THE WAY TO SUCCESS

OXYGEN CONSUMPTION (VO2), EFFORT AND WEANING IN MECHANICALLY VENTILATED PATIENTS IN THE INTENSIVE CARE UNIT

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Delft University of Technology
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The Way to Success

Oxygen Consumption (VO_2), Effort and Weaning in Mechanically Ventilated Patients in the Intensive Care Unit

by

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Preface

Dear reader,

In front of you lies the result of my master thesis, on which I started working in October 2022. With this thesis my life as a student has come to an end, a period I reflect upon with profound satisfaction, where I have evolved in a Technical Physician, striving for self-improvement. Driven by the curiosity in mechanical ventilation and supported by the enthusiasm I had developed during my ICU internship at LUMC, I contacted Dr. Bram Schoe, whose coincidental project was a perfect match for my aspirations. This project gave me the opportunity to refine both my clinical as technical skills. It also introduced me to the intricacies of study design and submission processes.

So I would like to start by thanking my medical supervisor, Bram. Thank you for your endless enthusiasm, thinking along, ensuring that I gained more experience in the clinical practice of mechanical ventilation, and your dedication to the project. Equally important is your patience in helping me to improve my English writing. In addition, I appreciate your belief in my potential and the opportunity to grow through this research into a PhD. To my technical supervisor, Susanne, your incisive perspectives have enriched my ideas. These insights always pushed me towards innovative solutions. Special thanks to my daily supervisor, Hubald. Our Monday meetings, while seemingly routine at times, were the cornerstone of my weeks. Your out-of-the-box ideas broadened my perspective, and your programming and technical insights were invaluable.

Apart from my supervisors, there have been a few others without whom this thesis would not have become what it is today. Mike and Jeanette, your patience and guidance during the METC application process was indispensable. Knowing that I could ask for your help or a talk at any time was very reassuring. Petra and Willem, your doors were always open for my inquiries, whether it was about a patient's ventilation or challenges I was facing. Willem, your ideas in forming a test setup and Petra, your dedication to a day of Douglas bag testing, made the testing phase much more enjoyable! I would also like to thank Jannes and Franciska. You were invaluable in conducting my literature review. You provided great help in screening the articles and giving feedback on the written article. Fransicka, I would also like to thank you for your critical eye, which improved the clarity of my concepts. Lastly, I would like to thank Rutger, thanks for you knowledge and experience with the Masimo and for all the times I could come to borrow stuff for the setup. Also thanks for thinking along and discussing problems.

To my friends and family, thank you for all the support, motivational talks, distractions, and study sessions. In particular, I would like to thank Janno, Rowan, Imane, Suus, Melissa, and Friso for all the hours of talking, post-lunch walks, and mental support during this thesis in the ICU.

As I reflect on these unforgettable moments, I am excited to see what the future holds.

Floor Smits
Leiden, September 2023

Contents

Nomenclature

Abbreviations

Abbreviation	Definition
APACHE	Acute Physiology and Chronic Health Evaluation
ADP	Adenosine diphosphate
ATP	Adenosine triphosphate
BbB	Breath-by-breath
Bpm	Breaths per minute
BTPS	Body temperature pressure saturated
CO_2	Carbon dioxide
ECMO	Extra Corporal Membrane Oxygenation
EE	Energy Expenditure
etO_2	End tidal oxygen concentration
FiO_2	Fraction of inspired oxygen
ICU	Intensive Care Unit
IND	"Independent Breath" algorithm
LUMC	Leiden University Medical Center
METC	Medisch Etische Toetsings Commissie
N_2	Nitrogen
NDIR	Non-dispersive infrared
O_2	Oxygen
PEEP	Positive End Expiratory Pressure
Pes	Esophageal Pressure
PTP	Pressure-time product
REE	Resting Energy Expenditure
RQ	Respiratory Quotient
RS232	Recommended Standard 232
RSBI	Rapid Shallow Breathing Index
SBT	Spontaneous Breathing Trial
STPD	Standard temperature pressure dry
VAP	Ventilator-Associated Pneumonia
VCO_2	Carbon dioxide production
VILI	Ventilator-induced lung injury
VO_2	Oxygen consumption
V_T	Tidal volume, in STPD conditions
WOB	Work of breathing

Symbols

Symbol	Definition	Unit
A	Area	cm^2
b_f	Breath frequency	$\mathrm{breaths/min}$
C	Compliance	$\mathrm{mL/cm\,H_2O}$
D	Diffusion coefficient	cm^2/s
E	Elastance	$\mathrm{cm\,H_2O/mL}$
I	Inertia	$\mathrm{cm\,H_2O/L/s}^2$
J	Diffusion rate	$\mathrm{mL/min}$
M	Molecular mass, density	$\mathrm{mol/g}$
ψ	Concentration	$\mathrm{mol/cm}^3$
PTP	Pressure-time product	$\mathrm{cm\,H_2O \cdot s}$
R	Resistance	$\mathrm{cm\,H_2O/L/s}$
R_i	Diffusion rate of gas i	$\mathrm{mL/min}$
t	Time	s
V	Volume	mL
$\dot{V}$	Flow	$\mathrm{mL/min}$
VO_2	Oxygen Consumption	$\mathrm{mL/min}$
V_T	Tidal Volume	mL
WOB	Work of breathing	$\mathrm{joules/L}$
X	Thickness of medium	cm
x	Distance	cm

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Introduction

1.1. Introduction

Critically ill, mechanically ventilated patients require a substantial amount of energy to meet their basic metabolic demands, as well as for their recovery, spontaneous breathing, gaining of strength, and weaning from the ventilator [1–3]. It is important for patients to use their energy as efficient as possible at all stages of the disease and recovery. Physicians need to estimate and match the energy cost of the treatment regimen with the patient's ability for energy expenditure. If the demands of the treatment regimen, such as weaning from the ventilator, are too high, it will lead to exertion and fatigue. On the other hand, if the patient is not challenged enough, it could lead to a slower recovery and prolonged admission to the Intensive Care Unit (ICU). For example, it is known that a too slow reduction in ventilator support can lead to atrophy of the diaphragm, resulting in prolonged ventilation time [4].

Predicting successful extubation is crucial for mechanically ventilated ICU patients. Prolonged intubation leads to prolonged mechanical ventilation, which is known to have adverse effects [5, 6]. Up to $20\,\%$ of all ICU patients fail to wean from mechanical ventilation [7]. Weaning failure and fatigue may be caused by a mismatch between the mechanical load on the respiratory muscles and the patient's endurance [8]. A spontaneous breathing trial (SBT) must be passed to determine whether a patient is ready for extubation [6, 9]. In addition to clinical parameters such as level of consciousness, cough ability, and muscle strength, the rapid shallow breathing index (RSBI) is a commonly used parameter to predict extubation success. The RSBI is the respiratory rate to tidal volume ratio (f/Vt) [10].

For the estimation of the effort in mechanically ventilated patients, the work of breathing (WOB) can be used. The WOB measures patient effort in Joules per breath or Joules per minute by integrating the volume over the esophageal pressure signal (Pes) [1, 11, 12]. In Figure 1.1 an overview of all pressures acting on the respiratory system is shown. Another measure for patient effort is the Pressure Time Product (PTP), expressed in cm $H_2O \cdot$ second, which is the time integral of the Pes signal [1, 13, 14]. In addition, the estimation of effort can be derived from transpulmonary pressure swings in the esophageal signal [1, 14]. Moreover, the Rapid Shallow Breathing Index (RSBI), which is already integrated into the existing weaning protocol, serves as a useful tool for effort estimation [10, 15, 16]. All these measures will be discussed in more detail below.

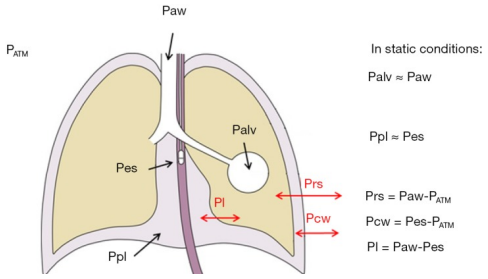


Figure 1.1: Model of the respiratory system. In red the relative distending forces are shown. P_{ATM}, atmospheric pressure; P_{aw}, airway pressure; P_{es}, esophageal pressure; P_{alv}, alveolar pressure; P_{pl}, pleural pressure; P_{rs}, transrespiratory pressure; P_{cw}, trans-chest wall pressure; P_l, transpulmonary pressure [1].

For an estimation of the actual energy expenditure, a summation of the resting energy expenditure (REE) and the energy necessary for other tasks must be made. Estimating the REE for mechanically ventilated patients has been challenging [3, 17–19]. Estimation of the energy on top of the REE to perform a task like exercise, a spontaneous breathing trial (SBT), or coping with stress or pain, is even more challenging.

Oxygen plays a significant role in the energy supply and survival of the human body [20]. Energy in human cells is generated through the conversion of adenosine triphosphate (ATP) to adenosine diphosphate (ADP) and cyclic AMP. ATP is produced using glucose, which is catabolized in three subsequent processes, glycolysis, tricarboxylic acid cycle and oxidative phosphorylation. Notably, this aerobic conversion is 19 times more efficient compared to

anaerobic ATP production [21].
A clear relationship exists between oxygen uptake and energy expenditure, enabling the estimation of resting and total energy expenditure [22]. Oxygen consumption (VO_2) is a measure of this relationship and is a direct measure of patient effort as it represents the total amount of oxygen consumed by tissue per minute [23]. Because it displays the instantaneous changes over time when comparing energy levels at rest and during activity, the usage of VO_2 is regarded as beneficial. This is particularly useful as accurate calculations of actual work or energy expenditure are difficult due to the various assumptions involved [1, 9]. Measurements of VO_2 can be derived from inspired and expired oxygen concentrations and minute volume [23–25]. Understanding these parameters and the techniques used to measure them is critical for accurate assessment of energy expenditure. Failure to meet the body's energy requirement may result in prolonged hospital stay, increased incidence of complications or increased risk of mortality [26].

It was hypothesized that the usage of oxygen consumption in critically ill, mechanically ventilated patients is an effective parameter to guide processes such as weaning from the ventilator, a spontaneous breathing trial, training with a physiotherapist, or other tasks that cost energy. However, before measuring VO_2, a reliable method must be established through extensive in vitro testing. This thesis will discuss the test setup and the process of measuring VO_2. First, some essential background information is provided below.

1.2. Parameters used to Estimate Energy and Effort

Several parameters can be used to estimate the energy or effort of a patient. These factors were briefly mentioned earlier, and will be discussed in more detail below.

1.2.1. Work of Breathing

Airway pressure is the pressure acting on the entire respiratory system. This is not the only pressure in the respiratory system, as shown in Figure 1.1. Often the esophageal pressure is used as a surrogate for the intrathoracic (pleural) pressure [13]. This can be used for differentiation of chest wall, lung and respiratory system mechanics. It can also be used in assisted mechanical ventilation to assess the contribution of the respiratory muscles. In order to derive the Pes, it is necessary to place an esophageal balloon in the esophagus of the patient.

Work of Breathing (WOB) can be explained as the energy required for spontaneous ventilation, i.e. to overcome the afterload on the respiratory system, which is generated by the mechanical properties of the lungs and chest wall [11, 12]. It is usually associated with the inspiratory effort, since expiration is a passive process [27]. Under normal conditions, the WOB is around $5\,\%$ of the total oxygen consumption. If a patient has respiratory failure, this percentage could increase to even $50\,\%$ [28]. Work of breathing is expressed as the area under the esophageal pressure-volume curve as

$$WOB = \int_{V_0}^{V_1} P(V) \cdot \mathrm{d}V, \tag{1.1}$$

where: WOB = Work of Breathing (in $\mathrm{cm\,H_2O \cdot cm^3}$), $P(V)$ = pressure at certain volume (in $\mathrm{cm\,H_2O}$), $\mathrm{d}V$ = change in volume (in mL), V_0 = start volume (in mL), and V_1 = end volume (in mL).

There are two components of WOB; elastic, which are the forces of the lung parenchyma and chest wall (tissue), and flow-resistive, which are the forces generated by the movement of gas through the airways [12, 13].

1.2.2. Pressure Time Product

The pressure time product (PTP) can be derived from the Pes measurement. It is a parameter which is related to the metabolic cost of breathing, which can be calculated as the product of the pressure developed by the respiratory muscles and the time of muscle contraction;

$$PTP = \int_{t_0}^{t_1} P(t) \cdot \mathrm{d}t, \tag{1.2}$$

where: PTP = Pressure Time Product (in $\mathrm{cm\,H_2O \cdot s}$), $P(t)$ = pressure at certain time (in $\mathrm{cm\,H_2O}$), $\mathrm{d}t$ = change of time (in s), t_0 = start time (in s), and t_1 = end time (in s) [1, 13, 14, 27]. The PTP was developed to account for energy expenditure during the dynamic and isometric phases of respiration [27]. PTP may be of more value in patients with ineffective respiratory effort, as WOB cannot be measured in these patients because there is no volume displacement [13, 14]. The PTP showed a significant increase in patients who failed their weaning trial [1, 29].

1.2.3. Transpulmonary Pressure Swings

By subtracting the esophageal pressure from the airway pressure, the transpulmonary pressure is derived. This is the pressure applied to the alveoli, remaining the lungs expanded and preventing it from collapsing. Swings are the differences within this derived pressure during a respiratory cycle. During the acute phase of illness the pressure swings should be $\leq 15\,\mathrm{cm\,H_2O}$. After this phase a value of $20\,\mathrm{cm\,H_2O}$ is accepted in the LUMC [1, 9, 14, 30].

1.2.4. Rapid Shallow Breathing Index

The rapid shallow breathing index (RSBI) is a parameter commonly used to predict extubation success, along with several other clinical parameters such as level of consciousness, the ability to cough and muscle strength. It can be calculated as

$$RSBI = \frac{RR}{V_t}, \tag{1.3}$$

where: $RSBI$ = Rapid Shallow Breathing Index (in $\mathrm{breaths/min/L}$), RR = respiratory rate (in $\mathrm{beats/minute}$), V_t = tidal volume (in L). The RSBI is associated with the WOB and the pressure time product [10, 27].

The most commonly used RSBI cut-off value ($105\,\mathrm{breaths/min/L}$) for predicting safe extubation misclassifies $15\,\%$ to $20\,\%$ of patients. This means that these patients require a further period of mechanical ventilation with possible adverse consequences [16].

1.2.5. Oxygen Consumption

A promising new parameter is the measurement of oxygen consumption (VO_2) as a measure of effort. Changes in VO_2 during an SBT may serve as an early indicator of patient effort and potential weaning failure [31, 32].

Oxygen consumption can be continuously monitored using direct or indirect calorimetry methods. Indirect calorimetry allows the measurement of changes in VO_2 and carbon dioxide

production (VCO_2) by analyzing respiratory gas concentrations. It has been used primarily in research settings but holds potential for clinical application in critically ill patients [31, 33].

In critically ill patients, monitoring VO_2 can have several potential benefits, including the ability to adapt nutritional support to changing metabolic needs during the course of ICU admission [17, 19, 22, 25, 34–53].

VO_2 is derived from indirect calorimetry methods using flow or volume measurements and oxygen concentration as

$$VO_2 = \frac{V_I O_2 - V_E O_2}{t}, \tag{1.4}$$

$$V_I O_2 = V_I \cdot F_I O_2, \tag{1.5}$$

$$V_E O_2 = V_E \cdot F_E O_2, \tag{1.6}$$

where: VO_2 = oxygen consumption (in $\mathrm{mL/min}$), $V_I O_2$ = inspired oxygen volume (in $\mathrm{mL/min}$), $V_E O_2$ = expired oxygen volume (in $\mathrm{mL/min}$), t = time of breath (in min), V_I = inspired volume (in mL), $F_I O_2$ = fraction of oxygen in the inspired air, V_E = expired volume (in mL), $F_E O_2$ = fraction of oxygen in the expired air [54].

Metabolic Demand

Monitoring oxygen consumption can provide insight into metabolic demand and patient effort, particularly during weaning from mechanical ventilation. Lower VO_2 values have been observed in patients who have successfully weaned, suggesting a possible relationship between oxygen consumption and weaning outcome [24, 50, 55].

In addition, measurement of VO_2 can help to identify cases of impaired oxygen delivery and consumption (oxygen deficiency) in conditions such as sepsis or after cardiac arrest, where the metabolic demands of the body are disrupted [56, 57].

The inclusion of VO_2 as a parameter in assessing patient readiness for extubation is advantageous because of its non-invasive nature. Unlike the measurements that require insertion of an esophageal balloon to measure esophageal pressures (WOB, PTP, and transpulmonary pressure swings), VO_2 monitoring offers a potentially less invasive alternative. This characteristic makes VO_2 a valuable consideration for inclusion in standard intensive care. Further investigation is warranted to determine its full clinical utility.

1.3. Sample and Measurement Methods of Oxygen Consumption

There are many different ways to measure oxygen consumption, each with its own advantages and disadvantages. The four most commonly used techniques will be described briefly. A comprehensive overview of the principles can be found in the literature review conducted as part of the thesis (see Appendix A) [58].

1.3.1. Douglas Bag

The Douglas Bag has been used to validate various measurements of both O_2, and CO_2 concentrations, and is the gold standard for VO_2 measurement [39, 40, 59, 60]. Gas is collected in a gas collection bag from the expiratory limb of the ventilator over a period of time. These concentrations can be analyzed using mass spectrometry [43, 59, 61, 62]. The volume of the bag can be measured using a Tissot gasometer [39, 61], the dilution technique by a water displacement method [59], or a portable constant-flow suction pump and aspiration through a fixed orifice [62]. A disadvantage is that, as with mixing chambers, it is essential that all exhaled gases are captured within the bag. If there is a small leak, the measurement will not be as accurate [63].

1.3.2. Mixing Chamber

The mixing chamber sampling technique is often used in an open circuit. There are two options for open circuit sampling. Subjects can either inhale from the atmosphere or they can inhale air supplied by a mechanical ventilator. In both cases, all exhaled air is collected in two air-filled chambers. The exhaled gases are drawn into the first chamber by rotameters [48, 60]. In this chamber, the exhaled gases are mixed with the air already present in the chamber. The mixed gas is transferred to a second chamber where samples are taken to determine the gas concentrations. As all exhaled air must be collected, there should be no leaks in the circuit (for a schematic representation, see Figure 1.2).

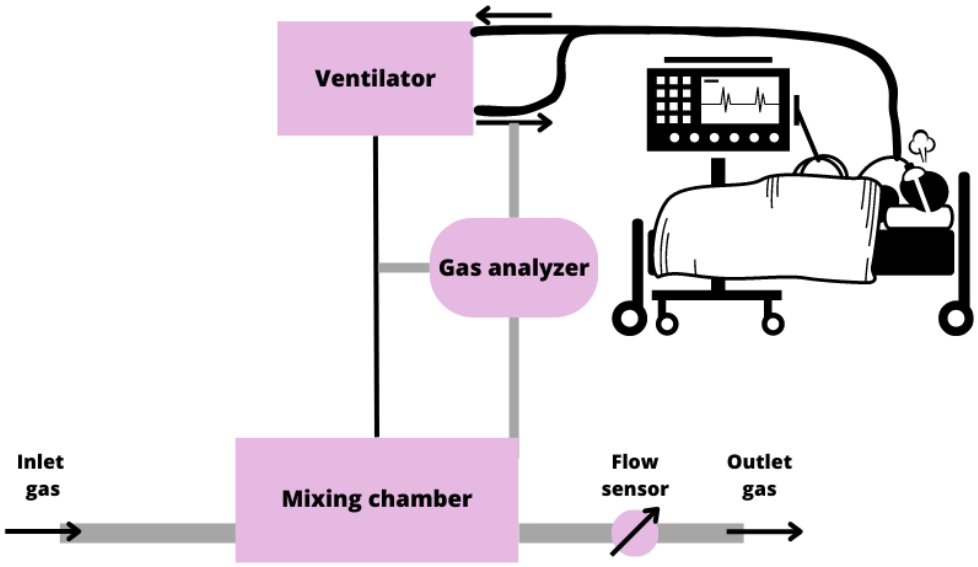


Figure 1.2: Schematic representation of a mixing chamber. This mixing chamber is connected to both the ventilator, as a gas analyzer, and the flow sensor. A reference gas is also present in the mixing chamber.

Flow can be measured using a variety of techniques. A dry gas meter, positive displacement meter, can determine flow by using a counter and rotation [48, 60]. Flow can also be monitored using the dilution technique or a pneumotachometer [38, 48], a vortex flow meter [51, 55] or a turbine flow meter [25] (see Figure 1.3). The dilution method uses a tracer gas that is delivered at a steady rate, allowing mass spectrometry to estimate fractional concentrations [41, 42, 64]. The vortex flow meter works with a bluff body which will result in a modification of the air flow.

To measure the flow rate, a vortex detector is employed. This detector is equipped with a pressure sensor located downstream from the bluff body. As vortices are repelled, they create pressure fluctuations, leading to pressure variations at the detector [65]. A disadvantage of the vortex flow meter is the fact that the accuracy is limited in the presence of humid air [48]. The turbine flow meter has blades that will rotate when air flows through the flow meter. A high flow will result in fast spinning of the turbine [66].

In general, expiratory volumes are affected by temperature and humidity [49]. If only the expiratory flow is measured, the Haldane transformation can be used to calculate the inspired volume;

$$\dot{V}_i \cdot F_iN_2 = \dot{V}_e \cdot F_eN_2; \tag{1.7}$$

$$\dot{V}_i = \frac{\dot{V}_e \cdot F_eN_2}{F_iN_2}; \tag{1.8}$$

$$F_eN_2 = 1 - (F_eO_2 + F_eCO_2), \tag{1.9}$$

where: $\dot{V}_i$ = Inspiratory flow (in $\mathrm{mL/s}$), F_iN_2 = Inspiratory nitrogen fraction, $\dot{V}_e$ = Expiratory flow (in $\mathrm{mL/s}$), F_eN_2 = Expiratory nitrogen fraction, F_eO_2 = Expiratory oxygen fraction, F_eCO_2 = Expiratory carbon dioxide fraction [48].

The Deltatrac (II) (Datex Instrumentation) is the most validated and extensively tested method using a mixing chamber, but is no longer manufactured. It can be used for both mechanically ventilated and non-mechanically ventilated patients [19]. For the latter group a canopy is required to take measurements [50]. The Deltatrac (II) is an open-circuit calorimeter with two fixed volume chambers [19, 22]. The device uses the gas dilution technique as described above [41, 64]. The inspiratory gas concentrations are measured from the inspiratory limb of the ventilator, while the expiratory gas concentrations are measured from the chambers using gas analyzers [50]. VO_2 can be calculated from the measured expired oxygen concentration, measured VCO_2, and respiratory quotient (RQ) [49, 67]. RQ and VO_2 can be derived using the Haldane transformation assuming equal nitrogen (N_2) concentrations between inspired and expired gases [22, 35, 37, 50, 64]. Data are collected at 1 minute intervals [35, 36, 39, 43, 49, 50, 67]. However, averages have been made over longer time periods, up to 12 hours [19, 64]. Unfortunately, this means that it is not possible to visualize small changes over a short period of time.

1.3.3. Breath-by-Breath

Increased numbers of newly developed devices use breath-by-breath analysis. A major advantage is that these devices require less calibration than devices using a mixing chamber [49]. In breath-by-breath devices, both flow and gas concentrations are measured during each breath cycle to determine VO_2, and VCO_2. As a sidestream sampling line is used to measure gas concentrations, an algorithm is required to synchronize flow and gas data [24, 37, 38, 42].

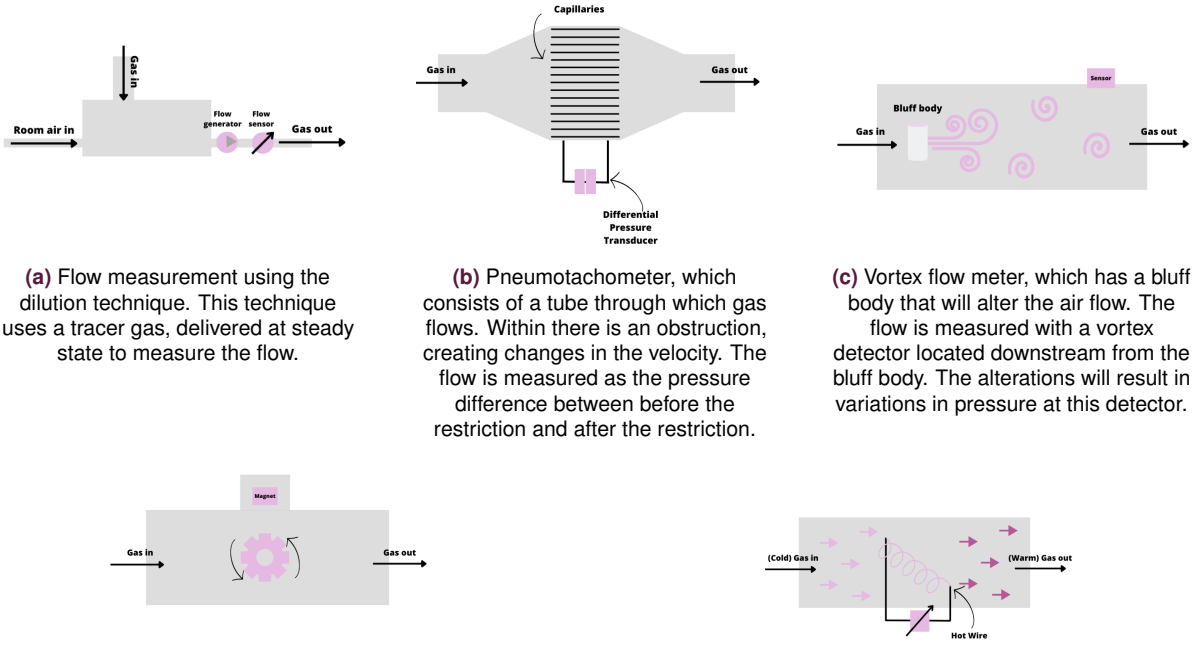
The sampling line is usually coupled to the endotracheal tube [35–37]. The flow meter, on the other hand, can be placed in different places. If it is connected to the expiratory port, both expiratory volume and bias flow (continuous circulating flow from the ventilator to the patient and back to the ventilator) are recorded, which will provide higher flow values [36]. When placed directly on the endotracheal tube, this bias current is eliminated [17, 35, 36].

For breath-by-breath analysis, there are also several options for flow measurement. These are the turbine flow meter (Figure 1.3d) [35–37], the pneumotachometer (Figure 1.3b) (both explained in the section about mixing chambers) [24, 35–37, 43, 56], and an anemometer (Figure 1.3e) [57]. The anemometer uses a hot wire to heat the air. The amount of current required to produce hot air is representative of the air flow [57]. A pneumotachometer could work as a bi-directional flow sensor, measuring both inspiratory and expiratory flow, eliminating the need for the Haldane transformation [68].

Some of the respiratory modules can be used in combination with monitors or other metabolic systems [34, 56, 57, 69].

1.3.4. Mass Spectrometry

The mass spectrometry principle relies on fixed collector technology, and can be paired with a mixing chamber to analyze or verify chamber samples [38, 39, 48]. This technique is also often used for analyzing exhaled gases in a Douglas Bag [59, 61, 62]. Gas samples taken from the patient's Y-piece in the breathing circuit can be mass spectrometrically analyzed to determine inspiratory concentrations. It is possible to measure expired flow using a pneumotachometer (Figure 1.3b) [39]. Recorded data is managed using a computer [38, 39, 46, 48, 59]. However, the output is adjusted by a predetermined factor to compensate for environmental factors, such as humidity, making it highly dependent on assumptions [39].



(a) Flow measurement using the dilution technique. This technique uses a tracer gas, delivered at steady state to measure the flow.

(b) Pneumotachometer, which consists of a tube through which gas flows. Within there is an obstruction, creating changes in the velocity. The flow is measured as the pressure difference between before the restriction and after the restriction.

(c) Vortex flow meter, which has a bluff body that will alter the air flow. The flow is measured with a vortex detector located downstream from the bluff body. The alterations will result in variations in pressure at this detector.

(d) Turbine flow meter with blades that rotate in response to air flow. The higher the flow, the faster the blades rotate.

(e) Anemometer that uses a hot wire to heat the air, the amount of current required to heat is representative of the airflow.

Figure 1.3: Schematic representation of different flow sensors commonly used in mixing chamber, breath-by-breath, and mass spectrometry devices.

Taking all these measurement methods into account, it was decided that a system using breath-by-breath analysis would be best. This method emerges as optimal due to its capability

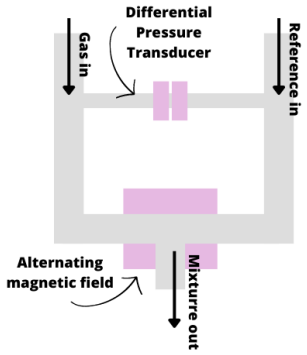
to capture rapid variations over a short time interval in VO_2 in situations where the patient is challenged, for example when undergoing a spontaneous breathing trial. In devices with a mixing chamber, the values will approach equilibrium. This is because it is measured over time rather than per breath. This will always give a steady state value rather than the current values. It is a suitable method for patients in a steady state but not when the energy state of the patient varies, which is often in ICU patients.

1.4. Oxygen Analyzers

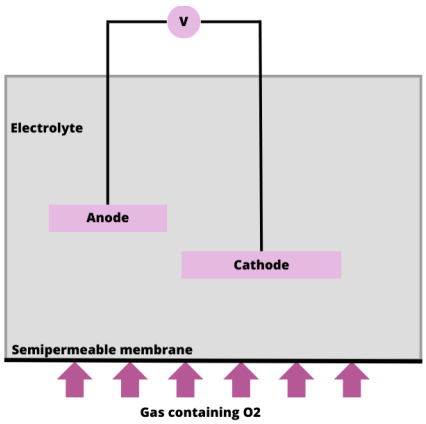
Within these different devices, oxygen is measured. This can be done using different sensors, explained below. The main disadvantage of O_2 sensors is that these are slower than CO_2 sensors, as CO_2 sensors have direct measurement capabilities [68, 70]. There are however, some differences between oxygen analyzers available.

A paramagnetic oxygen analyzer (Figure 1.4a) is commonly used to measure the concentration of exhaled oxygen. This analyzer can be used in both mixing chambers and breath-by-breath devices. These sensors use the paramagnetic properties of oxygen to attract it to a magnetic field. As oxygen molecules pass through the magnetic field, they are attracted to the magnets. By measuring how much they move with a differential pressure transducer, the oxygen concentration can be determined. This type of sensor has the advantage of the fastest response and rise time available on the market [68].

In addition to the paramagnetic oxygen analyzer, the (galvanic) fuel cell (Figure 1.4b) can be used. This sensor is based on the fact that oxygen molecules interact with the electrode. This will cause changes in electron flow and movement, which will result in an electric current. This current is proportional to the concentration of oxygen. This type of sensor reacts a bit slower than the paramagnetic sensors [68].



(a) Paramagnetic oxygen sensor that uses the magnetic properties of oxygen. This attraction to the magnet causes a displacement of the molecules, creating a differential pressure.



(b) The galvanic fuel cell uses the interaction of oxygen with an electrode. This interaction causes a change in the flow and movement of electrons, resulting in an electrical current. This current can be measured using a voltage sensor.

Figure 1.4: Schematic view of different types of oxygen sensors.

1.5. Master Thesis' Objectives and Outlines

The aim of this master's thesis was to develop an algorithm to measure the oxygen consumption in patients admitted to the intensive care unit using a breath-by-breath method. Here fore, an in vitro test setup was constructed that mimics VO_2 consumption, this will be described in Chapter 2. In Chapter 3 the development of the algorithm with the aid of the data, obtained from the in vitro test, will be described. In Chapter 4 the validation of the algorithm will be described using an improved test setup and simulated data. Chapter 5 will conclude the thesis and cast a perspective of the future.

2

In Vitro Test Setup

2.1. Introduction

As explained earlier, oxygen consumption (VO_2) is a direct measure of patient effort. It is defined as the difference between the amount of oxygen inhaled and exhaled over a predetermined time interval (Equation 1.4). Using end tidal oxygen (EtO_2) and fraction O_2 of inspired air (FiO_2) concentrations and volumetric calculations, it is possible to track breath-by-breath variations in VO_2 [71]. A change in oxygen consumption during an spontaneous breathing trial (SBT) could be an early indicator of patient effort and failure.

However, VO_2 is not yet used as a standard measure, and therefore it is necessary to make a setup for this purpose. Before it can be used in patients, this setup needs to be thought out and tested in vitro. An in vitro setup is also required to validate if the algorithm to synchronize gas concentrations and flow data is accurate. Therefore, it is necessary to develop a setup that represents the intensive care unit (ICU) patient as accurate as possible.

2.1.1. Objectives

When measuring VO_2 with a breath-by-breath device, the flow and gas concentration data must be synchronized. This requires an algorithm which must be evaluated before it is used in patients. Data from an in vitro test setup can be used for testing. This setup is designed to investigate different scenarios that may occur in intensive care patients that are mechanically ventilated. The purpose of this chapter is to describe the in vitro test setup and the choices that were made in its design.

2.2. Methods

Before an in vitro test setup was built, a plan of requirements was drawn up, to ensure that the in vitro setup was as close to reality as possible.

Despite the fact that many different factors will affect the patient and the outcome of VO_2, not every requirement was incorporated into the setup. Some differences in VO_2 are caused by differences in background, illness of patients or, for example, the likelihood of successful extubation.

2.2.1. Test Setup Goal

The SMART methodology was used to define the goal of this chapter [72].

- Specific: A test setup should be made that mimics the conditions of a patient on mechanical ventilation in the ICU as closely as possible, such as breathing frequency and different oxygen requirements. This setup will be used to generate data for creating an algorithm to measure oxygen consumption.
- Measurable: Using known conditions in the setup will verify the algorithm, by calculating the VO_2 manually using parameter data, the outcome of the algorithm can be compared.
- Achievable: Simulation methods, appropriate sensors and data acquisition systems are used to ensure that the test setup is technically feasible with the resources available.
- Relevant: The development of an accurate algorithm for measuring oxygen consumption is important because it can help to improve the care of mechanically ventilated patients in intensive care and for example by ensuring a safe transition to spontaneous breathing. To begin the evaluation of this measurement, it is first necessary to create an algorithm based on in vitro data.
- Time-bound: The test setup should be ready within three months, to create an algorithm based on the data and possible adjustments can be made to the test setup for new tests, if necessary.

2.2.2. Factors of Influence on Oxygen Consumption

Several factors can affect both the measurement and value of oxygen consumption:

1. Patient Specific Factors
   - Age
   - Underlying illness
   - Sleep quality
   - Neuromuscular blockage
   - Airway resistance
   - Accessory muscle use
   - Rib cage movements
   - Peristalsis
2. Technical Factors
   - Gas concentration measurement
   - Flow measurement
   - Technical specifications sensors
   - Sample frequencies
   - Breath-by-breath analysis
3. Oxygenation
   - Tidal volume
   - Respiratory rate
   - PEEP
   - FiO_2
   - Effort
   - Cough
4. Environmental Factors
   - Noise
   - Ambient light
5. Other
   - Nursing
   - Mobilization
   - Changes in medication

2.2.3. Plan of Requirements

Given the above factors affecting the measurement of VO_2, a plan of requirements was made. Considering this plan, a test setup was designed to be used in the development of an algorithm.

- Measurement requirements:
  - Flow rate measurement must be synchronized with gas concentration data (including CO_2 and O_2). This synchronization should not deviate by more than a quarter of a breath.
  - Must be able to measure breath-by-breath fluctuations.
- Equipment requirements:
  - Compact and cost-effective design.
  - Must be compatible with existing ICU equipment.
- Mimicking ventilated patient:
  - Connection to the same ventilator used in the ICU.
  - Incorporation of a component that can simulate ICU patient lungs.
- Oxygen consumption and settings:
  - Exhaled air must contain a lower oxygen percentage than the preset FiO_2.
  - Must be able to handle all variations in PEEP, FiO_2, tidal volume, respiratory rate and consumption.
- Environmental factors and portability:
  - Testing must be performed in an ICU patient room for similar conditions as compared to in vivo.
  - Size, weight, and ease of movement for the setup must be taken into consideration.
- Patient specific factors:
  - Patient specific factors and their influence should be tested in vivo, and were therefore considered as irrelevant for the in vitro setup.

A comprehensive version, using the SMART methodology, of all requirements can be found in Appendix B.

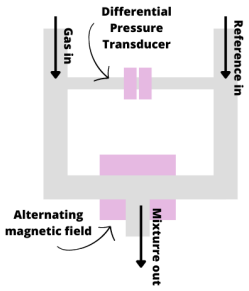
2.3. Results

2.3.1. Device Description

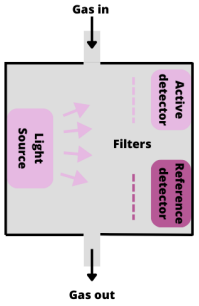
Based on the results of the literature review and the requirements set out in the methodology, a test setup was designed. It consisted of several components, which will be explained in more detail. A breath-by-breath system often requires synchronization between flow and gas concentration measurement. This is because most of these systems use a sidestream tube to measure gas concentrations, which causes a delay in the data. As it was already necessary to perform synchronization due to sidestream measurements, it did not seem important to have one device that measured both gas concentrations as flow. This choice resulted in a cheaper and smaller device, taking into account the existing mechanical ventilators in the ICU that measure flow.

Masimo ISA OR$^+$

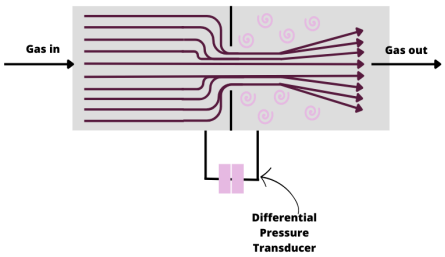
Among the breath-by-breath devices, the Masimo ISA OR$^+$ (Masimo Corporation, Irvine, USA), was chosen because it is compact, easy to use in the ICU and can be easily added to the ventilator circuit, which is within the intended use of the CE mark. The Masimo ISA OR$^+$ measures breath-by-breath oxygen and carbon dioxide concentrations through a (Nomoline) sidestream connected to the ventilatory circuit [73]. These concentrations are measured using a paramagnetic oxygen sensor and a non-dispersive infrared sensor, respectively [74]. Schematic representations of both sensors are shown in Figure 2.1.



(a) Paramagnetic oxygen sensor used in the Masimo device, which uses the magnetic properties of oxygen for the measurement of the oxygen concentration (for full explanation see Section 1.4 and Figure 1.4a).



(b) Non-dispersive infrared carbon dioxide sensor used in both devices. CO_2 is directly measured using infrared light which is absorbed by CO_2.



(c) Variable orifice flow meter in the Hamilton device. Within this sensor flow is slowed down due to the variable orifice. The flow is measured using the pressure differential between the two sides of the variable orifice. This sensor can be used bidirectional.

Figure 2.1: Schematic representation of the sensors used for gas concentrations and flow measurement.

The Masimo device only measures gas concentrations. Another device is therefore necessary to measure flow, to eventually obtain VO_2.

Hamilton C6 Mechanical Ventilator

The Hamilton C6 Mechanical Ventilator (Hamilton Medical, Bonaduz, Switzerland) is widely used in the LUMC. The Hamilton Medical ventilator measures flow using a variable orifice flow meter (Figure 2.1c) [75]. Bidirectional flow is allowed by the membrane in this sensor. During ventilation, the circuit is flushed with a mixture of gases to prevent clogging. Since the flow sensor is placed at the endotracheal tube, it does not have the problem of bias flow mentioned in Section 1.3. Due to the bidirectional measurement, both inflow and outflow are measured. For the measurement of the CO_2 concentration, the Hamilton C6 also uses a non-dispersive infrared (NDIR) sensor (see Figure 2.1b) [76].

2.3.2. Test Setup

The requirements plan resulted in the setup shown in Figure 2.2. Next to the devices explained above, the setup existed out of some other elements. For the setup, a cylinder containing a mixture of nitrogen (N_2) and carbon dioxide (CO_2) was chosen. The cylinder composition consisted of $95\,\%$ N_2, and $5\,\%$ CO_2. The choice of these gases was based on their capacity to simulate both oxygen consumption and carbon dioxide production. Nitrogen effectively mimics oxygen consumption by diluting O_2, while the introduction of CO_2 into the circuit replicates CO_2 production. This produces data that simulates metabolism and thus consumption [77–83].

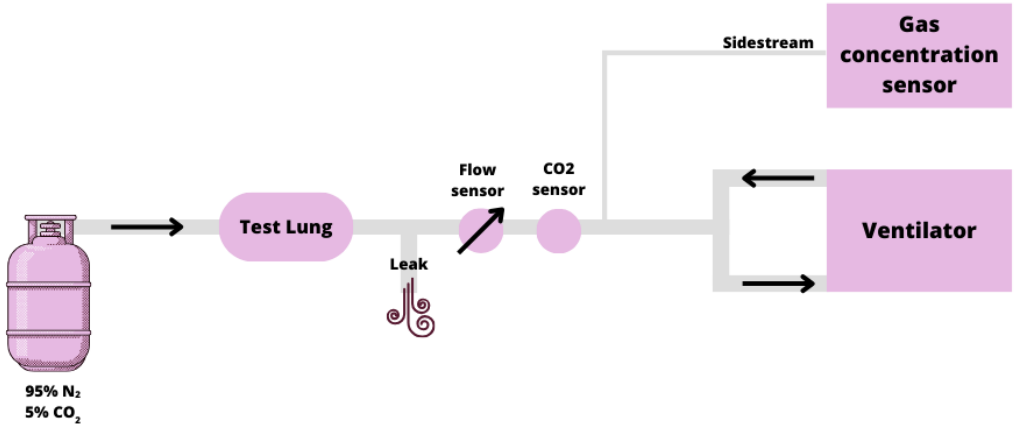


Figure 2.2: Schematic view of the setup for the in vitro tests with a sidestream connected to the Masimo ISA OR^+ to measure CO_2, and O_2 concentrations in the air. The cylinder containing $95\,\%$ N_2 and $5\,\%$ CO_2 is connected to a two liter AMBU test lung. A leak is implemented to compensate for the volume coming from the cylinder. After the leak the different sensors are placed. The flow and CO_2 sensors are coupled to the Hamilton, while the Masimo measures all gas concentrations using a sidestream tube.

A two liter AMBU breathing balloon was used to simulate the lungs [84]. An additional connection was made to the test lung to connect the cylinder to the circuit. This required an additional hole to ensure that the gases from the cylinder were completely mixed inside the balloon.

Due to addition of external gas, the end tidal volume was higher than the inspiratory volume in the circuit. A leak was added to the setup as compensation and was adjusted during the test to achieve (almost) equal inspiratory and expiratory volumes measured by the ventilator. This leak was made with three three-way stopcocks (Steritex 3W) to adjust the amount of leakage more precise.

The Masimo was connected to the ventilator circuit with a (Nomoline) sidestream, placed between the ventilator and the flow sensor. This positioning allowed for the direct measurement of all the flow reaching the balloon, without any volume loss caused by the Masimo device measuring through the sidestream. Pictures of this setup in real-life can be seen in Appendix C, Figure C.1 and Figure C.2.

2.3.3. Test Protocol

Gas exchange, encompassing both production (VCO_2), and consumption (VO_2), was simulated using the gas mixture of $5\,\%$ CO_2 and $95\,\%$ N_2. Different settings were used to simulate different scenarios.

The following tests were performed.

1. Baseline test
2. Different FiO_2 settings in combination with varying degrees of consumption
3. Changes in dead space volume
4. Several respiratory rates
5. Various tidal volumes
6. Addition of Pulmonary End Expiratory Pressure (PEEP)

Each test started with an expiratory hold of at least seven seconds. Since the flow stops during the hold and the gas concentrations achieve a plateau, it was thought to guide the synchronization. After the hold, the settings were maintained for five minutes. All settings per type of test can be found in Table 2.1.

Table 2.1: Overview of the different settings used for the test protocol to create different situations found in patients in the ICU. Variations in the parameters were made to simulate different changes in the previously established categories.

Type of Test	FiO_2 (%)	RR (min)	Vt (mL)	MV (L/min)	PEEP ($cm\,H_2O$)	Nitrogen Flow (L/min)
Baseline	40	15	300	4.5	5	1.4
Different FiO_2	40	15	300	4.5	5	1.4
	40	15	300	4.5	5	2.0
	40	15	300	4.5	5	3.5
	22	15	300	4.5	5	1.4
	22	15	300	4.5	5	2.0
	22	15	300	4.5	5	3.5
	60	15	300	4.5	5	1.4
	60	15	300	4.5	5	2.0
	60	15	300	4.5	5	3.5
	80	15	300	4.5	5	1.4
	80	15	300	4.5	5	2.0
	80	15	300	4.5	5	3.5
Changes in dead space volume	40	15	300	4.5	5	1.4
Changes in respiratory rates	40	15	300	4.5	5	1.4
	40	25	300	7.5	5	1.4
	40	35	300	11.5	5	1.4
	40	35	300	11.5	5	2.0
	40	35	300	11.5	5	3.5
Changes in tidal volumes	40	15	300	4.5	5	1.4
	40	15	200	3.0	5	1.4
	40	15	400	6.0	5	1.4
Changes in PEEP	40	15	300	4.5	5	1.4
	40	15	330	5.0	10	1.4
	40	15	375	5.6	15	1.4

In addition to the settings stated in Table 2.1, some other settings were used to obtain the data. These were not changed between tests, and were therefore excluded from the table. First, the

ventilation type was set to pressure-controlled ventilation (P-CMV+). In addition, the pressure support was set to $16\,\mathrm{cm\,H_2O}$ for all tests.

Using these settings, all scenarios as explained above were simulated. Especially the changes in FiO_2 percentage and N_2 flow were considered important, as those were thought to have the greatest effects on the oxygen consumption outcome.

2.4. Discussion

A plan of requirements was developed for the design of a test setup. Based on these requirements, a test setup was made that used N_2, and CO_2 to simulate usage necessary for the purpose of the setup. With different settings at both the cylinder and ventilation equipment, it was considered possible to mimic the breathing of an ICU patient.

2.4.1. Limitations

Despite managing to build a test setup that met the set requirements, there were some limitations. First of all, the reducing valve, used to regulate air flow from the cylinder to the balloon, was not very accurate. During an expiratory hold, the flow value of the cylinder was recorded as it remained stable at that particular moment, minimizing variability. The design of the scale also caused some inter- and intra-user variability. Another limitation occurring with the cylinder, was the fact that the setup did not mimic patients that accurate, as the CO_2 production was not (approximately) equal to the O_2 consumption. As the cylinder only contained 5 % CO_2, and the test lung was a passive object, this was not possible to match.

Secondly, the leak was designed using three-way stopcocks. The aim of this design was to achieve accurate leak adjustment and ease of tuning. The verification process involved monitoring the inspiratory and expiratory volumes measured by the ventilator. However, this approach proved to be imprecise due to the variations that occurred with each breath. A small deviation between the volumes was acceptable, considering that exhaled air occupies a relatively larger volume in humans. This phenomenon is attributed to the internal humidification and heating of the inhaled air within the body [85]. Since this was not built into the test setup, it was unlikely that the exhaled volume was higher if the leak was exactly compensating for the inflow from the cylinder.

Lastly, the test lung used was very stiff. As a result, it filled quickly. This resulted in abnormal volume curves, almost like the shape of a pressure curve in pressure control ventilation (see Figure D.1) [86]. This may have affected the measurements, as the breaths were in fact different as seen in patients in the ICU. Apart from the fact that the material of the test lung was not as good as desired, a hole was made in the other side to facilitate connection to the cylinder. This alteration resulted in an additional opening, increasing the likelihood of leakage.

2.4.2. Recommendations

The biggest recommendation in terms of the test setup would be to remove as much uncertainties as possible. There were too many assumptions and uncertainties, making it difficult to draw conclusions on the values that might come out of the algorithm. It is therefore suggested to measure the inflow from the cylinder and the leak using additional flow meters. In addition, it is recommended to use a different balloon. It would be useful to use a balloon where the compliance can be adjusted to create more reliable volume curves (see Figure D.1). Besides, even though it seemed like a good idea, it is not recommended to make any holes in the test lung. By keeping the test lung intact, the materials will be preserved better and the risk of

leakage is minimized. This way, every location where a possible leakage would be has been measured, resulting in less assumptions. To handle all these recommendations, a new test setup was made in order to create new data for the algorithm. However, the algorithm was first designed on the data derived from the test setup explained in this chapter. The algorithm will be explained in Chapter 3, and the new test setup with minimized assumptions in Chapter 4.

2.5. Conclusion

Using the predefined requirements, it was possible to design a test setup that could be subjected to various tests. It was therefore feasible to generate data that can be used to design an algorithm, using data from both the Masimo ISA OR^{+}, and the Hamilton C6 Mechanical Ventilator. Some adjustments to the setup are recommended before the algorithm can be fully validated on the generated data.

3

Synchronization and Measurement of Oxygen Consumption Signals

3.1. Introduction

As discussed in Chapter 2, achieving optimal data synchronization was critical due to the delay introduced by sidestream measurements. A comprehensive description of the equipment used was presented in that chapter. In order to provide insight into the rationale behind certain decisions made during the development of the algorithm, this current chapter provides additional information on the technical aspects of synchronization and oxygen consumption (VO_2) measurements. In addition, this chapter provides background information on various concepts including dead space volume, rise time and RS232 connections.

3.1.1. Background

Sidestream Measurements

As previously described, Masimo ISA OR$^+$ measures the gas concentrations sidestream using Nomoline sampling lines (Figure 3.1). These lines are multi-layered to ensure the accuracy of the gas samples. The Nomoline consists of a Nomoline cover, a hydrophilic wick, and a hydrophobic bacteria filter surrounding the sampling tube. These create a sampling line that is permeable to moisture and water, preserving the integrity of the samples collected [73]. In general, humidity poses a challenge to the performance of sampling devices [87]. By using such a system for the sidestream tube, the effects of humidity are greatly reduced [73].

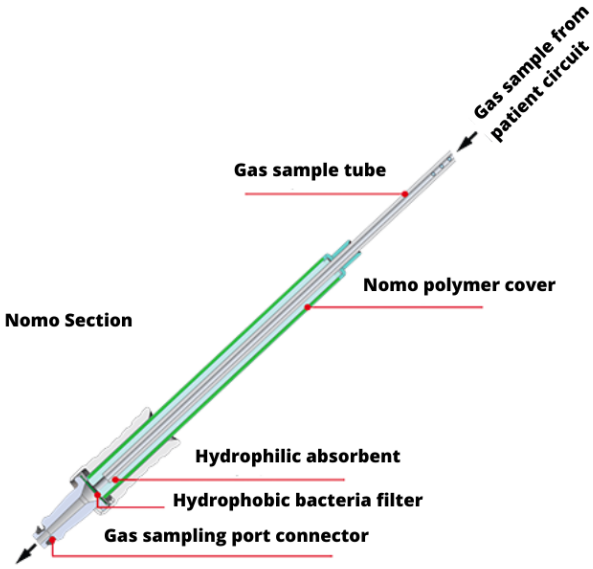


Figure 3.1: Schematic of the Nomoline sidestream used for gas concentration measurements in the Masimo ISA OR$^+$. This illustration shows the different layers used to reduce the effects of humidity and to filter the air.

Dead Space Volume

Different signals were obtained from the devices used in the developed test setup. However, these signals required preprocessing to guarantee proper synchronization. An important consideration was the presence of dead space volume in the ventilator circuit. Dead space consists of air that does not participate in gas exchange and contains some of the previously

inspired air. In humans the anatomical and ventilatory dead space is around $30\,\%$ of the normal tidal volume, equivalent to around $150\,\mathrm{mL}$ [88]. While the flow signal will not reflect the dead space volume, it will appear in the signal representing the gas concentrations, making synchronization of these two signals more complex.

Rise Time

Rise time refers to the time a signal takes to go from a specific low value to a specific high value, typically between 10 and $90\,\%$ of the total value (Figure 3.2) [89, 90]. The sensors in the devices have different rise times. The CO_2 sensors from Hamilton C6 and Masimo have rise times of $60\,\mathrm{ms}$ and $300\,\mathrm{ms}$ respectively, while the oxygen (O_2) sensor from Masimo has a slower rise time of $400\,\mathrm{ms}$ [74, 76]. This rise time variability adds complexity to data synchronization by affecting the timing of signal acquisition and processing.

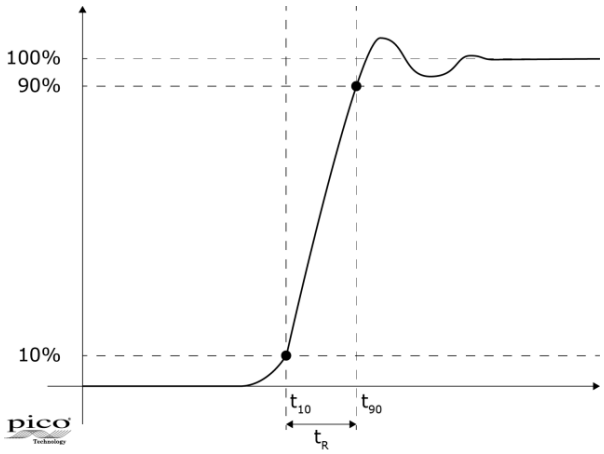


Figure 3.2: Drawing of the concept of rise time (t_R), which is the time a signal takes to go from 10 to $90\,\%$ of the total value.

CO_2 Analysis

The measurement of CO_2 relies in both devices on a sensor that generates infrared light to determine the CO_2 concentration. This light is absorbed by the CO_2 molecules allowing it to be converted to a concentration, as schematic represented in Figure 2.1b [74, 76, 91]. However, it is important to note that the rise time of the Masimo ISA OR$^+$ sensor is slower compared to the rise time of the Hamilton C6 Mechanical Ventilator sensor due to the distinction between mainstream and sidestream measurement techniques. Mainstream devices place the measurement head directly into the breathing circuit, while sidestream devices divert a sample of the air to a separate device located at a distance from the patient, offering a broader range of applications [73]. This difference in measurement method results in a time delay in the signal received by both devices. Despite this, all parameters obtained with each device are measured with consistent timing relative to the respiratory cycle. Since Hamilton C6 Mechanical Ventilator uses mainstream measurements and Masimo ISA OR$^+$ uses sidestream measurements for all parameters, it is possible that including CO_2 data in the synchronization process could facilitate further alignment [74, 76].

Recommended Standard 232 (RS232)

The data from Masimo is received through an RS232 connection and a laptop. Recommended Standard 232, commonly known as RS232, is a serial communication protocol frequently used for data transmission. Several configuration settings are supported, among which the

baud rate is particularly important as it determines the transmission speed, expressed as the number of bits that are transmitted per second. RS232 communication allows two devices to share data by initiating a send request and transmitting data back and forth once the request is acknowledged. A communication block protocol is required to interpret the meaning of each byte received [92].

3.1.2. Objectives

The purpose of this chapter is to provide an explanation of the algorithm developed to synchronize and analyze the data from both the Hamilton C6 and Masimo to eventually get values for oxygen consumption. To do this, the test setup described earlier was used to generate data to test the algorithm.

3.2. Methods

The algorithm was written in Python version 3.9.13 [93]. The overall algorithm can be divided into two main parts; data acquisition and synchronization, and determination of oxygen consumption. Each part is described separately, along with the decisions and considerations that were part of the process.

3.2.1. Data Acquisition

Data for algorithm evaluation was derived using the test setup described in Chapter 2. Data from the Hamilton C6 was retrieved using a MemoryBox (Hamilton Medical AG, Bonaduz, Switzerland) connected to the ventilator, which was later extracted and converted to waveform and breath-by-breath parameter data. Data was obtained from the Masimo device through an RS232 connection and stored on the laptop running the Python code for later analysis, as real-time analysis was not required for this study.

3.2.2. Preprocessing Data

Before using the raw data in the algorithm, certain preprocessing steps were performed to clean the data. These steps included unit conversions and interpolation.

Time Variable

The signals from both the Masimo as the Hamilton C6 had timestamps representing the time of each sample, but they used different formats. To synchronize the signals, it was ideal for both to start at t = 0 at the beginning of a test and to add the time difference between successive samples. Achieving this new timestamp required several steps:

First, the Hamilton timestamp was converted from Excel time to a more readable format expressing days, months, years, hours, minutes and seconds. Before conversion a value of 25569 was subtracted from each raw timestamp, which is the number of days between January 1, 1900 (Excel timestamp) and January 1, 1970 (Unix timestamp).

The Masimo timestamp was recorded in real time on the laptop where the data was collected. This data used the days, months, years, hours, minutes, and seconds from the laptop clock.

Since the time obtained with the Hamilton was the time set on the device, it may not have been the real time as it was set manually. It was therefore necessary to create a new uniform time constant for both devices. This time constant worked on the principle of adding the time difference between two samples as

$$T(t_{\mathrm{i}}) = T(t_{\mathrm{i}-1}) + \Delta t\,, \tag{3.1}$$

where: $T(t_{\mathrm{i}})$ = value of time constant on time t_{i} (in s), $T(t_{\mathrm{i}-1})$ = value of time constant on previous time $t_{\mathrm{i}-1}$ (in s), Δt = time difference between consecutive samples (in s), ensuring that both sets of signals spanned an equivalent total duration. This calculation took into account the different sampling frequencies of the two devices, thus achieving synchronization.

Gas Concentration Data

To achieve uniformity of units for all inputs and obtain the desired units for the parameter output (mL/min) from the algorithm, all concentrations were converted to fractions at the beginning instead of leaving them in percentages. This was performed by dividing the concentrations by 100 as,

$$\mathrm{Fraction} = \frac{\psi}{100}\,, \tag{3.2}$$

where: ψ = concentration in $\%$.

Sample Frequency

As mentioned in the section about time variables, each device operated at a different sampling frequency. The Hamilton C6 device collected waveform data at $50\,\mathrm{Hz}$, while the Masimo recorded waveform data at approximately $8\,\mathrm{Hz}$. In addition, the Hamilton's breath-by-breath parameter data was sampled at $100\,\mathrm{Hz}$, but averaged per breath, whereas the Masimo's parameter frequency was $1\,\mathrm{Hz}$. In order to ensure consistency in the number of samples for subsequent analysis, an interpolation method was applied to the waveform data. This solution involved using the existing time vectors for the waveform signals, which allowed the sampling frequencies to be harmonized and a uniform frequency to be achieved for the data. This harmonization facilitated further analysis.

3.2.3. Synchronization

Crop Data

Data was collected throughout the entire duration of all the different tests. It was therefore necessary to separate the data into parts for each test setting.
To achieve this, an expiratory hold of at least 7 seconds was conducted at the start of a new setting. This created a landmark in both the gas concentration data, and the flow signal [94]. This was identified in the algorithm through peak detection. If a hold occurred, the duration between the peaks exceeded 1.5 times the average duration between peaks, which indicated the initiation of a new configuration.

Cross-Correlation

In addition to the performed expiratory holds, cross-correlation was used to synchronize the signals. As CO_2 concentrations were measured by both devices, it was assumed that the shape of the CO_2 concentrations would be the same between the devices. Therefore, cross-correlation was used to determine the time lag between the signals.

Since the calculation of VO_2 requires both flow and O_2 concentration data, it was necessary to transfer this lag found in the CO_2 signals to the flow and O_2 concentration data. These data were moved relative to each other based on the delay in the CO_2 signal using the `numpy.roll` function. As mentioned earlier, the CO_2 signal was measured in each device at the same point as the signal of interest.

3.2.4. Oxygen Consumption Measurement

Once signal synchronization was completed, the data could be used to determine oxygen consumption.

Rise Time Compensation for Signal Alignment

Adjustments were implemented to the oxygen signal to minimize discrepancies between flow and concentration data due to the slow rise time of the O_2 sensor. These adjustments were based on the curve of the CO_2 signal measured with the fast responding Hamilton sensor. It was decided to use the CO_2 data instead of the start of expiration in the flow signal as the latter would not have accounted for dead space. Changes in the flow signal at the start of expiration was visible earlier than in the concentration signal. Based on the timing of the signal change in CO_2 concentration, a block-shaped signal was created for the O_2 curve. The magnitude of this signal was determined by the end tidal oxygen (etO_2) value as measured by the Masimo O_2 sensor. This approach effectively circumvented the challenge posed by the slower response time, while taking dead space into account.

Integral of the Product of Flow and Concentration

The determination of VO_2 required the integration of the product of flow and oxygen concentration, with the resulting oxygen consumption expressed in $\mathrm{mL/min}$. This was obtained by dividing the integral by the elapsed time derived from the flow, concentration and time variables;

$$\dot{V}O_{2,\mathrm{i}} = \frac{\int_{t_\mathrm{i}}^{t_{\mathrm{i}+1}} \dot{V}(t) \cdot FO_2 \mathrm{d}t}{t_{\mathrm{i}+1} - t_\mathrm{i}}, \tag{3.3}$$

where: $\dot{V}O_{2,i}$ = oxygen consumption of breath i (in $\mathrm{mL/min}$), $\dot{V}(t)$ = flow (in $\mathrm{mL/min}$), FO_2 = oxygen fraction at the mouth, t_i = time of start breath i (in sec), and $t_{\mathrm{i}+1}$ = time of start breath $\mathrm{i}+1$ (in sec). This calculation is called the mouth algorithm [95]. The integration for each breath was taken from the start of inspiration to the end of expiration for that particular breath. These time points were extracted from the ventilator status, provided in the waveform data. In this status parameter, each breath sample was assigned a numerical value, with 1 indicating expiration and 0 indicating inspiration. Consequently, a transition in this numerical sequence denoted the onset of inspiration or expiration.

To minimize the reliance on assumptions in Python, it was decided to perform the integration manually. As a result, all parameters of a sample were systematically multiplied, resulting in distinct "bars" characterized by specific heights and widths, corresponding to the integration. This method resulted in the calculation of a cumulative area, which was then divided by the total duration of the given respiratory cycle. This resulted in

$$V = \frac{\sum \dot{V} \cdot \mathrm{d}t}{2}, \tag{3.4}$$

$$VO_2 = \frac{(V_\mathrm{insp} \cdot FiO_{2,\mathrm{plat}}) - \|(V_\mathrm{exp} \cdot etO_{2,\mathrm{plat}})\| \cdot 60}{t_{\mathrm{i}+1} - t_\mathrm{i}}, \tag{3.5}$$

where: V = volume (in mL), $\dot{V}$ = flow (in $\mathrm{mL/sec}$), $\mathrm{d}t$ = change in time (in sec), VO_2 = oxygen consumption (in $\mathrm{mL/min}$), V_insp = inspired volume (in mL), $FiO_{2,\mathrm{plat}}$ = inspired oxygen fraction plateau, V_exp = expired volume (in mL), $etO_{2,\mathrm{plat}}$ = expired oxygen fraction plateau, $t_{\mathrm{i}+1}$ = time of start breath $\mathrm{i}+1$ (in sec), and t_i = time of start breath i (in sec).

3.2.5. Predicted Oxygen Consumption

Predicted values for oxygen consumption were calculated for each test. Initially, literature suggested the use of VN_2 washout,

$$VO_{2,\text{pred}} = \frac{VN_{2,\text{infused}} \cdot FiO_2}{1 - FiO_2}\,, \tag{3.6}$$

where: $VO_{2,\text{pred}}$ = predicted oxygen consumption (in mL/min), $VN_{2,\text{infused}}$ = infused nitrogen flow (in mL/min), and FiO_2 = fraction of inspiratory oxygen [77, 79, 81]. However, this method was designed to validate devices that did not measure expiratory O_2 concentrations. It was therefore decided not to use this method.

Instead the values derived from the two devices were used to obtain the predicted VO_2 values. As both the Masimo and Hamilton devices are already CE marked and validated, it was assumed that the sensors and parameter data were accurate [74, 76]. The predicted values were derived from the breath-by-breath parameter files of each device. The Hamilton parameter file provided values for both inspired and expired volumes per breath, while the Masimo parameter data included values for etO_2 and FiO_2. This predicted values were obtained as

$$VO_{2,\text{pred}} = ((FiO_2 \cdot V_{\text{insp}}) - \|(etO_2 \cdot V_{\text{exp}})\|) \cdot RR\,, \tag{3.7}$$

where: RR = breathing frequency (in $\text{breaths}/\text{min}$).

In addition to these predicted values, it was investigated what the predicted VO_2 values would be if the dead space volume was subtracted from the inspiratory and expiratory volumes. As the algorithm takes the dead space volume into account, it was necessary to include this in the predicted values as well in order to obtain more accurate results. Using the integral between the start expiration time in the flow signal and the point at which the CO_2 curve began to incline, the dead space volume was computed and subtracted as

$$V_{\text{dead}} = \int_{t_{\text{flow,exp}}}^{t_{\text{CO}_2,\text{exp}}} \dot{V}(t)\text{d}t\,, \tag{3.8}$$

where: V_{dead} = dead space volume (in mL), $t_{\text{flow,exp}}$ = time that flow starts expiration (in sec), $t_{\text{CO}_2,\text{exp}}$ = time that CO_2 signal starts expiration decline (in sec).

3.2.6. Data Analysis

The VO_2 values obtained from the algorithm were compared with the predicted VO_2 values derived from the parameter data. These values were compared using visual inspections.

3.3. Results

3.3.1. Data Acquisition

Data was successfully obtained from the Hamilton and Masimo devices, containing waveform and parameter data. The raw data for all tests can be found in Figure 3.3. Due to differences in data acquisition methods, the lengths of the data were uneven, as data from the Hamilton were recorded from the moment a connection was made with the ventilator, while data from the Masimo was received through a command on the laptop, which was not done at the same time.

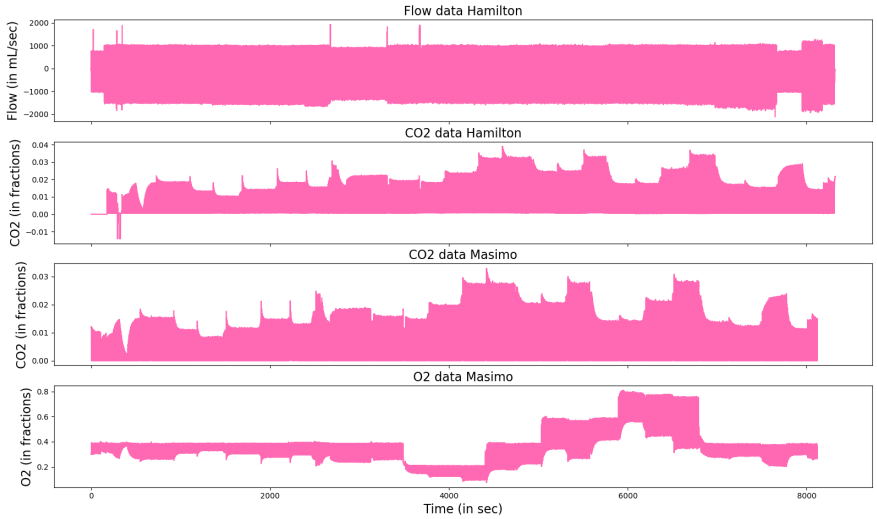


Figure 3.3: Raw signals as derived from the Hamilton and Masimo. These are the results of more than two hours of testing in order to perform all the tests stated in Table 2.1.

3.3.2. Preprocessing Data

During preprocessing, all parameters were standardized to a uniform unit scale. Time variables were initially set to 0 at the start of the test. To ensure consistency, adjustments were made at various intervals throughout the test to maintain a consistent starting point of $t = 0$. While the frequency of the Hamilton waveform data was set to $50\,\mathrm{Hz}$, the time difference between samples was not always exactly $200\,\mathrm{ms}$, varying approximately between $198\,\mathrm{ms}$ and $202\,\mathrm{ms}$. Consequently, a proprietary time vector with a fixed $200\,\mathrm{ms}$ interval between samples was not applicable, and time stamps were converted to account for the varying intervals.

In addition, all concentrations were converted to fractions by dividing the signals by 100. The signals' lengths were standardized using interpolation [96]. The result of interpolation is shown in Figure 3.4.

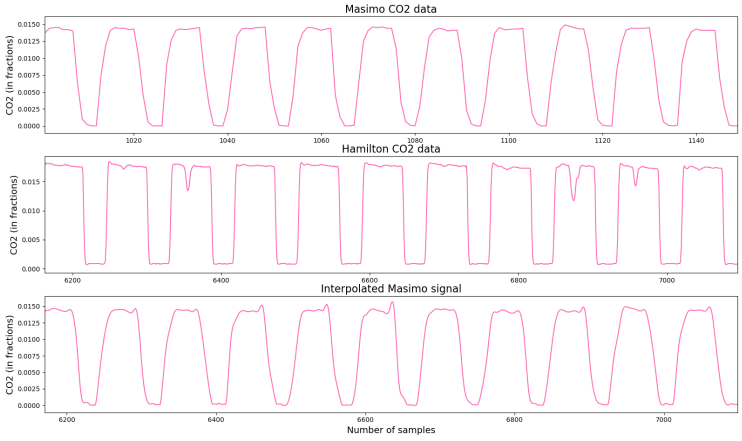


Figure 3.4: Results of interpolating the signal with the lowest sampling frequency. As the Masimo signal had the lowest sampling frequency, this signal is interpolated based on the timing of the Hamilton CO_2 signal. Therefore the x-axes of the subplots are not the same as the x-axis has the number of samples of each data set.

3.3.3. Synchronization

Crop Data

To compare the signals, the complete data set was segmented into individual tests per setting. This segmentation was accomplished by detecting the expiratory hold conducted at the beginning of the test through peak finding. Given that the test lung was ventilated at a constant frequency, the hold was easily identified as there would be no peaks during that period and the duration between the peaks would be longer at that time (see Figure 3.5).

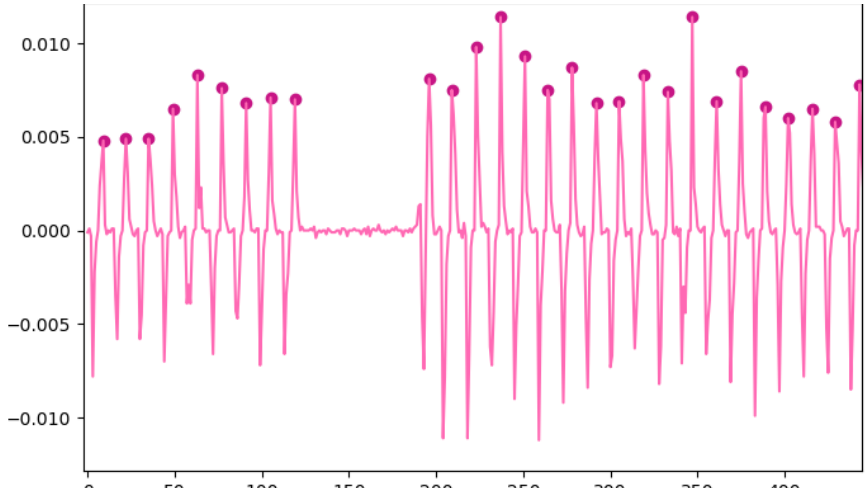


Figure 3.5: The results of peak finding in Masimo data to find the timing of the expiratory hold. As the peaks will have a longer duration between them during the hold, this can be used to find the start and end of a hold.

Cross-Correlation

After cropping and interpolating the signal, it was necessary to do a final timing check using cross-correlation (Figure 3.6). Due to the constant respiration in the signal, the lag signal was more sinusoidal than is typically seen in a cross-correlation lag signal.

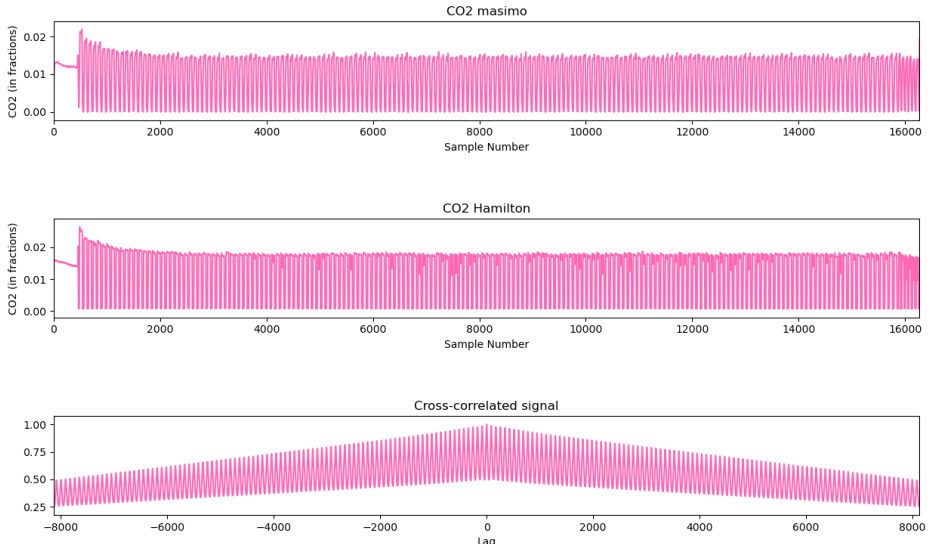


Figure 3.6: Result of the cross-correlation between the CO_2 signals of both devices, including the identified lag from one of the performed tests in the test protocol.

3.3.4. Oxygen Consumption Measurement

As explained in the Methods section, breath status was given in the Hamilton waveform data. These status numbers were used to indicate the start of both inspiration and expiration in the flow data. In Figure 3.7 start of inspiration and start of expiration are shown in the flow data.

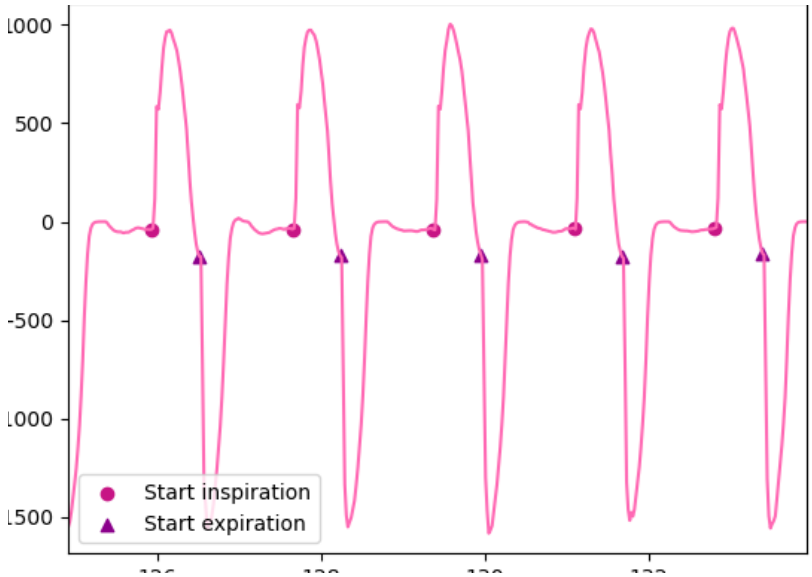


Figure 3.7: Part of the flow signal measured with the Hamilton C6 showing the start of inspiration and expiration based on the breath status as provided in the waveform data of the device.

After optimal data synchronization, it was necessary to compensate for the rise time of the oxygen sensor as explained in Section 3.1. Plateau data was created based on the timing of the Hamilton's CO_2 sensor. A part of the data with the result can be seen in Figure 3.8.

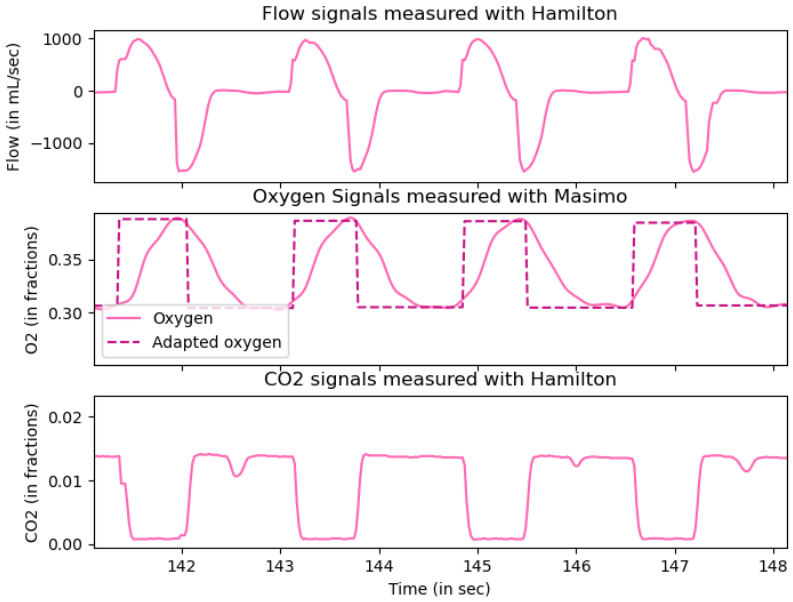


Figure 3.8: Part of the flow, O_2, and CO_2 signals, where the O_2 signal was adapted based on the timing of the CO_2 signal from the Hamilton. The original O_2 signal is depicted as a straight line, while the adapted signal is represented by the dashed line in the central plot.

Table 3.1: Description of all parameters derived from the test setup and the algorithm, where the FiO_2, etO_2, and the volumes were derived from the (breath-by-breath) parameter data of both devices. The algorithmic and predicted VO_2 were derived from the algorithm and the (breath-by-breath) parameter values.

Description of test	FiO_2 (fraction)	RR (min)	PEEP	EtO_2 (fraction)	Mean Volume Insp (mL)	Mean Volume Exp (mL)	Algorithmic VO_2 ($\mathrm{mL/min}$)	Predicted VO_2 ($\mathrm{mL/min}$)
Increase RR	0.39	25	5	0.31	309.43	310.15	131.35	613.31
Increase RR	0.39	35	5	0.30	306.06	333.84	43.91	672.34
Increase RR	0.39	35	5	0.28	302.19	335.63	157.34	841.90
Increase RR	0.39	45	5	0.30	320.61	342.28	-73.24	827.55
Increase RR	0.39	25	5	0.27	306.25	317.67	500.76	841.69
Extra dead space volume	0.39	15	5	0.24	349.18	315.26	474.57	911.55
Change FiO_2 + Consumption	0.21	15	5	0.15	323.08	306.97	6.37	327.2
Change FiO_2 + Consumption	0.21	15	5	0.12	307.63	310.66	189.83	409.84
Change FiO_2 + Consumption	0.21	15	5	0.10	297.25	317.72	180.09	459.76
Change FiO_2 + Consumption	0.39	15	5	0.18	301.02	319.19	358.68	899.10
Change FiO_2 + Consumption	0.39	15	5	0.22	310.70	313.79	462.48	782.09
Change FiO_2 + Consumption	0.58	15	5	0.34	313.92	316.82	632.77	1115.30
Change FiO_2 + Consumption	0.57	15	5	0.27	304.21	322.02	498.50	1296.89
Change FiO_2 + Consumption	0.59	15	5	0.41	320.74	314.88	621.71	902.02
Change FiO_2 + Consumption	0.79	15	5	0.56	324.41	318.46	904.14	1169.14
Change FiO_2 + Consumption	0.77	15	5	0.45	315.72	323.05	765.00	1465.67
Change FiO_2 + Consumption	0.76	15	5	0.35	307.88	338.40	696.88	1733.21
Increase in PEEP	0.38	15	10	0.28	334.47	332.53	260.39	509.83
Increase in PEEP	0.38	15	15	0.29	374.66	376.40	-28.68	495.60
Change in tidal volume	0.38	15	5	0.21	195	201.4	99.51	477.09
Change in tidal volume	0.38	15	5	0.29	395.79	404.19	53.99	497.80

Table 3.1 shows all values for different test setup settings. Alongside the values derived from the algorithm to obtain the 'algorithmic' VO_2, are the corresponding values from the parameter files (etO_2, FiO_2, inspiratory volume and expiratory volume). These parameters have been averaged over the whole test set. The lowest recorded VO_2 value was -73.24, and the highest 904.14. The mean VO_2 value was $330.30\,\mathrm{mL/min}$ with a $95\,\%$ confidence interval (CI) of $[222.19, 438.42]$.

In addition, the table includes extensive data on the type of test and respirator settings. Notably, as the mode was consistent in all cases, it is not shown in the table.

3.3.5. Predicted Oxygen Consumption

Predicted oxygen consumption values were derived from inspiratory and expiratory volumes in the Hamilton parameter file and the FiO_2 and etO_2 from the Masimo parameter file. The mean values for these parameters per test setting and the resulted predicted oxygen consumption value can be found in Table 3.2. As can be seen, one of the values was predicted to be negative. The lowest value was 327.2, the highest value 1733.21, and the mean value was $821.38\,\mathrm{mL/min}$ with a $95\,\%\,\mathrm{CI}$ of $[682.09, 960.66]$.

Table 3.2: All predicted VO_2 values and values for the FiO_2, etO_2, inspiratory (Insp), and expiratory (Exp) volumes derived from the (breath-by-breath) parameter data of the Hamilton and Masimo devices.

FiO_2	etO_2	Volume Insp (mL)	Volume Exp (mL)	Predicted VO_2 (mL/min)
0.39	0.30	309.43	310.15	613.31
0.39	0.30	306.06	333.84	672.34
0.39	0.28	302.19	335.63	841.90
0.39	0.29	320.61	342.28	827.55
0.39	0.27	306.25	317.67	841.69
0.39	0.25	349.18	315.26	911.55
0.22	0.16	323.08	306.97	327.2
0.21	0.12	307.63	310.66	409.84
0.21	0.10	297.25	317.72	459.76
0.38	0.17	301.02	319.19	899.10
0.39	0.21	310.70	313.79	782.09
0.57	0.32	313.92	316.82	1115.30
0.57	0.27	304.21	322.02	1296.89
0.59	0.40	320.74	314.88	902.02
0.79	0.54	324.41	318.46	1169.14
0.78	0.45	315.72	323.05	1465.67
0.75	0.35	307.88	338.40	1733.21
0.39	0.29	334.47	332.53	509.83
0.38	0.28	374.66	376.40	495.60
0.38	0.23	195	201.4	477.09
0.38	0.28	395.79	404.19	497.80

3.3.6. Data Analysis

The curves of both algorithmic and predicted VO_2 are plotted in Figure 3.9. Next to these two, the curve of the predicted value with a correction for dead space volume is plotted. The values of all tests can be found in Table 3.3

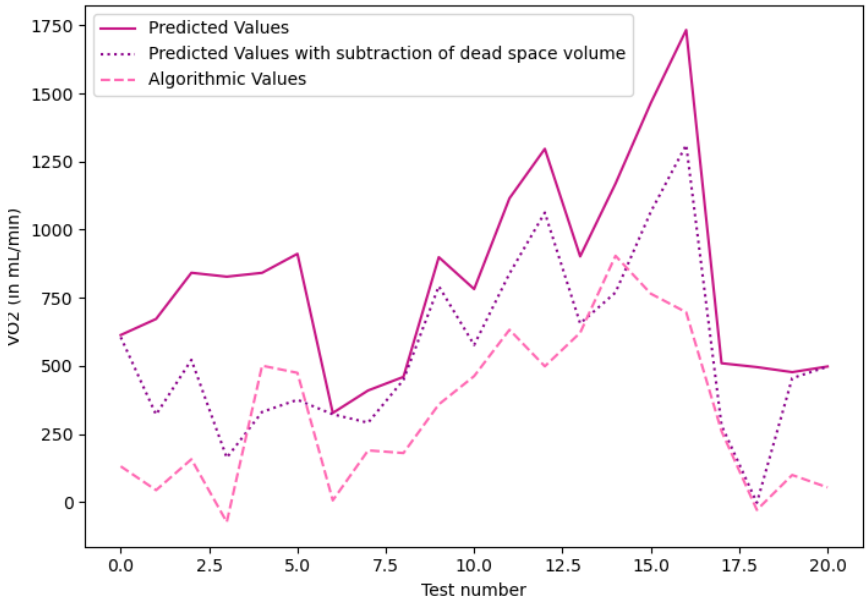


Figure 3.9: Curves displaying mean VO_2 values for each test as explained in Table 3.1. Both the algorithmic VO_2 values (dotted) and the predicted values (straight) were provided. Additionally, the predicted values were presented while considering the volume of dead space (dashed).

Table 3.3: Data analysis of algorithmic VO_2 values compared to the predicted VO_2 values and the predicted VO_2 values without dead space volume. Results are presented for these three values for each of the tests, as described in 3.1.

Algorithmic VO_2 (mL/min)	**Predicted VO_2** (mL/min)	**Predicted VO_2 without dead space volume** (mL/min)
131.35	613.31	605.32
43.91	672.34	321.27
157.34	841.90	522.16
-73.24	827.55	162.91
500.76	841.69	331.01
474.57	911.55	375.72
6.37	327.2	322.69
189.83	409.84	291.57
180.09	459.76	448.79
358.68	899.10	792.64
462.48	782.09	576.85
632.77	1115.30	838.93
498.50	1296.89	1062.75
621.71	902.02	655.79
904.14	1169.14	769.57
765.00	1465.67	1066.05
696.88	1733.21	1311.17
260.39	509.83	281.96
-28.68	495.60	-2.37
99.51	477.09	455.00
53.99	497.80	497.30

3.4. Discussion

The objective of this chapter was to create an algorithm using raw data obtained from the Hamilton and Masimo devices. Using several steps, the algorithm managed to synchronize and multiply the data from two devices to retrieve the VO_2. As seen in the results there was still a large difference between the algorithmic and predicted VO_2 values. This difference can be explained by the fact that both cases measured a situation in equilibrium. The data was generated by a balloon and preset settings, so there were no differences in this during the test. Unfortunately, the algorithm itself also had some limitations that must be taken into account.

3.4.1. Limitations

Firstly, O_2 sensors have a slower rise time than CO_2 sensors. To use the data obtained by the O_2 sensor, it was necessary to adjust the signal to compensate for this delay. As a result, important data may be lost, as the signal was adjusted to one value of the plateau for FiO_2 and etO_2. However, studies have shown that sensors shouldn't be used with rise times greater than $500\,\mathrm{ms}$. In addition to having a lower rise time, patients tested with the algorithm are not expected to breathe so quickly that the sensor can't reach the FiO_2 and etO_2 plateaus [70].

In addition, it is questionable whether cross-correlation was a good method in this imposed-breath setup. As a model, there was little variation between breaths. As a result, the cross-correlation lag curve was sinusoidal rather than having a clear peak at the lag of the signals. Therefore, it may be a good idea to have the cross correlation look at a smaller slice rather than the whole signal between two holds. As the signal was already synchronized on the hold, it was thought that this was not a major problem. The plotted results also did not show a very

large shift of the signals relative to each other.
On the other hand, there was an intriguing observation regarding the cross-correlation delay, which seemed to vary slightly between different test scenarios. Although this seemed unlikely given the expected synchronization of the signals from the start of data recording through all test iterations, there is a possible explanation. It is plausible that this divergence was due to small variations in the number of samples during the hold phase in each setting. This underlines the peculiar nature of the delay inconsistencies detected by the cross-correlation analysis, possibly due to the duration of the hold period.

Lastly, the VO_2 obtained from the algorithm was compared with the VO_2 extracted from the parameter data using FiO_2, etO_2 and volumes for inspiration and expiration (see Equation 3.7). These volumes were based on breath numbers. These breath numbers did not always change exactly at start of inspiration. Therefore, the volumes may differ slightly from the actual inspiratory and expiratory volumes calculated by the algorithm. This could have caused the error margins to differ from the values obtained. In addition, the parameter data does not take into account the dead space volume, which the algorithm does by basing the new O_2 signal on the curve of the Hamilton CO_2 signal. In the predicted values that did correct for the dead space volume, this limitation can be seen, as these values are closer to those of the algorithm. In Table 3.2 it can be seen that these inspiratory and expiratory volumes per breath were not even. This is however, as explained in Chapter 2 unlikely as there is no difference in temperature or humidity within the test lung. It is therefore plausible that this difference is due to a discrepancy between the flow from the cylinder and the flow disappearing through the leak, as already discussed as an expectation in the previous chapter.

3.4.2. Recommendations

Currently, the data was analyzed from the time the expiratory hold was recognized. In contrast, the hold created a different composition of gases in the test lung since the hold could only be applied to the ventilator and not to the flow from the cylinder. Therefore, it may be better not to determine the VO_2 over the entire test setting, but to average it from the moment the value does not change more than 10 %, in other words, has reached equilibrium.

It is also recommended to perform cross-correlation, as mentioned earlier, on a subset of the complete test data set. A possible improvement may be to perform this on the first breath after the hold. The lag found can then be used for the whole signal.

While existing literature has indicated the superiority of the independent breath algorithm (IND) over the mouth algorithm (Equation 3.3), it is thought that this generalization may not apply to this specific algorithm, developed using data from the Hamilton and Masimo devices. Studies suggest that the IND algorithm produces favorable results in patients breathing spontaneously, with reduced noise levels compared to alternative algorithms. The uniqueness of the IND algorithm lies in its individualized treatment of each breath cycle, taking into account potential overlaps between breaths. Unlike the mouth algorithm, which integrates over fixed start and end points, the IND approach considers the distinct inhalation and exhalation start and end points for each individual breath [95, 97–99]. In contrast, this is less relevant for the data obtained with the Hamilton, since every sample was already labeled reliably according to the ventilator activation. It could possibly be investigated whether the IND algorithm could still have a better outcome than the conventional mouth algorithm, but it is expected that this difference will be small.

Finally, sometimes a small dip occurred in the signal in the CO_2 signal measured with the Hamilton (Figure 3.8). As a result, occasionally this CO_2 signal contained more breaths than

there actually were. This may have caused the newly formed O_2 plateau data to be inaccurate since the indices correlated poorly. This problem could possibly be solved by filtering the CO_2 signal or comparing the amount of start inspirations in the CO_2 signal with the start inspirations found in the flow signal.

3.5. Conclusion

In conclusion, it has been possible to create an algorithm that can determine VO_2 based on data from the Hamilton and Masimo devices. This algorithm already seems to adjust and synchronize the signals well, but it still differed largely compared to the predicted VO_2. It is recommended that this algorithm is further tested on a different setup before it can be used on patients as there were too many assumptions in the setup. If these error margins do not improve, some adaptions should be made to the algorithm.

4

Validation of the Algorithm

4.1. Introduction

As explained in the previous chapters, a number of problems were found, mainly in the test setup. For this reason, it was decided to create another test setup in which an attempt was made to reduce the number of assumptions. This chapter will therefore focus on the design of this new setup. Before doing so, the previous assumptions will be evaluated in more detail. This is followed by a description of the new setup and tests carried out to reduce assumptions and obtain algorithmic results.

4.1.1. Questioning Assumptions

To understand why these assumptions may have caused problems in the previous setup and to obtain accurate VO_2 values, some concepts and physiological processes need to be explained. This will highlight the need to minimize the number of assumptions. To understand this a certain understanding of physiology is required.

A State of Complete Exhalation

Peak flow can be calculated using the equation of motion,

$$\Delta P_{\text{insp}} = E \cdot V + R \cdot \dot{V} + I \cdot \ddot{V} \,. \tag{4.1}$$

Since it is assumed that the inertia times the second derivative of the volume contributes almost nothing to the pressure, this equation can be transposed to

$$\Delta P_{\text{insp}} = E \cdot V + R \cdot \dot{V} \,, \tag{4.2}$$

where: ΔP_{insp} = difference in inspiratory pressure (in $\mathrm{cm\,H_2O}$), E = elastance (in $\mathrm{cm\,H_2O/L}$), V = volume (in L), R = resistance (in $\mathrm{cm\,H_2O/L/s}$), $\dot{V}$ = flow (in $\mathrm{L/s}$), I = inertia (in $\mathrm{cm\,H_2O/L/s^2}$), and $\ddot{V}$ = second derivative of volume (in $\mathrm{L/s^2}$) [27, 100].

In a ventilated patient, at the end of exhalation, the volume is zero since all air has been expelled. This allows the maximum flow, or peak flow, to be calculated as

$$\dot{V}_{\text{peak}} = \frac{\Delta P_{\text{insp}}}{R} \,. \tag{4.3}$$

However, this assumption was incorrect as there was also a constant flow from the cylinder in the test setup. Therefore, the volume in the test lung after exhalation was not zero and this part of the equation could not be neglected. If this is transposed into the peak flow equation, the peak flow will be lower as the part of the equation relating to elastance times the volume present must still be subtracted from the pressure;

$$\dot{V}_{\text{peak}} = \frac{\Delta P_{\text{insp}} - E \cdot V}{R} \,. \tag{4.4}$$

This principle is also shown in Figure 4.1 for all three curves commonly used in ventilation, i.e. flow, pressure and volume. The flow is lower, while the pressure and volume start at a higher level. In this figure, Vicy represents the volume coming from the cylinder.

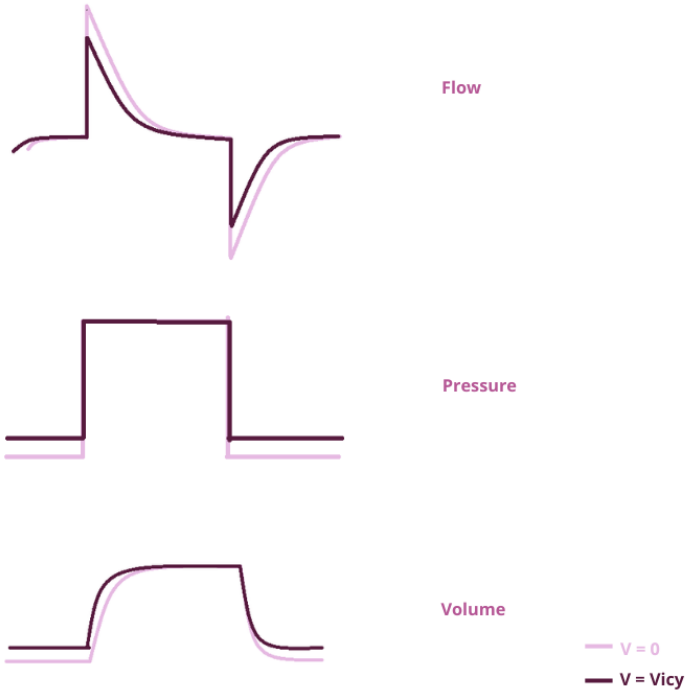


Figure 4.1: Representation of the different curves in case the mechanical ventilator flow is 0 ($V = 0$) and if the cylinder provides continuous flow ($V = V_{\mathrm{icy}}$).

Steady Flows through the Leak and from the Cylinder

It was also assumed that there was a constant flow from the cylinder to the test lung, delivering a constant amount of nitrogen. Would this have been the case, a constant amount of oxygen would be diluted by the nitrogen. However, there was a possibility that this would not be the case if the cylinder was used in conjunction with a respirator. This is because the mechanical ventilator provides inhalation and exhalation, resulting in varying pressures within the circuit. During inspiration, the flow from the cylinder will be lower because the pressure difference between the pressure in the cylinder and the pressure provided by the respirator is reduced, whereas during expiration it will be higher. Consequently, the flow could not be assumed to be constant. The same assumption of constant flow has been made for the setup's leak, but it is assumed that this will also fluctuate according to the pressures and therefore the flow provided by the ventilator. If this problem was indeed present, determining an predicted VO_2 using the N_2 flow (Equation 3.6) from the cylinder would not be feasible.

Cylinder and Leak Flow Equivalence

In addition to the assumptions mentioned above, another assumption was made about the cylinder and the leak. It was assumed that the flow coming from the cylinder was equal to the flow leaving the circuit through the leak. It was essential that this was the case, otherwise the volumes on inhalation and exhalation would not be the same, which would be important in determining VO_2. This difference was also seen in the results of the parameter data obtained from the Hamilton. Inspiratory and expiratory volumes vary slightly in humans due to body humidity and temperature. However, such variations were not expected in a test lung. To see the effect of these different flow rates, a number of equations are worked out below. In these equations all possible other leaks were assumed to be 0.

Flow is generated by the ventilator. However, because there is a leak built into the circuit, some of this flow will disappear through the leak. As a result, the total flow generated by the Hamilton is divided between the balloon and the leak. This is written out as

$$\dot{V}_{\mathrm{tot}} = \dot{V}_{\mathrm{iLH}} + \dot{V}_{\mathrm{ibH}}\,, \tag{4.5}$$

where: $\dot{V}_{\mathrm{tot}}$ = total flow from the Hamilton (in $\mathrm{mL/min}$), $\dot{V}_{\mathrm{iLH}}$ = inspiratory flow that goes from Hamilton through the leak (in $\mathrm{mL/min}$), and $\dot{V}_{\mathrm{ibH}}$ = inspiratory flow that goes from Hamilton into the balloon (in $\mathrm{mL/min}$).

Using the formula above, it is possible to determine the volume of the balloon. This determination is based on the integration of the flow from the Hamilton entering the balloon and the integration of the flow from the cylinder. The mathematical representation of this relationship is

$$V_{\mathrm{ib}} = \int \dot{V}_{\mathrm{ibH}} + \int \dot{V}_{\mathrm{iCy}}\,, \tag{4.6}$$

where: V_{ib} = inspiratory volume of balloon (in mL, $\int \dot{V}_{\mathrm{ibH}}$ = inspiratory volume from Hamilton into the balloon (in mL), and $\int \dot{V}_{\mathrm{iCy}}$ = inspiratory volume from cylinder into the balloon (in mL.

In addition, the volume from the Hamilton is an important factor as it can be set (in volume controlled mode) or read in the parameter file. Again, as in Equation 4.5, this can be divided into two parts, the balloon and the leak. These two volumes are determined by integrating the flows from the Hamilton and through the leak. This can be written as

$$V_{\mathrm{iH}} = \int \dot{V}_{\mathrm{ibH}} + \int \dot{V}_{\mathrm{iLH}}\,, \tag{4.7}$$

where:V_{iH} = inspiratory volume from the Hamilton ventilator (in mL), $\int \dot{V}_{\mathrm{ibH}}$ = inspiratory volume that goes from Hamilton into the balloon (in mL), and $\int \dot{V}_{\mathrm{iLH}}$ = inspiratory volume that goes from Hamilton through the leak (in mL).

Since both Equation 4.6 and Equation 4.7 include the volume of the balloon given by the Hamilton device, the question is whether the volume passing through the leak is the same as the volume entering the circuit through the cylinder. Only if this is true, the total volume read from the Hamilton would be precise and representative of the volume in the balloon, ensuring accurate VO_2 values.

4.1.2. Objectives

To address the problems identified with the test setup (discussed in Chapter 2) and the algorithm (described in Chapter 3), the primary objective of this chapter was to develop an improved setup with a minimized number of assumptions. This would improve the accuracy and validation of the algorithm's results. This improvement would be achieved by designing a revised setup and validating the algorithm results using theoretical analysis and additional measurements. Finally, simulation data were generated to create ideal data to further validate the algorithm.

4.2. Methods

The majority of steps regarding the methods, as explained in previous chapters, remained unchanged. The algorithm followed the same methodology, while the setup had some modifications incorporated to minimize uncertainties.

4.2.1. Improvements of the Test Setup

To reduce the number of assumptions, the test setup was modified. First, the problem of the hole in the test lung was solved. To connect the cylinder to the test lung, a hole had to be made. However, this introduced more uncertainty. It was therefore decided to place the cylinder between the ventilator and the test lung instead of after the test lung. It was also decided to replace the entire test lung. As mentioned before, the curves were not as expected in patients. This new test lung was the IMT Analytics SmartLung Adult, where the lung could be adjusted for resistance and compliance. Resistance was set to $5\,\mathrm{cm\,H_2O/L/s}$ and compliance to $30\,\mathrm{mL/cm\,H_2O}$ in the setup [101].

As well as the changes to the test lung, additional flow sensors were added. These flow sensors were placed at the cylinder inlet and at the leak. With these flow sensors, it was possible to analyze the flow at both points and potentially use this to verify the total flows and volumes at different points in the circuit. The flow sensors were two Sensirion SFM3400-33-D sensors with a range of $-33\,\mathrm{L/min}$ to $33\,\mathrm{L/min}$ and an accuracy of $3\,\%$ [102].

Finally, a $20\,\mathrm{L}$ Douglas bag was added to the set-up. As it seemed difficult to get the predicted VO_2, it was thought that this might be helpful. As mentioned in the first chapter, the Douglas bag is the gold standard for oxygen consumption device validation. The concentration of the Douglas bag was read with the Masimo. This way there was no uncertainty that a difference could be due to the use of a different oxygen sensor. By connecting the Douglas bag to the expiratory port, it was thought that this concentration in the bag could be used in combination with FiO_2 and tidal volumes to derive consumption.
The schematic representation of the improved test setup can be found in Figure 4.2. Pictures of the test setup can be found in Figure C.3, and Figure C.4.

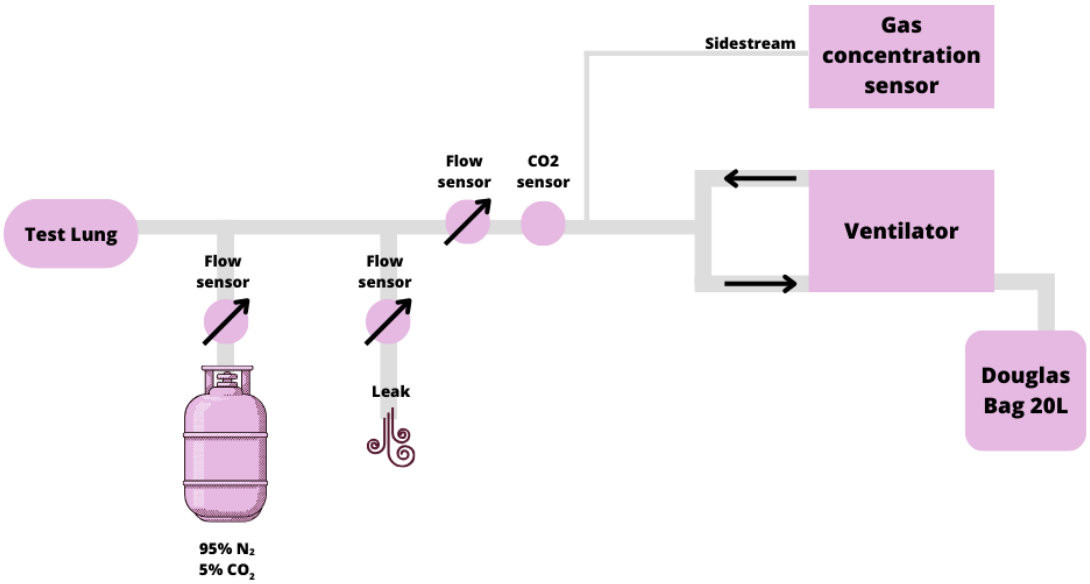


Figure 4.2: Schematic view of the setup for the in vitro tests with a Nomoline sidestream connected to the Masimo ISA OR$^+$ to measure concentrations of CO_2, and O_2 in the air. The cylinder containing $95\,\%$ N_2 and $5\,\%$ CO_2 is connected to the circuit with an additional Sensirion SFM3400-33-D flow sensor. This connection is located between the IMT Analytics SmartLung Adult test lung and the mechanical ventilator. To compensate for the volume coming from the cylinder, a leak is implemented into the circuit, which is similarly connected to the circuit with a Sensirion SFM3400-33-D flow sensor. The flow and gas concentration sensors were placed behind the leak. The flow and CO_2 sensors are linked to the Hamilton, whereas the Masimo used a Nomoline sidestream tube to measure all gas concentrations. After the mechanical ventilator, a Douglas bag is connected to the expiratory port to collect all exhaled gases.

4.2.2. Enhancements to the Test Protocol

In addition to the adjustments to the test setup, changes were made to the test protocol. First, the new setup was connected, followed by the use of the Sensirion Viewer to ensure average flow equivalence [103]. Once successfully connected, data was generated using a different protocol to the previous one. A notable change was the transition from pressure controlled to volume controlled ventilation. The aim of this change was to improve control of the volume within the circuit, thereby optimizing experimental conditions.

Furthermore, the extensive range of different tests was abandoned and replaced by an increased focus on rigorously testing a single configuration multiple times. This strategic adjustment aimed to facilitate the mitigation of outliers and reduce the reliance on isolated events within the circuit. The settings of this test were PEEP $5\,\mathrm{cm\,H_2O}$, P control $16\,\mathrm{cm\,H_2O}$, FiO_2 $40\,\%$, respiratory rate of $15\,\mathrm{min}$, an I:E ratio of $1:1$, and a tidal volume of $400\,\mathrm{mL}$.

4.2.3. Data Analysis

Data obtained from the setup was again analyzed by the algorithm. The same analysis was performed, comparing the VO_2 obtained from the algorithm with the predicted VO_2 calculated from the Hamilton and Masimo parameter data. In addition, the algorithmic VO_2 was compared with the VO_2 obtained using the algorithm and the old test setup. This comparison was based on the difference in the trends of the VO_2 in the different settings compared to the predicted value.

4.2.4. Exploring Dead Space Volume of the Breathing Circuit

Due to the results of the tests discussed above, it was decided to conduct an additional investigation into the possible effect of dead space and diffusion in the ventilation circuit [104].

It was thought that the length of the tubing might have an effect on the concentrations measured by the Masimo. For this reason, an additional study was conducted in which the tubing was cut progressively shorter. First, long sections of the 2-meter tube were cut off. These pieces were always $40\,\mathrm{cm}$ long, to measure a total of 5 different lengths. After these tests, another set of tests was carried out in which short pieces of between 2.5 and $10\,\mathrm{cm}$ were cut instead of $40\,\mathrm{cm}$. This was done for both the inspiration and expiration tubes simultaneously and for both tubes separately. The tests were performed both with the Douglas bag connected to the expiration port and with a Masimo Side Stream connected to the end of the expiration tube.

4.2.5. Simulation of Ideal Signals

To resolve the remaining discrepancies in the results, it was decided to simulate different ventilation signals using Python [93]. These theoretically ideal signals were used to validate the performance of the algorithm. Each of these signals had a total duration of five minutes for each specific setting.

The flow curve was simulated using a sine wave with a baseline of $0\,\mathrm{mL/min}$. To generate different test sets, the amplitude and respiratory rate were adjusted to align with a tidal volume ranging between four and eight times the weight $(80\,\mathrm{kg})$ [105]. The Hamilton CO_2 signal was simulated using a square wave, where inspiration was set to 0 and both inspiration and expiration were of equal duration. The Masimo CO_2 signal was also simulated using a square wave, but a slight offset was introduced to create a sloped curve, mimicking a slower rise time. For the O_2 signal, a Fourier decomposition technique was used. This involved superimposing multiple sine waves to capture the rise time, overshoot, and fluctuations in the O_2 values. The specific value of N in the Fourier decomposition was varied across tests.

In addition to these ideal signals, signals were generated with the same parameters but with a dead space volume introduced into the Hamilton CO_2 signal. Throughout the simulation process, only one test setting was simulated at a time.

Additionally, the predicted VO_2 was determined by integrating the flow signal and identifying the maximum and minimum values in the raw O_2 signal. This value was multiplied by the respiratory rate, according to the test settings as

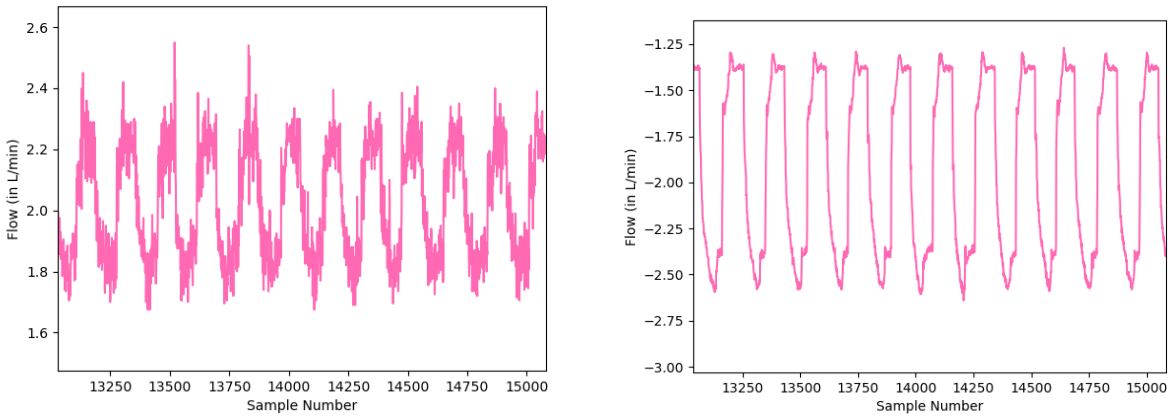
$$VO_{2,\text{pred}} = (\int (\dot{V}_{\text{insp}}(t) \cdot O_{2,\max})\text{d}t - \| \int (\dot{V}_{\text{exp}}(t) \cdot O_{2,\min})\text{d}t\|) \cdot RR\,, \tag{4.8}$$

where: $VO_{2,\text{pred}}$ = predicted oxygen consumption (in mL/min), $\dot{V}_{\text{insp}}(t)$ = inspiratory flow (in mL/sec), $O_{2,\max}$ = maximal oxygen fraction, $\dot{V}_{\text{exp}}(t)$ = expiratory flow (in mL/sec), $O_{2,\min}$ = minimal oxygen fraction, RR = breathing frequency (in breaths/min). Since this signal was constant, the calculation was performed for a single breath cycle. A corrected predicted VO_2 value was calculated, accounting for the dead space volume. This correction aimed to counteract any overestimation of the VO_2 value due to the dead space volume. The same methodology as in the in vitro test setup was employed to determine this dead space volume (see Equation 3.8), which was subtracted from both the inspiratory and expiratory values.

4.3. Results

4.3.1. Flow Sensor Measurements

First, the flow was checked before the test began. The flow signals showed that the signal was indeed fluctuating due to flow and pressure from the ventilator (see Figure 4.3). As mentioned above, the pressure was lower during inspiration than during expiration. It was also difficult to tell by eye whether the two flows were the same. It can be seen that the signal from the cylinder contained more noise than the signal from the leak. However, as analyzed afterwards, the mean flow was the same for both signals.



(a) Flow curve from the cylinder, showing a noisy signal.

(b) Flow curve for the air flowing trough the leak.

Figure 4.3: Flow curves of the flow sensors at both the cylinder and the leak.

4.3.2. Oxygen Consumption Measurement

Once the flows had been checked, the tests were carried out. Several tests were performed with the same settings, and the results are given in Table 4.2. Although the ventilator settings

were always the same, the VO_2 obtained by the algorithm differed each test. The lowest value was 465.56, the highest 693.93 and the mean $541.06\,\mathrm{mL/min}$, with a $95\,\%\,\mathrm{CI}$ of $[472.15, 609.97]$.

4.3.3. Predicted Oxygen Consumption Measurement

In addition, the predicted values were as in the old setup, obtained from the parameter data. Table 4.1 shows all the parameter values and the resulting VO_2. Again, although the settings were the same, there was a difference in the predicted VO_2. The lowest value was 930.45, the highest 1193.08 and the mean $1051.42\,\mathrm{ml/min}$, with a $95\,\%\,\mathrm{CI}$ of $[972.99, 1129.84]$.

Table 4.1: All predicted VO_2 values and values for the FiO_2, etO_2, inspiratory (Insp), and expiratory (Exp) volumes derived from the (breath-by-breath) parameter data of the Hamilton and Masimo devices.

FiO_2	etO_2	Volume Insp (mL)	Volume Exp (mL)	Predicted VO_2 ($\mathrm{mL/min}$)
0.41	0.25	389.40	390.43	930.45
0.42	0.22	397.67	397.64	1193.08
0.41	0.23	395.81	396.84	1065.24
0.41	0.24	393.46	396.69	991.65
0.41	0.22	395.48	397.13	1121.73
0.41	0.24	397.15	398.86	1006.35

4.3.4. Data Analysis

Comparisons were made between the predicted and algorithmic VO_2 values. Table 4.2 shows different values for each test for the predicted values with and without dead space volume, and the algorithmic VO_2 values. In addition, the VO_2 curves of both algorithmic, predicted and predicted without dead space volume are plotted in Figure 4.4. It can be seen that the trend of both signals is correlated.

Table 4.2: Data analysis of algorithmic VO_2 values compared to the predicted VO_2 values and the predicted VO_2 values without dead space volume.

Algorithmic VO_2 ($\mathrm{mL/min}$)	Predicted VO_2 ($\mathrm{mL/min}$)	Predicted VO_2 without dead space volume ($\mathrm{mL/min}$)
489.60	930.45	759.52
693.93	1193.08	995.74
522.03	1065.24	920.37
499.01	991.65	826.15
576.25	1121.73	931.18
465.56	1006.35	851.76

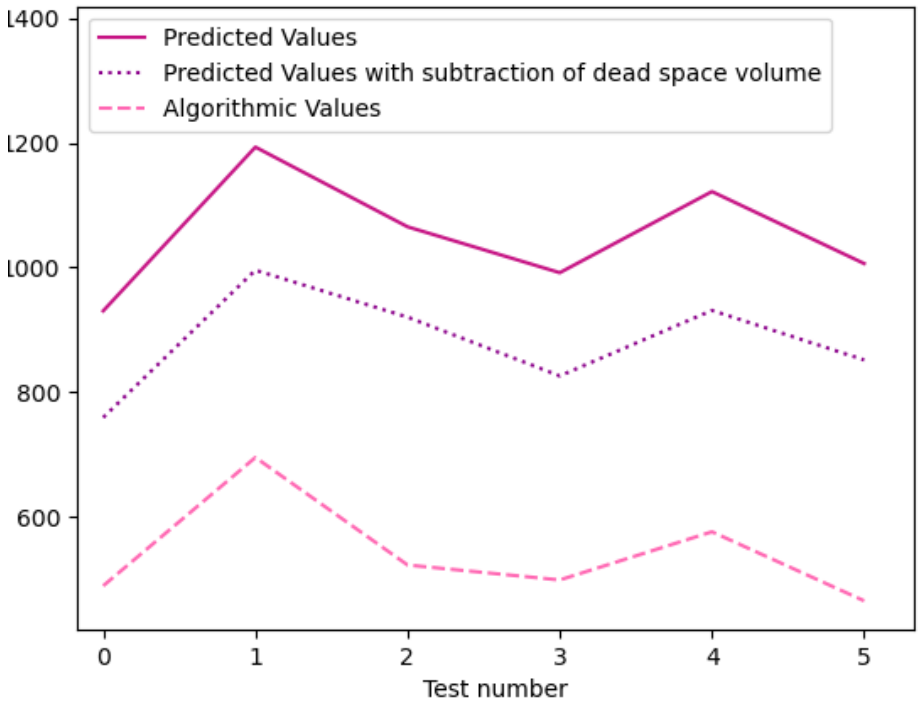


Figure 4.4: Curves of each mean VO_2 value per test. Both the predicted (straight) and algorithmic (dotted) values are shown, and the predicted values are also displayed when accounting for dead space volume (dashed).

When looking at the difference in the VO_2 curves (see Figure 3.9 and Figure 4.4), it can be seen that the data from the new setup has a better correlation with the trend of the predicted VO_2 values.

4.3.5. Dead Space Volume of the Breathing Circuit

As mentioned above, additional tests were carried out to check for the effects of dead space in the breathing circuits. This was suspected because the Douglas bag connected to the expiration port showed an expiratory O_2 of $30\,\%$ in each test. However, this was unlikely as the Masimo indicated an expiratory value of around $20\,\%$ where it was connected to the circuit. To test this hypothesis, tests were performed in which pieces of approximately $40\,\mathrm{cm}$ were cut each time. However, there was no change in the average etO_2 measured in the Douglas bag, which was approximately $31\,\%$.

The effect was therefore investigated by connecting the Masimo directly to the expiratory port to measure the gas concentration in the expiratory tube in real time, rather than the concentration in the Douglas bag, was investigated. This showed that the Masimo device measurement needs a respiratory cycle to distinguish between FiO_2 and etO_2 concentrations. There was a greater difference between the two values when the tube was cut shorter, while only one value ($30\,\%$) could be read at the full length.

4.3.6. Simulation of Ideal Signals

The simulation data from one of the ideal tests without dead space volume can be seen in Figure 4.5, showing all four curves formed as raw data for the algorithm. Figure 4.6 shows the result of changing the oxygen curve with the algorithm. Next to only ideal data, there was also

data created with dead space volume implemented. This volume was around $30\,\%$ of the total inspiratory volume [88].

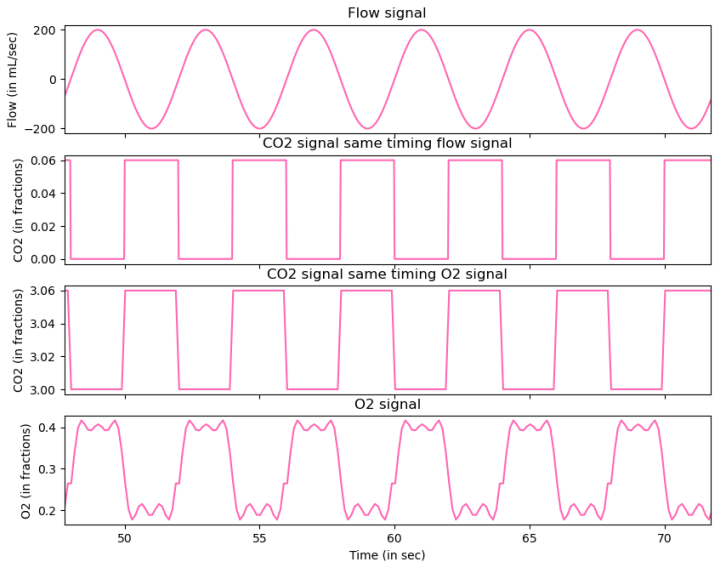
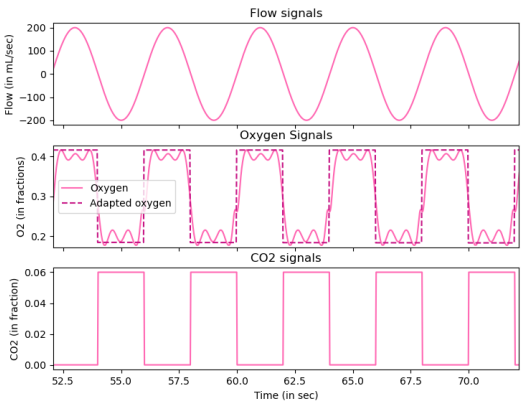
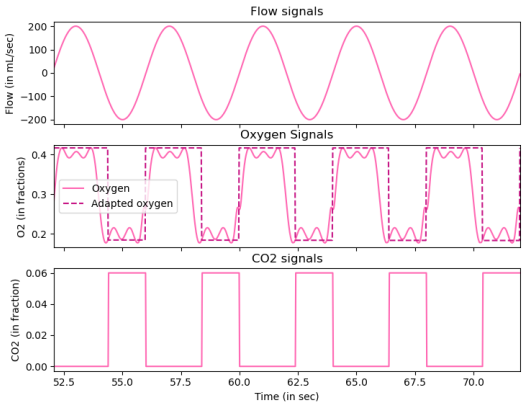


Figure 4.5: Raw simulated signals with a flow amplitude of 250 and a baseline of $0\,\mathrm{mL/sec}$ were obtained. The oxygen signal was subjected to Fourier decomposition with N = 5, a baseline of 0.30, and an amplitude of 0.10. The CO_2 signal for the Masimo simulation had an offset of 0.10. The breathing rate was set at $15\,\mathrm{breaths/minute}$.



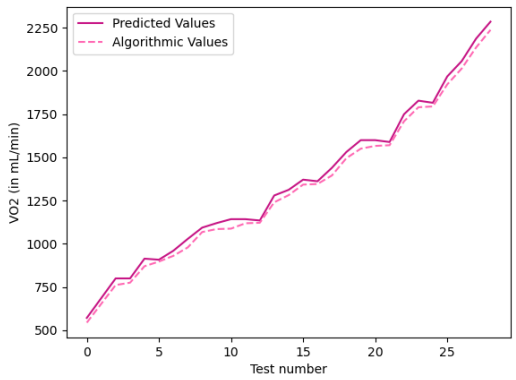
(a) Example of simulation data where no dead space volume was implemented in the CO_2 signal.



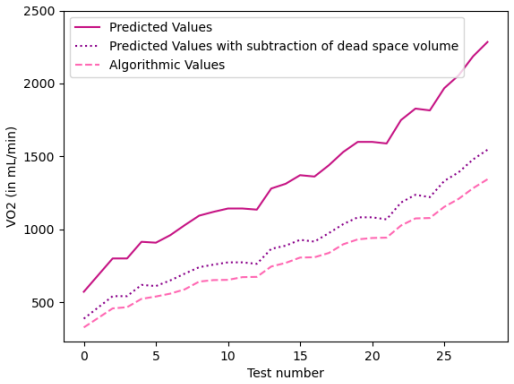
(b) Example of simulation data with 30 % dead space volume implemented in the CO_2 signal. The

Figure 4.6: Adapted simulated O_2 signals, based on the timing of the CO_2 signal. The original O_2 signal is depicted as a straight line, while the adapted signal is represented by the dashed line in the central plots of both subfigures.

Both predicted and algorithmic VO_2 values were obtained from the various simulations. The settings and results are shown in Table E.1 and Table E.2 in Appendix E. The results of the predicted and algorithmic values are visible in Table 4.3 and Table 4.4. In addition, the predicted (with and without dead space correction) and algorithmic values were plotted against each other to visualize the difference between the values (Figure 4.7).



(a) VO_2 values for simulation data with no dead space volume implemented in the CO_2 signal.



(b) VO_2 values in simulation data with 30 % dead space volume implemented in the CO_2 signal.

Figure 4.7: Curves showing algorithmic and predicted VO_2 values for the simulated test sets are presented, with the algorithmic values ranging from small to large for improved clarity. In the simulation with implemented dead space volume, a correction for this volume was also applied. The curves show the algorithmic (dashed), predicted (straight), and corrected predicted (dotted) VO_2 values.

Table 4.3: The values for the VO_2 for both the algorithm, and predicted values for the simulated data without dead space volume implemented in the CO_2 signal.

Algorithmic VO_2 (mL/min)	**Predicted VO_2** (mL/min)
1118.52	1142.32
1342.22	1370.79
1565.93	1599.25
1789.63	1827.72
2013.33	2056.18
2237.04	2284.65
775.00	799.61
930.01	959.54
1085.01	1119.46
1240.01	1279.38
1395.01	1439.30
1550.01	1599.23
543.73	571.13
652.48	685.36
761.23	799.59
869.97	913.82
978.72	1028.04
1087.47	1142.27
897.13	907.69
1121.41	1134.61
1345.69	1361.53
1569.97	1588.45
1794.25	1815.37
1067.68	1093.24
1281.22	1311.89
1494.76	1530.54
1708.29	1749.19
1921.83	1967.83
2135.37	2186.48

Table 4.4: The values for the VO_2 for both the algorithm, and predicted values with and without dead space volume correction for the simulated data with dead space volume implemented in the CO_2 signal.

Algorithmic VO_2 (mL/min)	**Predicted VO_2** (mL/min)	**Predicted VO_2 without dead space volume** (mL/min)
671.41	1142.32	772.75
805.69	1370.79	927.30
939.98	1599.25	1081.84
1074.26	1827.72	1236.39
1208.54	2056.18	1390.94
1342.82	2284.65	1545.49
465.21	799.61	540.91
558.25	959.54	649.09
651.29	1119.46	757.27
744.34	1279.38	865.45
837.38	1439.30	973.64
930.42	1599.23	1081.82
326.39	571.13	386.35
391.66	685.36	463.61
456.94	799.59	540.88
522.22	913.82	618.15
587.50	1028.04	695.42
652.77	1142.27	772.69
538.53	907.69	610.12
673.16	1134.61	762.65
807.80	1361.53	915.18
942.43	1588.45	1067.71
1077.06	1815.37	1220.24
640.88	1093.24	739.54
769.06	1311.89	887.45
897.24	1530.54	1035.36
1025.42	1749.19	1183.27
1153.59	1967.83	1331.18
1281.77	2186.48	1479.09

4.4. Discussion

The objective of this chapter was to create a new test setup that depended on fewer assumptions and could therefore be used to further validate the algorithm created. In addition, concepts were further tested to see whether there was a significant effect of diffusion within the tubes. Lastly, data was simulated to create ideal test data for a validation of the algorithm.

The results showed that the flow from the cylinder and through the leak did indeed fluctuated. It was expected that these differences were due to the pressure from the ventilator. This was assumed because it fluctuated with the ventilation pattern. As soon as the I:E ratio was changed to $2:1$, the fluctuations also occurred at on this ratio.

As can be seen from the results comparing the algorithmic values with the predicted values, there was still a difference. This was probably due to the fact that measures were calculated in a static situation, resulting in a small range of values. This was the case for both the algorithmic and predicted values, resulting in non-overlapping ranges. By examining the 95 % confidence intervals for both setups, coupled with the visualization of the VO_2 value curves, an inference can be drawn: the new test configuration yielded more reliable results compared to the previous one. In particular, the new setup showed a corresponding trend with the predicted values, thus improving the overall reliability of the results. Next to the predicted values, the dead space volume was subtracted from the inspiratory and expiratory volumes in order to account for this air. This showed lower values than the predicted values. Although these values do not overlap completely, there is a good chance that the large difference between the predicted value and the algorithmic value is partly due to dead space. However, this dead space correction was not a fully valid validation as it required data from variables selected by the algorithm. In order to determine the dead space volume, it was necessary to know how long had elapsed between the onset of flow and the CO_2 signal. As this onset was determined by the algorithm, this value was less objective as validation of the algorithm.

The abnormal expiratory concentration of oxygen within the Douglas bag was hypothesized to be due to a combination of diffusion and the presence of a singular CO_2 concentration in the Douglas bag (i.e. the absence of a respiratory cycle). This condition posed a challenge to the Masimo device, impairing its ability to effectively differentiate between inhalation and exhalation and consequently reducing its performance. It was plausible that this problem could have been caused by the test setup and equipment used. In particular, a cylinder was used containing only 5% CO_2, resulting in lower etCO_2 value compared to those observed in patients.
In addition to these potential CO_2-related factors, another consideration was the likelihood of a higher percentage of oxygen in the expiratory tube and consequently in the Douglas bag. This could be due to the constant admixture of 40% FiO_2 through the inspiration port. As there is no physical separation in the Y-piece connecting these tubes, some of the gas may be diverted into the expiratory tube instead of following the intended path through the circuit into the test lung. This phenomenon is known as diffusion of gases and can be explained by several equations outlined in Appendix F. Analysis of these equations shows that there is a difference in the diffusion rate of CO_2, O_2 and N_2, where $N_2 > O_2 > CO_2$. This may explain these observed concentrations.

However, it is important to note that the Douglas bag may not be necessary in this context, as the Masimo device is already CE marked, indicating compliance with the essential health and safety requirements. As a result, the O_2 and CO_2 sensors in the Masimo device do not require additional validation using the Douglas bag.

As with the data from the new test setup, Figure 4.7 again showed trends that were very similar across settings. To best simulate the real situation and test whether the algorithm

could accurately shape the timing of the adjusted O_2 signal, dead space volume was included in these data. It is clear that the projected value and the algorithmic value differ. When the dead space is removed, the values are closer together. The VO_2 values follow the same trend. Therefore, it is thought that the algorithm can correctly measure the VO_2 for different situation and ventilator settings.

4.4.1. Limitations

As no changes have been made to the algorithm, it was subject to the same limitations as discussed in the previous chapter.

An additional limitation arose from the lack of an alternative approach to derive the predicted VO_2. This was partly influenced by the incongruity of using the Douglas bag in this setup. As the Masimo could no longer distinguish between inspiration and expiration, it did not produce a correct etO_2 value that could be used to generate an predicted VO_2. In addition, the formula outlined in the previous chapter (see Equation 3.6), which depended on the VN_2, could not be applied for this calculation due to previously mentioned reasons. For this reason, there was no deviation from the method previously used to obtain the predicted VO_2. However, it could still be that the difference found in the data was due to a small error in this calculation, possibly in the volumes obtained in the parameter data. In addition, the predicted value method did not take into account dead space, which had an effect in the algorithm, as the algorithm was based on the timing of the CO_2 curve and not the flow curve, which was proved to be true as the curves became closer to each other after correcting for dead space volume. As all the curves did follow the same trend, dead space volume was expected to be the reason for the overestimation of the predicted values.

4.4.2. Recommendations

As only one setting had been tested this time, it would be advisable to see if it was necessary to try the other settings. Of course, these had already been tested in the old test setup, and it did not appear that the algorithm had more difficulties with other settings than baseline. Of course, for future research, it would be good for the results to test all these different settings several times. This way, both comprehensiveness and the possibility of outliers were ensured.

In addition, an improvement might be to add perturbations to the in vitro data. For example, a spontaneously breathing patient might cough or move and this might produce data that is more difficult for the algorithm to interpret. This, on the other hand, is very difficult to mimic in the current setup, and might only be possible when real patient data is collected.

Finally, a good addition would be to improve the Douglas bag validation method. At the moment there is still a leak in the set-up, which leaves a small uncertainty. This was taken for granted because it was assumed that diffusion would be the same everywhere, so the concentrations would be the same everywhere. Instead, it would be even better to place another Douglas bag to capture the gases coming from the leak. These Douglas bags would then have to be read correctly, using an accurate flow sensor to measure the volume of the Douglas bag and a gas concentration device. This way all gases and flows are correctly measured and a total comparison of all flows can be made. Although it seemed plausible to validate this using the Masimo oxygen sensor, there were too many problems to validate the algorithm at this moment with the Douglas bag.

4.5. Conclusion

In conclusion, it was possible to improve the setup by reducing the number of assumptions. The new test setup gave better results, but still showed a difference between the algorithmic and predicted VO_2 value. However, as the trend of the values was the same, it is hypothesized that this is mainly due to an overestimation of the predicted value by not taking dead space into account in this calculation. In addition, diffusion was investigated and its possible effect in the ventilation tubes, but this appeared to be mainly due to the fact that the Masimo could no longer distinguish between inspiration and expiration. As a result, the Douglas bag did not prove to be a viable validation method of the algorithm. The algorithm was also validated using simulated data. Within this simulated data, the algorithm showed high correlations with the predicted values, making it reliable for use in clinical practice.

5

Future Perspectives and Conclusions

5.1. Discussion

Critically ill, mechanically ventilated patients admitted to the intensive care unit (ICU) require continuous monitoring to ensure optimal care and treatment. To measure energy expenditure in these patients, oxygen consumption (VO_2) should be considered. This measure is thought to be efficient as it is directly related to cellular function and aerobic adenosine triphosphate (ATP) conversion. Accurate assessment of VO_2 could provide valuable insight into a patient's energy expenditure and metabolic status, leading to better informed clinical decisions and improved patient outcomes.

Despite the potential benefits, measuring VO_2 in mechanically ventilated patients is challenging. It requires monitoring both flow and oxygen concentrations throughout the respiratory cycle. Achieving breath-by-breath measurements of VO_2 often requires synchronization, adding further complexity to the process. The primary objective of this thesis was to develop a robust algorithm capable of measuring oxygen consumption in critically ill, mechanically ventilated patients, as described in Chapter 3. To achieve this, an in vitro setup was designed as described in Chapter 2 to closely mimic the respiratory cycle of these patients in the ICU. However, this setup offered room for improvement caused by certain assumptions made in the development. The improved setup was described in Chapter 4.

5.2. Future Perspectives

Oxygen consumption measurement holds great promise for advancing personalized care in the ICU. However, a number of challenges need to be effectively addressed before the Masimo device and associated data synchronization algorithm can be implemented.

The main requirements for implementation have been addressed and it would be best to test the algorithm further, ideally on real patient data. The question is whether it will be necessary for these VO_2 values to be identical to the predicted VO_2 since there seemed to be some limitations with that value as well, as explained in Chapter 3 and Chapter 4.

Despite these mentioned limitations, it seems plausible that this algorithm might be used in the future on patients admitted to the ICU. Prior to implementation, the algorithm must be tested on real patient data. For this reason, a protocol has been written and is awaiting Medisch Etische Toetsings Commissie (METC) approval. The aim of this research is to assess whether failure criteria of a spontaneous breathing trial (SBT) can be improved. Currently, up to $20\,\%$ of ICU patients fail to wean from the ventilator even though they are ready for extubation according to the established protocol (see Appendix G) and the failure criteria [6, 7, 16]. So despite all measures, it still seems very difficult to find the optimal extubation timing.

The addition of oxygen consumption as a measure seems interesting to provide better treatment guidance. It is hypothesized that the group of patients who will pass extubation at baseline will have a lower VO_2, but a greater difference in consumption between rest and SBT. This means that these patients will consume less oxygen at rest, but will be able to consume more oxygen when required [24].

If oxygen consumption measurement in weaning from the mechanical ventilator is proven to be successful, the VO_2 can be studied further and possibly used for weaning from Extra Corporal Membrane Oxygenation (ECMO). Requiring ECMO support provides a totally different situation since oxygenation is not only obtained through the ventilator. Understanding the patient's independent oxygen consumption could help optimizing the weaning process. This will allow measurement of oxygen consumption and oxygenation at the level of the ECMO as well as the lungs.

In addition to its use in weaning, VO_2 has also been shown to guide personalized care for patients in intensive care. This could include, for example, the care of the physiotherapist. Being able to see the patient's oxygen consumption could help the therapy plan. It could also help, for example the psychiatry or pain team to see if a patient is experiencing stress, anxiety or pain. It is expected that oxygen consumption while in rest will be increased in these situations.

For these applications, it is recommended that VO_2 can also be obtained real time. Currently, the algorithm can only provide this value in retrospect. This is mainly due to the fact that a MemoryBox must be connected to obtain the Hamilton data. An important improvement would be to obtain this data via an RS232 connection. If both the Masimo and Hamilton data can be obtained through an RS232 connection, it is possible to project data in real time with the use of an Arduino. ICU patients can then be monitored in real time and the trend of the consumption can be shown, rather than only the oxygen consumption at certain times.

Further research is needed before real time monitoring of VO_2 can be achieved. This will take time and some financial investment. This thesis has made a promising start by providing a working in vitro test setup and an algorithm to synchronize data from two different devices and use this synchronized data to derive VO_2.

5.3. Conclusion

In conclusion, this thesis has made significant progress towards achieving personalized care in the ICU by developing an algorithm to measure oxygen consumption in critically ill patients. The designed in vitro test setup demonstrated the feasibility of mimicking patient breathing cycles, and the algorithm successfully synchronized flow and oxygen concentration data while accounting for dead space volume and slower rise time. However, the algorithm was based on several assumptions and further research and testing in patients is required. The potential of oxygen consumption (i.e. the algorithm) to improve weaning from both mechanical ventilators as ECMO machines, as well as its applications in personalized care, holds promise for improving patient outcomes. Although challenges remain, this research lays the groundwork for obtaining real time VO_2 measurements and advancing critical care practice.

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A

Literature Review

An Overview of Oxygen Consumption Measurements in Mechanically Ventilated Critically Ill Patients: A Literature Review

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Abstract

Background More than half of all patients admitted to an ICU receive mechanical ventilation within the first 24 hours of admission. To determine if someone is ready for extubation, a spontaneous breathing trial (SBT) must be performed. Changes in consumption during an SBT can be an early indicator of patient effort and weaning failure. Oxygen consumption (VO_2) can be monitored by metabolic monitoring using indirect calorimetry. In recent years there has been increased interest in the use of indirect calorimetry. There are many different ways of measuring VO_2, each with its own advantages and disadvantages.

Objectives The objective of this review is to give an overview of these options and to assess the best way to implement VO_2 in mechanically ventilated intensive care patients during weaning.

Methods A literature search was performed using five databases, PubMed, Embase, Web of Science, Cochrane Library, and Emcare. The reports had to be published before the 18th of October 2022, and mention the sampling method, the sensor for the oxygen measurement, the validation and the purpose of the VO_2 measurement. Articles had to be published in English and could not be case reports.

Results In total 653 unique reports were found, of which 34 articles were included in the review. Different techniques and purposes were used of which the mixing chamber and breath-by-breath techniques were used the most. Of these techniques, it was found that it could provide multiple monitor purposes and has a wide variety in values seen in ICU patients.

Conclusion The most commonly used techniques have evolved over time with the disappearance of the Deltatrac mixing chamber. VO_2 is a valuable parameter to include in the standard of care and to use to monitor critically ill patients, providing clinicians with more detailed information about the condition of ICU patients. Further research should be conducted on weaning using breath-by-breath techniques.

1. Introduction

More than half of all patients admitted to an Intensive Care Unit (ICU) receive mechanical ventilation within the first 24 hours of admission. (1) Weaning from mechanical ventilation is often a difficult step. (2) Prolonged ventilation and too early extubation causing extubation failure (i.e. the necessity to reintubate the patient), can result in a longer ICU stay, higher costs, and even increased morbidity and mortality. (3-6) It is therefore important to predict extubation success as early as possible with a low extubation failure percentage. Currently the prediction of extubation success is done with a spontaneous breathing trial (SBT), initially described by Tobin et al., in which the rapid shallow breathing index pays a prominent role. (7, 8) However, even with a proper execution of an SBT, 15-20% of patients experience extubation failure. It is therefore

necessary to investigate if better parameters can be found to improve the SBT. (9, 10)

One of the promising new parameters is the measurement of oxygen consumption as a measure of effort and/or metabolic demand. Changes in consumption during an SBT, which is required to determine whether a patient is ready for extubation, can be an early indicator of patient effort and weaning failure. (11, 12) Oxygen consumption can be monitored by metabolic monitoring with indirect calorimetry. Metabolic monitoring has been used in critically ill patients for decades, although mostly in research settings. (11, 13) In theory, it has several advantages, including matching nutrition to the metabolic needs, which vary during ICU admission, monitoring patient effort during weaning from the ventilator, and monitoring patient's effort during exercise. (14, 15)

Unfortunately, metabolic monitoring of ICU patients, has proven to be difficult and expensive. Resting energy expenditure (REE) can be approximated mathematically. This method, however, has repeatedly failed to show good correlation with measured values. This has led to an increased interest for the use of indirect calorimetry in recent years. (14, 16-19)
Indirect calorimetry has made it possible to continuously measure changes in oxygen consumption (VO_2), and carbon dioxide production (VCO_2). These parameters can be used to assess both cardiac output and nutritional status. (16-18) VO_2 is derived from indirect calorimetry using flow or volume measurements and oxygen concentration. (20)

There are many different ways to measure oxygen consumption, each with its own advantages and disadvantages. The aim of this research is to provide an overview of the different ways of measuring VO_2 in mechanically ventilated ICU patients. The results will be used to assess the best way to implement indirect calorimetry in patients during weaning.

2. Methods

2.1. Search Strategy

On October 18th, 2022, a search strategy was conducted. PubMed, Embase, Emcare, Cochrane Library, and Web of Science were all used in the search. The search query included the terms VO_2, oxygen consumption, Intensive Care Unit (ICU), Mechanical Ventilation, Adults, and synonyms. The search strings can be found in Appendix I.

2.2. Study Screening

All publications were independently evaluated for suitability for full text analysis by two of three reviewers (F.S., F.V. or J.O.) based on title and abstract.
Any persistent disagreements were resolved by author A.S.
The following inclusion and exclusion criteria were used for title and abstract screening, as well as full text analysis.

The inclusion criteria were:

- Adults on mechanical ventilation in the ICU.
- Describes all criteria about the VO_2 measurement mentioned below.
    - The sampling method (breath-by-breath, mixing chamber and other examples)
    - The sensor which is used to measure the O_2 concentration
    - Where the VO_2 was used for
    - The validation of the technique or device, to ensure the quality of the device.

The exclusion criteria were:

- No full text available
- Case reports, review, clinical trials, posters or abstract presentations
- Pediatric patients
- Only in vitro analysis

2.3. Data Extraction

Data extraction was carried out on the included publications by F.S., F.V., and J.O., and included extensive information about the articles, including the authors' names, year of publication, journal, and study design. They also gathered essential information about the study's demographic, sample size, setting, potential interventions, objectives, and outcome measures of the study. VO_2 measurement information, including sampling technique, sensor used, device name and manufacturer, purpose of VO_2 measurement, validation, was also retrieved. Test lung settings, calibration and number of calibration required, accuracy and VO_2 values of the devices and studies were documented where applicable.

2.4. Outcome Measures

As the aim of the research is to provide an overview of the different VO_2 measurements, these were the main findings.

Some incidental findings (the literature-based VO_2 values, the calibration procedures and the calculations) were also noted, as they may add to the knowledge base when making a conscious choice.

3. Results

3.1. Study Selection

The search strings lead to the following number of articles: PubMed: 409, Embase: 304 of which 185 were unique, Web of Science: 72 of which 15 unique, Cochrane Library: 37 of which 22 unique, Emcare: 105 of which 22 were unique. In total 653 references were included for title and abstract screening.

Of these articles, 146 were assessed for full text analysis. 34 met all criteria and were included for data extraction. The PRISMA flow diagram of the selection process is depicted in Figure 1.

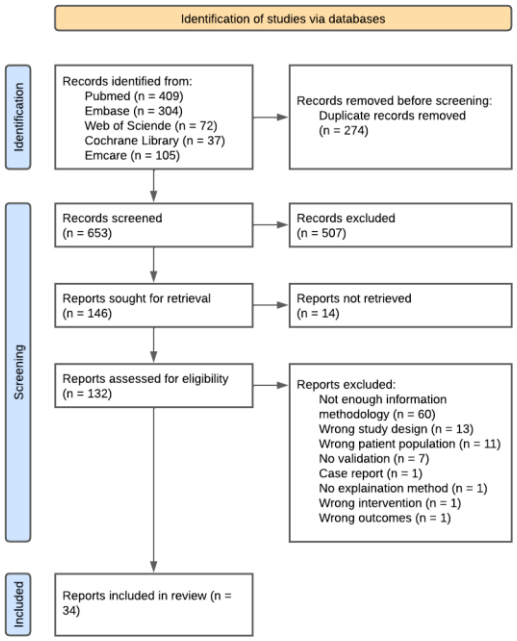

Figure 1 PRISMA Flow Diagram of Selection Process

3.2. Study Characteristics

All articles were published between December 1981 and February 2022. A complete overview per article is stated in Appendix A.

All articles conducted their study in the intensive care unit. However, some articles further specified this as a general intensive care unit (21-23), critical care unit (24), surgical and medical critical care unit (25-30), a surgical intensive care (31, 32), surgery-anesthesiology intensive care unit (33), and one in collaboration with a pediatric intensive care unit (29).

3.3. Purpose

Measurements of oxygen consumption and indirect calorimetry can be utilized for several tasks. It is mostly used for better understanding of energy expenditure and to keep track of the patient's nutritional or metabolic status. (21-23, 26, 28, 29, 31, 34-47) This could lead to more personalized care, which could be beneficial in terms of the number of infections found in critically ill patients. (26) In most papers, the recommended method for measurement of REE is the use of indirect calorimetry. (22, 26)

VO_2 measurements can also serve as an indicator for the impairment between oxygen delivery and consumption (oxygen deficiency). (27, 31-33, 42, 43, 48) This can help in monitoring patients with sepsis or after cardiac arrest. (27, 32) Additionally, it can be used for monitoring the critically ill in general by providing more information on gas exchange or as a metric to predict death. (24, 25, 29, 30, 41, 44-46, 48-52)
Lastly, it was also used as a parameter to guide in decision making during weaning. (47, 53, 54)

3.4. Methods for VO_2 Sampling

The publications used a variety of techniques. These are all covered in the following sections. In addition, various devices regularly used within these methods are described, as well as their specific operation. A complete overview per article can be found in Table 2, in Appendix B. The different set ups used in the articles can be found in Appendix H.

3.4.1. Mixing Chamber

A mixing chamber sampling technique is often used in an open circuit. There are two options for the open circuit. Subjects can either inhale from the atmosphere or they breathe in air supplied by a mechanical ventilator. A complete overview of the used mixing chambers, can be found in Appendix C.1, Table 3.

The mixing chamber technique uses two chambers filled with air. The exhaled gases are drawn to the first chamber with rotameters (44, 49). In this chamber the exhaled gases are mixed with the already present air in the chamber. The mixed gas is transported to a second chamber where samples are collected to determine the gas concentrations. All exhaled air must be collected and there should be no leaks in the circuit.
A dry gas meter can determine flow by using a counter and rotation. (44, 49) Flow can also be monitored using the dilution technique or a pneumotachometer. (29, 44) The dilution method uses a tracer gas that is delivered at a steady rate, allowing mass spectrometry to estimate fractional concentrations. (37) In addition, expiratory flow can be measured using a vortex flowmeter (31, 53) or a bias turbine volume transducer (46). Unfortunately, the accuracy of the vortex flowmeter is comprised in the presence of humid air. The Haldane transformation can also be used to calculate the inspired volume. (44)

Contrary to what has been stated above, Gonzaléz-Arevalo et al. used a mixing chamber as part of a closed-anesthesia circuit. In a closed circuit, the amount of O_2 delivered to the patient is equal to the amount consumed by the patient. In addition, CO_2 is completely eliminated. (25)
This system was based on a closed-circuit spirometer, but, the spirometer was replaced by a chamber. The flow rate was used to keep the oxygen concentration within the chamber constant, which was equal to the patient's oxygen consumption. As an additional check, it measured the inspired oxygen concentration in order to compare it to the prefixed FiO_2 to ensure that all of the oxygen required for compensation was actually consumed. (25)

Deltatrac (II)

The Deltatrac (Datex Instrumentation) is the most validated and extensively tested method. It can be used for both mechanically ventilated and non-mechanically ventilated patients. (21) For the latter group a canopy is required to take measurements. (47)
The Deltatrac (II) is an open-circuit calorimeter with two chambers of a fixed volume. All exhaled air is collected and mixed in the first chamber. (21, 43) All exhaled, mixed air is transported at a constant flow rate to the next chamber (gas dilution technique). (36, 48) The inspiratory concentrations are measured from the inspiratory limb of the ventilator, while the expiratory gas concentrations are measured from the chambers using the analyzers. (47) VO_2 can be calculated using the measured

expired oxygen concentration, measured carbon dioxide production (VCO_2), and the respiratory quotient (RQ). (25, 45) The RQ and VO_2 can be derived using the Haldane transformation assuming that nitrogen is equal between the inspired and exhaled gasses. (23, 28, 43, 47, 48) A complete overview of different calculations, can be found in Appendix G. Data is collected over 1 min intervals. (23, 25, 26, 34, 38, 45, 47) However, averages were made over longer time periods, up to 12 hours (21, 48).

Engström Metabolic Computer

Another frequently used device which uses a mixing chamber is the Engström Metabolic Computer (EMC). The EMC is a microprocessor connected to the Engström Erica Ventilator, with a mixing chamber connected to the expiratory side, for elimination of variations. The EMC samples and processes the data to measure VO_2, VCO_2, and RQ as a mean of different time periods. (24, 33, 39, 51).

3.4.2. Breath-by-Breath

All devices using a breath-by-breath technique found in the included papers are stated in Appendix C.2. In these devices, each respiratory cycle both flow and gas concentrations are measured. With the use of a side stream sampling line for measurement of gas concentrations, an algorithm is necessary for synchronization of flow and gas data. (28, 54)

E-sCOVX

The E-sCOVX (GE Healthcare) uses a sampling line and a pneumotach flowmeter, both connected to the Y-piece of the ventilator. (27, 28)

This respiratory module can also be used in combination with the CARESCAPE B650 Monitor. (27) Furthermore, this technique is used in the GE S/5 metabolic system (22).

The M-COVX (Datex-Ohmeda) metabolic module, which is an earlier version of the E-sCOVX, can only be used for mechanically ventilated patients. (22) The inhaled and exhaled volumes and concentrations are monitored and averaged over 60 second intervals in the same way as previously described. VO_2 is calculated using the Haldane transformation. As the inhaled volume is less susceptible to external influences, it is used in the conversion rather than the exhaled volume. (45)

Quark RMR

The Quark RMR is a device manufactured by Cosmed. The sampling line is connected to the endotracheal tube, and the flow is measured using a turbine flowmeter at the expiratory port of the ventilator. (23, 26, 28) Expiratory volume and bias flow (continuous circulating flow from the ventilator to the patient, back to the ventilator) are both included in the collected flow. (26)

CCM Express

The CCM Express (Medgraphics Corp) uses a pneumotach flowmeter connected directly to the endotracheal tube (which eliminates the effect of bias flow), and gas analysis is performed with a sampling line. (23, 26)

MGU, Medgraphics Ultima

Within this device, a bi-directional flow sensor is used to measure both inspiratory and expiratory flow, eliminating the requirement for the Haldane transformation. All collected flow and concentration data is averaged as the middle five of seven breaths. (38)

Metabolic Cart

Metabolic modules can be used within the ventilator or monitor. (52)

One of these is the M-CAiOVX (General Electric). The connection is close to the patient with a side stream and a pneumotachometer. (54)

Also the Metabolic Monitor 7250 can be integrated in a ventilator (Ventilator 7200 (Nellcor Puritan Bennett)). This construction is an open circuit, as seen in the Deltatrac. Expiratory volume can be measured using the anemometer in the ventilator. (32)
Lastly, the Mindray module measures the O_2 concentrations with a paramagnetic technology and a respiratory-mechanics analyzer. (22)

3.4.3. Douglas Bag

The Douglas Bag has been used to validate various measurements of both O_2 and CO_2 concentrations, and is the gold standard for VO_2 measurement. (24, 34, 35, 49)
Gas is collected in a gas collection bag from the expiratory limb of the ventilator over a period of time. A blood gas analyzer is used to analyze 20 milliliters of gas using 50 mL syringes and three-way valves. Before use, these syringes and three-way valves must be flushed with 100 ml of gas from the Douglas bag. (38) The collected concentrations can be analyzed by mass spectrometry. (30)
The volume of the bag can be measured using a Tissot gasometer (30, 34), using the dilution technique by a water displacement method (24), or using a portable constant-flow suction pump and aspiration through a fixed orifice (50).

3.4.4. Mass Spectrometry

The mass spectrometry principle works with the fixed collector technology. It can be used in conjunction with a mixing chamber to analyze or verify samples from the chamber. (29, 34, 44)
Furthermore, it is often used to analyze the expired gases in the Douglas Bag. (24, 50)
Gas samples can be taken from the patient's y-piece in the breathing circuit to perform a mass spectrometric analysis of the inspiratory concentrations. It is possible to gauge expired flow using a pneumotachometer. (34)
A computer is used to record data. (24, 29, 34, 41, 44)

3.5. Oxygen Analyzers

A paramagnetic oxygen analyzer is commonly used to measure the concentration of exhaled oxygen. This is used in both mixing chambers and breath-by-breath devices. These sensors rely on the paramagnetic properties of oxygen to attract it to a magnetic field. The amount of current displaced within the gas mixture determines the concentration. (21-23, 25-28, 34, 36, 38, 41, 43, 45, 47-49, 52, 54)

Besides the paramagnetic oxygen analyzer, the (galvanic) fuel cell can be used. This sensor relies on the fact that the flow of electrons is proportional to the concentration of oxygen. (23, 24, 26, 32, 33, 38-40, 51)
Other methods to measure the oxygen concentration are mass spectrometry (24, 29, 30, 34, 37, 41, 44, 50), zirconium oxide analyzer (31, 53), polarographic oxygen sensor (35, 46) and even blood gas analysis (30).

3.6. VO_2 Values

27 of 34 articles reported VO_2 values.
However, not all articles used the same unit. Although many articles reported VO_2 in ml/min, some articles have also expressed it in ml/min/kg (27, 52) or ml/min/m2 (42, 43, 48). To provide a consistent overview, only the ml/min values were included. Table 5 (Appendix D) shows these VO_2 values from the articles that stated VO_2 in ml/min; the range was 172 ml/min to 409 ml/min.

4. Discussion

The purpose of this literature review was to provide an overview of the different options for measuring oxygen consumption in mechanically ventilated critically ill ICU patients, in order to make a decision on what could potentially be used in research in patients weaning from mechanical ventilation. We found that VO_2 measurement can be used in many areas of monitoring. VO_2 was most frequently used to provide a better understanding of the nutritional and metabolic

state of ICU patients. Henderson et al. stated that VO_2 could also be used as a prognostic factor when used as a measure for energy expenditure. (44) Different outcome measures were defined in the studies that used weaning as an endpoint. One of the outcomes was the ability of patients to breathe at Continuous Positive Airway Pressure (CPAP) for one hour. (54) A responder was also described as a patient where therapy resulted in CPAP within the last 24 hours after the beginning of the process, and no additional mechanical ventilatory support was required until extubation. (53)

Several techniques can be used to measure oxygen consumption. Some studies used different devices to compare their accuracy. (23, 26, 28, 38, 45) Not all devices provided the same level of precision. This disparity could be attributed to the fact that these devices were frequently compared to the most validated device, the Deltatrac, which uses a mixing chamber, although the device itself used breath-by-breath technology. (28) Breathing patterns of critically ill patients were (often) irregular, what could have influenced the results of the different techniques. (27, 38)
Another explanation could be the fact that mixing chambers use the gas dilution technique. This technique requires the collection of all expired gas, whereas the breath-by-breath technique requires the collection of a sample. This makes it more difficult to compare different devices simultaneously. (45)

Making measurements or computations in patients with extremely high ventilatory conditions, such as high FiO_2, or high positive end-expiratory pressure (PEEP), is exceedingly challenging. This is because FiO_2 is expressed as a percentage, so the effect of inaccuracy is greater at higher FiO_2. As a result, there is less difference between the percentage of inspired and expired oxygen, which increases the rate of error. (29, 31, 44, 47, 48, 50)

4.1. Mixing Chamber

The Haldane transformation is commonly used to calculate the VO_2 using the Deltatrac and mixing chamber. However, expiratory volumes are affected by temperature and humidity assumptions, making the inspiratory volume a more reliable parameter to use. (45)
The Deltatrac uses special Nafion tubing to counteract the effects of humidity. In all sample lines, this tubing equalizes the humidity to that of the surrounding air. (34)

Unfortunately, it is necessary to calibrate the device before each test or analysis when using the mixing chamber technique or a Deltatrac, which is time consuming (see Appendix F).

Values for the oxygen concentration, thus consumption, are always a mean over a certain period of time. Therefore, it is not possible to visualize small changes that happen within short time.
To compensate for the breath-by-breath fluctuations, a large volume chamber is necessary, which is one of the reasons why the response time is slow. (44)

Since a mixing chamber does not measure flow nor volume, it is not affected by flow-by, which is often the case in the breath-by-breath devices. (38)

4.2. Breath-by-Breath

In breath-by-breath techniques, a sampling line was often used for the gas analysis. However, when a sampling line is used to sample gas concentrations, a delay occurs and synchronization is required, which can be difficult if there is a long delay between these measurements. (28, 29, 37) Moreover, synchronization becomes more difficult as the respiratory rate increases. (28) In addition, signal processing is required to synchronize these as accurately as possible while minimizing artefacts and other noise effects. (37)

Another problem with this technique relates to the flow meter, where there may be a bias flow, a continuous 'background' flow. This is created by the ventilator, to maintain mean airway pressure and must be compensated for when measuring VO_2 (55). Not all ventilators use bias flow, since some have different methods of achieving flow triggering. (56) When measuring at the endotracheal tube, the bias flow can be neglected. (17, 23, 26) If measurements are taken elsewhere, it should be taken into account and a compensation made for VO_2 and VCO_2. (23, 28)

A disadvantage of metabolic modules like the Mindray module is the fact that it requires stable breathing patients.
Nevertheless, a great advantage of this technique is that it is possible to make an integration with the mechanical ventilator.

Many studies required calibration less frequently (see Appendix F). While with the mixing chambers it was needed for every test, with the devices that used breath-by-breath technique it was often only needed once a day or even once a half year. (45)

Of the 14 articles published from 2000, nine used the breath-by-breath technique. This could be due to the fact that the Deltatrac is no longer manufactured. In some articles it was even stated that breath-by-breath gas exchange analysis is the new gold standard for measuring energy expenditure. (57)

4.3. Douglas Bag

Although the Douglas bag is the gold standard, the VO_2, VCO_2, and REE need to be calculated, while calculations were found to result in lower values in comparison with measurements. (38)
As in the mixing chambers, it is essential that all expired gases are captured within the bag. If there is a small leak, the measurements will not be as accurate. (58)

These could be the reasons it is mostly used as an extra validation or comparison (see Appendix E), instead of the main measurement device.

4.4. Mass Spectrometry

Mass spectrometry is known for its fast response time. This is beneficial when breath-by-breath analysis is pursued. (29)
However, the output is multiplied by a predetermined factor to account for environmental factors (such as humidity). This factor ensures that all gases in the mixture are measured, with the exception of water vapor. This makes it highly dependent on assumptions. (34)

4.5. Oxygen Analyzers

Temperature and humidity are thought to affect the gas analyzers used. It has been found that when exposed to humid air, the sensors become unstable and may give false readings. It is possible that this effect is greater with breath-by-breath methods due to the placement within the breathing circuit. (26) However, it is possible to measure with sampling lines that are more resistant to the humidity.

4.6. VO_2 Values

27 out of 34 articles stated their VO_2 values. A wide range was seen in the values. However, since it was used for multiple purposes, it was hard to draw concrete conclusions on the measured VO_2 values and the trends seen in these values. Nevertheless, it is notable that most of the lower values found all came from studies with weaning. These lower values were mostly of the patients who had a weaning success, while the failure group had a higher mean VO_2. This could mean that VO_2 could indeed be a good predictor of extubation success. (53, 54)
The fact that critically ill ICU patients are a group with high heterogeneity means that this has contributed to the difficulty of drawing conclusions from the values. (18)

4.7. Limitations

Despite the attempt to be as comprehensive as possible, there were some limitations.
The quality of the articles was not reviewed as inclusion was only based on the used methods. Therefore, it is not clear what the quality of the reports was.
In addition, there was no limit to the year in which an article could have been published. Which resulted in a lot of old articles. Techniques described in these articles could be outdated. However, as the aim was to acquire a complete picture of all possible methods, it was decided to include all articles and not to set a minimum year limit.

5. Conclusion

Several techniques for measuring VO_2 are described in literature. However, they all have drawbacks and advantages, which is why careful consideration must be given to determine what is the best device for the purpose for which it will be used. In addition, it was found that the breath-by-breath technique was used more in more recent years possibly due to the disappearance of the Deltatrac. Moreover, it seems that the VO_2 values for patient who succeeded their weaning trial were lower, however, not much articles used this purpose for the measurement of the oxygen consumption. For this reason, more research is recommended in the combination of weaning and oxygen consumption using the breath-by-breath technique.

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B

Plan of Requirements

Measurement Requirements

VO_2 measurement requires both flow and gas concentration data. At least O_2 and CO_2 should be measured. If the flow and gas concentrations cannot be measured with the same device, the data should be synchronized externally. As explained in the introduction, it is desirable to measure on a breath-by-breath basis to identify variations, since it is plausible that the ICU patients of interest are not in a steady state.

- **Specific**: The measurement setup must collect both flow and gas concentration data, with a focus on oxygen (O_2) and carbon dioxide (CO_2).
- **Measurable**: The data collected will provide accurate breath-by-breath information allowing the identification of variations in non-steady-state ICU patients. A maximum delay between the signals of a quarter of the breath.
- **Achievable**: This requirement is achievable with appropriate sensors and data synchronization methods.
- **Relevant**: Accurate breath-by-breath measurements are relevant for understanding and monitoring variations in the condition of ICU patients.
- **Time-bound**: Measurements are made on a breath-by-breath basis during the patient's ventilation cycles.

Equipment Requirements

In the context of equipment, the device must not be too large or expensive. It could be that in a later stadium it will be purchased on a large scale for the ICU. In addition, there is already a lot of equipment in the patient room on the ICU, so it should be as compact as possible.

- **Specific**: The equipment should be compact, cost-effective and adaptable for potential large-scale use in intensive care units.
- **Measurable**: The size and cost of the equipment can be measured against other devices used in the ICU.
- **Achievable**: The design and selection of equipment can ensure compactness and affordability.
- **Relevant**: Compactness and affordability are relevant to practical ICU integration and use in clinical practice.
- **Time-bound**: Equipment design and procurement should be alighned with future ICU deployment plans.

Mimicking Ventilated Patient

As the aim is to mimic ventilated patients, it is necessary that the setup can be connected to the same ventilator as used in the ICU. This way, human breath cycles will be mimicked, and the breath-by-breath principle can be tested. Furthermore, any possible factors induced by the ventilator will be eliminated. Next to the fact that it should be connected to the ventilator, the setup should include a component that can be connected while mimicking lung movement. These movements should simulate realistic breathing patterns.

- **Specific**: The setup should be compatible with the ICU mechanical venilator and simulate human breathing cycles.
- **Measurable**: The simulation of the setup can be measured by comparing its behavior with real ventilated patients.
- **Achievable**: Connection to the ventilator and integration of lung movement simulation are achievable through proper design.

- **Relevant**: Simulation of ventilated patients is relevant for accurate testing and data generation.
- **Time-bound**: The facility should be connected to the ventilator and the simulation capabilities should be implemented within 10 minutes of the start of the experiment.

Oxygen Consumption and Settings

Although it is an in vitro setup, there must be oxygen consumption in addition to lung movement. This requires the exhaled air to contain a lower percentage of oxygen than the FiO_2 set on the ventilator. Otherwise, no valuable data will be generated to create an algorithm.

To validate if the algorithm can be used in all patients, it is necessary that it could handle different values for oxygen consumption. It must be possible to perform different oxygenation levels as this will affect the VO_2 value. To create these different oxygenation levels, the setup must be able to handle different levels of PEEP, FiO_2, tidal volume, and respiratory rate.

- **Specific**: The exhaled air must contain less oxygen than the FiO_2 set on the ventilator, allowing oxygen consumption measurements.
- **Measurable**: The end tidal oxygen concentration can be measured using a device that can measure gas concentrations breath-by-breath.
- **Achievable**: The required difference in oxygen concentration can be achieved by adjusting the gas composition within the circuit of the test setup.
- **Relevant**: The measurement of oxygen consumption is directly relevant to the research objective.
- **Time-bound**: The setup's oxygen concentration adjustment should be operational during each breath.

Environmental Factors and Portability

In order to account for the influence of environmental factors, it is recommended to set up and perform the tests in a patient room in the intensive care unit. In this way, these factors, such as temperature, and humidity, are the same in vivo as in vitro.

To easily get the setup to the patient room, it is necessary that it is easy to move, but in addition, it should not be too heavy or too large. This way it is movable and not tied to a fixed spot.

- **Specific**: Tests should be conducted in an intensive care unit to account for environmental factors.
- **Measurable**:
- **Achievable**: Setting up the experiment in an ICU room and replicating the conditions is achievable.
- **Relevant**: Testing in the ICU environment ensures that results are relevant to real-world scenarios.
- **Time-bound**: The setup should be transported and operational within 10 minutes of the start of the test.

Patient Specific Factors

Although the aim of this research is to create an algorithm that can eventually be used to measure oxygen consumption in patients for research, most patient specific factors are less important for the in vitro setup. It is expected that these factors will influence consumption, but this will be further investigated in future research.

- **Specific**: Although less critical for the in vitro setup, the influence of patient specific factors on consumption should be investigated.
- **Measurable**: The effect of patient specific factors can be measured with future research.
- **Achievable**: Investigating the influence of these factors is feasible in future studies using ICU patients.
- **Relevant**: Understanding these factors is relevant to the clinical applicability of the algorithm.
- **Time-bound**: Detailed investigation of patient specific factors is planned for future research.

C

Pictures of Test Setups

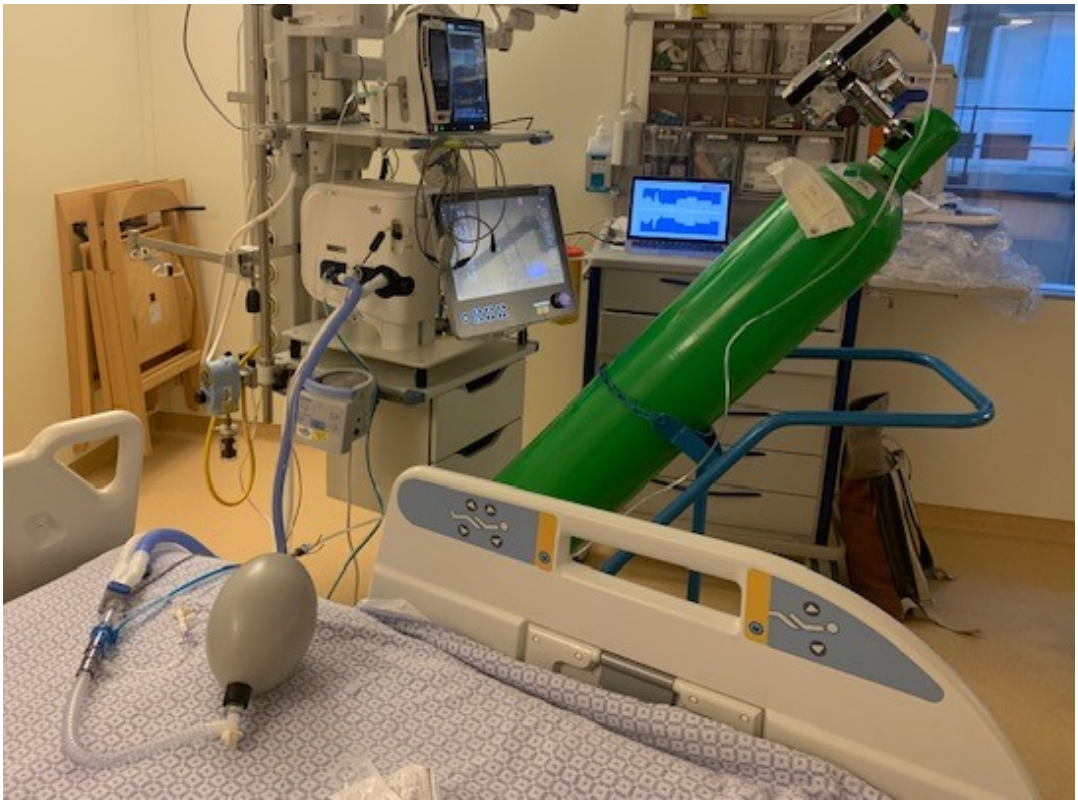


Figure C.1: Picture of the result of the first designed test setup. The green cylinder is connected to the two liter AMBU test lung which is connected to the Hamilton C6 Mechanical Ventilator and the Masimo ISA OR^{+}.

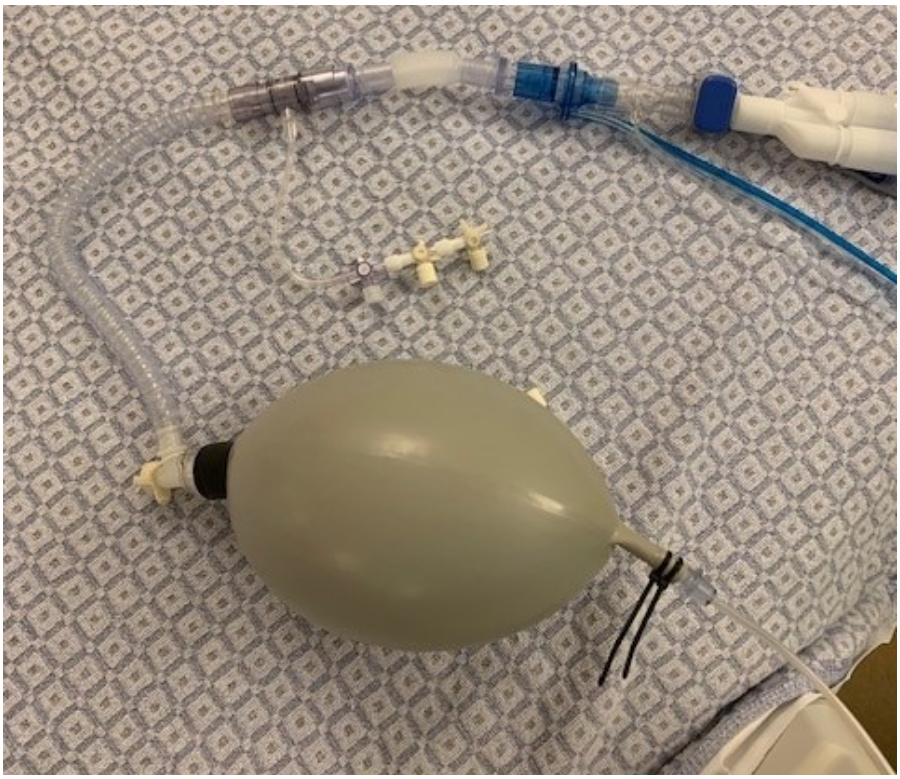


Figure C.2: Close-up picture of the connection from the cylinder to the test lung and from the test lung to the mechanical ventilator and the Masimo.

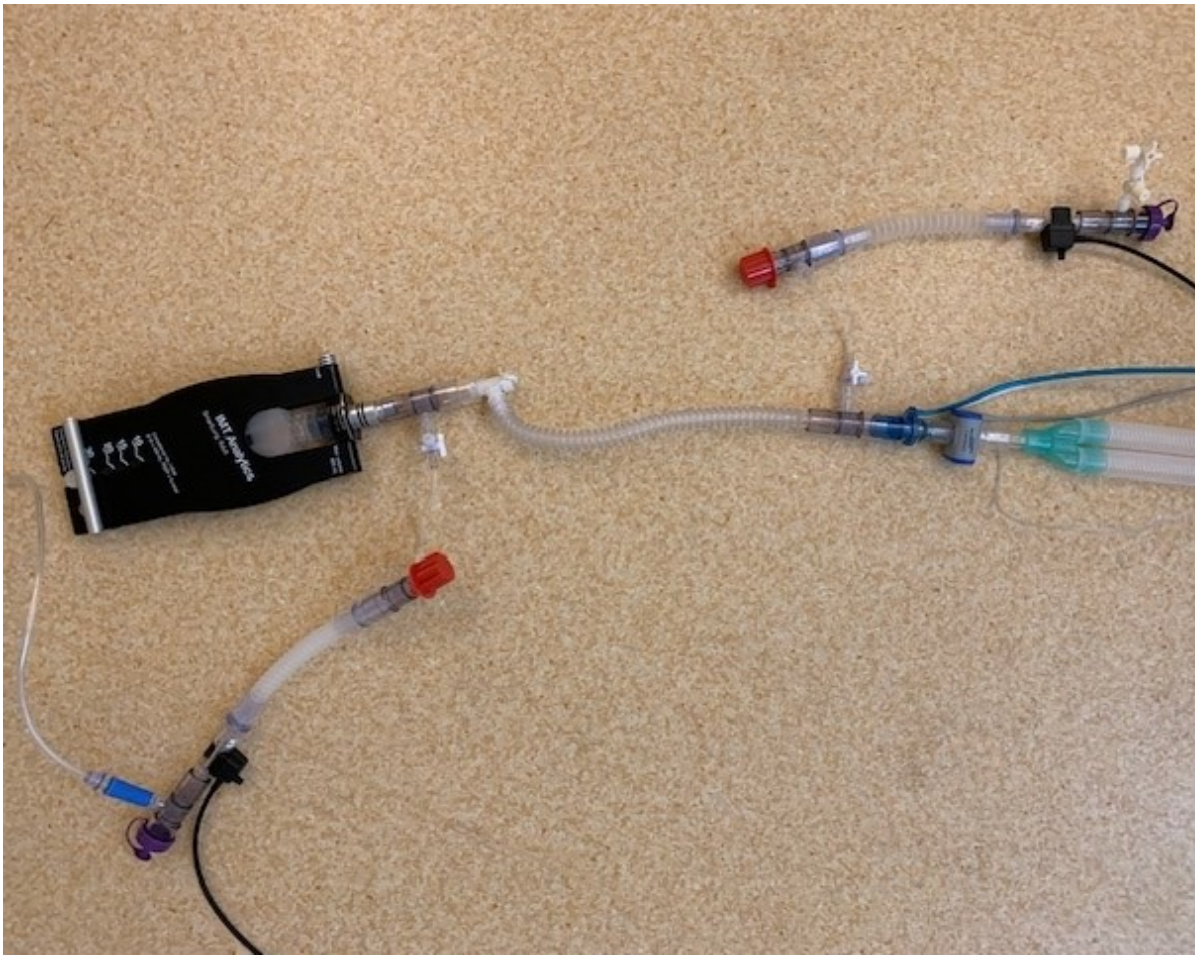
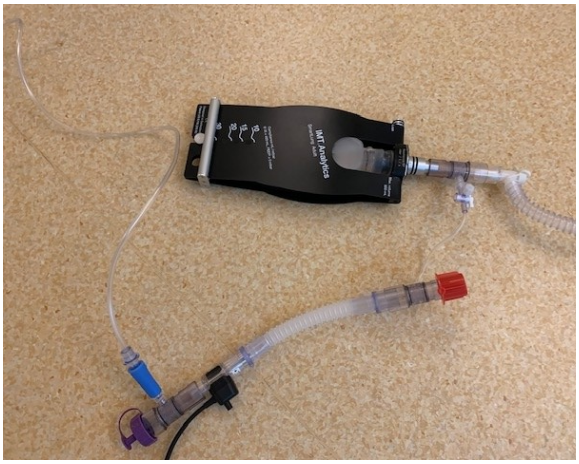
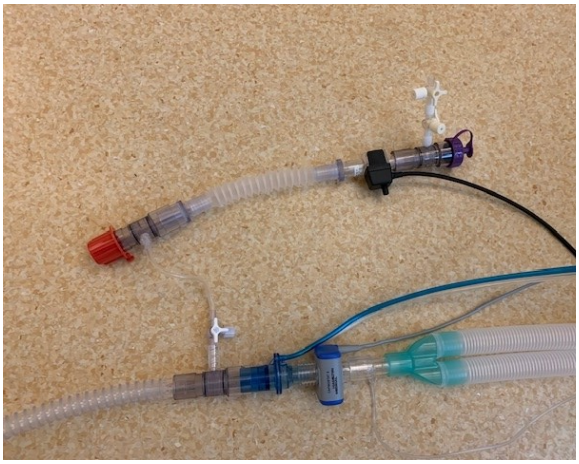


Figure C.3: Picture of the improved test setup. The same cylinder has been used, however, there were new Sensirion flow sensor added to the setup and a new test lung has been used. The test lung also does not have a hole anymore, and is changed to the IMT Analytics SmartLung Adult test lung, resulting in both the connection of the cylinder and the leak placed between the test lung and the ventilator.



(a) Connection of the IMT Analytics Smartlung Adult test lung to the cylinder inlet which was connected with a Sensirion flow sensor to the circuit.



(b) Connection of the leak with the Sensirion flow sensor and the Hamilton flow and CO_2 sensors and the Masimo sidestream.

Figure C.4: Close-ups of the improved test setup.

D

Volume Curves Old Test Setup

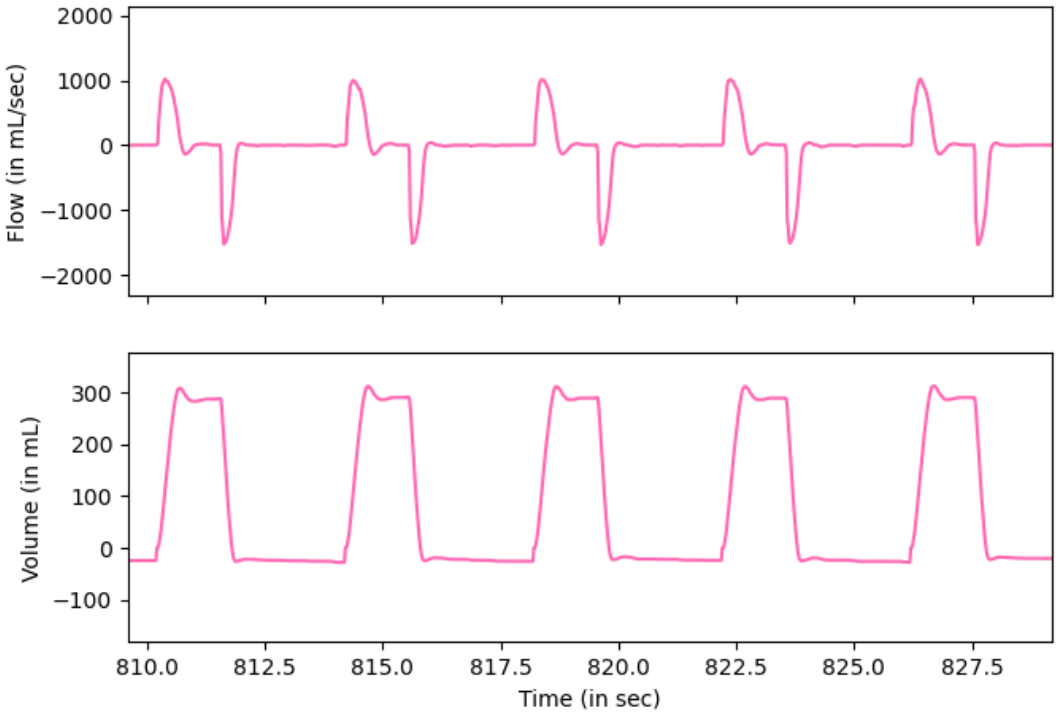


Figure D.1: Volume and flow curves measured with the Hamilton mechanical ventilator in the old test setup using the two liter AMBU test lung. The volume curves have this steep slope as a result of the high compliance of the test lung.

E

Simulated Data Results

Table E.1: Results of the different simulated settings to validate the algorithm with the predicted values. These settings were used for simulated data without dead space volume implemented in the CO_2 signal.

Breathing Frequency (bpm)	**Flow Amplitude** (mL/sec)	**Maximal O_2**	**Minimal O_2**	**N in Fourier Decomposition**	**Algorithmic VO_2** (mL/min)	**Expected VO_2** (mL/min)
15	250	0.417	0.177	5	1118.52	1142.32
15	300	0.417	0.177	5	1342.22	1370.79
15	350	0.417	0.177	5	1565.93	1599.25
15	400	0.417	0.177	5	1789.63	1827.72
15	450	0.417	0.177	5	2013.33	2056.18
15	500	0.417	0.177	5	2237.04	2284.65
15	250	0.582	0.414	5	775.00	799.61
15	300	0.582	0.414	5	930.01	959.54
15	350	0.582	0.414	5	1085.01	1119.46
15	400	0.582	0.414	5	1240.01	1279.38
15	450	0.582	0.414	5	1395.01	1439.30
15	500	0.582	0.414	5	1550.01	1599.23
15	250	0.808	0.689	5	543.73	571.13
15	300	0.808	0.689	5	652.48	685.36
15	350	0.808	0.689	5	761.23	799.59
15	400	0.808	0.689	5	869.97	913.82
15	450	0.808	0.689	5	978.72	1028.04
15	500	0.808	0.689	5	1087.47	1142.27
12	200	0.416	0.178	5	897.13	907.69
12	250	0.416	0.178	5	1121.41	1134.61
12	300	0.416	0.178	5	1345.69	1361.53
12	350	0.416	0.178	5	1569.97	1588.45
12	400	0.416	0.178	5	1794.25	1815.37
15	250	0.413	0.183	7	1067.68	1093.24
15	300	0.413	0.183	7	1281.22	1311.89
15	350	0.413	0.183	7	1494.76	1530.54
15	400	0.413	0.183	7	1708.29	1749.19
15	450	0.413	0.183	7	1921.83	1967.83
15	500	0.413	0.183	7	2135.37	2186.48

Table E.2: Results of the different simulated settings to validate the algorithm with the predicted values and the predicted values with a correction for the dead space volume. These settings were used for a signal with 30 % dead space volume implemented in the CO_2 signal.

Breathing Frequency (bpm)	**Flow Amplitude** (mL/sec)	**Maximal O_2**	**Minimal O_2**	**N in Fourier Decomposition**	**Algorithmic VO_2** (mL/min)	**Expected VO_2** (mL/min)	**Predicted VO_2 with dead space correction** (mL/min)
15	250	0.417	0.177	5	671.41	1142.32	772.75
15	300	0.417	0.177	5	805.69	1370.79	927.30
15	350	0.417	0.177	5	939.98	1599.25	1081.84
15	400	0.417	0.177	5	1074.26	1827.72	1236.39
15	450	0.417	0.177	5	1208.54	2056.18	1390.94
15	500	0.417	0.177	5	1342.82	2284.65	1545.49
15	250	0.582	0.414	5	465.21	799.61	540.91
15	300	0.582	0.414	5	558.25	959.54	649.09
15	350	0.582	0.414	5	651.29	1119.46	757.27
15	400	0.582	0.414	5	744.34	1279.38	865.45
15	450	0.582	0.414	5	837.38	1439.30	973.64
15	500	0.582	0.414	5	930.42	1599.23	1081.82
15	250	0.808	0.689	5	326.39	571.13	386.35
15	300	0.808	0.689	5	391.66	685.36	463.61
15	350	0.808	0.689	5	456.94	799.59	540.88
15	400	0.808	0.689	5	522.22	913.82	618.15
15	450	0.808	0.689	5	587.50	1028.04	695.42
15	500	0.808	0.689	5	652.77	1142.27	772.69
12	200	0.416	0.178	5	538.53	907.69	610.12
12	250	0.416	0.178	5	673.16	1134.61	762.65
12	300	0.416	0.178	5	807.80	1361.53	915.18
12	350	0.416	0.178	5	942.43	1588.45	1067.71
12	400	0.416	0.178	5	1077.06	1815.37	1220.24
15	250	0.413	0.183	7	640.88	1093.24	739.54
15	300	0.413	0.183	7	769.06	1311.89	887.45
15	350	0.413	0.183	7	897.24	1530.54	1035.36
15	400	0.413	0.183	7	1025.42	1749.19	1183.27
15	450	0.413	0.183	7	1153.59	1967.83	1331.18
15	500	0.413	0.183	7	1281.77	2186.48	1479.09

F

Laws of Diffusion

Fick's Laws of Diffusion

These laws provide insight into the diffusion process. Fick's first law of diffusion describes the rate of transfer of a substance across a given area in a medium. This can be expressed as,

$$J = -D \cdot A \cdot \frac{\mathrm{d}\psi}{\mathrm{d}x}\,, \tag{F.1}$$

where: J = diffusion rate (in $\mathrm{mL/min}$), D = diffusion coefficient (in $\mathrm{cm^2/s}$), A = surface area (in $\mathrm{cm^2}$), ψ = concentration (in $\mathrm{mol/cm^3}$), x = distance (in cm). The negative sign in front of the diffusion coefficient indicates that diffusion occurs from regions of higher concentration to regions of lower concentration [104].

Fick's second law of diffusion goes one step further by considering how the concentration of a diffusing substance changes over time as well as space. The formula is

$$\frac{\mathrm{d}\psi}{\mathrm{d}t} = D \cdot \frac{\mathrm{d}^2\psi}{\mathrm{d}x^2}\,. \tag{F.2}$$

It describes how the concentration changes in both space and time. This equation states that the concentration changes more rapidly in regions where the concentration gradient is steeper [104].

The diffusion coefficient is influenced by factors such as molecular size, medium viscosity, and temperature. It varies according to the gas through which it diffuses. For example, the diffusion coefficient for CO_2 in O_2 is 0.170 [106].

Graham's Law

Graham's law gives another perspective and highlights how the molar mass of a gas affects its diffusion rate. It can be written as

$$\frac{R_1}{R_2} = \sqrt{\frac{M_2}{M_1}}\,, \tag{F.3}$$

where: R_1 and R_2 are the diffusion rates of gas 1 and gas 2, respectively (in $\mathrm{mL/min}$), M_1 and M_2 are the molecular masses (in $\mathrm{g/mol}$).

This equation emphasizes that lighter gases diffuse more quickly due to their higher average speeds and kinetic energies [104]. According to Graham's law, the diffusion rates for different gases used will follow the order: N_2 > O_2 > CO_2 [107].

G

Spontaneous Breathing Trial Protocol - Dutch Version

Beademing, spontaneous breathing trail [SBT] bij volwassenen (Intensive Care) (Versie 1)

Inleiding

Elke slotfase van weantraject begint met een Spontaneous Breathing Trial (SBT); of deze slaagt en hoeveel pogingen nodig zijn om patiënt succesvol van de beademing te weanen bepalen of er sprake is van een eenvoudige, lastige of moeilijke weaning. Het tijdig herkennen of een patiënt klaar is voor een SBT is cruciaal.

Algemeen

Wanneer een patiënt voldoet aan de ingangscriteria voor een SBT dient de patiënt deze te ondergaan, tenzij anders bepaald door IC-arts. Mocht het bewustzijn een probleem vormen dan dient te worden overwogen of patiënt in aanmerking komt voor extubatie, zo niet dan wordt er geen SBT verricht.

De kliniek van de patiënt wordt getoetst aan faalcriteria beschreven in het algoritme. Na een geslaagde SBT kan een patiënt geëxtubeerd worden. Voorafgaand aan de extubatie moet overleg plaatsvinden met de arts.

Obstructieve longaandoeningen

Patiënten met obstructief longlijden vallen onder hoog risico patiënten en de vraag is dan ook of deze patiënten een afwijkende strategie nodig hebben voor het toewerken naar extubatie. Wat bekend is van obstructief longlijden is dat de longen ver oprekken door de hoge compliantie waardoor effectief uitademen moeilijk is en patiënten dus kortademig worden. Een voorbeeld is een patiënt met astma/COPD waarbij de lagere luchtwegen de grootste weerstand bieden doordat de totale diameter van de luchtwegen sterk is afgenomen. Bij COPD patiënten is er juist bij de uitademing een hoge weerstand en bij de inademing niet, bij inademing gaat de lucht er zeer makkelijk in, vanwege de hoge compliantie.

Patiënten met acute respiratoire insufficiëntie ten gevolge van exacerbatie van chronische luchtwegobstructie hebben baat bij positieve eind expiratoire druk. Dit is bewezen door middel van een onderzoek onder patiënten met longlijden. De SBT werd uitgevoerd met CPAP en zonder drukondersteuning. Hierbij werd gekeken naar de metingen: luchtwegopeningsdruk, gasstroom en dus ademhalingspatroon, zuurstofopname, koolstofdioxide-excretie, arteriële bloedgassen, dyspneu en ademhalingsdrang (P.01) (Goldberg et al., 1995, p. 1898). De conclusie is dat bij chronische luchtwegobstructie, CPAP helpt om een SBT vol te houden. Door de eind expiratoire druk wordt er een langzamere, diepere ademhaling bevorderd en zo de kooldioxide-afvoer makkelijker gemaakt. Echter doordat CPAP helpt om een SBT vol te houden, kan het juist na de extubatie zwaarder zijn voor bijvoorbeeld een COPD patiënt. Dit omdat de patiënt het dan zonder enige drukondersteuning moet doen.

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de patiënten die waarschijnlijk hun extubatie falen, het starten van non invasieve ventilatie na extubatie her-intubatie voorkomt.

Omdat een SBT met PEEP een minder voorspellende waarde hij bij de COPD patiënt, adviseren wij als beademingswergroep om bij COPD'ers het SBT over te slaan en direct na extubatie NIV (non-invasieve ventilatie) toe te passen.

Bij ernstige COPD of twijfel van slagen van NIV kan er gekozen worden om een SBT met kunstneus uit te voeren.

Hartfalen

De overgang van CPAP naar ademen zonder drukondersteuning (los van de beademingsmachine of zonder tube) kunnen drie belangrijke cardiovasculaire effecten te weeg brengen die kunnen leiden tot een falend SBT:

- De afname in de intrathoracale druk leidt ook tot afname van de druk in het rechteratrium waardoor de veneuze return toeneemt en dus de preload van de rechterventrikel. De output van de rechterventrikel neemt toe en hiermee de preload van de linkerventrikel.
- De afname van de intrathoracale druk verhoogt echter ook de afterload van de linkerventrikel. Vooral bij een slechte linkerventrikelfunctie kan dit leiden tot hartfalen en ontwikkelingen van longoedeem.
- Verhoging van de ademarbeid tijdens een SBT leidt, vooral bij ongunstige ademmechanica, tot een hogere zuurstofconsumptie van de ademspieren. Bij onvoldoende cardiale reserve kan ischemie ontstaan in vitale organen zoals de hartspier. Door toename van de sympathische tonus (emotionele stress, hypoxemie, hypercapnie) tijdens een SBT zal de systemische bloeddruk toenemen en neemt de afterload van de linkerventrikel verder toe.

Diverse studies hebben ondertussen aangetoond dat zowel systolisch als diastolisch hartfalen frequente oorzaken zijn van falende ontwenning van de beademing (Roesthuis & Heunks, 2015,.p. 22). Zowel Ter Haar (2017) als Sklar et al (2017, p 1483) geven aan dat een SBT met kunstneus of T-stuk een duidelijke voorkeur heeft bij patiënten met hartfalen, met name linkerventrikel falen. Bij een SBT met beademingsmachine heeft het linkerventrikel de voordelen van de postieve beadmeing terwijl het rechter ventrikel het echter juist iets zwaarder hebben doordat de positieve druk voor een verhoogde afterload zorgt. De verhoogde afterload voor de rechterventrikel zal zorgen voor een verlaagde preload voor de linker ventrikel waardoor er een grotere kans is om te slagen voor een SBT aan de beademingsmachine en vervolgens geëxtubeerd zal worden. Het is waarschijnlijk dat na extubatie de linker ventrikel preload en afterload gaan toenemen waardoor de patiënt alsnog kan decompenseren en mogelijk opnieuw geïntubeerd moet worden. Wanneer de SBT uitgevoerd wordt met kunstneus kan bij decompensatie verschijnselen de tube weer aangesloten worden aan de beademingsmachine en voorkomt zo een re-intubatie (Ter Haar, 2017).

Quick Wean Hamilton

In ontwikkeling

Voorwaarden SBT

Onderstaande tekst is nog in ontwikkeling - het kan zijn dat sommige onderdelen nog niet werkzaam zijn. Om een SBT uit te kunnen voeren moet de patiënt aan een aantal criteria voldoen. Deze zijn onderverdeeld in respiratoire, hemodynamische en neurologische voorwaarden. Vanuit het PDMS krijg je een melding om te checken of patiënt klaar is voor een SBT.

deze melding krijg je als bepaalde beademingsvoorwaarden voldoende aan de respiratoire voorwaarden voor het SBT. Bij deze melding dien je de overige readiness criteria te checken. Voldoet de patiënt aan alle voorwaarden dan kan er theoretisch gezien een SBT worden uitgevoerd, indien er wordt afgezien van een SBT dient de reden hiervan beschreven te worden in het PDMS. (dit onderdeel moet nog in PDMS worden verwerkt - bekeken moet worden of je bij bepaalde voorwaarden automatisch deze pop up krijgt)

Respiratoire voorwaarden

FiO2	**< 40%**
SaO2	**> 92%**
PaO2/FiO2 ratio	**≥ 26 kPa**
PEEP	**≤ 8 cmH2O**
Pressure Support (PS) / Inspiratoire druk (Pinsp)	**5-7 cmH2O**
Ademhalingsfrequentie	**< 25 /min**
Rapid Shallow Breathing Index	**≤ 105**
Ademminuutvolume	**< 10 liter/min**
Arterieel bloedgas (ABG)	**Ph > 7.35**

Hemodynamische voorwaarden

Hartfrequentie	**≤ 140 bpm**
Systolische bloeddruk	**90-160 mmHg**
Temperatuur	**< 38 graden**
Geen of lage dosis vasopressie	**< 0.2 y**

Neurologische voorwaarden

Glascow come scale	**≥ 8**
Intacte luchtwegreflexen	**Hoest- en slikreflex**
Geen sedatie	**Of adequaat bewustzijn onder sedatie**

Uitvoering SBT

Regulier SBT Een SBT houdt in dat de patiënt 30 minuten lang met 5 tot 8 cmH2O PEEP ademt.

- Spontane modus (Hamilton C6, C3 of C1/MR1)
- De ASV- of I-ASV modus heeft geen SBT mogelijkheid
- Geen pressure support
- FiO_2 is maximaal 40% tenzij anders afgesproken.

Faalcriteria

Faalcriteria	
Ademfrequentie	**> 35/min**
SpO2	**< 90 %**
F/Vt (RSBI)	**> 100**
Respiratoire acidose	
Hartfrequentie	**> 140/min ***
Systole RR	**> 180 mmHg * of < 90 mmHg**
Vegetatieve verschijnselen	**Angst, zweten, etc.**
*** of 20% toename**	

Bij hartfalen

Bij patiënten met hart falen (LVEF < 30%) voeren we het SBT bij voorkeur niet uit aan de beademingsmachine, maar leggen we de patiënt los van de machine met een kunstneus en zuurstof. Deze SBT houdt in dat de patiënt 30 minuten lang met 0 cmH2O PEEP ademt. De zuurstof flow wordt ingesteld op 5 ltr/min via de kunstneus, tenzij anders is afgesproken. Dezelfde faalcriteria gelden hier als bij het regulier SBT.

Bij COPD

Een SBT heeft weinig voorspellende waarde bij ernstig obstructief longlijden. Indien een patiënt voldoet aan de criteria van het SBT is het advies om de patiënt te extuberen zonder de uitvoering van een SBT. En direct post extubatie aan de non invasieve beademing te leggen. Dit kan intermitterend worden toegepast.

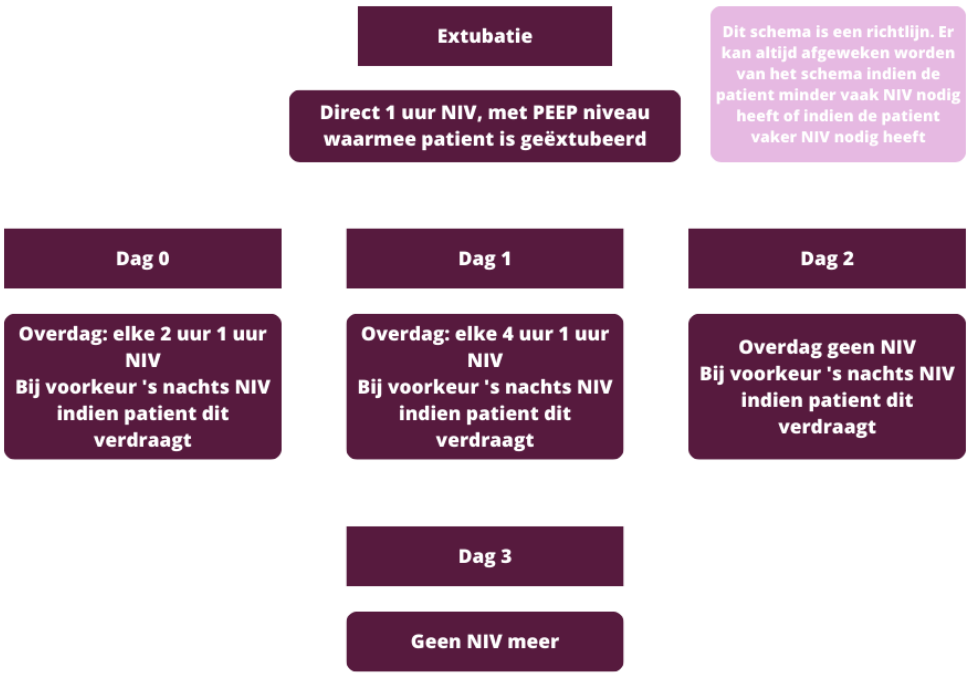
Post-extubatie

Patiënten die de SBT goed hebben doorstaan kunnen worden beoordeeld voor extubatie. Een geslaagde SBT is nooit een garantie voor een succesvolle extubatie (Ter Haar, 2017), 13-23% moeten ondanks een geslaagde SBT toch weer geïntubeerd worden (Boles et al., 2007, p. 1051). Een geslaagde extubatie is als de patiënt niet binnen 48uur weer geïntubeerd moet worden

Obstructief longlijden

Bij patiënten met obstructief longlijden en welke > 7 dagen geïntubeerd zijn geweest passen we post-extubatie intermitterend NIV toe. Dit om de kans van slagen van de extubatie te vergroten. De extubatie van patiënten met obstructief longlijden verloopt ook anders.Daarvoor verwijzen we je naar het protocol: Beademing, Extubatie

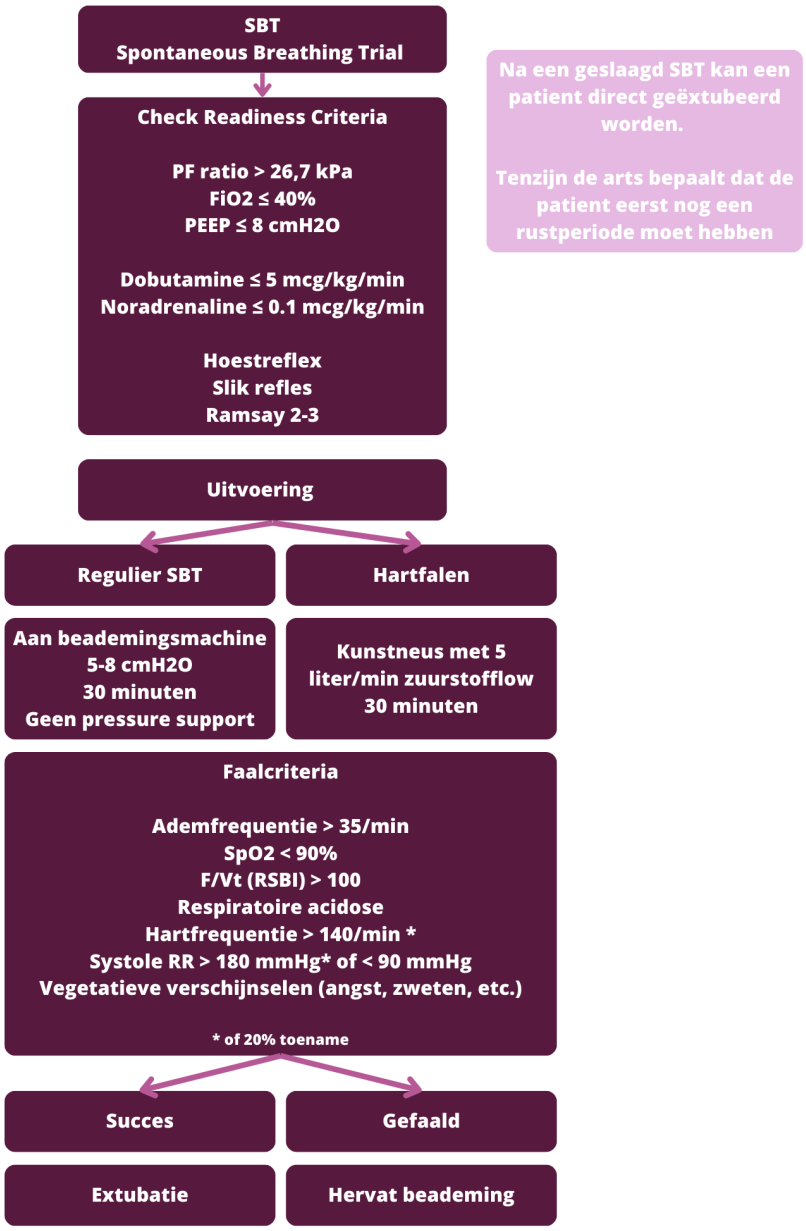
Handelswijze
Direct post- extubatie wordt er 1 uur NIV toegepast met het PEEP niveau waarmee de patiënt is geextubeerd Uit een systematic review van Yeung et al. (2018) blijkt dat de inzet van NIV post- extubatie specifiek bij COPD patiënten leidt tot verlaging van de ziekenhuis mortaliteit, de incidency van VAP en de opname duur op de IC.



Niet geslaagd SBT

Als de patiënt faalt dan moet altijd overleg plaatsvinden met de IC-arts. • In sommige gevallen kan toch geoordeeld worden de patiënt te extuberen. Beargumentatie dient vastgelegd te worden in het medisch/verpleegkundig dossier De veiligheid van patiënten staat voorop. Als de patiëntveiligheid dat vereist kan van bovenstaande worden afgeweken. Bij een niet geslaagde SBT en de beademing wordt voortgezet. Wordt de oorspronkelijke beademingsvorm weer hervat en na 24 uur wordt het opnieuw geprobeerd. Er dient beoordeeld te wordne wat de reden was van eht niet slagen van het SBT. Dit dient gedocumenteerd te worden in het PDMS. In het protocol Beademing, analyse weaning kan handvatten geven voor het zoeken van de oorzaak van falen.

Flowchart SBT



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