Diploma thesis

Intensive care of COVID-19 patients: Importance of 3D-printing for the development of emergency respirators

submitted by

Marcell Krall

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FA Dr.med.univ. Thomas Wegscheider

and

Univ.-Prof. Dr.rer.nat. Ute Schäfer

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Affidavit

I hereby declare that the following diploma thesis is the result of my own work. I did not receive any assistance from third parties. Furthermore, I confirm that all sources applied are listed and specified in the thesis.

Graz, 15.07.2021 *Marcell Krall eh*

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Abbreviations

ACE-2	Angiotensin-converting enzyme 2
ALT	Alanine aminotransferase
ARDS	Acute respiratory distress syndrome
ASB	Assisted spontaneous breathing
BE	Base excess
CRP	C-reactive protein
CPAP	Continuous positive airway pressure
CT	Computer tomography
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
ERV	Expiratory reserve volume
FiO2	Inspiratory oxygen fraction
FRC	Functional residual capacity
ICU	Intensive Care Unit
IMC	Intermediate Care
IRV	Inspiratory reserve volume
LDH	Lactate dehydrogenase
MIT	Massachusetts Institute of Technology
NEU	Neutrophil granulocytes
NIV	Noninvasive
pCO2	Carbon dioxide partial pressure
PEEP	Positive end-expiratory pressure
pMax	maximum pressure
pO2	Oxygen partial pressure
RNA	Ribonucleic acid
RQ	Respiratory quotient
RT-PCR	reverse transcription polymerase chain reaction
RV	Residual volume
sO2	Oxygen saturation
TLC	Total lung capacity
TV	Tidal volume
VC	Vital capacity

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Zusammenfassung

Anfang April 2020 hatten rund 200 Länder mit den Auswirkungen des Ausbruchs von SARS-CoV-2- zu kämpfen. Viele dieser Länder berichteten, dass die Intensivstationen bereits ihre Kapazitäten erreicht hätten. Triagen wurden initiiert und mit Hilfe des Militärs wurden beispielsweise in Italien Notfallkrankenhäuser errichtet. Zu diesem Zeitpunkt war die Pandemie auch in Österreich angekommen. Die Meldesysteme berichteten damals von über 13.000 mit SARS-CoV-2 infizierten Menschen. Diese Überlegungen veranlassten das Unternehmen HAGE-Sondermaschinenbau GmbH & Co KG, gemeinsam mit der Medizinischen Universität Graz, ein Notfall-Beatmungsgerät für den überbrückenden Einsatz in Krisengebieten zu entwickeln.

Ziel dieser Studie war es, einen geeigneten Testaufbau für die Bewertung eines Notfall-Respirators zu schaffen. Die Überprüfung einer suffizienten Beatmung von Großtieren (Schweinen) sollte anhand einer Pilotstudie durchgeführt werden. Im Rahmen eines iterativen Entwicklungsprozesses wurde eine kontinuierliche Adaptierung des Prototyps, auf Grundlage der Ergebnisse von den Versuchen, angestrebt.

In den ersten beiden Experimenten wurden Tidalvolumina (TV) von <480 ml erreicht. Maximaler Inspirationsdruck und PEEP konnten nicht aufrechterhalten werden. Der pCO2-Spiegel stieg auf maximal 64 mmHg. Durch den Lern- und Iterationsprozess konnten die Komponenten auf Grundlage der ersten Ergebnisse angepasst werden. Im dritten Experiment war eine ausreichende Beatmung nach unseren Kriterien für eine Dauer von 30 Minuten möglich. Es war möglich, ein angemessenes TV> 800 ml bei einem Gewicht von 93 kg aufrechtzuerhalten. Die Oxygenierung wurde stabilisiert. Der pCO2-Gehalt von 47 mmHg reduzierte sich auf einen Wert von 43 mmHg. Die Sauerstoffsättigung betrug fast 100% bei einem FiO2 von 35%.

Die Ergebnisse zeigten, dass es grundsätzlich möglich ist, ein Schwein unter physiologischen Bedingungen mit einem kontrollierten Beatmungsmodus für eine Dauer von 30 Minuten zu beatmen. Wir konnten eine stabile Sauerstoff- und Stoffwechselsituation in den Tieren nachweisen.

Wenn spezielle Entwöhnungsverfahren implementiert werden können und die Langzeitanwendung in weiteren Studien getestet werden kann, kommt der Autor zu dem Schluss, dass eine vorübergehende Beatmung von mit SARS-CoV-2 infizierten Patienten möglich sein könnte.

Dies sollte jedoch nur in Notfällen erfolgen, in denen alle anderen Ressourcen bereits erschöpft sind und ein Triage-System installiert wurde.

Abstract

At the beginning of April 2020, around 200 countries were struggling with the effects of the SARS-CoV-2 outbreak. Many of them reported that intensive care units (ICU) had reached their capacities. Caring systems were initiated, and with help of military, emergency hospitals were installed for example in Italy. At this point in time, the pandemic had also arrived in Austria with over 13,000 people infected with SARS-CoV-2. These considerations led the company HAGE-Sondermaschinenbau GmbH & Co KG to take the initiative, together with the Medical University of Graz, to develop an emergency respirator for temporary use. This was contrived by using 3D-printet components.

The aim of this study was to create a suitable test set-up for the evaluation of an emergency respirator. The verification of adequate ventilation of a large animal (pig) should be tested on the basis of a pilot study. As part of an iterative development process, a continuous adaption of the prototype was strived. This was based on the results of the experiments.

In the first two experiments, tidal volumes (TV) of <480 ml were achieved. Maximum inspiration pressure and PEEP could not be maintained. Level of pCO_2 increased to a maximum of 64 mmHg. As a result of learning- and iterative process, the components could be adapted. Sufficient ventilation measured on our criteria for duration of 30 minutes was feasible in the third experiment. Maintaining adequate TV > 800ml by a weight of 93kg was possible. The oxygenation was stabilized. The pCO_2 level of 47mmHg decreased to a level of 43mmHg. The oxygen saturation was almost 100%, by a FiO_2 of 35%.

The results showed that it is basically possible to ventilate a pig under physiological conditions with a controlled ventilation mode for duration of 30 minutes. We were able to show maintenance of a stable oxygenation and metabolic situation.

If special weaning procedures can be implemented in further development and long-term use can be tested in further studies, the author concludes, that a temporary ventilation of patients infected with SARS-CoV-2 could be possible.

However, this should only be done under emergency circumstances where all other resources have already been exhausted and a triage system has been installed.

1 Introduction

As of April 9, 2020, around 200 countries worldwide were affected by the outbreak of COVID-19 disease caused by the SARS-CoV-2 pathogen. To date, there are a total of approximately 1.5 million confirmed cases, 90 thousand deaths and 1.2 million active cases, of which around 4% are critical [1].

Many countries have faced unprecedented healthcare tasks since the onset of the disease. Hospitals, especially intensive care units, have reached their limits or must prepare to reach them soon. According to the report by the German Institute for Disaster Medicine (DIFKM) for the Interior Ministry of Baden-Württemberg, on the situation in the French coronavirus epicenter, over 80-year-old patients are no longer ventilated due to the lack of capacity [2]. In Italy, a triage system is used to decide who receives a place in the intensive care unit. Only one of ten patients, who need intensive care, is getting a place at the intensive care unit (ICU). A triage system is used for the decision [3]. With the help of the military, the Italians managed to build up a few field hospitals in a short time, but the situation makes it clear, that not only the beds and personal capacity play a decisive role, also all the important equipment must be produced in sufficient quantities. For this reason, the pope donated 30 ventilators to hospitals in the regions, which are most affected by COVID 19 [4].

On April 9, 2020, there were 13,120 positive test results of COVID 19, in Austria. 266 patients required intensive care and 295 people died due to the consequences of the SARS-CoV-2 pathogen [5]. According to different forecast models, Austria could soon face the same challenges as Italy, Spain, and France. Capacity problems with devices like ventilators could result [6].

To prevent supply shortages in Austria, the Austrian industry has already been requested by the Federal Ministry for Digitalization and Business Location (BMDW) together with the Association of Industrialists to contribute their know-how and expertise [7].

These considerations led the company HAGE-Sondermaschinenbau GmbH & Co KG to take the initiative, together with the Medical University of Graz, on the basis of a long-term collaboration in the field of medical 3D printing [10], to provide an emergency ventilator for temporary use in crisis areas [8,9].

The scientific goal of this study was to evaluate a prototype of an emergency respirator referring on sufficient ventilation of patients infected with SARS-CoV-2. For this we aimed to create a suitable test set-up. The verification of adequate ventilation of a large animal (pig) should be tested on the basis of a pilot study. As part of an iterative development process, a continuous adaption of the prototype was strived. This was based on the results of the experiments

Since the SARS-CoV-2 infection is not gender-specific, the significance of the results of this work is equally important for both males and females.

1.1 COVID-19

COVID-19 is an acute respiratory disease caused by the SARS-CoV-2.

Corona viruses were first described in the 1930s. Seven of the numerous strains of coronavirus cause diseases in humans. Four of them, 229E, OC43, NL63 and HUK1, are known to cause cold symptoms. Three of the seven coronavirus strains, SARS-CoV, MERS-CoV and SARS-CoV-2, cause respiratory diseases with much more severe courses. In the end of 2019, COVID-19 was registered in the Chinese city Wuhan for the very first time [11]. As the disease continued to spread, it was declared to a worldwide pandemic by the WHO, on March 12, 2020. [12]

1.1.1 Infection kinetics

Currently, it is assumed that SARS-Cov-2 passed from animals to humans in December 2019 [14]. The paper from Liang K. "Mathematical model of infection kinetics and its analysis for COVID-19, SARS and MERS" showed that the growth rate of SARS-CoV2 is about twice as high as that of SARS-CoV or MERS-CoV. The parametric analysis showed that the doubling cycle of SARS-CoV-2 is about two to three days. This indicates that the number of people affected doubles every two to three days without human intervention [13], which subsequently leads to an exponential growth curve [14]. The growth rate in the early stages of the disease determines the prevalence. The work clearly shows that the infection inhibition constantly correlates with the preventive measures [13].

1.1.2 Symptoms

In most patients, first symptoms appear after an average incubation period of about five to six days. 80% of the cases show mild and around 20% have severe symptoms. About 5% of the patients need intensive care therapy. Mortality is given around 1-2% [14].

COVID-19 is an infection of the upper and lower respiratory tract. The main symptoms are fever, cough, and fatigue. Many of those who are affected with a mild course show no- or typical cold symptoms. 15% of patients with COVID-19 develop severe general symptoms including pneumonia and 5% are in critical condition with the development of sepsis, septic shock, and multi-organ failure. The classic picture of an ARDS can develop in critically ill patients [14].

Table 1: Outline of symptoms and course of the disease

Severity	Symptoms
Mild (outpatient care / normal word)	No symptoms. Fever Cough Fatigue
Severe (Intermediate Care-IMC)	Dyspnea Respiratory rate ≥ 30 / min $sO_2 \leq 93\%$ Oxygen partial pressure (pO_2) / Inspiratory oxygen fraction (FiO_2) <300 Lung infiltrates> 50% within 24 - 48 h
critical (ICU)	Lung failure septic shock Multi organ failure

References: inspired by Bein et al. [14]

Not only typical respiratory symptoms can occur during the COVID-19 disease. Some authors also describe neurological symptoms such as cerebrovascular diseases, impaired consciousness, dizziness or loss of taste and smell [15, 25]. Neurological involvement has already been known in SARS and MERS. SARS-CoV was first detected in cerebrospinal

fluid during an autopsy in 2002/3. SARS-CoV-2 has so far not been detected in the liquor, but pathologists observed hyperemia and nerve damage during the autopsy [25]. Diarrhea is also described in over 10% of patients. SARS-CoV-2 uses Angiotensin-converting enzyme 2 (ACE-2) and the serine protease TMPRSS2 for S-protein priming. ACE-2 is not only found in the lungs, but also expressed in the small intestine epithelium [16].

1.1.3 Diagnosis

The diagnostic procedure relates primarily to the patient's medical history, a clinical examination, and a blood test [14]. Laboratory parameters can help to screen COVID-19 cases. The authors around Madrian concluded, that lactate dehydrogenase (LDH), c-reactive protein (CRP), alanine aminotransferase (ALT) and neutrophil granulocytes (NEU) levels can be used to predict SARS-CoV-2 infections [16]. Also contact persons were defined to estimate the probability of an infection. First-degree contact persons are defined as persons who cumulatively had face to face contact with secured COVID-19 patients for at least 15 minutes. In the presence of a clinical suspicion of an infection with SARS-CoV-2, the Robert Koch Institute (RKI) recommends taking smears from the upper and lower airways, to detect virus-ribonucleic acid (RNA) by using reverse transcription polymerase chain reaction (RT-PCR) [14].

1.1.3.1 Imaging

COVID-19 patients should receive imaging to check the expected morphology and to be able to estimate infection or treatment consequences. Due to the radiation exposure, daily x-ray checks are not indicated for stable intubated patients. If patients have functional impairment and/or hypoxemia after recovery from COVID-19, a Computer tomography (CT) is indicated. Although CT imaging of a COVID-19 infection is not specific, the team led by Rubin describes its importance if there are no better alternative diagnostic methods available. However, it is unclear whether the CT scan should be used as a standalone screening tool [17]

1.1.4 Therapy

In about 20% of patients suffering from an infection with SARS-CoV-2, severe symptoms develop as part of the course of the disease. Approximately 5% of COVID-19 patients require intensive medical therapy [14].

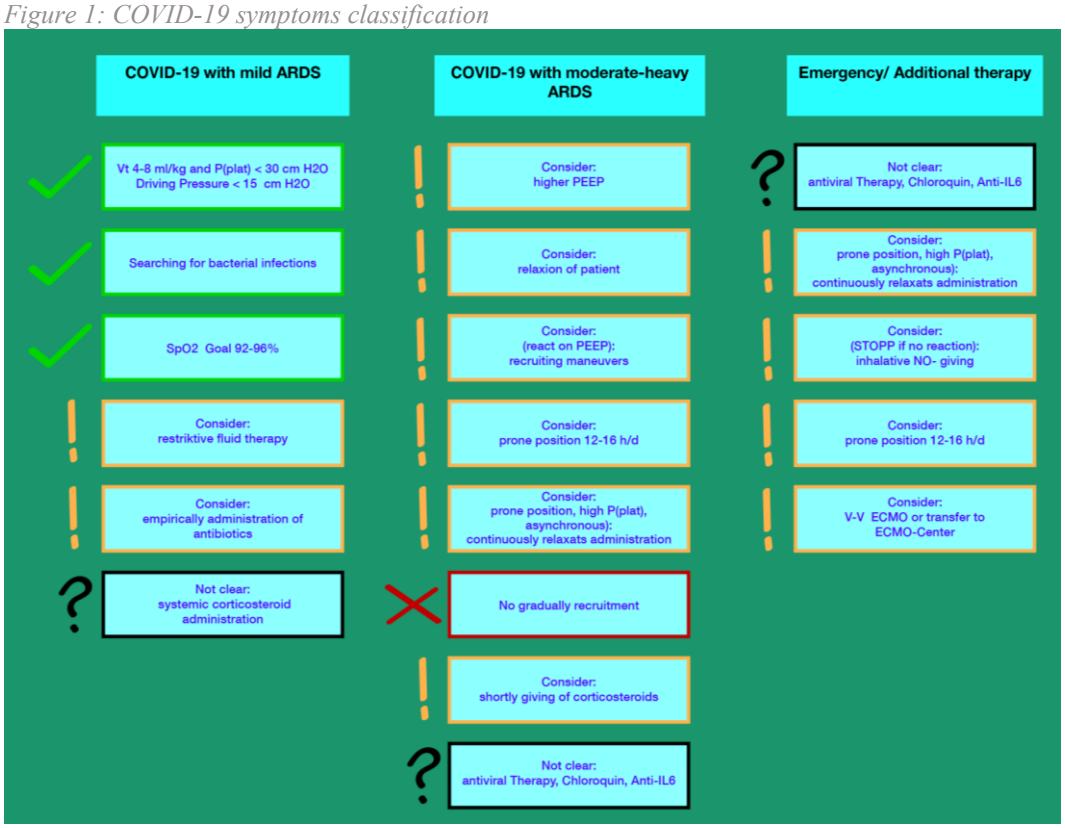
The lungs react to the SARS-CoV-2 pathogen in a similar way to other viruses that affect the respiratory system. Basically, the evidence-based therapy recommendation for ARDS applies [14].

However, separate recommendations were made for the following measures:

- No dopamine
- Lung protective ventilation (V_t 4-8ml / kg, positive end-expiratory pressure (PEEP) >10 cm H2O, No gradual recruitment)
- Oxygen administration with an Oxygen saturation (sO_2) <90%, also not be> 96%

In addition, measures such as special positioning (prone position) or restrictive hydration etc. can be considered [14].

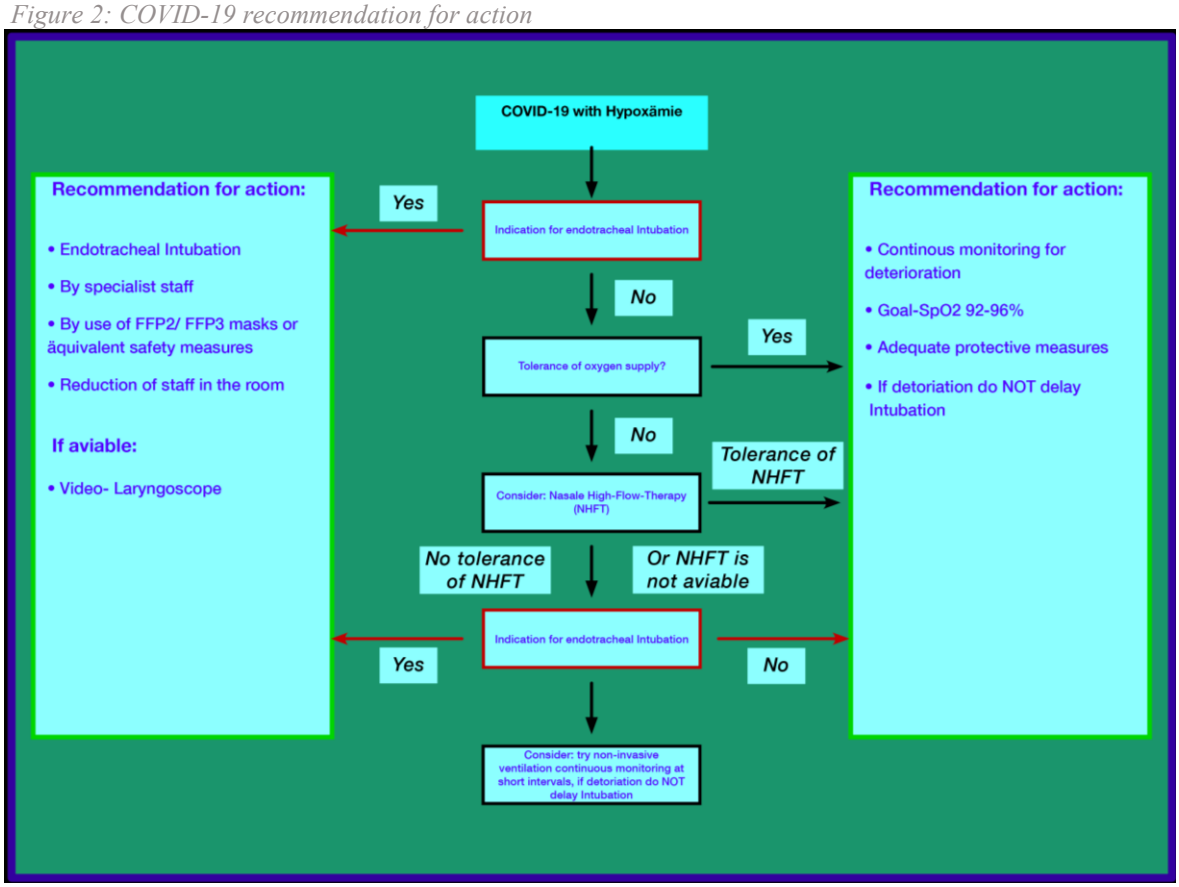
Figure 1: COVID-19 symptoms classification



References: Own representation, inspired by Robert Koch Institute [58]

The primary focus is on performing non-invasive ventilation using high-flow masks, noninvasive (NIV) masks or NIV-helmets. However, if treatment with non-invasive measures is no longer sufficient, invasive ventilation by an endotracheal tube is indicated. [14]

Figure 2: COVID-19 recommendation for action



References: Own representation, inspired by Robert Koch Institute [58]

Due to the formation of aerosols, invasive ventilation therapy is preferred over non-invasive ones [24].

Paracetamol or metamizole is recommended by the RKI to lower fever. To control restrictive fluid therapy, transpulmonary thermodilution is recommended [14]. Ibuprofen's data seems unclear. However, as of March 18, 2020, the WHO no longer advised against taking ibuprofen in connection with COVID-19 [23].

In addition to the evidence-based therapy options, there are experimental approaches for the treatment of COVID-19 patients [14].

Remdesivir (pharmaceutical entrepreneur: Gilead Sciences, Inc.) is an antiviral substance originally developed to treat infections caused by the Ebola virus [14]. In Grein et al., symptomatic improvement was observed in over 68% of patients using Remdesivir [21]. Furthermore, positive effects are reported in over 100 patients using **Chloroquine** in a Chinese multicenter study. An improvement of the radiological imaging as well as a shortening of the duration of the illness and the prevention of the exacerbation are described [20].

However, based on evidence, no recommendation can currently be made for any of these therapies [14, 22].

1.2 Acute respiratory distress syndrome - ARDS

Acute Respiratory Distress Syndrome is the name given to the massive response of the lungs to various damaging factors [26]. The typical picture of ARDS can appear because of a difficult course during an infection with SARS-CoV-2 [14]. Among other things, this is a life-threatening impairment of lung function triggered by sepsis, pneumonia, lung injuries, aspiration, multiple transfusions, etc. The more factors appear together at the same time, the higher the probability of developing an ARDS [18].

ARDS is defined by an acute hypoxemic respiratory failure with bilateral condensation in the imaging. A cardiac cause must be excluded [19].

1.2.1 Pathophysiology

ARDS typically proceeds in three phases: (1) the exudative phase, (2) the proliferative phase and (3) the fibrotic phase. In the first phase, the **exudative phase**, inflammatory mediators are released, and leukocytes migrate. Together with the damage of the alveolar cells this is the reason for the loss of the barrier function between capillaries and alveoli. Plasma proteins and defective surfactant clump together to form hyaline membranes. This leads to atelectasis and a higher dead space volume. The decrease in the alveolar 02 concentrate leads to vasoconstriction. The result is a pulmonary high pressure with strain on the right heart. If the patients survive the first seven days, they start to recover somewhat in the **proliferative phase**. The neutrophils are replaced by lymphocytes. The

type II alveolar epithelial cells begin to produce new surfactant and then differentiate into type I alveolar epithelial cells. Some of the patients subsequently develop pulmonary fibrosis in the **fibrotic phase**, which leads to the appearance of bullae typical of emphysema and is associated with an increased mortality [18-19].

1.2.2 Clinical presentation

The ARDS is a serious clinical picture that can lead to artificial ventilation within a few hours. Dyspnea, tachypnea, and hypoxemia usually occur 12-96 hours after the triggering event, followed by multi-organ failure [27].

1.2.3 Diagnosis

A cardiac cause must be excluded, because only then it can be defined as ARDS for sure [26].

The following applies to the diagnostic procedure:

- Pulmonary capillary occlusion pressure (PCWP, wedge pressure) <18mmHg, or there is no clinical evidence of increased pressure in the left atrium or an echocardiographic exclusion of left heart failure [26]
- pO_2 (oxygen partial pressure in the arterial blood) / FiO_2 (oxygen content in the breathing air) ≤ 200 mmHg (Horovitz quotient) [26]
- Acute pulmonary edema without cardiac cause [27]
- Bilateral pulmonary infiltrate [27]

1.2.4 Therapy

The primary objective is to treat the triggering cause and to use ventilation that is as gentle as possible with a relatively high PEEP, but with moderate medium pressures. This serves to protect the still intact tissue. A permissive hypercapnia up to a carbon dioxide partial pressure (pCO_2) value of 100 mmHg is tolerated. In exceptional cases and very difficult courses, an extracorporeal membrane oxygenation (ECMO) can also be considered [27].

In addition, supportive therapy such as certain positioning maneuvers (prone position) and a restrictive fluid balance can be considered. Glucocorticoids are only indicated in the fibroproliferative phase [27].

1.3 Physiological background of breathing

The human body consists of two lungs, which are divided into three lobes on the right and two on the left. Bronchial-arterial segments can be defined within the lobes. These can again be divided into lobes. The air flows through a branched bronchial system and evenly ventilates the organ [28, 29].

The main task of the lungs is to ensure that the blood is sufficiently enriched with O_2 from the atmosphere and, at the same time, to release the CO_2 resulting from metabolisms. This gives the lungs an essential role in regulating the pH value. This task is controlled by so-called chemoreceptors, which are subdivided into peripheral ones located in the carotid fork (Glomus caroticum) and located in the aortic arch (Glomus aorticum) and central chemoreceptors located in the area of the medulla oblongata. These measure the pO_2 as well as that of pCO_2 and the concentration of H^+ (H_3O^+) to detect the pH value in the blood and in the brain liquid. The transport of breathing gases in the blood occurs mainly in bound form. The task of breathing regulation is to adapt the ventilation to the respective demand (energy requirement, help regulate the blood pH value). [28, 39].

The gas exchange exclusively takes place in the alveoli. These are lined with type I and type II pneumocytes. Those of the type I represent the barrier between the alveoli and the capillaries, and those of the type II, on the other hand, are used to produce surfactant. This reduces the tension in the alveoli and is essential for physiological compliance. Various disorders can hinder breathing in such a way that sufficient O_2 uptake and CO_2 release is no longer possible [28, 29, 39].

1.3.1 Compliance

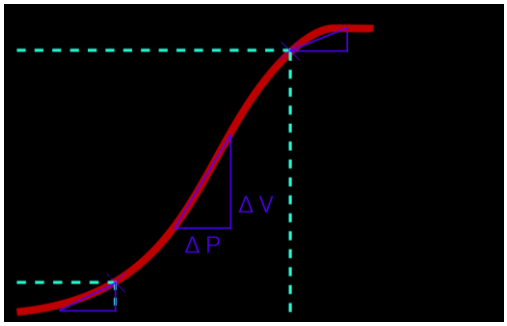
The lungs and the thorax have very different elastic properties.

For the **lungs**:
The compliance of the lungs is determined by two factors. On one hand from the elastic and collagen fibers, which counteract the expansion of the lungs, and on the other hand – which is the more important factor - from the surface tension of the alveoli. This is mainly determined by the surfactant [28, 29].

For the **thorax**:
The compliance of the thorax results from the difference between the pressure that acts on the chest from the inside and the outside. It is mainly influenced by the passive properties of the ligaments and muscles [28, 29].

To determine the overall compliance of the lungs and thorax, the relationship between intrathoracic volume and wall pressure (difference between alveolar pressure and external wall pressure) must be recorded. The curve is S-shaped and covers a range of approximately 8 kPa. If the alveolar pressure is the same as the external pressure, this denotes the resting position. In this state there are still approximately 3L of air in the organ. This is the functional residual capacity. The compliance is the steepening of the curve in the area of the resting breathing position. In healthy people it is 0,1L x cmH_2O^{-1} [29].

Figure 3: Pressure-volume curve



References: Own representation

1.3.2 Age-related change in compliance

Due to age-physiological changes, elastic connective tissue fibers are increasingly being replaced by collagen fibers. This leads to a steady decrease in the compliance with increasing age. Exogenous noxae such as the consumption of nicotine or the inhalation of fine dust can accelerate this process. The age-related stiffening of the thoracic skeleton also contributes to the age-related decrease in compliance [29].

1.3.3 Breathing mechanics

The respiratory mechanics describe the pulmonary functional variables pressure, volume and breathing gas flow and their relationship to one another. The process of inspiration and expiration and thus the transport of the air are described by ventilation. The driving force is the pressure gradient. To allow air to flow into the lungs, a pressure differential must be built upby enlarging the lungs. Since the organ does not have any muscles, it must be moved indirectly. The most important respiratory muscle is the diaphragm. Additional expansion of the bony thorax is enabled by the so-called auxiliary breathing muscles, which are formed by the intercostal muscles and muscles of the chest wall, the back, and the muscular abdominal wall. In contrast to inhalation, exhalation usually takes place passively through the relaxation of the muscles that act as inspiration. Expiratory muscles are only activated, when breathing is forced. Due to the dynamic airway compression, however, this does not lead to any significant increase in expiration [28, 30, 31, 41].

1.3.4 Airway resistance

The airway resistance is localized in the supplying, increasingly branching airways and offers the airflow a resistance that is defined in analogy to Ohm's law, $R=\Delta P/V$ and, according to the Hagen-Poiseuille law, deliberately determined by the diameter of the airways affected. This is mainly effective in the expiration. For healthy lungs, the resistance to breathing at rest is about 0.15 kPa x l^{-1} x s [29].

Dependence on the airway diameter: This decreases in the airways leading from (trachea) 12mm to 0.1mm (bronchioli terminales). The Hagen-Poseuille law means that there is much higher resistance in a single terminal bronchiolus than in the trachea. However, the numerous bronchioli terminales represent resistances connected in parallel in the sense of the flow, so that the total amount of air resistance is only approximately 20%. 40% are in the larger bronchi with fewer branches and the last 40% come from the upper airway [29].

Dependence on respiratory flow strength: With increasing breathing flow, turbulence develops in the air flow. This happens both at the branches and in the straight sections. In large parts these are stronger. The increased energy requirement to convey the turbulent air is further expressed in increased airway resistance [29].

Dependence on the breathing cycle: The airway resistance is also heavily dependent on the filling level of the length and on the alveolar pressure. As the lung volume increases, the upper airways are widened by elastic fibers and the airway resistance drops sharply [28, 29].

The regulation of airway resistance is controlled by the autonomic nervous system. The activation of the sympathetic system via the stimulation of the β2 adrenoceptors by the hormone adrenaline leads to a relaxation of the smooth muscles and thus to an expansion of the bronchi in the lungs. This mechanism results in a decrease in airway resistance and increases the strength of the breathing flow during physical work [28, 32].

1.3.5 Lung volumes and lung capacity

The normal values of these parameters greatly vary depending on age, body size and gender.

The following values are shown for a young man with healthy lungs. In women these are 10-20% smaller.

While some people achieve a vital capacity of 6 liters, competitive swimmers may achieve values of over 8 liters, in extreme cases even up to 10 liters. At the age of around 20 years,

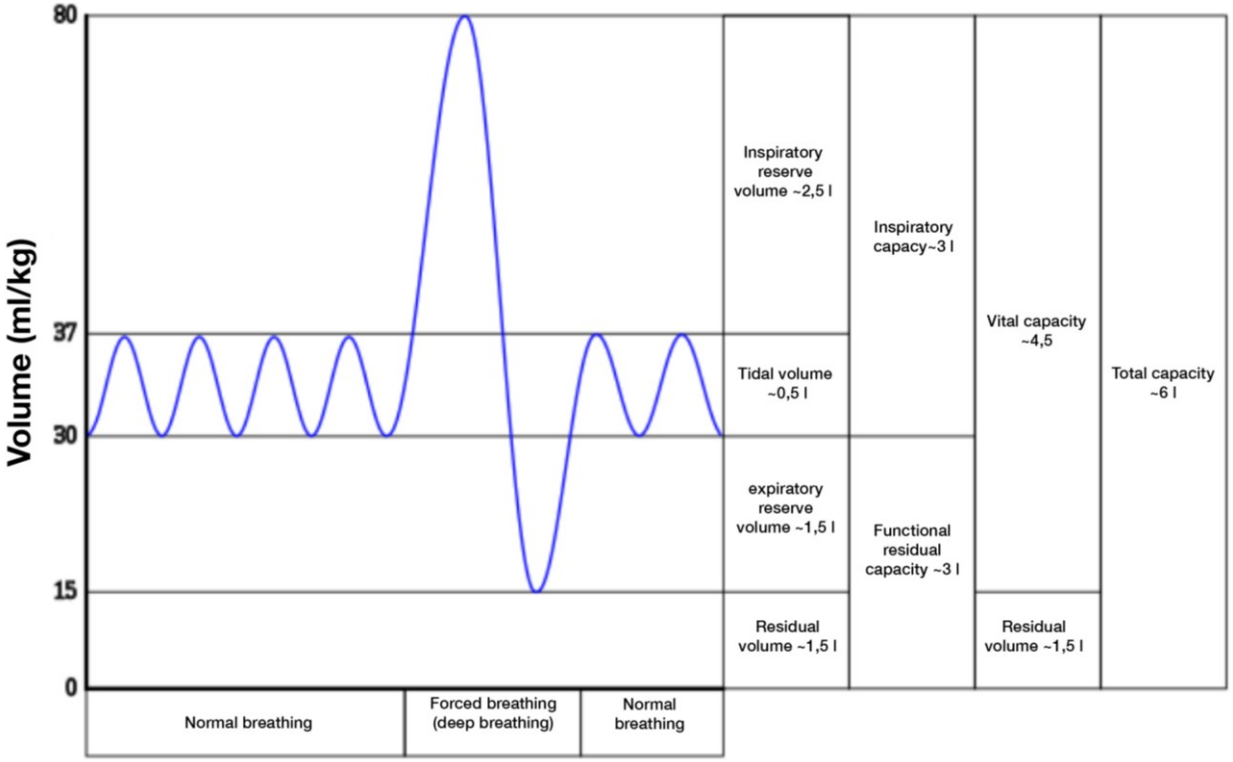
humans reach their maximum vital capacity of around 3-4 liters. This can drop to values of less than 2 liters with age. This decrease in old age is due to a loss of elasticity in the lungs and restricted mobility of the thorax. The total lung capacity (TLC), however, remains constant. This leads to an increase in the residual volume. The non-functional residual capacity is around 3.0 liters for young men and around 3.4 liters for older men [28, 33].

Table 2: Lung volumes and capacities

Designations	volume	Explanation
Total lung capacity (TLC)	6,0 l	The maximum gas volume of the lungs is called the total capacity.
Tidal volume (TV)	0,5 l	Describes the volume inhaled and exhaled with each breath
Inspiratory reserve volume (IRV)	2,5 l	Defines, how much can be inhaled maximally beyond the normal breath.
Expiratory reserve volume (ERV)	1,5 l	This is the volume that can be exhaled to a maximum beyond breathing rest.
Vital capacity (VC)	4,5 l	Is the sum of TV, IRV and ERV.
Residual volume (RV)	1,5 l	Describes the volume that remains in the lungs after maximum expiration.
Functional residual capacity (FRC)	3,0 l	This is the volume that is still in the lungs during normal exhalation.

References: Own representation, inspired by Behernds J.C. et al. [28]

Figure 4: Lung volumes and lung capacity



References: Own representation, inspired by Behernds J.C. et al. [28]

1.3.6 Dead space ventilation and alveolar ventilation

The gas volume of the lungs is composed of the anatomical dead space and the alveolar space. The **anatomical dead space** extends from the mouth to the 16th division of the bronchial tree. In this section, there is no gas exchange, only conduction. In adults, one speaks of approximately 150ml (2ml / kg body weight). The remaining 3-4 L (when breathing is resting) is the gas-exchanging alveolar space [28].

1.3.7 Alveolar gas exchange

The pulmonary gas exchange is divided into 3 sub-processes: ventilation, diffusion, and perfusion [42].

As part of **ventilation**, oxygen-rich air is transported into the lungs and the alveolar gas mixture containing CO_2 is removed from the organ. This process happens in adults under physiological conditions and is performed 12-18 times per minute at rest. A breathing rate

of more than 18 breaths per minute is called tachypnea and less than 12 times per minute is called bradypnea. [42,46].

The amount of substance transported by **diffusion** per time depends on numerous factors that are considered in Fiksch's law of diffusion.

$$V = (P1 - P2) \times (A / d) \times D$$

P1 defines the gas partial pressure in the alveolar space, while P2 defines it in the capillary. A stands for the cross-sectional area, d for the membrane thickness and D describes the diffusion coefficient. This applies to all gases that are absorbed or released through the lungs Partial pressure describes the pressure of an individual component or fraction in an (ideal) gas mixture [28].

Table 3: Typical partial pressure values

Localization	O_2 partial pressure in mmHg	CO_2 partial pressure in mmHg
Atmospheric air	158.8	0.3
Upper airways	149.0	0.3
Alveolar space	100	40
Pulmonary artery	40	46
Pulmonary vein	90	40

References: Own representation, inspired by Behernds J.C. et al. [28]

Lung **perfusion** is performed over the pulmonary artery. At rest, there is a decrease in perfusion from the base of the lung to its top due to the force of gravity and better ventilation of the upper lung. In the course of this an increased pressure in the tip of the lung is created, to compress the capillaries and thus to reduce blood flow.

During physical work, the increase in cardiac output and thus blood pressure leads to increased arterial pressure in the capillaries; this overcomes the enables better perfusion of the upper airways.

When ventilation decreases in parts of the lungs, hypoxia occurs. This leads to the reflex narrowing of the blood vessels, which then allows the perfusion to be adapted to the ventilation. This is called the Euler-Liljestrand mechanism. Under pathological conditions (obstructive pulmonary disease, ARDS), chronic hypoventilation of lung areas occurs. The Euler-Liljestrand mechanism leads to reflex vasoconstriction, which further causes pulmonary hypertension. If left untreated, right heart strain and further right heart failure may develop [39, 44, 45, 46, 47].

1.3.8 Respiratory quotient

The respiratory quotient (RQ) is the ratio of CO_2 production to O_2 uptake. The normal value is approximately 0.8. This means that more oxygen is absorbed from the alveoli into the blood than CO_2 is released from the blood into the alveolar space. Since part of the CO_2 is eliminated via the kidneys and, under physiological conditions, the CO_2 production is lower than the O_2 uptake, the expiratory minute volume is somewhat less than the inspiratory.

The RQ is largely dependent on the composition of the diet. A high-fat, low-carbohydrate diet can lower the RQ to 0.7, whereas a high-carbohydrate, low-fat diet can increase the RQ to 1.0.

A high-fat, low-carbohydrate diet should therefore be selected for patients with global respiratory insufficiency or who are difficult to wean from the respiratory system [34].

1.4 Acids bases household

A largely constant concentration of cations and anions is essential for the cells to work properly. In the acid-base balance, the proton (H^+, actually H_3O^+) is the focus. In pure water its concentration is 10^{-7} mol/l. In arterial blood plasma, we speak of a concentration of $10^{-7,35}$-$10^{-7,45}$ mol/l. The pH value corresponds to the negative decadic logarithm of the H_3O^+ concentration. Under physiological conditions, this results in a pH value in the arterial blood of 7.35-7.45 [35,37].

The body is exposed to a constant acid load, which results from the oxidative breakdown of fats and carbohydrates, the absorption of acid equivalents through food, the metabolism of amino acids and anaerobic glycolysis [36].

Since enzymes act as molecular switches for metabolic pathways, they must be carefully controlled, and their activity is normally adapted to the situation. These can only work optimally within a certain concentration of H_3O^+ ions. This is the reason why the human body has developed mechanisms to keep the pH constant in the very narrow range of 7.35-7.45. A pH value <7.35 is called acidosis and> 7.45 is called alkalosis. These can have

both respiratory and metabolic causes and, if the cause is respiratory, it can be compensated metabolically and vice versa. [36, 38, 40].

Buffer system

Buffers are a mixture of weak acids and bases, as well as their salts. They can absorb H_3O^+ and HO^- ions. This can compensate a change of the concentration of H_3O^+ ions and thus minimize changes in the pH value. The total buffer capacity of humans is 15mmmol / kg body weight [36].

Carbonic acid-bicarbonate buffer system

The protons generated by metabolic processes react with bicarbonate to form carbonic acid. This then breaks down to H_2O and CO_2. Since CO_2 does not dissolve in the blood but is exhaled continuously through the lungs, the pH value changes only minimally despite the addition of H_3O^+ ions [36, 48].

$H^+ + HCO_3^- \rightarrow H_2CO_3 \rightarrow H_2O + CO_2$

Non-bicarbonate buffer

This system includes hemoglobin, phosphate, and protein buffer, which comprise about 25% of the total buffer capacity. The amino acid histidine in the hemoglobin found in erythrocytes has a ring structure in its side chain that can bind protons. In the plasma, the plasma proteins take on the role of the buffer, mainly the albumin. Since the concentration of phosphate in the plasma is very low, its contribution is only 0.4% of the total buffer effect [36].

The lungs, kidneys and liver regulate the acid-base balance. As already mentioned, the lungs continuously exhale the resulting CO_2. By changing the minute volume, the lung can participate in the acid-base regulation. This mechanism is very efficient. Compared with the kidneys, 100 times more acid equivalents can be excreted per unit of time, based on the lungs [36].

1.4.1 Blood gas analysis

The following values apply to arterial blood:

Table 4: Blood gas analysis

Designation	Reference values
pH	7.35-7.45
pO_2	65-100 mmHg
pCO_2	35-45 mmHG
HCO_3^-	22-26 mmol/l
Base excess (BE)	(-2)-(+2) mmol/l

References: Own representation, inspired by Renz-Polster et al. [36]

Base Excess (BE)

This value indicates the amount of acid or base that must be added to the blood to restore the pH to 7.4. A positive BE indicates an excess of bases or a lack of acids, while a negative BE indicates a lack of bases or an excess of acids [38].

1.4.2 Metabolic and respiratory disorders

In case of a **respiratory** disorder, the base or acid equivalents result from increased or decreased breathing activity. This primarily leads to a change in the pCO_2. In case of a **metabolic** disorder, on the other hand, acid or base equivalents are produced by a metabolic disorder or by impaired renal excretion. This leads to a change in the bicarbonate and the BE. In case of combined disturbances, the pCO_2, the HCO_3 and BE will change. The respiratory acidosis is **compensated** by a metabolic increase of the bicarbonate and the respiratory alkalosis by a metabolic reduction of the same. If, on the other hand, a metabolic alkalosis or acidosis occurs, the body tries to compensate that by regulating the pCO_2 through the lung [36, 48].

1.5 Difference between spontaneous breathing and ventilation

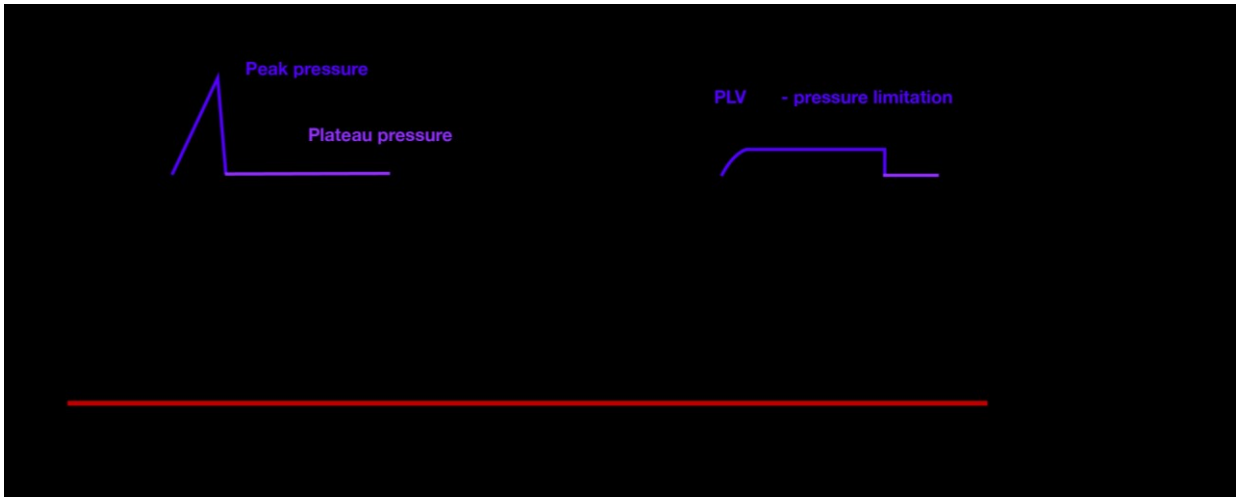
Regardless of whether ventilation occurs through spontaneous breathing or artificial respiration, in both cases the ventilation of the alveoli results from periodic changes in the intrathoracic pressure conditions [43].

Inspiraton:
As described above, the air flows along the lower pressure gradient resulting from the increase in volume through the diaphragm into the lungs during spontaneous breathing. With mechanical ventilation, however, this is achieved by applying positive pressure to the airways. This creates a pressure gradient in the direction of the alveoli. By applying a PEEP, the breathing medium position can be increased. This leads to an increase in the functional residual capacity and can normalize it again with reduced compliance due to atelectasis [28, 30, 31, 41, 43].

Expiration:
This is a passive process in both spontaneous breathing and mechanical ventilation.

With mechanical ventilation, the pressure applied from outside creates a gradient. We therefore differentiate between two pressure levels, a higher inspiratory pressure and a lower expiratory pressure or PEEP, in the lungs. This difference in turn results in a tidal volume [43].

Figure 5: Pressure curve respirator



References: Own representation, inspired by Oczenski et al. [43]

1.5.1 Forms of ventilation / ventilation techniques

A basic distinction is made between controlled and assisted forms of ventilation.

The ventilation pattern is determined by the following parameters on the respirator [49]:

- Inspiratory pressure or tidal volume
- Respiratory rate
- PEEP
- Inspirations: Expiratory relationships
- FiO_2

With **volume-controlled** ventilation, the volume of the inspiratory breath and the PEEP are defined. The inspiratory pressure results from the inhaled tidal volume. Forms of ventilation are e.g. (S) IMV [50, 51, 49].

In the **pressure-controlled** variant, the pressure that prevails in the lungs is specified. A tidal volume results from the difference between inspiratory pressure and expiratory pressure [50, 51, 49].

There are also **mixed forms** in which both parameters can be defined and controlled, e.g. volume controlled and pressure regulated. In this variant, a tidal volume and an upper pressure limit are specified. This is important for the prevention of trauma in the lung tissue [50, 51, 49].

With **continuous positive airway pressure (CPAP)**, the patient must breathe independently. He is only provided with pressure in the ventilation system. The PEEP increases the gas exchange surface [50, 51, 49].

Finally, there is the option of so-called **assisted spontaneous breathing** (**ASB**). By that, the patient specifies the breathing rate by means of an adjustable trigger. The respirator supports this with a definable support [50, 51, 49].

1.6 Monitoring

The following sections describe the options for patient monitoring within the framework of mechanical ventilation. The primary task of monitoring is to recognize potentially dangerous situations for the patient by acoustic and optical signals.

1.6.1 Pulse oximetry

Pulse oximetry is a non-invasive form of continuous measurement of arterial oxygen saturation and pulse rate.

Working principle

Oxygenated and reduced hemoglobin have different colors due to their different light absorption behavior. Reddish from 660 nm is absorbed by oxygenated hemoglobin much less than by reduced hemoglobin. For light with a wavelength of 940 nm, the absorption behavior is approximately the same. The Pulsoxy now alternately sends both wavelengths from different diodes and detects them on a photocell, which converts the unabsorbed light into an electrical signal. The strength of the signal is directly proportional to the oxygen saturation [49].

The limits for arterial oxygen saturation are between 94-97%. However, the limits should be set individually [52, 53].

1.6.2 Capnometry

Capnometry is the measurement and display of the pCO_2 in the exhaled air.

Working principle

Measurements are performed using infrared spectroscopy. The measurement is based on the absorption of infrared light. CO_2 molecules absorb light in proportion to the number of particles. The measuring chamber is compared with the absorption of a CO_2-free gas. With the sidestream method, a breathing gas sample is sucked off between the tube and the Y-piece over a thin plastic line and the CO_2 concentration is measured in a measuring chamber. With the main flow method, a measuring cuvette is placed between the tube and the Y-piece, onto which a CO_2 sensor is attached [54].

2 Material and Methods

The aim of this study was to create a suitable test set-up for the evaluation of an emergency respirator. The target was to implement a pilot study, which provides sufficient ventilation of large animals (pig). As part of an iterative development process, a continuous adaption of the prototype was strived. This was based on the results of the experiments.

2.1 Technical background of the respirator

The technical structure of the respirator significantly changed during the three animal experiments. At the beginning, a resuscitation bag variant was chosen based on the respirator developed by Massachusetts Institute of Technology (MIT) [55]. However, since the first experiment did not allow a sufficient ventilation of the pig due to the insufficient volume of the bag, this idea was changed to a cylinder version. This also avoided the problem of the poor availability of utensils at the time (March-April 2020). In the second experiment, a cylinder volume of 750ml was used. Since this turned out to be too small, a cylinder volume of 1.000ml was selected in the final experiment. In the following, the technical structure of the final prototype is described, as this was the goal of development.

Figure 6: Prototype resuscitator 1

References: Own representation

Figure 7: Prototype resuscitator 2

References: Own representation

The valves described below were replaced by self-constructed industrial valves instead of conventional PEEP valves. Here, too, availability played a key role. At the same time, this process also made it possible to achieve better controllability and tightness. These also had to go through a development process. Up until the last animal experiment, it was possible to produce sufficient valves and to us them as integrated (by software) switchable components.

Figure 8: PEEP ventil

References: Own representation

Figure 9: Prototype PEEP ventil (3D printed)

References: Own representation

Thanks to the possibility of 3D-printing, many ideas and prototypes could be implemented overnight. The components described below correspond to industrial components, but their applicability was checked in advance in the development process of only 2-3 weeks by using 3D-printed components.

Figure 10: Prototype cylinder

References: Own representation

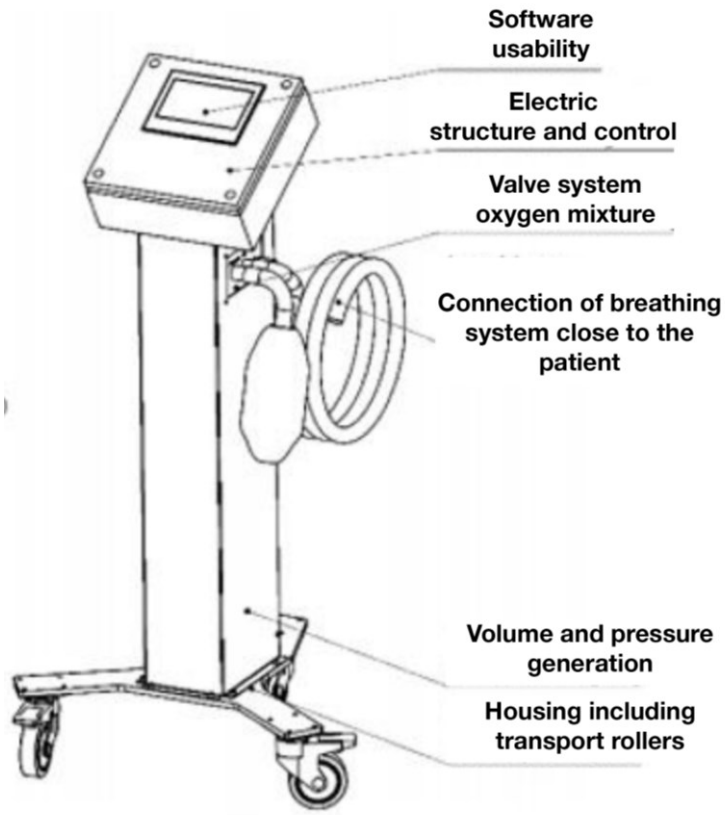
The final respirator is technically composed of several units. For a better understanding, the device is divided into the following mechanical subsystems:

- Housing including transport rollers
- Volume and pressure generation system
- Oxygen mixing valve system
- Breathing system close to the patient

The respirator also has an industrial control system including a graphic touch panel for operation. The systems are composed as follows:

- Electrical structure and control
- Software and usability
- Sensor technology and monitoring functions
- Security functions

Figure 11: Construction respirator

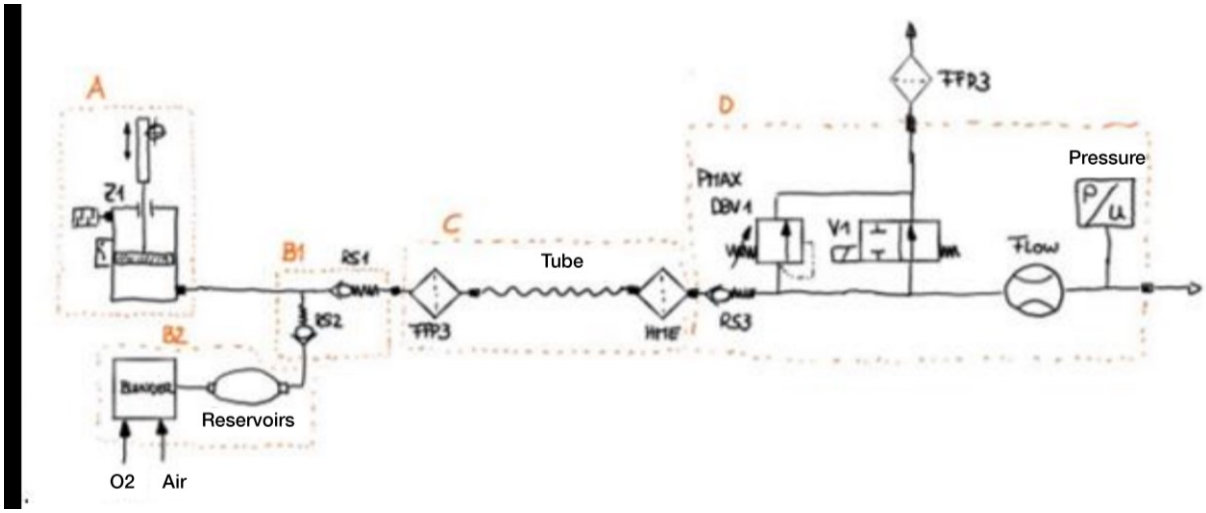


References: Own representation

2.1.1 Schematic structure

The following figure shows the schematic structure of the respirator, whichcan essentially be divided into 4 units made up of the systems described above.

Figure 12: Schematic structure References:



References: Own representation

- **Unit A:** volume and pressure generation system
- **Unit B1:** valve system
- **Unit B2:** medical oxygen and compressed air mixer
- **Unit C:** system filter and connection technology (hose)
- **Unit D:** Breathing system close to the patient including sensors and safety Components

2.1.2 Filters

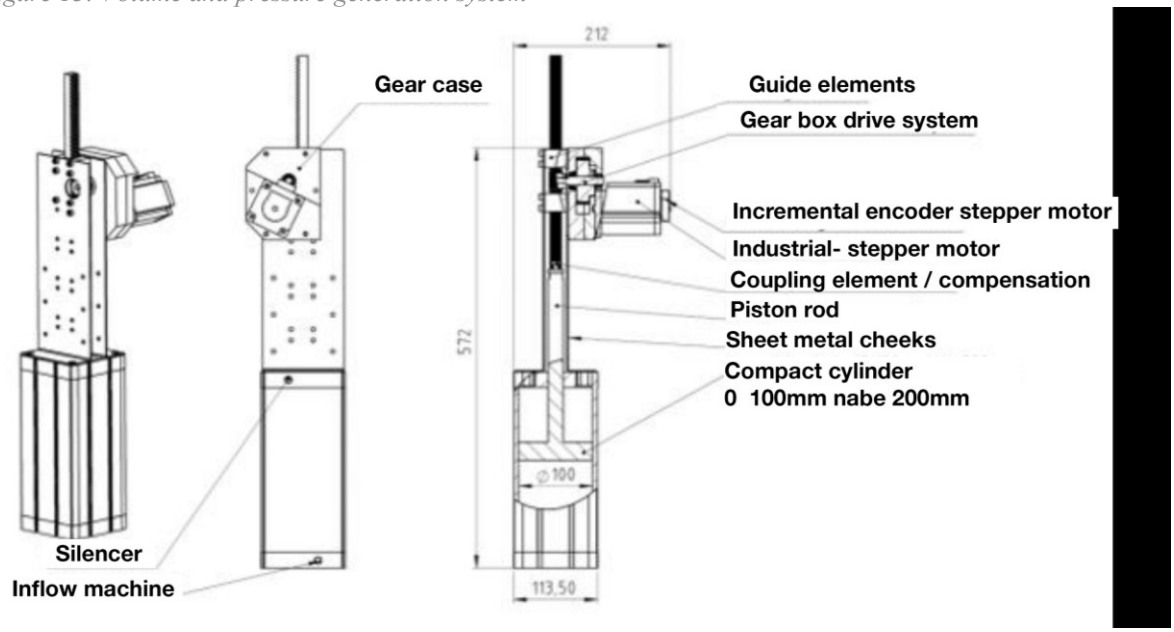
For optimal humidification of the breathing air and to prevent the distribution of infectious aerosols, FFP3 and HME filters were used as shown in Chapter 2.1.1.

2.1.3 Volume and pressure generation system

This system forms the basis of the controlled volume and pressure generation. The central element is a standard pneumatic cylinder with a clearly defined displacement. Contrary to the typical use, in which the cylinder is moved from applied pressure to perform an action or movement as an actuator, the piston is set in motion mechanically in order to be able to generate a defined volume flow. Along with the volume flow, there is also a corresponding pneumatic system pressure.

The cylinder is driven by means of a toothed rack mounted on the piston rod, which is also guided on the outside so that it can be moved along the piston axis with low friction. The drive pinion including an appropriately dimensioned single-stage gear forms the connection to a powerful regulated stepper motor. A reed contact is installed on the cylinder for referencing and is approached using the control, when the machine is initiated.

Figure 13: Volume and pressure generation system



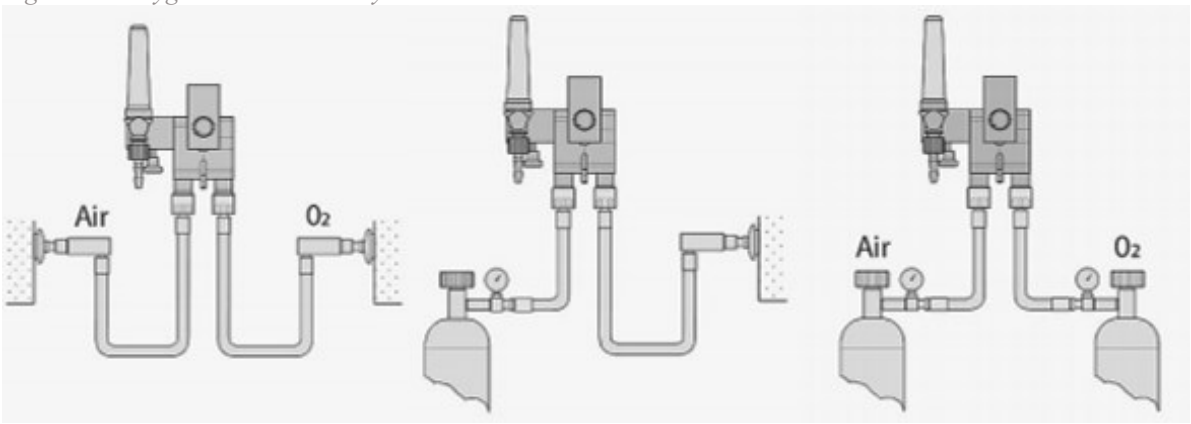
References: Own representation

2.1.4 Oxygen mixture/valve system

By moving the piston rod down, volume is released into the piping system. After this phase, the stepper motor controls the backward movement, and the previously ejected volume must be refilled. In the case of controlled ventilation, it is important to form an appropriate mixing ratio from the ambient air and the connected pure oxygen, which can be actively drawn into the cylinder, remain there and then fed into the ventilation circuit. An oxygen-air mixer is used for this, which is already used in ventilation technology.

The mixer used can regulate the FiO_2 according to an adjustable default value and make this constantly available to the machine. As a compensation element, a compensation bag is installed between the mixing unit and the non-return valve, which can be pre-filled in the active phases. Figure 14 shows the various connection and operating options for the gas supply. Depending on availability, the machine can be operated from full supply from the hospital's central gas system to offline operation with pressure bottles.

Figure 14: Oxygen mixture/valve system



References: Own representation

2.1.5 Breathing system close to the patient

Connected by a hose system, the breathing system close to the patient forms the closing element. The main task of this system is to enable the oxygen-enriched gas to be supplied with low resistance during the ventilation phase (volume and pressure are built up). After the desired inspiratory pressure has been reached, the pressure generated must be kept tight for a definable time to enable a corresponding inspiration in the lungs. This phase is followed by controlled and low-resistance exhalation. An integrated switchable valve positioned directly at the outlet of the breathing system minimizes dead space, and prevents rebreathing into the hose system. Further prevention is possible by an additional, integrated non-return valve between the supplying ventilation hose and the breathing valve close to the patient.

2.1.6 Sensor technology and monitoring functions

Sensors are built into the system to measure the pressure, volume, and oxygen content in the ventilation air. With the help of these measuring systems, on the one hand, a graphical visualization of the time courses can be generated, and, on the other hand, various monitoring functions can be defined.

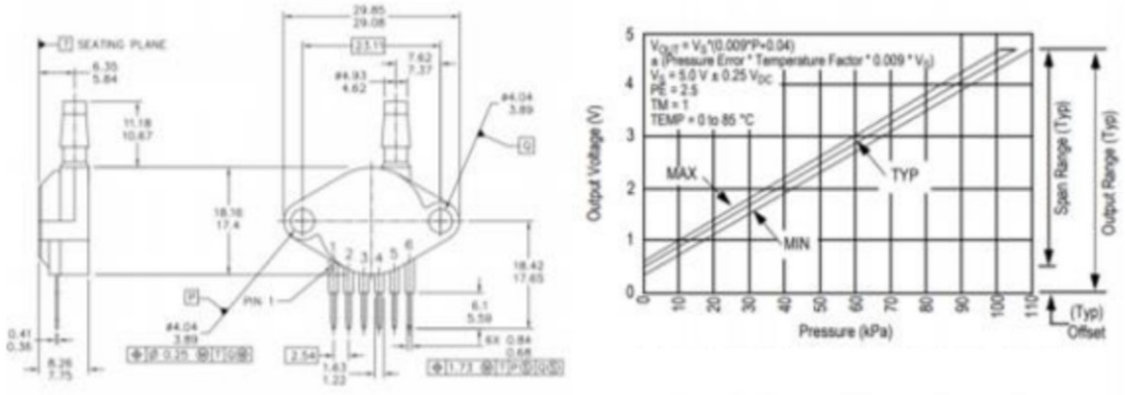
Used measurement technology:

1. System pressure breathing valve
2. Flow breathing valve
3. Oxygen mixture sensor

With the help of the pressure sensor in the breathing valve (1), the active pressure at the outlet of the breathing valve can be measured. This transducer is an element from NXP with the type designation MPX5100AP.

A SFAH-50U-G18FS-PNLK-PNVBA-M8 flow sensor from Festo is used to determine the volume flow (2). The volume flowing through can be calculated by integrating the measured flow over time.

Figure 15: Sensor technology and monitoring functions



References: Own representation

2.1.7 Alarms

Alarm limits can be specified for the parameters r**espiratory frequency, inspiratory pressure, maximum pressure, PEEP, minute volume, tidal volume and FiO_2**. If the defined minimum / maximum values are exceeded or fallen below, there is an acute and visual signal.

2.1.8 Ventilation mode

A pressure-controlled or volume-controlled and pressure-regulated form was selected as the ventilation mode with a view to its use as an emergency ventilator in crisis situations.

Pressure-controlled ventilation

With this type of ventilation, following parameters are variable: PEEP, inspiratory pressure, FiO_2, respiratory rate, I: E. The parameters tidal volume and minute volume result from the pressure differences and the respiratory rate. If pressure values are above the inspiratory pressure, e.g. due to insufficient sedation of the patient, one will get an acoustic and visual signal. In addition, a maximum pressure (pMax) can be defined. When this is reached, the respirator automatically stops the inspiration. An overpressure valve is additionally installed, which allows additional volume to escape. Thus, barotrauma can be prevented under all circumstances.

Volume controlled pressure assisted

With this variant, the inspiratory tidal volume is specified. The inspiratory pressure is also defined as a protective function. If this reaches a lower volume than defined, the inspiration stops and one gets a visual and acoustic signal. The parameter pMax can also be defined to prevent trauma. The following values are given by the therapist: PEEP, respiratory rate, FiO_2, I:E.

2.1.9 Console

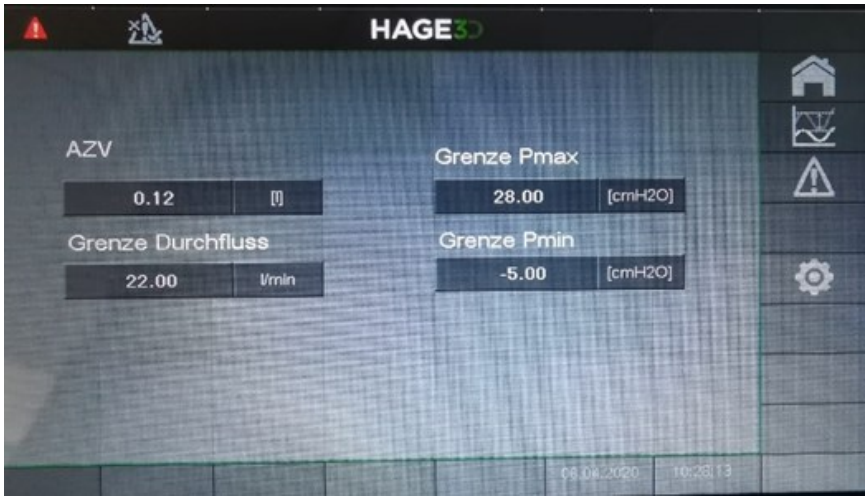
All parameters mentioned above as well as the ventilation mode can be entered by the user on a console with a touch function. This also provides a flow volume curve. The data is displayed in absolute numbers as well as a graphic representation. The following information is given by the console:

- FiO_2
- Tidal volume
- Minute volume
- Breathing rate
- PEEP
- Inspiratory pressures

Figure 16: Console 1

References: Own representation

Figure 17: Console 2



References: Own representation

2.2 Animal experiment

Relevant data was collected as part of a large animal experiment over a period of 30 minutes each, using the sedoanalgesia mentioned here.

The weight of the animals was:

Pig 1 60kg
Pig 2 75kg
Pig 3 93kg

2.2.1 Anesthesia

To ensure controlled ventilation, experiments were carried out under general anesthesia of the animals. The following method was chosen for this.

The **premedication** was administered intramuscularly approximately 15 minutes before the planned attempt and was composed as follows:

- 0.5mg / kg midazolam (Midazolam®)
- 2.5mg / kg azaperone (Stresnil®)
- 10 mg / kg ketamine (Ketasol®)
- 0.2 mg / kg butorphanol (Butomidor®)

Induction of anesthesia:

After the skin had been disinfected, an indwelling venous catheter was placed.
After sufficient pre-oxygenation, induction of anesthesia was performed as follows:

- Propofol 1% (Propofol "Fresenius" ®) 3 mg / kg / body weight bolus (if necessary, for deepening before intubation)
- Intubation: spiral tube 8.0-9.0 ID, long Miller's spatula, stylet

The ventilation was done as IPPV (ventilation with intermittent positive pressure - pressure-controlled mechanical ventilation), I: E ratio 1: 2 with a tidal volume of 10-15 ml / kg body weight at a respiratory rate of 12-20 / min and a PEEP of 5 cmH2O . The exact adjustment was made by measuring the end-tidal CO_2, which physiologically should be between 35 and 45 mmHg. The carrier gas consists of an oxygen-air mixture (initially in a ratio of 50:50), whereby the inspiratory oxygen content (FiO_2) was chosen in a way that the blood's pO_2 (oxygen partial pressure) was constantly around 95-100 mmHg.

Maintenance of anesthesia:

Anesthesia was kept by intravenous administration of the following substances over perfusors:

- Propofol (Fresenius ®) 1% 2-5 mg / kg / h (after effect)
- Fentanyl (Fentanyl-Hammeln ®) 20 µg / kg / h

Volume (EloMel Isoton, approx. 10 ml / kg / h in the 1st hour, then 3 ml / kg / h) was administered by a second venous catheter.

Pigs were treated by eye ointment (Aqua Tears®) to protect the cornea from drying out and were kept at constant, physiological temperature range (37-39 ° C) using heating mats.

2.2.2 Data collection:

Monitoring of the vital parameters was carried out during the entire anesthesia as follows:

- Pulse oximetry on the tail
- ECG
- Blood gas analysis every 15 minutes
- Capnometry
- Ventilation pressures, ventilation volumes and respiratory rate

Collected data was entered in a table in the Microsoft® Excel®, version 2005 spreadsheet program and saved on a data carrier owned by the Medical University of Graz, which is located in the 3D printing laboratory of the FE Experimental Neurotraumatology.

2.2.3 Euthanasia:

No euthanasia was done during or after the experiments.

2.2.4 Use of endpoints that are as painless as possible (termination criteria)

If, contrary to expectations, unforeseen emergencies (pain that cannot be treated, weight loss, loss of appetite and / or lethargy) occured before the attempt, the responsible veterinarian (Section 16 (2) no.3 TVG 2012) would decide on how to proceed and, if necessary, the professional euthanasia of the animal. This would be done in a separate room in order to avoid additional stress in the other animals.

2.2.5 Description of the housing, keeping and care conditions for the animals

The experimental animals were housed and kept under standard conditions at the Medical University of Graz, Department of Biomedical Research (Hahnhof). The animals there have to get used to at least 7-14 days in order to get used to the new environment. During this time, the animals were looked after by the responsible animal care staff and routinely checked for their health by the veterinary team.

2.2.6 Reduction, avoidance, and alleviation of all suffering from birth to death

The male, adult pigs were taken to the Department of Biomedical Research about 7-14 days before the start of the experiment (operation) and kept there until the experiment. If, contrary to expectations, unforeseen emergencies (non-treatable pain, weight loss, loss of appetite and / or lethargy) occured before the attempt, the responsible veterinarian (Section 16 (2) no.3 TVG 2012) would decide on how to proceed and, if necessary, the professional euthanasia of the animal. This would be done in a separate room to avoid additional stress in the other animals.

At the beginning of the experiment, the animals were anesthetized and remained under anesthesia until the end of the experiment. No euthanasia was done during or after the experiments.

2.2.7 Ventilation mode

A pressure-controlled ventilation mode was chosen for all 3 experiments. The parameters respiratory rate, I: E, PEEP, inspiration pressure, maximum inspiration pressure and FiO_2 were defined. The parameters tidal volume and minute volume resulted from the pressure differences and were graphically displayed on the ventilation monitor and saved by means of an alarm.

Experiment 1:

Table 5: Experiment 1

Parameter	**Values**
Respiratory rate	13 /min
I:E	1:2.0
PEEP	5 mmHG
Inspiration pressure	15 mmHG
Tidal volume	640 ml
Minute volume	9.4 l
FiO_2	40%

References: Own representation

Experiment 2:

Table 6: Experiment 2 References:

Parameter	**Values**
Respiratory rate	14 /min
I:E	1:2.0
PEEP	5 mmHG
Inspiration pressure	20 mmHG
Tidal volume	440 ml
Minute volume	8 l
FiO_2	50%

References: Own representation

Experiment 3:

Table 7: Experiment 3

Parameter	Values
Respiratory rate	18 /min
I:E	1:2.0
PEEP	5 mmHG
Inspiration pressure	22 mmHG
Tidal volume	860 ml
Minute volume	15 l
FiO_2	35%

References: Own representation

2.2.8 Monitoring

Blood gas analysis

Blood gas analysis was performed using EPOC®

Technical Specifications:

Table 8: Technical Specifications of EPOC®

Designation	Information
Sample volume	At least 92l
Analysis time	1 min
Quality control	urotrol GAS-ISE quality control; Eurotrol hematocrit control
Calibration	Performed automatically before each test.
Storage	15-30°
Durability	Up to 5 months
Integrated barcode scanner	Patienten-ID und Benutzer-ID; 1D- und 2D-Barcode-Format
operating system	MICROSOFT Windows Mobile 6.5 Classic
Communication	Wirelessly via POC data management solution

References: Own representation

Capnometry

The capnometry was carried out using Datex Ohmeda accessories.

As described in Chapter 1.6.2, CO_2 absorbs light in the infrared range. This is also absorbed by other compounds such as H_2O or N_2O, but not by O_2 and N_2. Precautions must therefore be taken to consider the effects of H_2O and N_2O. The Datex device uses an absorption band at 3.9 µm for N_2O measurement.

3 Results

3.1 Animal experiment: 1

Date: April 4th, 2020

Time: 08.30 am – 09.00 am

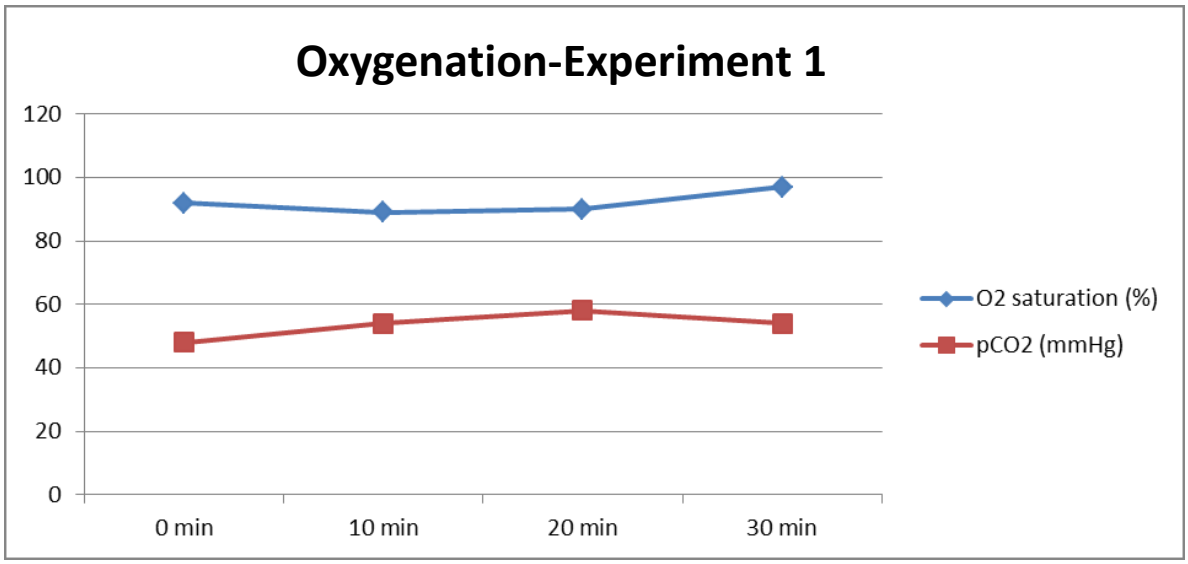
Weight: 60 kg

Table 9: Animal experiment 1; Illustration of the ventilation parameters

	Pig 1			
Time	**0**	**10**	**20**	**30**
Respiratory rate/min	13			
I:E	01:02,0			
PEEP (mmHg)	5	4	3	4
Inspiration pressure (mmHg)	15	14	12	18
Tidal volume (ml)	480	430	390	470
Minute volume (l)	6,2	5,6	5	6
FIO_2 (%)	40		50	
O_2 saturation (%)	92	89	90	97
HF/min	65	40	55	55
pCO2 (mmHg)	48	54	58	54
PH	7,43			7,37
pO_2 (mmHg)	401			481
pCO_2 (mmHg)	48			55
SO_2 (%)	100			100
Lactate (mmol/l)	0,8			2,39
ABE (mmol/l)	7,5			6,5
HCO_3 (mmol/l)	31,4			31,7

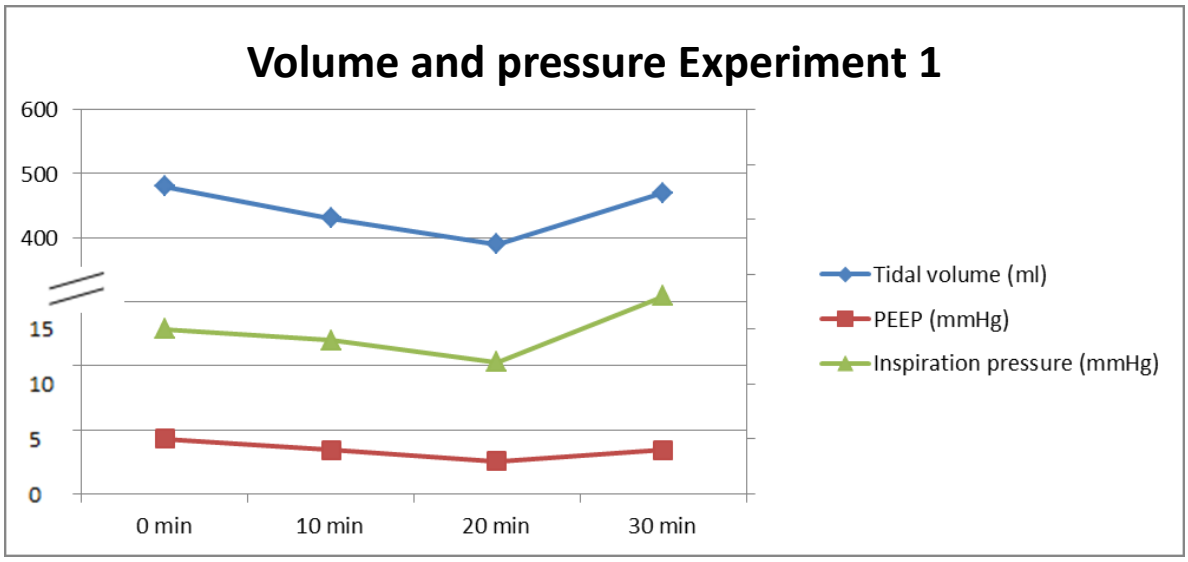
References: Own representation

Figure 18: Oxygenation-Experiment: 1; ***Representation of the oxygenation with pO_2 and PCO_2 every 10 minutes.***



References: Own representation

Figure 19: Tidal volume-Experiment: 1; ***Representation of the tidal volumes, inspiratory pressures and PEEP.***



References: Own representation

The animal experiment on April 4th, 2020 was performed with the first prototype. As described in chapter "*2.1 2.1 Technical background of the respirator*", a resuscitation bag with mechanical valves was therefore installed.

Tidal volumes of < 400 -500 ml (Fig. 19) were achieved. Inspiratory pressures and PEEP could not be maintained (Fig. 19). The animal was taken over from the anesthesia machine with pCO_2 values of 48mmHg. These increased in the next 30 minutes to a maximum of 58 mmHg (Fig. 18). The oxygen saturation could be stabilized with a FiO_2 adaptation from 40% to 50% from a minimum of 89% to 97% (Fig. 18).

The blood gas analysis showed a metabolically compensated pH value with a pCO_2 maximum of 55mmHg (Tab. 10).

Animal experiment: 2

Date: April 9th, 2020

Time: 08.00 am – 08.30 am

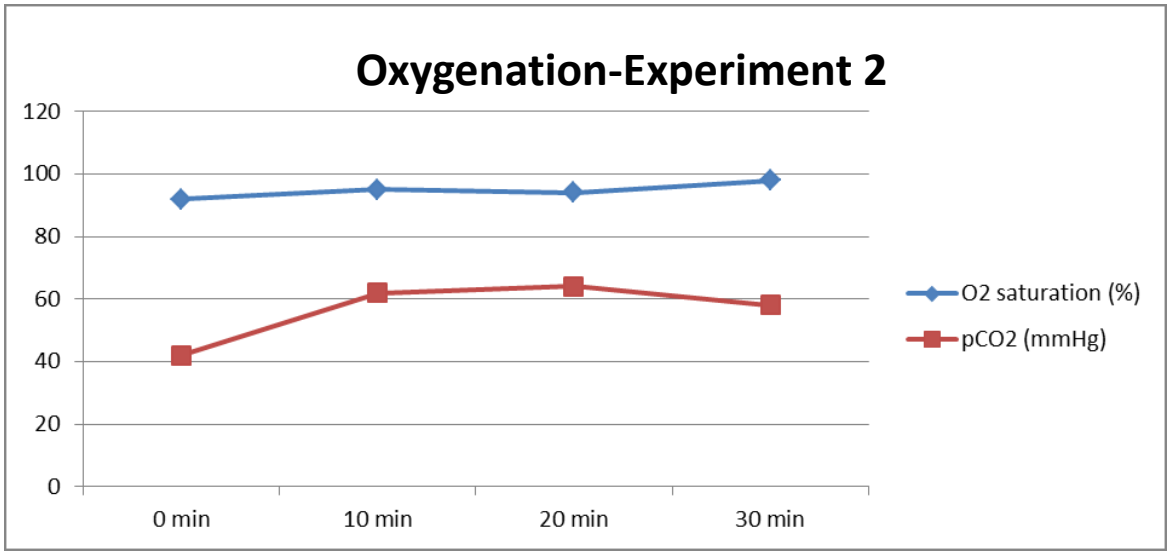
Weight: 75 kg

Table 10: Animal experiment 2; Illustration of the ventilation parameters

	Pig 2			
Time	**0**	**10**	**20**	**30**
Respiratory rate/min	14			
I:E	01:02,0			
PEEP (mmHg)	5	4	4	5
Inspiration pressure (mmHg)	20	15	13	17
Tidal volume (ml)	440	410	400	430
Minute volume (l)	6	5,7	5,8	5,9
$FIO_{2\,(\%)}$	50			
O_2 saturation (%)	92	95	94	98
HF/min	70	65	72	68
pCO2 (mmHg)	42	62	64	58
PH	7,45			7,35
pO_2 (mmHg)	323			530
pCO_2 (mmHg)	40			60
SO_2 (%)	99			100
Lactate (mmol/l)	2,4			0,75
ABE (mmol/l)	4			7,7
HCO_3 (mmol/l)	28			33

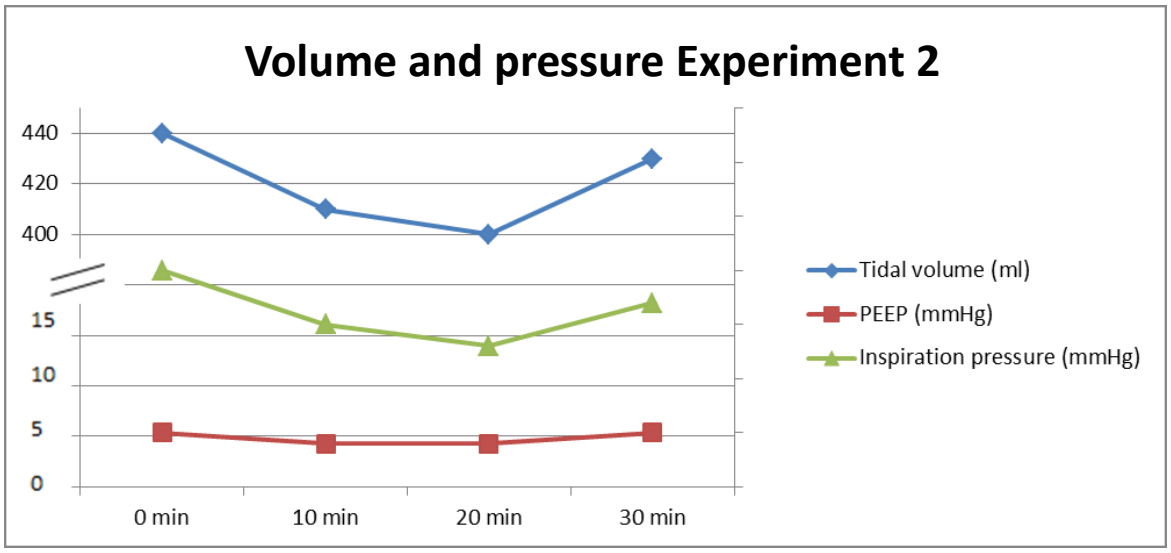
References: Own representation

Figure 20: Oxygen-Experiment: 2; ***Representation of the oxygenation with pO_2 and PCO_2 every 10 minutes***



References: Own representation

Figure 21: Tidal volume-Experiment: 2; ***Representation of the tidal volumes, inspiratory pressures and PEEP.***



References: Own representation

For the experiment on April 9th, 2020, the prototype was converted to a cylinder version with a volume of 750ml. The inspiratory pressures of 20 mmHg and PEEP of 5mmHg could not be maintained (Fig. 21). Tidal volumes of <450 ml (Fig. 21) were presented. The animal was taken over from the anesthesia machine at 8 a.m. with a pCO_2 value of 42mmHg. These increased to a maximum of 64 mmHg over the next 30 minutes (Fig. 20). Oxygen saturation of 90% (Fig. 20) was measured. FiO_2 was 50%.

The blood gas analysis showed a metabolically compensated pH level with a pCO_2 maximum of 60mmHg. The oxygen saturation was 100% (Tab. 11).

Date: April 17th, 2020

Time: 08.15 am – 08.45 am

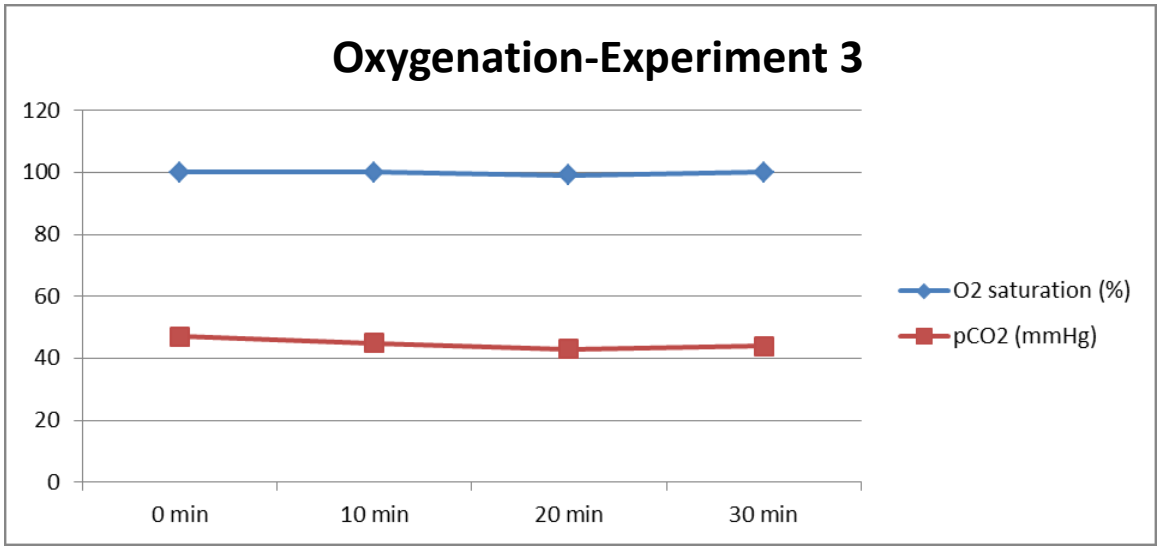
Weight: 93 kg

Table 11: Animal experiment 3; Illustration of the ventilation parameters

	Pig 3			
Time	**0**	**10**	**20**	**30**
Respiratory rate/min	18			
I:E	01:02,0			
PEEP (mmHg)	5	5	5	5
Inspiration pressure (mmHg)	22	24	26	25
Tidal volume (ml)	860	880	910	890
Minute volume (l)	15,4	15,8	16,3	16
$FIO_{2\,(\%)}$	35			
O_2 saturation (%)	100	100	99	100
HF/min	70	75	66	72
pCO2 (mmHg)	47	45	43	44
PH				
pO_2 (mmHg)				
pCO_2 (mmHg)				
SO_2 (%)				
Lactate (mmol/l)				
ABE (mmol/l)				
HCO_3 (mmol/l)				

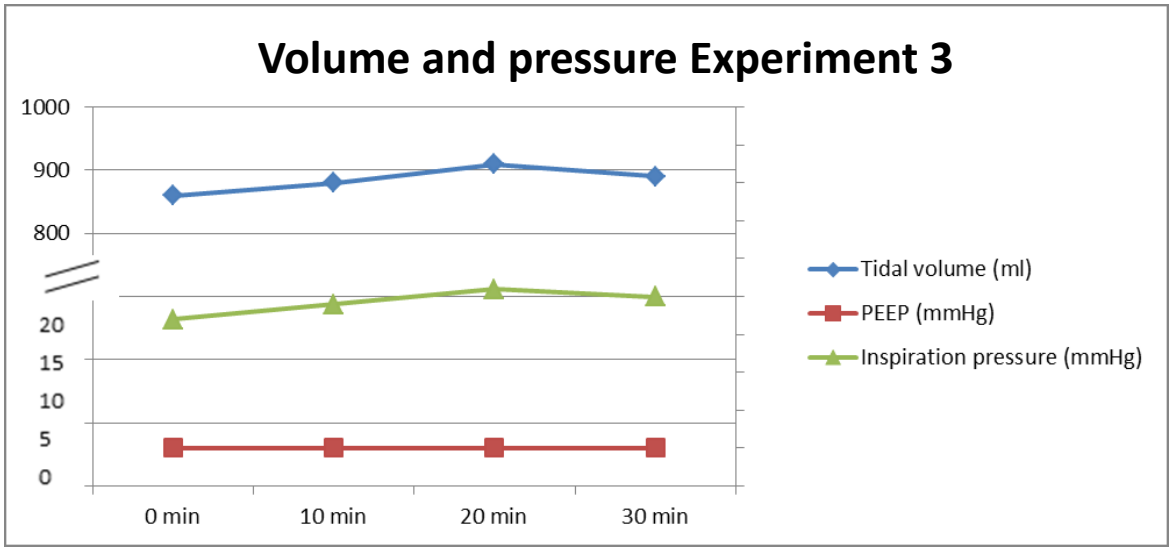
References: Own representation

Figure 22: Oxygen-Experiment: 3; ***Representation of the oxygenation with pO_2 and PCO_2 every 10 minutes.***



References: Own representation

Figure 23: Tidal volume-Experiment: 3; ***Representation of the tidal volumes, inspiratory pressures and PEEP.***



References: Own representation

The 3rd and final experiment was done with the final prototype as described in chapter 2.1 "*Technical background of the respirator*". A cylinder with a volume of 1,000ml and self-designed valves was used. Inspiratory pressure of > 22 mmHg and PEEP of 5mmHg were maintained (Fig. 23). TV was > 800 ml (Fig. 23) and MV was > 15 l (Tab. 12). The weight of the pig was 93 kg.

Level of pCO2 decreased from 47mmHg to a minimum of 43mmHg. The oxygen saturation was almost 100%. FiO_2 was 35%.

The blood gas analysis had to be dispensed due to technical problems.

4 Discussion

4.1 Discussion of the methods and results

The reason for HAGE-Sondermaschinenbau GmbH & Co KG's initiative to develop an emergency respirator was based on Austria´s situation in April 2020 [6]. They were inspired by the work of the MIT, which developed a machine to periodically compress a resuscitator to generate ventilation in patient's lungs [55].

The scientific goal of this study was to evaluate a prototype of an emergency respirator referring on sufficient ventilation of patients infected with SARS-CoV-2. For this we wanted to create a suitable test set-up. The verification of adequate ventilation of a large animal (pig) should be tested on the basis of a pilot study. As part of an iterative development process, a continuous adaption of the prototype was strived. This was based on the results of the experiments

Our study design scheduled three large animal experiments. As part of an iterative development process, a continuous adaption of the prototype was strived. This adaption was based on the results of the experiments. Due to this, we tested three different prototypes. This explains different results in our experiments. This kind of development process is common. A similar approach to develop and evaluate their respirator was used by King et al. [59].

This form of iterative development process was only able through 3D-printing. Prototypes could be adapted, based on our results, overnight. The fact that most of the medical components were not available on the market in April 2020 made a development without 3D-printing almost impossible. Thanks, on this, many components could be produced in-house. Nevertheless, this required a high level of expertise from a wide variety of disciplines, such as software developers, engineers, and computer-aided design.

In the first two experiments, tidal volumes (TV) of <480 ml were achieved. Maximum inspiration pressure and PEEP could not be maintained. Level of pCO_2 increased to a maximum of 64 mmHg. As result of learning- and iterative process, the components could be adapted. Sufficient ventilation measured on our criteria for duration was feasible in the third experiment. This was done with our final prototype. Maintaining adequate TV > 800ml by a weight of 93kg was possible. The oxygenation was stabilized. The pCO_2 level of 47mmHg decreased to a level of 43mmHg. The oxygen saturation was almost 100%, with a FiO_2 of 35%.

4.2 Discussion of collected parameters

To check sufficiency of respiration, the effects of ventilation, diffusion and perfusion were observed. The study included only animals with healthy lungs. Hereby it can be assumed, that perfusion and diffusion are not the factors of limitation for physiological oxygenation. From this point of view, ventilation remains as a limiting but influenceable factor [31].

Under this consideration, an increased pCO_2 and decreased pO_2, out of reference values, show the picture of insufficient ventilation [36, 48]. On this account the focus was placed on parameters pCO_2 and oxygen saturation, measured by capnometry and pulse oximetry.

Maintaining proportionate pressures and volume is also a criterion of adequate ventilation. The difference between PEEP and maximum inhalation pressure results in TV [49]. This should be 7-8 ml / kg body weight. MV is defined as product of TV and respiratory rate [28, 32]. The physiological range of respiration rate is between 12 and 20 times per minute [31]. Additional to pCO_2 and pO_2 attention was paid on PEEP, maximum inspiration pressure, TV and MV.

Our criteria of sufficient performed ventilation were based on above-described considerations. These comprised the possibility of maintaining the following parameters: pCO_2 between 33 and 43 mmHg, oxygen saturation > 92%, PEEP of 5 mmHg as well as inspiration pressure of 15 mmHg in experiment 1, 20 mmHg in experiment 2, and 22 mmHg in experiment 3. Due to the described reference ranges TV volumes of 420-480 ml in experiment 1, 525-600 ml in experiment 2, and 651-744 ml in experiment 3 were

assumed as physiological. Our goal was to maintain these parameters in reference range for at least 30 minutes, without the need of increase in FiO_2.
Referring on this definition the first two experiments were not successful with regard to sufficient ventilation. Due to a unique iterative development process the prototype could be adapted in a way that sufficient ventilation was able in the final measured on our criteria.

For standardized evaluation of the parameters pCO2 and oxygen saturation, measured by capnometry and pulse oximetry, blood gas analysis was used. This also provided us information about animal's metabolic situation [38]. King et al. also used capnometry as a continuous control parameter and they evaluated it by using blood gas analysis. [59]. Via this method measurement errors could be foreclosed.

The operation and approval of ventilators in Austria is regulated by the Medical Devices Act [56]. The notified agency is responsible for licensing and decides on the safety by checking the standards and norms [57]. This is a time-consuming and complex process under regular circumstances. This is done for patient's safety. Licensing is also a very important tool for companies and user's safeness. Thus, they can refer to this in case of patient harm. This has an important impact on legal situation for everyone involved. Emergency licensing is on this account difficult. The usage without approval is called off-label use. In this case the user (physician) is liable.

The aim of this work was not to check all standards and norms of law. Our study should only show the possibility of adequate ventilation to initiate further studies and give scientific background for emergency license.

The study also showed that the respirator can be connected to conventional systems such as O_2 connection. The presence of alarms is an important safety aspect which prevents complications.

It is recommended that a ventilator must be able to provide a PEEP of 10–20 cm H_2O, a tidal volume of at least 300–600 ml, and minute ventilation of 10–15 l / min [65]. Data of this study showed feasibility of described volumes. To check possibility of maintaining PEEP between 10-20 cm H_2O, further study is necessary.

4.3 Limitations

As described, for development of the respirator we used an iterative process. To save time and infrastructure, this is a common way in scientific developing and was also utilized by King et al. [59]. This led to the situation that we could only test our final prototype once, and the results should be interpreted as a case report.

Proceeding of King et al. led to a comparable situation. They also could test their final prototype only once. By this consideration, comparability of the evidence between our and Kings data should be discussed.

The fact that each animal had a different weight should be considered. But this was each time comparable with humans. The animal of the 3rd experiment had a weight of 93kg. Because we judged the last testing as success in form of sufficient ventilation, we could show that artificial respiration on a tall human male should be possible. The achieved and maintained TV underpinned this thesis. Animals with low weight are difficult to compare with human. Stable achievement and maintenance of pressures and volumes in taller individuals and therewith bigger lungs would not be verified then [67, 68]. King et al., did also not describe different weight as exclusion criterion. They had animal weighed between 90-127 kg [59].

With cylinder volume we used (1.000 ml) it is not possible to guarantee requirements of specification for this type of medical devices. The possibility of sufficient ventilation in terms of enough cylinder capacity and rapid pressure build-up could be shown in the 3rd experiment. Since we developed emergency respirator for special situations, the authors agreed this capacity is sufficient in this context. Other variants of emergency respirators like bag variant developed by MIT had the same problem [55]. They even used lower capacity, because of the small volume of resuscitators. Such variant complicate special maneuvers in treatment of patients with ARDS. Specific operations are still not possible with bag variants [66]. Data of our first experiment corroborate this. Sufficient ventilation was not possible with our first prototype, a resuscitator variant.

To evaluate the effects of ventilation a duration time of 30 minutes was intended in our protocol. This should give us an idea of the possibility of sufficient ventilation. The data should be seen as initiator for further studies. To justify the usage on humans and especially in individuals infected with SARS-CoV-2 further research is necessary.

King et al. had longer ventilation times than our protocol, but they used several pigs because those animals which developed respiratory acidosis were exchanged. Therefore they hat a maximum of four hours of continuous ventilation [59]. This is longer than ours, but does still not provide any long-term data. On this account comparability to our data could be discussed.

Nevertheless, due to the special needs of ARDS patients, maneuvers with PEEP of up to 12 mmHg and the feasibility of long-term ventilation must be checked in further studies [60-64].

In contrast to other emergency respirators, the development was only sufficient for a controlled invasive form of ventilation. King et al. were also able to show a non-invasive variant with bilevel positive airway pressure. During the animal experiments, they could also show the possibility of ventilation with low sedation. [59]. This is an important point relating to the weaning procedures of ventilated patients.

Since assisted ventilation and therefore weaning are not feasible, the treatment is only suitable in the initial phase of intensive care. For long-term ventilation, the triage system would have to be adapted, in form of changing conventional respirators to patients with better prognosis. However, this form of ventilation is essential for a weaning procedure and should be part of further development for the HAGE respirator.

4.4 Conclusion

The results showed that it is basically possible to ventilate a pig under physiological conditions with a controlled ventilation mode for duration of 30 minutes. We were able to show maintenance of a stable oxygenation and metabolic situation.

When all other resources have already been used up and a triage system has been installed, a situation could arise where patients could not be treated anymore. In this case and if special weaning procedures can be implemented in further development and long-term use can be tested in further study's [60-64], the author concludes, that a temporary ventilation of patients infected with SARS-CoV-2 could be possible. From this point of view, the use would also be ethically justified.

The COVID-19-crisis brought an increase in development of "emergency" respirators. However, most of them have only minor functions. The usage of emergency ventilators should be viewed very critically.

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6 Appendix

Project Plan approved by the Department of Animal Experimentation and Genetic Engineering, Austrian Federal Ministry of Education, Science and Research

1. **Nichttechnische Projektzusammenfassung (gemäß § 31 TVG 2012)**

Inhalt

Es dürfen keine personenbezogenen Daten enthalten sein. Es müssen enthalten sein:

1. Angaben über die Projektziele, einschließlich des zu erwartenden Schadens und Nutzens,
2. Anzahl und Art der zu verwendenden Tiere,
3. Angaben über die Erfüllung der „3R" (Vermeidung, Verminderung und Verfeinerung). Umfang: in den meisten Fällen werden ca. 500 Worte ausreichen.

Hinweis

Durch die nichttechnische Projektzusammenfassung sollen objektive Informationen über Tierversuchsprojekte im Internet öffentlich zugänglich gemacht werden. Dadurch sollen allerdings weder Rechte des geistigen Eigentums verletzt noch vertrauliche Informationen preisgegeben werden. **Es ist die Aufgabe der Antragsteller beim Ausfüllen der Zusammenfassung ihre Rechte zu wahren.**

2. **Zweck des Tierversuchs (gemäß § 5 TVG 2012): Grundlagenforschung**

3. Angaben über Projektziele, einschließlich zu erwartender Schaden und Nutzen

Diese Pilotstudie dient dazu, ein neu entwickeltes Beatmungsgerät auszutesten, wodurch ein Engpass in diesem Bereich verhindert werden könnte und somit die intensivmedizinische Notfallbehandlung schwerst erkrankter COVID-19 Patienten unterstützt werden könnte. Ein Austesten der Methode im lebenden Organismus ist notwendig, um untersuchen zu können, ob die Methode funktioniert und ob diese in Notsituationen auch im Patienten eingesetzt werden könnte.

zu erwartender Nutzen: Wenn im Rahmen dieses Tierversuchs bestätigt werden kann, dass die neue Methode zufriedenstellende Ergebnisse liefert, könnten die Geräte sofort in großer Stückzahl produziert werden und die Kapazitäten in den österreichischen Intensivstationen könnten aufgestockt werden.

zu erwartender Schaden für die Tiere: Die Tiere werden wie für einen chirurgischen Eingriff in Narkose intubiert und beatmet. Wenn der Versuch beendet ist, werden die in tiefer Narkose befindlichen Tiere wiedererweckt. Falls es notwendig ist, werden auftretende Schmerzen der Tiere therapiert.

4. Art und Anzahl der Tiere

Für diesen Tierversuch werden drei Duroc-Schweine verwendet.

5. Erfüllung der „3R" (Vermeidung, Verminderung und Verfeinerung)

Vermeidung: Eine Vermeidung des beantragten Tierversuchs ist nicht möglich, da die Fragestellung nur in vivo zu beantworten ist.

Da es sich bei diesem Versuch um eine eventuelle Bewältigung der COVID-19 Problematik handelt, kann der Tierversuch nicht vermieden werden und muss unbedingt durchgeführt werden, um optimalerweise so rasch als möglich Notfallpatienten intensivmedizinisch betreuen zu können.

Verminderung: Die Versuche erfolgen mit der kleinstmöglichen Versuchsgruppe, mit welcher es möglich ist, trotzdem aussagekräftige Daten zu erhalten.
Es geht hier nur darum, eine Aussage zu treffen, ob das entwickelte Beatmungsgerät funktionsfähig ist und ob es im lebenden Organismus angewandt werden kann. Da die Tiere davor bereits in einem anderen Versuch verwendet wurden, reduziert sich die Anzahl an Tieren, die für Tierversuche verwendet werden.

Verfeinerung: Während der Eingewöhnungszeit der Tiere von 7-14 Tagen wird neben standardmäßiger fachkundiger Betreuung durch geschultes Tierpflegepersonal eine Bereicherung („enrichment“) in Form von Bällen, Gummiringen, Stroh, etc. zur Verfügung gestellt. Auch werden die Tiere durch vermehrten Kontakt an die TierpflegerInnen gewöhnt, um den Stress der Tiere weiter zu reduzieren. Die Tiere werden während des gesamten Versuchszeitraums engmaschig überwacht und routinemäßig von Tierärzten auf ihren Gesundheitszustand kontrolliert. Die Tiere werden nicht für den Versuch angekauft, sondern werden von einer anderen Forschungsgruppe zur Verfügung gestellt. Das bedeutet, dass die Eingewöhnungszeit trotz der Dringlichkeit des Experiments gegeben ist.

Gegebenenfalls von der Behörde zu ergänzen:
Eine rückblickende Bewertung ist bis spätestens …… vorgesehen.

Medizinische Universität Graz

Tierversuchsantrag

Titel:

Austestung 3D-gedruckter Beatmungsgeräte zur intensiv- medizinischen Versorgung von COVID-19 Patienten

Beantragt von: Univ.-Prof. Dr. Ute Schäfer
FE Experimentelle Neurotraumatologie
Universitätsklinik für Neurochirurgie Medizinische Universität Graz

Graz, April 2020

Bedeutung und Begründung des Projekts, Projektziele

Bedeutung und Begründung des Projekts

Derzeit sind etwa 200 Länder weltweit vom Ausbruch der **COVID-19 Erkrankung** durch en Erreger SARS-CoV-2 betroffen. Mit Stand 31.03.2020 gibt es insgesamt rund 786.000 bestätigte Fälle.

Viele Länder sind seit dem Ausbruch der Erkrankung mit noch nie dagewesenen Aufgaben im Gesundheitsbereich konfrontiert. Krankenhäuser, insbesondere Intensivstationen, sind an ihre Belastungsgrenzen gestoßen bzw. müssen sich darauf vorbereiten, bald an diese zu stoßen. Nicht nur die Betten und personelle Kapazität spielt eine entscheidende Rolle, sondern allem voran das Equipment, welches es gilt, in ausreichenden Mengen zu produzieren. Auch Österreich könnte bald vor denselben Herausforderungen stehen wie Italien, Spanien und Frankreich und Kapazitätsprobleme von Beatmungsgeräten könnten die Folge sein. Um solche Versorgungsengpässe möglichst umgehen zu können wurde die österreichische Industrie auch bereits vom Bundesministerium für Digitalisierung und Wirtschaftsstandort (BMDW) gemeinsam mit der Industriellenvereinigung um Einbringung ihres Know-Hows und ihrer Expertise ersucht. Um in dieser Notfallsituation eine adäquate intensivmedizinische Behandlung schwerstkranker Patienten gewährleisten zu können, wurde in einer schon länger bestehenden Zusammenarbeit zwischen der Medizinischen Universität Graz (Medizinisches 3D-Druck Labor) und der Firma HAGE-Sondermaschinenbau GmbH & Co KG in Obdach ein Beatmungsgerät entwickelt, das basierend auf zur Verfügung stehenden Materialien wie Atmungsbeutel, Schläuche, etc. automatisiert mechanisch bedient werden kann. Die Funktionalität und Sicherheit des Beatmungsgeräts soll in einem ersten Schritt durch eine Überprüfung vordefinierter intensivmedizinischer Parameter im Rahmen eines Pilotprojekts an zwei Großtieren getestet werden.

Für den Versuch werden drei Schweine in Narkose versetzt, intubiert und mit dem entwickelten Gerät künstlich beatmet, um die respektiven intensivmedizinischen Parameter zu erheben.

Die **Entwicklung eines praktikablen, einfachen und kostengünstigen 3D-gedruckten Beatmungsgeräts** soll dazu dienen, tausende **Notfallpatienten intensivmedizinisch versorgen** zu können – im Optimalfall nicht nur in Österreich, sondern auch in anderen Ländern, in welchen das Gesundheitssystem an die Grenzen seiner Kapazitäten kommt.

Projektziele

Ziel des Pilotprojekts an drei Schweinen ist es, die **Funktionalität des entwickelten Beatmungsgeräts am lebenden Organismus auszutesten**.

Nach dem Tierversuch ist es das **weitere Ziel, eine druckkontrollierte Beatmungsform vorliegen zu haben, die auch für die intensivmedizinische Betreuung von Patienten, die schwerst an COVID-19 erkrankt sind, eingesetzt werden kann**.

Das Beatmungsgerät funktioniert druckkontrolliert und maschinell. Um dies zu erreichen, wurden von der Firma HAGE-Sondermaschinenbau GmbH zwei Prototypen für das Beatmungsgerät entwickelt:

VARIANTE 1 – auf Basis eines Beatmungsbeutels:

Bei dieser Variante wird ein Beatmungsbeutel in eine eigens dafür konstruierte Haltevorrichtung eingespannt. An dieser befindet sich ein über ein Scharnier befestigter Kompressionsarm. Dieser komprimiert den Beatmungsbeutel über einen Motor, welcher dann über eine Steuerkonsole zu bedienen ist. Einstellbar über diese Konsole mit Touch- Display sind die Atemfrequenz, sowie die Inspirations- und Expirationszeiten, woraus sich ein Inspirations- und Expirationsverhältnis ergibt, welches grafisch dargestellt wird. Die im Beatmungsbeutel befindliche Luft kann über ein Schlauchsystem inkl. Reservoir mit O_2 angereichert werden. Die FiO_2 Konzentration richtet sich nach der zugeführten O_2 Menge pro Minute. Die durch den Motor komprimierte Luft wird in ein Schlauchsystem weitergleitet, welches über ein doppeltes Ventilsystem die Drücke regelt.



VARIANTE 2 – auf Basis eines Pneumatikzylinders:

Aufgrund der derzeit schlechten Verfügbarkeit von Beatmungsbeutel und Zubehör, entwickelte HAGE-Sondermaschinenbau GmbH in Zusammenarbeit mit der Medizinischen Universität Graz eine zweite Variante des Prototyps. Anstelle des Beatmungsbeutels findet sich hier ein pneumatischer Zylinder (1.000 ml), welcher über einen Motor komprimiert wird. Durch diesen Vorgang wird die Luft in ein Schlauchsystem weitergleitet, welches über ein doppeltes Ventilsystem die Drücke regelt. Die im

Kolben befindliche Luft kann über ein Schlauchsystem inkl. Reservoir mit O_2 angereichert werden. Die FiO_2 Konzentration richtet sich nach der zugeführten O_2-Menge pro Minute.

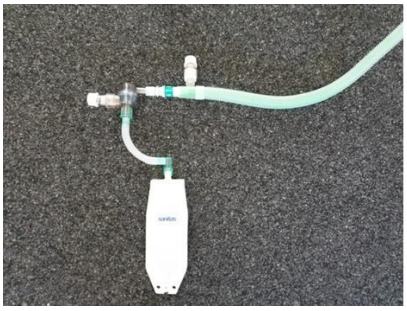
Bei beiden Varianten werden die Drücke über ein patientennahes Ventilsystem im

Beatmungsschlauch geregelt und mittels Sensoren kontrolliert. Die detektierten Werte werden grafisch auf der Konsole angezeigt und können mit einem Alarm (bei Abweichung der definierten Sollparameter) gesichert werden.

Das patientennahe Ventil fungiert als PEEP-Ventil. Dieses öffnet bei Expiration über dem eingestellten Druckniveau. Dadurch kann eine Positive EndExpiratory Pressure erzeugt und gleichzeitig die Expirationsluft patientennahe abgeatment werden, was zu einer deutlichen Reduktion des Totraumvolumens führt.

Über ein zweites, patientenferneres Ventil kann der inspiratorische und gleichzeitig maximale Druck vorgegeben werden. Bei Erreichen des eingestellten Drucks entweicht jede weitere zugeführte Luft. Dadurch können auch in Situationen wie Husten oder Pressen Barotraumata verhindert werden.

Die in der Druckdifferenz zugeführte Luft ergibt das Atemzugsvolumen, welches mittels Flowsensor gemessen und auf der Konsole grafisch dargestellt wird.



Während des gesamten Versuchs wird auch ein Facharzt für Anästhesiologie dabei sein, um die Funktionalität der Methode aus klinischer Sicht zu beurteilen.

Begründung für die Verwendung der Tiere, einschließlich Art, Anzahl und Lebensabschnitte

Die geplante Fragestellung ist nur durch die Untersuchung im Großtiermodell zu beantworten. Aufgrund der Zeitknappheit wurden keine Vorversuche getätigt; ein Versuch an einem Dummy ist jedoch angedacht.

Aufgrund der Dringlichkeit der COVID-19 Problematik ist es notwendig, die Methode so rasch als möglich in vivo auszutesten, um im Optimalfall schnellstmöglich intensivmedizinische Patienten behandeln zu können. Für die in vivo Austestung eignen sich am besten Schweine, da Schweine physiologisch am ehesten mit dem Menschen

vergleichbar sind.

Für diese Studie werden **drei Duroc-Schweine** verwendet. Das Gewicht der Tiere ist für den Versuch nicht relevant, muss aber vor Ort für die Einleitung und Aufrechterhaltung der Narkose bestimmt werden.

Drei Schweine sind für diesen Versuch ausreichend, da bereits mit dieser geringen Tierzahl eine

Aussage darüber getroffen werden kann, ob die Beatmungsmethode funktioniert oder nicht und im Notfall eingesetzt werden kann.

Versuchs- und Beobachtungsstrategien sowie statistische Gestaltung zur Minimierung der Zahl der Tiere, der Schmerzen, des Leidens, der Ängste und gegebenenfalls der Umweltauswirkungen

In diese Studie werden zwei männliche, erwachsene Schweine eingeschlossen.
Ziel der Studie ist es, die **Funktionalität des entwickelten Beatmungsgeräts am lebenden Organismus auszutesten**.
Nach dem Tierversuch ist es das **weitere Ziel, eine druckkontrollierte Beatmungsform vorliegen zu haben, die auch für die intensivmedizinische Betreuung von Patienten, die schwerst an COVID-19 erkrankt sind, eingesetzt werden kann**
Dazu werden die Schweine in Narkose gelegt, intubiert und beatmet. (Schweregrad: leicht). Nachdem die Beatmung abgeschlossen ist, werden die in tiefer Allgemeinanästhesie wieder erweckt und werden dann nach Salzburg gebracht, wo sie ihr Leben weiter führen können. Nach der Hautbiopsie, also zwischen dem Ende des Versuchs der Gruppe Kamolz und unserer Verwendung der Tiere erfolgt grundsätzlich keine Therapie. Falls es notwendig ist, können die Tiere jedoch einmalig analgetisch mittels Carprofen 4 mg/kg abgedeckt werden. So können Schmerzen, Leiden und Angst als Folge ausgeschlossen werden. (Schweregrad: leicht).

Für diese Studie werden nur drei Schweine beantragt. Die Tierzahl kann gering gehalten werden, da nur eine Aussage darüber getroffen werden soll, ob das entwickelte Beatmungsgerät im lebenden Organismus funktioniert oder nicht.
Zu statistischen Zwecken ist keine Einhaltung einer bestimmten Tierzahl notwendig, da es sich um eine reine Beobachtungsstudie handelt und lediglich die Anwendbarkeit einer Methode ausgetestet werden soll.
Das Leid und der Schmerz der Tiere kann gering gehalten werden, da sie vor der Intubation bzw. Beatmung unter Narkose gesetzt werden und direkt im Anschluss – ohne von der Narkose wieder aufgeweckt zu werden – euthanasiert werden. Auf diese Weise werden eventuelle Schmerzen vermieden.

Einsatz von Anästhesie, Analgesie und anderer schmerzlindernder Methoden

Einleitung der Narkose

Die Prämedikation soll ca. 15 Minuten vor dem geplanten Versuch intramuskulär verabreicht werden und sich wie folgt zusammensetzen:

- 0,5mg/kg Midazolam (Midazolam®)
- 2,0mg/kg Azaperon (Stresnil®)
- 10 mg/kg Ketamin (Ketasol®)

- 0,2 mg/kg Butorphanol (Butomidor®) – falls

notwendig Einleitung

Nach der Hautdesinfektion werden zwei Venenverweilkatheter in die V.v. auriculares gelegt.

Nach ausreichender Präoxygenierung soll die Einleitung wie folgt stattfinden:

- Propofol 1% (Propofol "Fresenius"®) 3 mg/kg/KG Bolus (bei Bedarf zur Vertiefung vor der Intubation)
- Intubation: Spiraltubus 8,0-9,0 ID, langer Millerspatel, Mandrin

Die Beatmung erfolgt als IPPV (Beatmung mit intermittierend positivem Druck - druckkontrollierte maschinelle Beatmung), I:E Ratio 1:2 mit einem Atemzugvolumen von 10-15 ml/kg KGW bei einer Atemfrequenz von 12 - 20/min und einem PEEP von 5 cmH2O. Die genaue Anpassung erfolgt über die Messung des endtidalen CO_2, welches physiologischer Weise zwischen 35 und 45 mmHg liegen soll. Das Trägergas besteht aus einem Sauerstoff-Luft-Gemisch (zunächst in einem Verhältnis von 50:50), wobei der inspiratorische Sauerstoffgehalt (FiO_2) so gewählt wird, dass das Blut einen konstanten pO_2 von 95-100 mmHg aufweist.

- ***Aufrechterhaltung der Narkose***

Die Narkose wird aufrechtgehalten durch intravenöse Applikation von den folgenden Substanzen mittels Perfusoren:

- Propofol (Fresenius ®) 1% 2-5 mg/kg/h (nach Wirkung)
- Fentanyl (Fentanyl-Hammeln ®) 20 µg/kg/h – falls

notwendig sowie mittels zusätzlicher Verabreichung von

- Isofluran (1-2%) in der Beatmungsluft.

Über einen zweiten Venenkatheter wird Volumen (EloMel Isoton, circa 10 ml/kg/h in der 1. Stunde, dann 3 ml/kg/h) verabreicht.

Die Schweine bekommen eine Augensalbe (Aqua Tears®) zum Schutz vor Austrocknung der Hornhaut und werden mittels Heizmatten in einem konstanten, physiologischen Temperaturbereich (37-39°C) gehalten.

Das Monitoring der Vitalparameter soll während der gesamten Narkose wie folgt durchgeführt werden:

- Pulsoxymetrie am Schwanz
- Blutdruck invasiv (während Aufrechterhaltung), A. femoralis sinistra sive dextra
- Kapnometrie
- Temperatursonde (Ösophagus)
- EKG

Analgesie und andere schmerzlindernde Methoden

Die Schweine werden unter Narkose operiert und unmittelbar danach wiedererweckt. Sie werden dann nach Salzburg gebracht, wo sie ihr Leben weiterführen können. Nach der Hautbiopsie, also zwischen dem Ende des Versuchs der Gruppe Kamolz und unserer Verwendung der Tiere erfolgt grundsätzlich keine Therapie. Falls es notwendig ist, können die Tiere jedoch einmalig analgetisch mittels Carprofen 4 mg/kg abgedeckt werden. So können Schmerzen, Leiden und Angst als Folge ausgeschlossen werden. Aus diesem Grund ist während des Versuchs nicht mit Schmerzen zu rechnen und eine Schmerztherapie ist nicht notwendig.

Anwendung möglichst schmerzloser Endpunkte (Abbruchkriterien)

Sollte es wider Erwarten vor dem Versuch zu unvorhergesehenen Notfällen (nicht therapierbare Schmerzen, Gewichtsverlust, Appetitlosigkeit und/oder Lethargie) bzw. während oder nach dem Versuch (z.B. Probleme bei der Regelung des Beatmungsdruckes) kommen, entscheidet der verantwortliche Tierarzt (§ 16 Abs. 2 Z 3 TVG 2012) über das weitere Vorgehen und leitet, falls nötig, die fachgerechte Euthanasie des Tieres ein. Dies geschieht in einem separaten Raum, um zusätzliche Stressauslösung bei den anderen Tieren zu vermeiden.

Angabe zu den Tötungsmethoden

Die Tiere werden nach dem Versuch wiedererweckt und werden dann nach Salzburg gebracht, wo sie ihr Leben weiter führen können. Nach der Hautbiopsie, also zwischen dem Ende des Versuchs der Gruppe Kamolz und unserer Verwendung der Tiere erfolgt grundsätzlich keine Therapie. Falls es notwendig ist, können die Tiere jedoch einmalig analgetisch mittels Carprofen 4 mg/kg abgedeckt werden. So können Schmerzen, Leiden und Angst als Folge ausgeschlossen werden.
Sollte eine Sakrifizierung unumgänglich sein, wird das in tiefer Allgemeinanästhesie befindliche Tier durch eine Überdosierung von Kaliumchlorid euthanasiert.

Angabe zur Anwendung der „3R“

Vermeidung:

Eine Vermeidung des beantragten Tierversuchs ist nicht möglich, da die Fragestellung nur in vivo zu beantworten ist.

Da es sich bei diesem Versuch um eine eventuelle Bewältigung der COVID-19 Problematik handelt, kann der Tierversuch nicht vermieden werden und muss unbedingt durchgeführt werden, um optimalerweise so rasch als möglich Notfallpatienten intensivmedizinisch betreuen zu können.

Verminderung:

Die Versuche erfolgen mit der kleinstmöglichen Versuchsgruppe, mit welcher es möglich ist, trotzdem aussagekräftige Daten zu erhalten.

Es geht hier nur darum, eine Aussage zu treffen, ob das entwickelte Beatmungsgerät funktionsfähig ist und ob es im lebenden Organismus angewandt werden kann.

***Verfeinerung*:**

Während der Eingewöhnungszeit der Tiere von 7-14 Tagen wird neben standardmäßiger fachkundiger Betreuung durch geschultes Tierpflegepersonal eine Bereicherung („enrichment“) in Form von Bällen, Gummiringen, Stroh, etc. zur Verfügung gestellt. Auch werden die Tiere durch vermehrten Kontakt an die TierpflegerInnen gewöhnt, um den Stress der Tiere weiter zu reduzieren. Die Tiere werden während des gesamten Versuchszeitraums engmaschig überwacht und routinemäßig von Tierärzten auf ihren Gesundheitszustand kontrolliert. Die Tiere werden nicht für den Versuch angekauft, sondern werden von einer anderen Forschungsgruppe zur Verfügung gestellt. Das bedeutet, dass die Eingewöhnungszeit trotz der Dringlichkeit des Experiments gegeben ist.

Beschreibung der Unterbringungs-, Haltungs- und Pflegebedingungen

Die Versuchstiere werden an der Medizinischen Universität Graz in der Abteilung für Biomedizinische Forschung (Hahnhof) unter Standartbedingungen untergebracht und gehalten. Die Tiere haben dort eine Eingewöhnungszeit von mind. 7-14 Tagen, um sich an die neue Umgebung zu gewöhnen. In dieser Zeit werden die Tiere vom zuständigen Tierpflegepersonal gepflegt und vom Tierärzteteam routinemäßig auf ihren Gesundheitszustand kontrolliert.

Verminderung, Vermeidung und Linderung jeglichen Leidens von der Geburt bis zum Tod

Die männlichen, erwachsenen Schweine werden etwa 7-14 Tage vor Versuchsbeginn (Operation) an die Abteilung für Biomedizinische Forschung gebracht und bis zum Versuch dort gehalten (*siehe Punkt g*).

Sollte es vor dem Versuch wider Erwarten zu unvorhergesehenen Notfällen (nicht therapierbare Schmerzen, Gewichtsverlust, Appetitlosigkeit und/oder Lethargie) kommen, entscheidet der verantwortliche Tierarzt (§ 16 Abs. 2 Z 3 TVG 2012) über das weitere Vorgehen und leitet, falls nötig, die fachgerechte Euthanasie des Tieres ein. Dies geschieht in einem separaten Raum, um zusätzliche Stressauslösung bei den anderen Tieren zu vermeiden.

Vermeidung einer nicht gerechtfertigten doppelten Durchführung von Tierversuchen

Nicht zutreffend