In some cases, the flow rate was adjusted to the patient who breathes comfortably. During high inspiratory flow, the airflow was initially adjusted to 60 L/min. No further modification of the HFNC settings was made during the investigation (figure 2).

Each subject went through 3 treatment phases:

Phase 1 (HFNC): Oxygen was administered using only HFNC for 30 minutes. After that, if the subject remained stable, arterial blood gases were measured using the arterial catheter.

Phase 2 (HFNC + DTM): The clinician placed the DTM over the nasal prongs, without changing the settings of HFNC (figure 1). Arterial blood gases were measured after 30 min. Subjects in whom the PaO_2 increased by at least 10% were considered as "responders."

Phase 3 (HFNC): The DTM was withdrawn while HFNC was continued with the same settings. Arterial blood gases were again measured after 30 min.

The respiratory and haemodynamic statuses were also reassessed at the end of each study phase. The subjects did not receive any instruction regarding opening or closing their mouth during any of the study phases.

Statistical analysis

Data were analysed with the Sigma plot program (Version 12.0 Systat™ Software Inc., Salisbury Road, Hounslow, London, UK). Data are presented as the mean ± standard deviation for normally distributed variables, and median and interquartile range for non-normally distributed variables. The distribution of data was evaluated with a Kolmogorov Smirnov test. Differences between variables across study phases were tested by one-way

analysis of variance (ANOVA) for repeated measures for parametric data and by a one-way repeated measures ANOVA on ranks for non-parametric data. Pairwise multiple comparison procedures (Tukey test) were performed when statistically significant differences were found between groups.

In the absence of data allowing for the estimation of sample size, we decided to enrol 15 subjects in this exploratory study, with the hypothesis that this number would be sufficient to detect a significant variation in PaO_2.

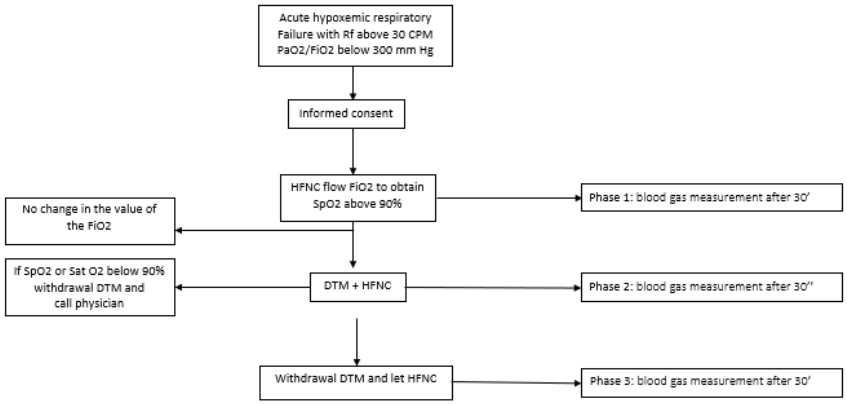


Figure 3: Enrolment and follow-up of the study participants in a cross over design

HFNC indicates therapy with high-flow oxygen through a nasal cannula. DTM + HFNC denotes the addition of the Double Trunk Mask over the HNFC nasal cannula. FiO_2 denotes fractional inspired in oxygen and partial pressure of carbon dioxide in arterial blood ($PaCO_2$).

III. Results

The subjects are described in table 1. Fifteen subjects were included: 13 men (86%) and two women (13%). The age was 67 ± 16 years, and body mass index was 26 ± 6 kg/m². At enrolment, all subjects had a PaO_2/FiO_2 of less than 200 mmHg with thirteen (87%) less than 100 mmHg. The ROX index was equal to 6.3 ± 1.9. The flow during HFNC was 51 ± 6 L/min (range 40 to 60 L/min). No adverse events were observed during the study.

Compared with HFNC alone, HFNC + DTM increased PaO_2 from 68 ± 14 to 85 ± 22 mmHg ($p<0.001$) and did not affect $PaCO_2$ ($p=0.18$) (tables 1 and 2, figure 4). In the 11 responders, the PaO_2 increase from 63 ± 12 to 88 ± 23 mmHg ($p<0.001$). After removal of the DTM, all variables returned to the baseline values.

Subject	Age (years)	Sex	BMI	Set FiO2 (%)	Flow (L/min)	SOFA Score on admission	Etiology of AHRF	Bilateral infiltrates	Immunodeficiency	Current or past smoking	ROX index
1	59	Male	34	80	50	4	CAP	YES	NO	NO	4.8
2	63	Male	18	55	60	5	HAP	NO	NO	NO	8.02
3	67	Female	21	80	60	4	HAP	YES	YES	NO	5.68
4	44	Male	31	50	50	4	CAP	NO	NO	NO	9.2
5	67	Male	24	100	60	4	CAP	YES	YES	YES	4.65
6	86	Male	22	80	50	5	CAP	YES	NO	NO	5.27
7	62	Male	28	70	50	3	CAP	YES	YES	NO	9.33
8	23	Male	21	80	50	5	ES	YES	NO	NO	6.86
9	54	Female	34	90	50	8	CAP	YES	NO	YES	5.63
10	82	Male	23	100	50	4	CAP	YES	YES	NO	4.45
11	73	Male	25	70	40	6	CAP	YES	NO	NO	6.71
12	71	Male	31	70	40	5	CAP	YES	NO	YES	9.05
13	76	Male	35	70	50	5	CAP	YES	NO	NO	6.43
14	82	Male	23	90	50	5	CAP	YES	NO	NO	4.31
15	76	Male	19	80	50	11	CAP	YES	NO	NO	3.71
Total or mean ± SD	67±16	13 male	26±6	78±14	51±6	5±2	12 CAP	13 yes 2 NO	3 yes 12 NO	3 yes 12 NO	6.3±1.9

Table 1: Subject descriptions. BMI: body mass index (Kg/m^2) – FiO_2: Fractional inspired oxygen – SOFA: Sequential organ failure assessment - AHRF: Acute hypoxaemic respiratory failure - CAP: Community-acquired pneumonia, HAP: Hospital-acquired pneumonia, ES: Extrapulmonary sepsis - ROX index is defined as the ratio of pulse oximetry per fraction of inspired oxygen to respiratory rate

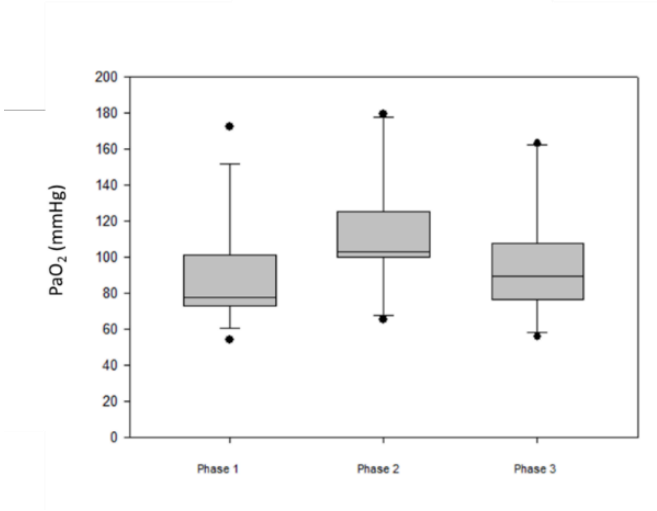


Figure 4: PaO_2 comparisons by Friedman test between only HFNC during phase 1, HFNC with the addition of DTM during phase 2, only HFNC during phase 3. The boxes illustrate IQR, P25, P50, and P75; the whiskers correspond to the 5th and 95th percentiles, dots are outliers. PaO_2 levels show a statistically significant increase in phase 2 compared to phase 1 (+26%). When the mask was removed, the PaO_2 returned to the baseline values during the washout periods and subsequently during the recovery period

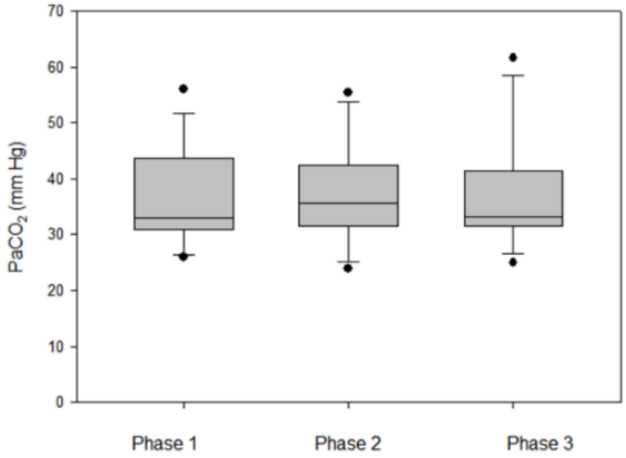


Figure 5: $PaCO_2$ comparisons by Friedman test between phase HFNC (Phase 1), HFNC + DTM (phase 2), and only HFNC (phase 3). $PaCO_2$ levels did not show any statistical difference between all phases (P = 0.18)

IV. Discussion

The present study shows that in subjects with moderate (n=4) and severe (n=11) AHRF already receiving HFNC oxygenation, the addition of DTM to HFNC increased the PaO_2 from 68 ± 14 to 85 ± 22 mmHg ($p<0.001$) and did not affect $PaCO_2$ ($p=0.18$). In the 11 responders, the PaO_2 increased from 63 ± 12 to 88 ± 23 mmHg ($p<0.001$). The increase in PaO_2 can be explained by the removal of the contamination of inspired gas by room air when inspiratory flow value is above the gas flow delivered by HFNC and when the nasals prongs are not correctly located in the nostrils. Such contamination by room air is known to decrease the true, delivered FiO_2 (352,354–360,366,377,378). When the DTM is added, inspired gas is no longer contaminated by room air, but by the oxygen-enriched mixture collected in the additional tubes (374,379). Actual FiO_2 increases closer to the set FiO_2, thereby increasing the subject oxygenation. However, there were four non-responders. We believe this is due to the differences in the patient's inspiratory flow (not measured because of technical limits) and/or due to the air contamination through leaks around the mask. Few studies have examined the inspiratory flow values during acute respiratory failure. Two studies have examined the role of inspiratory flow in healthy volunteers receiving HFNC at rest and during exercise (5,28). The authors concluded that HFNC could not be considered a constant oxygen administration system because the accuracy of the system depends on the wearer's breathing pattern, especially if the inspiratory flow is above the HFNC gas flow value.

In our study, the $PaCO_2$ remained unchanged despite the increase of dead space. This observation can be explained by the tubes washout by gas coming from the HFNC (376). Indeed, with gas flow from HFNC of 60 L/min (i.e., 1000 mL/sec), the total trunk volume of 120 mL is entirely washed-out in about 0.12 seconds. Even with the high respiratory rate and short expiratory duration of subjects with HARF, this limited duration is appropriate to wash out the expired CO_2 from the tubes. According to our calculations, a respiratory rate higher than 60 breaths per min would be required to result in CO_2 rebreathing.

Another issue relates to our classification of subjects with acute hypoxaemic respiratory failure (AHRF). The primary determinant of our subject's classification into mild, moderate, and severe AHRF subgroups is the PaO_2/FiO_2. Our data show that actual FiO_2 is overestimated in many subjects with AHRF, resulting in factitious low PaO_2/FiO_2 values. The use of DTM may reverse this confounding effect by minimising the difference between set FiO_2 and actual FiO_2 and restoring a more real PaO_2/FiO_2 ratio.

In a general way, hyperoxaemia is related to the poor outcome (380); moreover severe hypoxaemia is deleterious to patients and should be considered as an indication for positive airway pressure and mechanical ventilation (381). The DTM should thus not be used only to delay intubation and prolong the duration of critical hypoxaemia. Suggested indications

would be transient hypoxaemia (e.g., related to cardiogenic pulmonary oedema expected to respond rapidly to medical therapy), pre-oxygenation before intubation, haematological patients (in whom invasive mechanical ventilation carries specific risks) or do-not-intubate patients. The DTM has an obstructive design that can cause discomfort. Although few subjects complained, DTM could be used in respiratory distress, especially when the inspiratory flow reach up over 60 L/min or during refractory hypoxaemia.

The study has limitations. The number of included subjects is small, and the male/female ratio is high, which may not be representative of general ICU populations. The sequence of treatments was not randomised, but time effects can be reasonably excluded thanks to the double cross-over design. On the other hand, subjects were included in the study only when investigators were present in the ICU. The results thus deserve to be confirmed in a more extensive set of ICU subjects with hypoxaemic acute respiratory failure.

V. Conclusion

Our data show that in AHRF subjects already receiving HFNC oxygenation, the addition of DTM to HFNC does increase the PaO_2 without significantly changing the $PaCO_2$. The DTM can thus be useful in subjects during transient hypoxaemia, pre-oxygenation before intubation, in haematological patients and do-not-intubate patients, and following stressful events, or other conditions associated with an increase in inspiratory flow.

e) Study V: Improvement of arterial oxygenation using the Double Trunk Mask above low flow nasal cannula: A pilot study

F Duprez, S. Cocu, A Legrand, S Brimioulle, S Mashayekhi, G Bodur, A Bruyneel, Jean Roeseler, G Cuvelier and G Reychler

To the Editor,

The Double Trunk Mask (DTM) is an original mask (figure 1) which boosts the inspired fraction in oxygen (FiO_2) during oxygen therapy with a high flow nasal cannula (HFNC) (382). In a previous study, the association of the DTM over HFNC showed an increase of the PaO_2 without $PaCO_2$ increase despite an added dead space of 210 ml due to the mask and the trunks (382). It can be explained principally by the washing of the trunks by the high flow (until 60 L/min). However, few studies have examined the effect of DTM on PaO_2 and $PaCO_2$ during oxygen therapy at low flow. Indeed, the use of low flow oxygen should lead to a risk of CO_2 rebreathing (383). In fact, during expiration, the additional oxygen does not escape but is collected in the two trunks. During inspiration, the patient receives this oxygen-enriched gas mixture from the trunks instead of the air in the room. The DTM thus acts like a "reservoir" and results in increased FiO_2. However, thanks to its dead space volume, the DTM could also contribute to increasing $PaCO_2$ by increasing rebreathing (383). Therefore, we prospectively investigated the effects of the DTM and its dead space on arterial blood gases in hypoxaemic patients already receiving low flow oxygen through NC. The study was conducted in the ICU of the Epicura Hospital (Hornu, Belgium) between June and November 2018. Patients were eligible if they were at least 18 years-old, had respiratory symptoms, received oxygen via NC but remain hypoxaemic (PaO_2 < 75mmHg) (36,384–386), and were not considered for intubation or tracheotomy. Exclusion criteria were COPD, hypercapnia ($PaCO_2$ >45 mmHg), heart failure, shock or hypotension (vasopressor therapy), obesity-associated hypoventilation, and altered consciousness (Glasgow Coma Scale score < 13).

Oxygenation was ensured through standard NC (model 1616-21, Convatec™, Auckland, New Zeeland) or through standard NC with an additional DTM. The DTM is made of an aerosol mask (model 01.000.01.120 (CE0123), Dahlhausen, Köln, Germany) and two corrugated tubes with a 22 mm diameter and 15 cm length ("Trunks" - ref 13.801.01.016, Dahlhausen, Köln, Germany) inserted into the lateral holes of the aerosol mask (figure 1). Age, height, weight, heart rate, respiratory rate, arterial blood pressure, arterial blood gases, sepsis-related organ failure assessment (SOFA) were collected upon admission. Patients were placed in a semi-recumbent position and were received oxygen at a rate initially adjusted to obtain a pulse oximetry (SpO_2) value equal to or above 90%, and this then maintained unchanged during the investigation. Each patient went through three phases of 30 minutes: (1) NC alone, (2) NC + DTM over the NC (NC + DTM), (3) NC alone (NC). The patients did not

receive any instructions regarding opening or closing their mouths during the study. At the end of each phase, blood gases were collected again. Data were analysed with SigmaPlot programs (Version 12.0, Systat™ Software Inc., London, UK). Data distribution was evaluated with the Kolmogorov-Smirnov test. Overall differences were tested by 1-way ANOVA for repeated measures for parametric data, and by a Friedman test for non-parametric data. In the presence of significant differences, comparisons between specific phases were evaluated with the Tukey test. A sample size of fifteen patients was calculated to detect a clinically significant difference in PaO_2 increase at least 25% with an α of 5% at 80% power. Ten men and five women were included. The age was 69 ± 14 years, and the body mass index 27 ± 8 kg/m². The SOFA score was 6 ± 2, and the oxygen flow rate of 5 ± 3 L/min. Along the three study phases, PaO_2 increased from 60 ± 7 mmHg (NC) to 90 ± 14 mmHg (NC + DTM) and then decreased to 59 ± 7 mmHg (NC) ($p < 0.001$). $PaCO_2$ increased from 39 ± 5 mmHg to 42 ± 6 mmHg and then decreased to 38 ± 5 mmHg ($p < 0.001$). Arterial pH decreased from 7.42 ± 0.03 to 7.39 ± 0.03 and then increased to 7.42 ± 0.03 ($p < 0.001$) (figure 1). No statistical difference was found in the respiratory rate, heart rate, or mean arterial pressure.

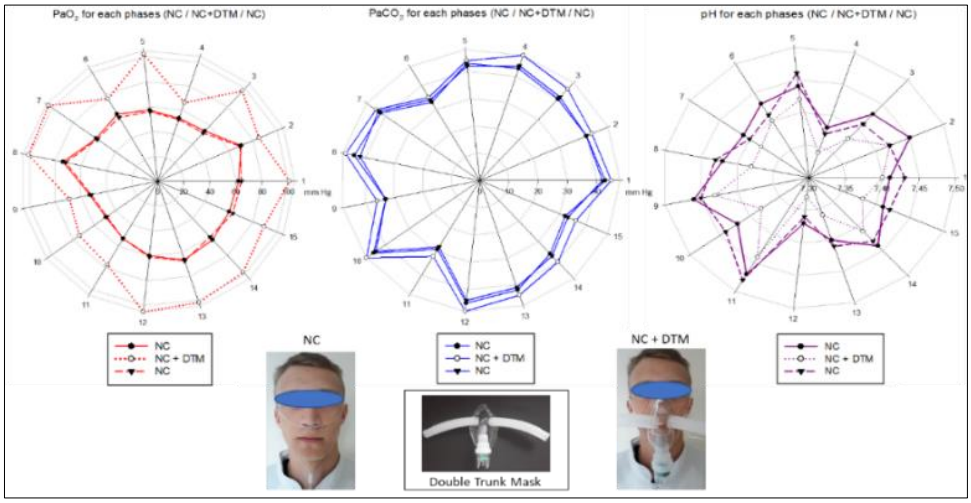


Figure 1: Schematic representation of individual changes in PaO_2, $PaCO_2$, and pH. Numbered lines 1–15 represent the 15 patients. Concentric values denote the individual values of PaO_2 (0-100 mmHg), $PaCO_2$ (0-40 mmHg) and pH (7.30-7.50) obtained during the three phases (NC alone, NC + DTM, NC alone)

The study shows that, in patients with hypoxaemic respiratory failure who receive oxygen by NC at low flow and remain slightly hypoxaemic, the addition of DTM over NC (at the same

oxygen flow rate) strongly increases the PaO_2 and minimally affects the $PaCO_2$ and pH. The observed increase in $PaCO_2$ could be explained by the Haldane effect and/or by a reduction of hypoxic pulmonary vasoconstriction, as well as by the increasing $FiCO_2$ due to the device's dead space (238,383,387). Indeed, it has been shown that when the $FiCO_2$ is increased by 2% in healthy subjects, compensatory hyperventilation is incomplete, and the $PaCO_2$ increases by 0.25kPa (1.8 mmHg) (388). As a unique mechanism, >50% rebreathing would be needed to explain the mean $PaCO_2$ increase of 3 mmHg. However, the dynamic apparatus dead space of the masks is not always equal to their static volume (389), which could also explain the limited increase of $PaCO_2$ during the DTM phase.

Moreover, on the one hand, the leaks between the DTM and the face allow the expiratory flow to escape readily and consequently decrease rebreathing (390).

On the other hand, the continuous oxygen flow could play a role in the dead space washing during the expiration phase (2).

On the third hand, the $PaCO_2$ is normal when initially receiving oxygen via NC. Thus, it is probably that compensatory hyperventilation was likely not to be present at the start of this study.

In the end, this limited increasing of the $PaCO_2$ could also be due to a successful increase of the tidal volume (Vt) to readjust the dead volume/tidal volume ratio (387,391,392). Whatever the mechanism, the increase in $PaCO_2$ was small and probably without clinical relevance.

The positive effects reported here should be confirmed through a study with a more extensive set of patients with hypoxaemic respiratory failure. As such, the effects of DTM could also be tested: During more prolonged periods of application, in more severe COPD patients, in obesity-associated hypoventilation, during pre-oxygenation before intubation, in "do-not-intubate" patients, and possibly in mass casualty events (sudden increase in oxygen demand but limited resources). HFNC treatment is increasingly being used in ICU medicine in hypoxaemic patients not sufficiently oxygenated using oxygen administration via NC. The positive effects of the DTM at low flow oxygen NC in hypoxaemic patients should be compared with HFNC to detect a potential benefit.

It should be noted that severe hypoxaemia is deleterious and is an indication for mechanical ventilation. Moreover, over-oxygenation is deleterious during heart failure. The DTM is not recommended in patients with critical hypoxaemia needing mechanical ventilation.

f) Study VI: ROX index calculation could be affected by the difference between actual and required FiO_2 delivered by high flow nasal cannula and by the lack of repeatability of SpO_2 and respiratory rate measurements.

Submit to Anaesthesia and Intensive Care journal

F Duprez, G Reychler, S Mashayekhi, A Bruyneel, X Witebole

To the Editor,

We read with interest the article by Roca and colleagues who highlighted the importance of three repeated evaluations of the ROX index during high flow nasal cannula (HFNC) use to predict HFNC failure and subsequent need for mechanical ventilation (MV) (330). The ROX index is defined as the ratio of SpO_2/FiO_2 to respiratory rate (RR). The authors found that patients with a ROX index ≥ 4.88 at different time points of HFNC therapy were less likely to require MV.

Although the measures of ROX parameters seem easy to perform, it might not always be the case in some clinical conditions.

First, SpO_2 measurement is not always accurate and reliable. Factors that can affect the accuracy of the measurement are the physiologic, environmental, technology failures and human error. For instance, it was shown that the measure of SpO_2 with a finger probe had the lowest agreement with SaO_2 than the earlobe site (393). Moreover, for Ritchie et al. there was a significant lack of agreement between SpO_2 measurements and SaO_2 (394). In their Study, Roca et al. do not specify where the measurement site is and if it was always the same in the studied patient.

Second, the required FiO_2 delivered by HFNC is not always an accurate parameter. In a randomised cross-over study, Duprez et al. included fifteen ICU patients receiving conventional HFNC, and found that the addition of a special mask with a large dead space (the Double Trunk Mask) over the nasal prongs had some impact on PaO_2 by the optimisation of FiO_2 (consequently, the SpO_2 was increasing). Differences observed on PaO_2 with and without the Double Trunk Mask ranged from -11% to 58% (395).

Moreover, both inspiratory flow and open mouth can affect the actual FiO_2: On the one hand, in patients with severe respiratory failure, the inspiratory flow rate can vary from 30 to above 120 L/min (396). In the last case, if the HFNC flow rate is equal to 60 L/min (max value), a high inspiratory flow above this threshold will have an impact on the actual FiO_2 because ambient air will be inhaled. On the other hand, in a bench study, Chikata et al. have

studied measured FiO_2 under various breathing patterns. They conclude that high tidal volume can affect actual FiO_2 during HFNC therapy (397). Finally, Ritchie et al. have studied the effect of high inspiratory flow on decreasing FiO_2 delivered by HFNC. They conclude that HFNC should not be considered as a fixed oxygen administration system because of the accuracy of the system depends on the breathing pattern (370).

Finally, respiratory rate is highly variables parameter; inspiratory flow is not constant and varies breath-by-breath. Emotion, pain, acidaemia, or hypoxia may also interfere with respiratory rate. While there is a good agreement between observers in respiratory rate measurement, inter-observer variability may account for a difference of up to 6 breaths min(-1) (398). This respiratory rate measurement difference could have a dramatic impact on the decision to initiate aggressive treatment or not after ROX calculation.

Because of the above reasons, in a clinical situation, the calculation of ROX index could be sometimes over or underestimate.

According to the study of Roca et al., a difference between actual and required FiO_2 (0.6 vs. 0.7) in five virtual patients with an SpO_2 equal to 96% with RR ranging from 29 to 33 cpm led to intubation in one patient in the "actual FiO_2 group" (Rox index < 4.88) compared to five patients in the "required FiO_2 group". This ROX index difference dramatically increases with increasing difference between actual and required FiO_2.

Further studies should be undertaken to evaluate the inter-observer repeatability of the ROX index calculation. Moreover, the agreement between actual and required FiO_2 delivered by HFNC should be studied thoroughly.

Chapter 8: General discussion and conclusion

Background

It is currently well-documented that oxygen therapy improves the oxygen status of the majority of hypoxaemic patients. However, its clinical effectiveness is limited during hypoxemia. Oxygen therapy is often a primary medical treatment and should be delivered precisely and accurately to avoid harmful effects. The goal of oxygen therapy is to maintain SpO_2 or PaO_2 within physiologic limits by titrating the flow rate. It may cause harm when used inappropriately (43).

This thesis highlighted the importance of some factors which can affect the quality of oxygen administration, including the accuracy of oxygen flow meters, oxygen tubing circuit leaks, inspiratory flow values for both low and high oxygen flow, mask dead space (Double Trunk Masks), and position of the mouth.

By reviewing the literature, this thesis has highlighted the lack of repeatability of oxygen administration assessment measures in intensive care such as FiO_2, SpO_2, respiratory rate, and ROX index.

The oxygen quality administration is dependent on the following variables, as described in the sections below.

A) Accuracy of oxygen flow meters

1) Thorpe Tube (TT):

TT flow meters are the most frequently used device for oxygen administration. At low flow, their accuracy is aleatory. Moreover, flow meters set at high flow rates can result in excessive administration of oxygen and subsequent hyperoxia. Hyperoxia can be harmful when occurring for more than a brief time (399). A study on the accuracy of oxygen administration conducted across two medical units showed that of the 206 patients included, only 90 were receiving oxygen as prescribed. The Thorpe Tubes were inaccurate, and the range of flows being delivered as a percentage of the indicated flow varied from 15% at 8 l/min to 40% at 1 and 2 l/min (43,275,399,400). In a large, multi-centre study evaluating the accuracy of wall-mounted oxygen flow meters in common conditions of use, we have observed that delivered oxygen flows are generally close to desired oxygen flow at low flow rates. However, with increasing flow, the oxygen flow rate dispersion increases. These results were obtained in a European setting and confirm the results from the study by Davidson et al. using South American-brand oxygen flow meters (275).

What are the reasons for this inaccuracy?

When the flow meter leaves the factory, its accuracy in standard conditions is guaranteed by the manufacturer. With time and usage, its accuracy can become altered and the delivered flow can differ from the required flow. Based on international standards (ISO 15002), a significant error in the delivered flow is so frequently observed that nearly 33 ± 8% of oxygen flow meters should be removed from use (401). The inaccuracy of oxygen flow meters might raise concerns any time the device has to be changed. This may occur when a patient has to move from one hospital department to another, or when a flow rate determined at hospital has to be applied at home. The absence of reproducibility between devices can lead to a variation in the oxygen flow actually delivered and to the over- or under-oxygenation of patients. Clinicians must be aware of these inaccuracies. Long-term oxygen therapy at home showed its ability to correct haemodynamics in hypoxaemic COPD patients and to improve their chances of survival (264). However, it has also been shown that an inadequate oxygen supply was ineffective in increasing the life expectancy of these patients. During acute hospital or chronic oxygen therapy, under-oxygenation problem can easily be addressed by checking the transcutaneous oxygen saturation (SpO_2) each time a new device is used, and by adapting the required flow rate to the new situation. Over-oxygenation is more problematic for the following reasons. First, some COPD patients and patients with obesity hypoventilation syndrome can develop a hypercapnic decompensation with respiratory acidosis when an excessive oxygen flow is delivered, even when transcutaneous saturation initially reaches the target value. Both hypoxaemia-hypoxia and hyperoxygenation can be deleterious. It is therefore important to have accurate and reliable devices available, especially when blood gas analysis is not directly accessible (401). Finally, inappropriate flow can cause logistical problems. This supply problem can be critical during transport outside the hospital or when oxygen therapy is used to increase mobility and ambulation time (402).

These results confirm the limited accuracy of wall-mounted oxygen flow meters when studied in hospital settings. Inaccuracy could lead to inappropriate oxygenation, particularly at low rates of flow. re-establishing the proper flow rate is therefore mandatory after each change of device. Furthermore, a periodic assessment of flow meters should be recommended in order to discard the more deviant devices. Respiratory therapists should trained properly on these inaccuracies and on the importance of correctly reading the value of oxygen flow on the rotameters (horizontal reading in the centre of the ball). The use of the same brand of flow meters in the same institution should be recommended. Using Thorpe Tubes should be avoided for the following reasons: parallax error, static electricity, wear of time, height at which the TT is placed (parallax error). In general, TTs in our clinic are at a height of 210 cm.

2) Oxygen flow restrictors (OFRs):

Our study shows that oxygen flow restrictors were more accurate when compared to Thorpe Tubes. However, for both TTs and OFRs, the dispersion of values increases on both sides of the actual flow as the required flow is elevated. We have also concluded that when the hospital unit is equipped with a central electronic checking of main oxygen pressure the error measurements were limited. In hospital settings, we recommend using oxygen flow restrictors to limit inaccuracies of oxygen administration.

3) Oxygen flows delivered by oxygen cylinders (OGC):

Oxygen flows delivered by oxygen cylinders appear more accurate than OFR. However, oxygen cylinders with double stages are more accurate than those with single stages. For all devices (TT, OFRs, OGC), oxygen flow inaccuracies are deleterious at high flow in adult patients as they can lead to over- or under-oxygenation. In paediatrics, even at low flow, these inaccuracies are deleterious because low inspiratory flows generated by an infant lead to the production of high FiO_2. Few health practitioners are aware of these inaccuracies and, consequently, the risks of adverse effects during oxygen therapy, especially when changing oxygen administration systems. To limit these adverse effects, we think it is necessary to change the prescription modalities in the administration of oxygen based on a target value of SpO_2 rather than a prescription of oxygen flow. In order to avoid the variability of oxygen administration, SpO_2 verification should be highlighted by health practitioners during daily clinical use.

4) Length of oxygen tubing:

The length of oxygen tubing has not been studied specifically in this thesis. Many groups have studied this topic (403–405); they conclude that the length of the oxygen tubing does not matter as long as it does not exceed 30 metres.

However, with portable oxygen concentrators (POCs) which deliver pulse oxygen flow, strict respect of the manufacturer's recommended oxygen tubing length is crucial. Triggering sensitivity for flow administration can be adjusted for a specific tubing length; an increase in tubing length will lead to the non-detection of inspiratory flow by POCs. When a POC with pulse volume administration is used with a parallel device for the administration of continuous positive airway pressure, the POC will not detect the patient's inspiratory effort and will not deliver the required oxygen flow (406).

Finally, in order to increase the length of the tubing, some patients use fittings to attach two pieces of tubing. These fittings are a source of oxygen leakage. This is the same for the connection of the oxygen tubing to the oxygen humidification system. Clinical and home practitioners must be aware of the risks of leakage at the connections of the tubing which will decrease the quality of oxygenation.

B) Effect of inspiratory flow on FiO2 in the oxygenated patient who receives oxygen at low flow and who breathes spontaneously:

This thesis confirm that FiO_2 is often unknown and highly variable in oxygenated patients both at low and high oxygen flow. Prediction equations have been used for several decades to determine FiO_2 in low-oxygenated patients (349). Our work has shown that these equations were relatively accurate, but only for healthy, normal-sized adults at rest.

However, if the minute ventilation value changes, then these equations are incorrect and can lead to the risk of over- or under-oxygenation. Our equation considers the minute ventilation (and the inspiratory flow) to more adequately predict the FiO_2 value.

FiO_2 decreases during hyperventilation and increases during hypoventilation, and thus two main clinical applications derive from this formula.

Firstly, in paediatrics, because of low inspiratory flow, oxygen flow must be administered at (very) low flows to avoid hyperoxaemia.

Secondly, in adults, high inspiratory flow will decrease the FiO_2 as in COPD rehabilitation. In this case, it is necessary to strongly increase oxygen flow to avoid hypoxaemia. In contrast, low inspiratory flow will increase FiO_2 and lead to hyperoxaemia, as, for example, during rest in COPD or obesity-associated hypoventilation.

Our formula explains why the FiO_2 is never continually the same in patients oxygenated at low flows.

However, in clinical practice, the minute ventilation is unknown in non-intubated patients, and thus, clinical application of our formula could be difficult to implement.

C) The effect of inspiratory flow on FiO2 in the oxygenated patient who receives oxygen via a high flow nasal cannula:

Use of the Double Trunk Mask above nasal prongs (high flow nasal cannula) demonstrated that HFNC therapy can be improved. This mask increases the PaO_2 in hypoxaemic patients. While HFNC therapy is considered to delivering stable FiO_2, our work shows that is not always the case.

This new information has led us to question the actual FiO_2 delivered by HFNC. We wondered about some scientific articles which base their study on FiO_2 stability. Using simulations, we have calculated the ROX index and concluded that under certain conditions, using ROX index can lead to inadequate medical decisions in some hypoxaemic patients.

D) Double Trunk Mask:

The Double Trunk Mask (DTM) is a new device that serves to increase the concentration of oxygen delivered by a classical nasal cannula or catheter. The Double Trunk Mask (DTM) is a modified tusk mask described by Hnatiuk (70). The DTM is composed by a normal aerosol mask with 22 mm diameter lateral holes and 38 cm-long flexible tubing inserted into each leak of the mask. The mask is applied to the face of the patients who already receive O_2 through a nasal cannula or catheter. The DTM was modified in 2015 by Duprez, who modified the arbitrary length of the trunk from 38 cm to 15 cm. The DTM can be used at low and high oxygen flow.

1) At low oxygen flow:

In this case, DTM can is used with nasal cannula or oxygen catheter.

2) At high oxygen flow:

In this particular case, the DTM is only used during high flow oxygen therapy. In both cases, DTM strongly increases the PaO_2 with a limited impact on $PaCO_2$, despite the increase in dead space from the trunk's volume. In general, hypoxaemia is deleterious to patients and severe hypoxaemia should be considered as an indication for positive airway pressure and mechanical ventilation. The DTM should thus not be used to prolong the duration of critical hypoxaemia and delay intubation in severely ill patients who will need mechanical ventilation. It is better suited to conditions of moderate hypoxaemia, transient hypoxaemia, or contraindications to intubation and mechanical ventilation. Suggested indications would be for transient cardiogenic pulmonary oedema (rapid response to medical therapy), atelectasis (rapid response to physiotherapy or fibro-aspiration), pre-oxygenation before intubation, hypoxaemia in haematological patients (reluctance to invasive mechanical ventilation), or do-not-intubate patients. Occasionally, the DTM could also be useful to limit the need for oxygen in mass casualty events where the suddenly increased oxygen demand would exceed the available oxygen supplies.

Futures investigations

Complementary research that could extend from this thesis includes:

1) Determine the effects of the association of DTM with HFNC on intubation frequency

2) Investigate DTM using both HFNC associated with a Positive End Expiratory Pressure (PeeP) in order to increase effect on PaO_2

3) Investigate DTM use in COPD patients using portable oxycentrator for walking. The DTM could boost oxygenation

4) Evaluate DTM use in patients with a high risk of hypercapnia (COPD, obesity-associated hypoventilation Syndrome) with particular regards to the effects on $PaCO_2$. Determine the mechanisms that, in some cases, increase the $PaCO_2$

5) To avoid rebreathing risks, determine the trunk volume of the DTM in regards to ideal body weight

6) Compare the DTM with other oxygen administration methods such as non-rebreathing masks. Determine the effects of use of the DTM in cluster headaches

Conclusion:

Even if oxygen delivery seems to be an easy treatment to perform, many factors can affect quality and efficiency of the therapy. These factors significantly influence effective oxygen delivery and could therefore lead to over or under oxygenation of the patient. As FiO_2 reflects in the most adequate way true oxygen delivery, a predictive equation of this variable is proposed in this thesis work to help clinicians deliver right oxygen flows. Throughout our FiO_2 predictive equation we also highlighted importance of inspiratory flow. This work has additionally focused on characterization of FiO_2 through DTM masks, which seems to be particularly effective to improve oxygenation of hypoxemic patients. Hence, this work proved efficiency of the DTM masks to improve oxygenation at low and at high oxygen flow rates.

Appendixes:

Posters presented at international conferences:

Poster N°1: Evaluation of FDO_2 between nasal cannula and nasal oxygen catheter

Poster N°2: Variability of FDO_2 with nasal cannula

Poster N°3: Dup-Reyg, a new system to increase the FiO_2 with a Boussignac system

Poster N°4: What is the effect on FiO_2 when the prongs of the nasal cannula overlap a nostril and the cheek?

Poster N°5: What is the effect on FiO_2 of mouth closed breathing vs mouth open breathing with nasal cannula? A bench study.

Poster N°6: Inspiratory negative pressure in simulated spontaneous breathing with a bag valve mask: A bench study

Poster N°7: Evaluation of inspiratory negative pressure in simulated spontaneous breathing with a bag valve mask and intubate tube: A bench study

Poster N°8: New system to control FDO_2 with bag valve mask for premature infants

Patent : Insufflateur manuel à FiO_2 constante

Poster 1:

Evaluation of FDO_2 between nasal cannula and nasal oxygen catheter

F Duprez, T Bonus, G Cuvelier, S Ollieuz, S Machayekhi, F Paciorkowski, G Reychler. Annals

of Intensive Care 2017, 7(Suppl 1):P194

Introduction: Oxygen therapy is the main supportive treatment of hypoxaemia. Nasal cannulas (NCs) and nasal oxygen catheters (NOCs) were used to administer oxygen therapy in hypoxaemia. Few studies have examined the difference in fractional delivered oxygen (FDO_2) between these two systems. The aim of our study was to compare the difference in FDO_2 between NCs and NOCs.

Materials and methods: On a bench study, a two-compartment model of adult lung (Dual Test Lung DTL, Michigan Instrument) was connected to a Servo i® Ventilator. The ventilator was set in volume-controlled mode. Three-minute ventilations (MV: 6/9/12 l/min at Ti/Ttot = 0.33) and two oxygen flow rates (OFR: 2 and 4 l/min) were analysed. OFR was analysed with a thermal mass flow meter Vogtlyn™ Red Y. The compliance of the artificial lung was set to 0.07 L/cmH_2O and the resistance set to 5 $cmH_2O/l\ s^{-1}$. The FDO_2 and MV measurements were made using an iWorx® acquisition system (GA207 gas analyser and analogue/digital IX/228 s) and LabScribe II® software. To simulate the anatomic dead space of the nasopharynx (±50 ml for an adult) we have used a 15 cm length corrugated tubing ISO 22 mm (CT22) at the level of inflow of DTL. NC was introduced at the entry of the CT22 while the NOC was introduced totally into the CT22. Statistics: ANOVA on ranks followed by Student–Newman–Keuls post Hoc test.

Results:

FDO2 (with SD) between nasal cannula and nasal oxygen catheter Oxygen flow rate 2 and 4 L/min and Minute Ventilation : 6 - 9 - 12 L/min				
MV (L/min)	Nasal Cannula 2 L/min	Nasal Oxygen catheter 2 L/min	Nasal Cannula 4 L/min	Nasal Oxygen catheter 4 L/min
6	31% (0.5)	37% (0.5)	38% (0.5)	43% (0.5)
9	29% (0.7)	34% (0.6)	34% (0.7)	39% (0.7)
12	26% (0.6)	30% (0.6)	30% (0.6)	34% (0.5)

Table of results: FDO2 between NC and NOC at OFR 2 and 4 L/min and VE: 6 – 9 – 12 L/min

Conclusion: In oxygen therapy, with NC or NOC, for a Ti/Ttot = 0.33, FDO_2 is influenced by MV, OFR and oxygen system delivery. For the same level of OFR and system delivery, when MV increases, FDO_2 decreases (see table of results). For the same MV and level of OFR, FDO_2 was more efficient with NOC than NC. The differences in FDO_2 between NOC and NC decrease with increasing MV. The FDO_2 fluctuations according to the value of the MV are greater with the NOC to 4 L/min. In clinical situations, the NOC is less used than the NC. Compared to the NC, the NOC is an alternative to increase the FDO_2 with the same OFR. NOC is more efficient than NC because anatomical dead space fills with O_2 during expiratory time, which increases the FDO_2. However, if the respiratory frequency increases then expiratory time decreases, filling with O_2 decreases which reduces FDO_2. Note that NOC may become uncomfortable at OFR greater than 5 L/min.

Poster 2:

Variability of fractional delivered oxygen (FDO_2) with nasal cannula

F Duprez, T Bonus, G Cuvelier, S Machayekhi, S Ollieuz, G Reychler. Annals of Intensive Care 2017, 7(Suppl 1):P195

Introduction: A nasal cannula (NC) is an option to deliver oxygen therapy. According to the American Thoracic Society (ATS), standard NC delivers a fractional delivered oxygen (FDO_2) of 24–40% at supply oxygen flows ranging from 1 to 5 L/min. An equation was proposed by ATS to predict oxygen delivery: FDO_2 = 20% + (4 X O_2 L/min). Moreover, for ATS, FDO_2 is also influenced by respiratory frequency (Rf), tidal volume (Vt) and ratio Ti/Ttot. However, the equation of ATS does not take into account these parameters. Our hypothesis is that these parameters can significantly affect the FDO_2. The aim of this study was to determine the effect of Rf, Vt and Ti/Ttot on FDO_2.

Materials and methods: The study was conducted on bench with NC connected to a two-compartment adult lung model (Dual Test Lung®) (DTL) controlled by a Maquet Servo I® ventilator. One oxygen flow rate (OFR) (5 L/min) and 3-minute ventilations (MV: 6/9/12 L/min) with two Ti/Ttot (0.33 and 0.25) were investigated. All settings of MV were generated by modifying Rf (10–40 CPM) and Vt (0.3 and 0.6 L). The inspiratory flow rate (IFR) obtained with settings ranged from 18 to 48 L/min. The OFR was analysed by a thermal mass flow meter Vogtlyn™ Red Y. FDO_2 and MV measurements were made using an iWorx® acquisition system (GA207 gas analyser) and LabScribe II® software. Compliance of DTL was set to 0.07 L/cmH_2O and resistance to: 5 cmH_2O/L s^{-1}.

Results: FDO_2 comparisons between: Ti/Ttot 0.33 and 0.25 and three MV: 6–9–12 L/min at OFR: 5 L/min.

FDO2 (SD) comparisons between:
Ti/Ttot 0.33 and 0.25 and three MV: 6 - 9 -12 L/min (with inspiratory flow) at OFR: 5 L/min

MV (L/min)	Ti/Ttot = 0.33						Ti/Ttot = 0.25					
	Rf x Vt (L)		FDO2	Rf x Vt (L)		FDO2	Rf x Vt (L)		FDO2	Rf x Vt (L)		FDO2
6	10 x 0.6 (IF=18 L/min)	a	41% (+/-2)	20 x 0.3 (IF=18 L/min)	d	42% (+/-2)	10 x 0.6 (IF=24 L/min)	g	36% (+/-1)	20 x 0.3 (IF=24 L/min)	j	37% (+/-1)
9	15 x 0.6 (IF = 27 L/min)	b	36% (+/-1)	30 x 0.3 (IF = 27 L/min)	e	35% (+/-1)	15 x 0.6 (IF = 36 L/min)	h	32% (+/-2)	30 x 0.3 (IF = 36 L/min)	k	32% (+/-3)
12	20 x 0.6 (IF = 36 L/min)	c	31% (+/-2)	40 x 0.3 (IF = 36 L/min)	f	30% (+/-1)	20 x 0.6 (IF = 48 L/min)	i	30% (+/-1)	40 x 0.3 (IF = 48 L/min)	l	29% (+/-1)

Conclusion: IFR and OFR are the main determinants of FDO_2. Equation of ATS is correct when IFR is equal to 18 L/min. When IFR is different to this value, the equation of ATS is not appropriate. In our experiment, with an OFR of 5L/min, when IFR = 18 L/min (MV = 6 L/min and Ti/Ttot = 0.33), the FDO_2 is equal to 41% (±1%) (see Table 5). To this value of IFR, the FDO_2 is in accordance with the formula of ATS, but when IFR increase beyond 18 L/min, the FDO_2 decrease and the formula is not in accordance with ATS. This can be explained because room air (fractional oxygen = 0.21) entry in the airway during the inspiratory phase mixes with OFR (FO_2 = 1), which modifies the FDO_2. In this case, when IFR increase then FDO_2 decrease and vice versa. Medical and paramedic staff must be aware that with patients who receive OFR by nasal cannula, any change in OFR and/or inspiratory flow changes the FDO_2. In this case, to maintain the same FDO_2, it is necessary to modify the value of OFR.

Poster 3:

Dup-Reyg: A new system to increase the FiO_2 with a Boussignac system.

Duprez F, Cuvelier G, Ebogo T, Jacques JM, Mashayekhi S, Reychler G. Annals of Intensive Care, 2018;8, 51.

Introduction: Boussignac system (BS) generates a continuous positive airway pressure (cpap). With BS, FiO_2 value is approximatively equal to the ratio between O_2 flow and inspiratory flow (IF). To limit the FiO_2 decrease during IF increase, we developed a new system: The Dup-Reyg system. The aim of this study was to test the Dup-Reyg system connected to a BS during IF increases.

Method: The study was conducted on bench with a BS connected to a two-compartment adult lung model (Dual Test Lung®- DTL) controlled by a Maquet Servo I®ventilator. Three-minute ventilations (MV 10 / 20 and 30 L/min) with a Ti/Ttot = 0.33 were investigated. FiO_2 and MV measurements were made using an iWorx® GA207 gas analyser. Three Positive End Expiratory Pressure (Peep) were analysed: 3, 5 and 10 cm H2O. The BS was supplied with an O_2 flow. In order to increases the FiO_2 during IF increases, we have evaluated the impact of the addition of the Dup-Reyg system (two corrugated tubing ISO 22, length: 18 cm for each Trunk) connected to expiratory way of BS. Statistics: Friedman test followed by a Holm-Sidak method were used to compare data. Results: Means are expressed with their SD.

Ti/Ttot = 0,33	MV 10 L/min		MV 20 L/min		MV 30 L/min	
	BS alone	BS with Dup-Reyg	BS alone	BS with Dup-Reyg	BS alone	BS with Dup-Reyg
						
PEEP 3 cm H2O	(a) 82% (+/- 0.6)	(b) 99%(+/-0.6)	(c) 55%(+/-1)	(d) 76%(+/-0)	(e) 45%(+/-0.6)	(f) 67%(+/-0.6)
PEEP 5 cm H2O	(g) 88%(+/-0.5)	(h) 99%(+/-0.6)	(i) 66%(+/-0.6)	(j) 83%(+/-0.6)	(k) 52%(+/-0.6)	(l) 74%(+/-1)
PEEP 10 cm H2O	(m) 94%(+/-0.6)	(n) 99%(+/-0.4)	(o) 80%(+/-0.6)	(p) 99%(+/-0.6)	(q) 63%(+/-0.7)	(r) 82%(+/-0.6)

Figure 1: FiO_2 obtained with BS at three MV (10, 20, 30 L/Min) and three PEEP (3, 5, 10 cm H_20). No statistical differences (p>.05) were found between (a-j/j-r/h-p/h-n/b-h/i-f/a-r/b-n/b-p/n-p) (figure 1). Higher the MV, lower the FiO_2 (p<0.05). Moreover, higher the peep, higher the FiO_2 (p<0.05). The addition of the Dup-Reyg system at the entry of BS increases FiO_2 (p<0.05). The impact of the Dup-Reyg addition is more important with high MV. In our study, FiO_2's absolute difference observed were equal from 5 % to 17%

Conclusion: The addition of a Dup-Reyg system to the expiratory way of a BS increases FiO_2 significantly. This system could be implemented to increase the FiO_2 when the oxygen flow delivery is limited (ambulance, disaster situations, war zone …).

Poster 4:

What is the effect on FiO_2 when the prongs of the nasal cannula overlap a nostril and the cheek?

Mandianga JM, Cuvelier G, Mashayekhi S, Duprez F. Annals of Intensive Care, 2018;8, 51.

Introduction: Nasal cannula (NC) are used for O_2 administration to treat hypoxemia. Sometimes, the prongs of the NC slip on the face and can be found overlapping a nostril and the cheek. Moreover, the patient's mouth can be open or closed during this time. The purpose of the bench study was to determine the impact of these situations on the FiO_2.

Material and methods: The study was conducted on bench with NC connected to a two-compartment adult lung model (Dual Test Lung®) (DTL) controlled by a Maquet Servo I®ventilator. One O_2 flow rate (OFR: 4 L/min) and a four-minute ventilation (MV: 7, 10, 14, 17 L/min) with Ti/Ttot = 0.33 were investigated. FiO_2 and MV measurements were made using an iWorx® acquisition system (GA207 gas analyser) and LabScribe II® software. Compliance of DTL was set to 0.07 L/cm H_2O and resistance to 5 cm H_2O/L/sec. To simulate closed mouth, we blocked an extremity of T piece, while the open mouth, was simulated by remove this obstruction. Four different approaches were analysed: A closed mouth (CM) with either a NC overlap on one nostril or not. A totally open mouth (TMO) with either a NC overlap on one nostril or not.

Results: When the MV increases, the FiO_2 decreases. When the mouth opens, the FiO_2 decreases. When the prongs are overlapping one nostril the FiO_2 decreases slightly (mean: 5% +/- 2% in absolute value).

	O_2 : 4L/min			
	Closed mouth		Open mouth	
				
MV	FiO_2	FiO_2	FiO_2	FiO_2
7 L/min	(a) 44 % (+/- 0.9%)	(e) 40 % (+/- 0.8%)	(i) 37 % (+/- 0.5%)	(m) 31% (+/- 0.9%)
10 L/min	(b) 41% (+/- 0.7%)	(f) 35 % (+/- 0.7%)	(j) 35 % (+/- 0.8%)	(n) 30 % (+/- 0.4%)
14 L/min	(c) 36 % (+/- 0.6%)	(g) 29 % (+/- 0.9%)	(k) 31% (+/- 0.6%)	(o) 27 % (+/- 0.3%)
17 L/min	(d) 33 % (+/- 0.5%)	(h) 26 % (+/- 1%)	(l) 29 % (+/- 0.8%)	(p) 26 % (+/- 0.2%)

Statistical differences were found between closed and open mouth and between overlap on one nostril and not ($p<.05$), except between TMO and CM at two MV (14 and 17 L/min) when NC overlap on one nostril.

Conclusion: When the prongs of NC are not correctly placed in the nostrils, the FiO_2 decreases, but this impact is limited except at MV 14 L/min with CM. The impact of MV increases and mouth opening on the FiO_2 values is also important.

Poster 5:

What is the effect on FiO_2 of mouth closed breathing vs mouth open breathing with nasal cannula? A bench study.

N Bahar, S Mashayekhi, G Cuvelier, F Duprez. Annals of Intensive Care, 2018;8, 51.

Introduction: Nasal cannula (NC) are used for O_2 administration during low and middle hypoxia. Sometimes, the patients receive O_2 through NC breathing with their mouth open or mouth closed. During this time, their SpO_2 values can modify. The purpose of this bench study was to determine the impact of closed mouth breathing or open mouth breathing on FiO_2. Material and methods: The study was conducted on bench with NC connected to a two-compartment adult lung model (Dual Test Lung®) (DTL) controlled by a Maquet Servo I®ventilator. One O_2 flow rate (OFR) (4.5 L/min) and three-minute ventilation (MV: 7, 12, 20 L/min) with Ti/Ttot = 0.33 were investigated. FiO_2 and MV measurements were made using an iWorx® acquisition system (GA207 gas analyser) and LabScribe II® software. Compliance of DTL was set to 0.07 L/cm H2O and resistance to: 5 cm H2O/L/sec. In order to simulate the anatomic naso-buccal area, we have used a T piece connected to a 15 cm long corrugated tube ISO 22 mm (CT22) at the level of inflow of the DTL. The NC was introduced at the entry of the CT22. Three different situations were analysed: A totally open mouth (TMO), a half open mouth (HOM) and a closed mouth (CM). To simulate HOM, we have used a flow restrictor piece which include an aperture of 10 mm in the centre of this piece.

Results: When MV increases, FiO_2 decreases ($p<0.05$). FiO_2 was highly with a half open mouth regardless MV ($p<0.05$). With totally open mouth, the FiO_2 decreases strongly ($p<0.01$). If we consider half open mouth and totally open mouth, the gap of FiO_2 value decreases with MV increases.

Oxygen flow 4.5 L/min	FiO2		
	MV 7 L/min	MV 12 L/min	MV 20 L/min
Half Open Mouth	(a) 49% (+/-0.5%)	(d) 42% (+/-0.6%)	(g) 33% (+/-1%)
Totally Open Mouth	(b) 38% (+/-0.8%)	(e) 34% (+/-0.9%)	(h) 28% (+/-0.9%)
Closed Mouth	(c) 45% (+/-1%)	(f) 39% (+/-0.5%)	(i) 31% (+/-1%)

Conclusion: In oxygen therapy with NC, the FiO_2 is influenced at the same time by the MV and the opening of the mouth. If the MV increases, the FiO_2 decreases. The FiO_2 is lower when the mouth is totally open and higher when the mouth is half open. These results are in contrast with the Wettstein's results. Those authors found out that patients breathing with open mouths reached a significantly higher FiO_2, compared to those breathing with their closed mouths.

Poster 6:

Inspiratory negative pressure in simulated spontaneous breathing with a bag valve mask: A bench study.

F. Duprez, Cuvelier, S. Mashayekhi, S. Ollieuz, G. Reychler. Crit Care. 2017; 21(Suppl 1): 57.

Introduction: In emergency care, oxygen therapy can be administered directly with a bag valve mask (BVM). In some cases, this method is applied to patient with a spontaneous breathing. The purpose of this study was to evaluate inspiratory negative pressure (INP) during spontaneous breathing through three different bag valve masks.

Methods: Three BVM (Ambu®Oval, MR100®, Ambu® Mark IV; without oxygen reservoir bag) were analysed. Spontaneous breathing was simulated on a bench study. A two-compartment model of adult test lung (Dual Test Lung® DTL, Michigan Instrument) was connected to a Servo i® ventilator. One compartment of DTL was moved by Servo i®, the other as the driving compartment which simulated breathe. Servo i® was set in volume-controlled mode. Three-minute ventilation (MV) (Respiratory frequency (Rf): 10, 20, 30 cpm with tidal volume (Vt) of 0.45 L were analysed. The compliance of DTL was set to 0.06 L/cm H_2O and the initial resistance set to 5 cm H_2O/L/sec. The change in inspiratory pressure was measured by an analogue IWorx station/digital IWx/214 LabScribe II ® software. Three consecutive measurements were performed for each MV. Parameters were compared over time using ANOVA for each MV ($p < 0.001$). Results: For all MV, no significant statistical differences were raised between Ambu®Oval and Ambu® Mark IV (ANOVA: $p < 0.001$).

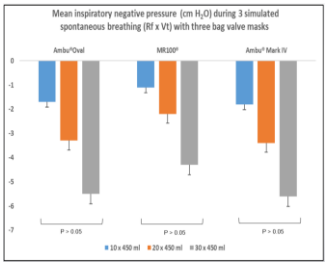


Table 1: Mean inspiratory negative pressure with SD (cm H_2O) during simulated spontaneous breathing with three bag valve masks

Conclusions: For a same BVM, when MV increases, INP increases. For all MV, MR100® is the BVM is one who offers the lower resistance. This is most likely due to the type of patient valve of the BVMs, because the AMBUs® patient valve is a mushroom valve concept, while the MR100® patient valve is a duckbill valve concept.

Poster 7:

Evaluation of inspiratory negative pressure in simulated spontaneous breathing with a bag valve mask and intubate tube: A bench study

T. Bonus, F. Duprez, G. Cuvelier, S. Mashayekhi, Reychler Crit Care. 2017; 21(Suppl 1): 57

Introduction: Bag valve masks (BVMs) are frequently used in emergency units or with intubated patients breathing spontaneously. The mask and the intubation tube are thought to increase resistance and thus inspiratory resistance. The purpose of the present study is to evaluate: The impact of BVM on the inspiratory negative pressure (INP) during simulated spontaneous breathing with intubate tube. The additional effects of the intubation tube size and minute ventilation on the INP.

Methods: In a bench study, a bag valve mask (Ambu® Mark 4, without oxygen reservoir bag) was tested with three intubation tubes (Internal Diameter 7, 8, 9 mm). Spontaneous breathing was simulated with a two-compartment model of an adult test lung (Dual Test Lung® DTL, Michigan Instrument). DTL was connected to a Servo i® ventilator in volume-controlled mode. One compartment of DTL was moved by Servo i®, the other as the driving compartment which simulated breathing. Three-minute ventilations (MV) (Respiratory frequency: 10, 20, 30 cpm with tidal volume = 0.5 L) were analysed. The compliance of DTL was set to 0.06 L/cm H_2O and the initial resistance set to 5 cm H_2O/L/sec. The change in inspiratory pressure was measured at entry of DTL, by an analogy IWorx station/digital IWx/214 LabScribe II ® software. Three consecutive measurements were performed for each MV. Parameters were compared using ANOVA for each MV.

Results: For MV (10 × 500 ml): No statistical differences were found between A2 and A4, A5 and A1, A6 and A4, A3 and A1, A5 and A3. - For MV (20 × 500 ml) and (30 × 500 ml): Statistical differences were found between all group's ANOVA ($p < 0.001$).

MV (Rf x Vt) (cpm x L)	Mean inspiratory negative pressure with SD (cm H2O) during simulated spontaneous breathing with three bag valve masks		
	Ambu®Oval	MR100®	Ambu® Mark IV
10 x .450	-1.7 (+/-.23)	-1.1 (+/- .28)	-1.8 (+/- .08)
20 x .450	-3.3 (+/-.10)	-2.2 (+/- .10)	-3.4 (+/-.18)
30 x .450	-5.5 (+/- .15)	-4.3 (+/- .15)	-5.6 (+/- .13)

Conclusions: With a bag valve mask, in spontaneous breathing, when the MV increases, INP increases. Moreover, when the intubation tube size decreases, the INP increases. For the same intubation tube size, when MV increases, INP increases. For the same MV and same intubation tube size, the addition of a BVM increases INP.

Poster 8:

New system to control FDO_2 with bag valve mask for premature infants

F Duprez, T Bonus, G Cuvelier, S Mashayekhi, M Maka, S Ollieuz, G Reychler

Crit Care. 2017; 21(Suppl 1): 56.

Introduction: According to the recommendations of the European Resuscitation Council (ERC), cardio-pulmonary resuscitation (CPR) in premature infants must be made with a fraction of delivered oxygen (FDO_2) not exceeding 30%. Bag valve masks for premature infant (BVMp) can be used for ventilation and oxygenation during CPR. In such a case, even with a low oxygen flow rate (OFR), a BVMp delivers higher FDO_2 than recommended. Indeed, with a BVMp, FDO_2 rises proportionally to OFR but decreases inversely proportionally to minute ventilation (MV). Therefore, in neonatology resuscitation, controlling and maintaining the FDO_2 below 30% is very difficult, even with a low OFR. To meet the ERC recommendations, we developed a new system aimed at delivering adequate FDO_2 with a BVMp: the DupRey system. This system uses the Venturi effect to provide a stable air-oxygen mixture to a BVMp. The present study was aimed at evaluating the actual FDO_2 between bag valve masks for premature infants used conventionally or used with the DupRey system.

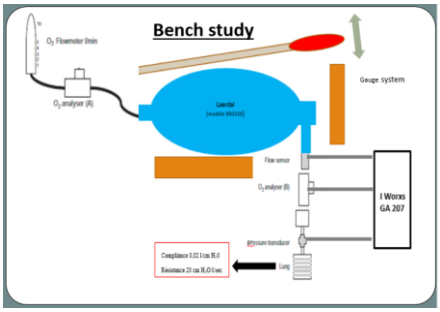


Figure 1: Bench test

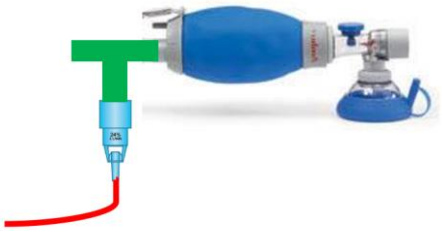
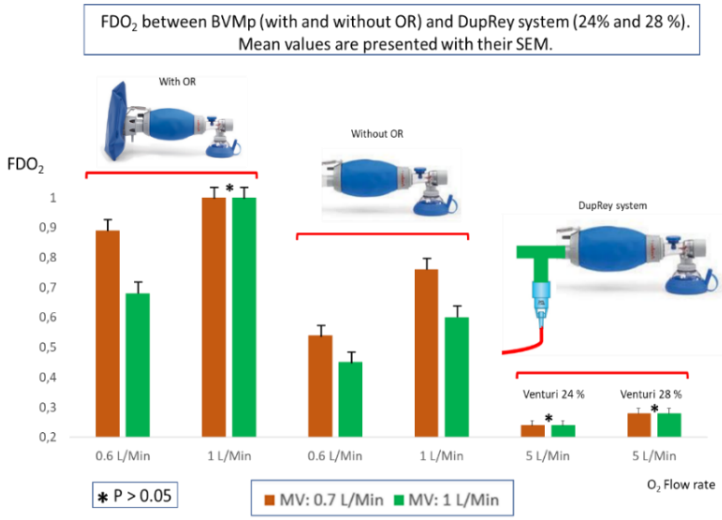


Figure 2: DupRey system

Methods: On a bench study, a BVMp (Laerdal™ for premature infant type 850150) was connected to a test lung (Maquet™ VA800 - compliance 0.02 L/cm H_2O - resistance 20 cm H_2O/L/sec. With the BVMp, two MV (0.7 L/min and 1 L/min) were generated. A metronome gave the frequency of insufflations. The BVMp was tested both with and without an oxygen reservoir (OR) and the pop off valve was closed. Two OFRs, 0.6 and 1 L/min were analysed and compared to the DupRey with Venturi 24% and 28% (OFR: 5 L/min). OFR were analysed by a thermal mass flow meter Vogtlyn™ Red Y. The FDO_2 and MV measurements were made

using an analogue iWorx® acquisition system (GA207 gas analyser associated with digital IWx 214) and LabScribe II ® software.

Results: Statistical differences ($p < 0.001$) were found between A5-A6 / B5-B6 and all other columns. However, no statistical differences were found between: B2 and A2, A6 and B6, B5 and A5.



Conclusions: For an oxygen flow ranging from 0.6 to 1 L/min and two MV analysed, a bag valve mask for premature infants with an OR delivers very high FDO_2(>86%). Without OR, at same OFRs, FDO_2 decreases but they maintain high values (>44%). The DupRey delivers FDO_2 <30% regardless of the MV. The DupRey system is easily accessible for medical teams who do not have access to modern technology.

Patent: brevet d'invention DupRey:

economie
SPF Economie, PME, Classes Moyennes & Energie
Office de la Propriété intellectuelle

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Date de délivrance : 09/05/2017

BREVET D'INVENTION

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INSUFFLATEUR MANUEL A FRACTION INSPIREE D'OXYGENE CONSTANTE

La présente invention concerne un dispositif médical permettant de contrôler la fraction inspirée d'oxygène (Fi02) d'un patient ventilé à l'aide d'un Ballon Auto-remplisseur a Valve Unidirectionnelle (BAVU). On prévoit un accélérateur Venturi (32) dont une extrémité est apte à être connectée a une source d'oxygène (33) sous pression et dont l'autre extrémité est reliée à une voie d'un connecteur creux (30) à trois (au moins) voies, p.e. un raccord en T, reliant l'accélérateur Venturi et le BAVU.

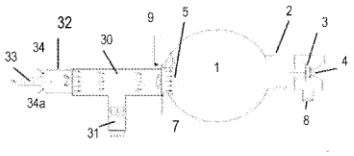

FIG. 2

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"C’est une folie de haïr toutes les roses parce qu’une épine vous a piqué, d’abandonner tous les rêves parce que l’un d’entre eux ne s’est pas réalisé, de renoncer à toutes les tentatives parce qu’on a échoué.

C‘est une folie de condamner toutes les amitiés parce qu’une d’elles vous a trahi, de ne plus croire en l’amour juste parce qu’un d’entre eux a été infidèle, de jeter toutes les chances d’être heureux juste parce que quelque chose n’est pas allé dans la bonne direction.

Il y aura toujours une autre occasion, un autre ami, une force nouvelle.

Pour chaque fin il y a toujours un nouveau départ.

Fais de ta vie un rêve, et d'un rêve, une réalité."

Antoine de Saint-Exupéry (1943)