RESCIUS_DMP

DMP TITLE

ADMIN DETAILS

Project Name: RESCIUS_DMP - DMP title
Project Identifier: C3/21/074
Principal Investigator / Researcher: Marc Sabbe
Project Data Contact: Dr. Michiel Stiers
Description: Introduction and background During the COVID-19 pandemic many healthcare providers and healthcare systems were strained to their limits. Even the well-established Belgian healthcare system was challenged, where 17% of the hospitals faced a ventilator surge capacity problem during the first COVID-19 wave. The shortage of ventilators forced physicians to decide which patients would get a ventilator and thus a survival chance. Since the number of available ventilators was a serious bottleneck, a worldwide race started to solve the ventilator surge capacity problem. (REF) The known concept of splitted ventilation or shared ventilation, where two patients share the same ventilator via a splitted ventilation circuit, was proposed as one of the possible solutions. The set-up is simple: by splitting a ventilator circuit with a y-piece, two patients can be ventilated using only one ventilator. The term shared ventilation is preferred over splitted ventilation, since unlike the simplicity of the set-up, the procedure of shared ventilation is challenging. (REF) Simply connecting patients in parallel to a ventilator without considering their individual ventilation requirements has potentially disastrous consequences, as it can cause ventilator induced lung injury (VILI).(REF) Therefore, patients need to be paired according to their ventilation requirements when ventilator sharing is initiated. However, it is difficult to find within one hospital two suited patients with an equal body constitution and lung pathology severity. Moreover, it is highly unlikely that the initially well-matched patients will remain so throughout the course of their disease. To tackle the problem of pairing and to facilitate lung protective ventilation, Stiers et al. founded the concept of Individualized Shared Ventilation (ISV). The modified ventilator circuit, ISV-circuit, allows for individualization of tidal volumes by using a flow restrictor, adding PEEP, and adjusting oxygen fraction. (REF) These crucial ventilation parameters are the cornerstone of lung protective ventilation and the proper management of different patients with an evolving disease severity. (REF) Nevertheless, the individualization of the ventilation volumes was still difficult, due to a very short regulation interval of the tidal volumes with the existing diaphragm valve. (REF) To overcome this problem, we aim to develop a 3D-printed flow restrictor that allows precise and predictable titration of tidal volumes. Shared Ventilation was already an existing domain and regained interest due to the COVID-19 pandemic, however, the concept of ISV is novel, and our research group was at the roots with a pioneering proof of concept. COVID-19 clarified that ventilator surge capacity is a very actual problem. In addition, many other situations with an increasing incidence, such as terrorist attacks, casualties in military operations and disaster situations of any kind, can result in a ventilator surge capacity problem. Although this is often

temporary in high-income countries, in low-income countries resources are scarce on a daily basis. At this moment, there is no certified ventilator circuit available that allows for ISV, neither there is a profound scientific evaluation of ISV carried out. This results in an ongoing discussion on this topic concerning: the individualization per patient, safety and monitoring, indications, and the ethical aspects. The RESCIUS-project has the aim to develop a validated ISV-circuit, with a 3D-printed flow restrictor, conform a medical IIb device and a clinical protocol enabling the physician to safely use the ISV-technology clinically. ISV will be a daily game changer in developing countries and a fire-extinguisher on the wall for the Western World. ? General hypothesis and specific aims of the project The overall hypothesis of this research project is that it is feasible and safe to individualize tidal volumes, PEEP and oxygen fraction with the ISV-circuit and newly developed 3D-printed flow restrictor in vitro and that ISV can be used safely in combination with our ISV-protocol in a large animal model. The RESCIUS-project scientifically aims to: 1) Design and develop a 3D-printed flow restrictor 2) Verification and validation of the 3D-printed flow restrictor in vitro and in vivo 3) Investigate the feasibility, safety, and performance of ISV in vitro and in vivo 4) develop a clinical protocol. We will use the following outcome parameters: 1) accurate delivery of individualized tidal volumes, PEEP, and FiO2% according to ventilator settings, 2) precise in bench interaction between ventilator settings and ISV-circuit, 3) in vivo interaction between ISV-circuit and animal model (ventilation and oxygenation, VILI and hemodynamics). Research methodology Two distinct consecutive studies are planned to achieve the proposed research objectives divided into 4 work packages: an in vitro bench study and an in vivo study with a large animal model. We will use a Dräger Savina 300 ICU-ventilator dedicated to the project. Data collection in vitro is provided by the Citrix H5 and in vivo by the FluxMed GrE. These devices are high-end ISO-certified monitors and will not be part of the validated ISV-circuit. Bench study with artificial lungs The Citrix H5 registers all the relevant ventilation parameters every 20ms, for at least 30 breath cycles to be statistically significant. Data will be synchronized by LabView and analyzed using MATLAB software. The artificial lungs (IMT, Smart2000) can simulate different lung pathologies by adjusting the airway resistance and lung compliance. In vivo study with a large animal model Domestic pigs will be used, ethical approval will be filed after completion of WP 1. ARDS will be induced by a 2-hit model following our in-house ARDS-protocol and will give a stable mechanical animal model with different levels of lung injury. Data collection will be done using the FluxMed GrE, monitoring vital parameters, arterial blood gas analyses, lung imaging and biomarkers after bronchial lavage. We estimate, based on previous experiment within the lab, that we will need a maximum of 36 domestic pigs with a worst-case ARDS induced mortality of 50%. Power calculation for the protocol development can be done after WP2. • Work package 1 (WP 1): Optimization of the ISV-circuit Goal: to develop a 3D-printed flow restrictor conform the intended use as a medical IIb device and design inputs. This R&D and bench testing will be performed in collaboration with the research laboratory of prof. ir. Benoît Marinus (RMA). Deliverables: 1) Prototype of the 3D-printed flow-restrictor 2) Bench testing with design freeze of the 3D-printed flow restrictor • Work package 2 (WP 2): Flow restrictor verification and validation. Goal: to verify and validate the flow restrictor against the intended use, conform regulatory requirements of a medical IIb device. Deliverable: 1) Verification and validation process in vitro and in vivo, conform medical IIb device. 2) Final 3D-printed flow restrictor, printed by external partner, Materialise. • Work package 3 (WP 3): ISV validation and pre-clinical protocol development Goals: 1) Individualize tidal volumes, PEEP, and oxygen with our optimized ISV-circuit in bench. 2) Define a pre-clinical ISV-protocol that can be

used to manage healthy lungs in bench. 3) Define a clinical protocol for different types of lung injury in bench. Deliverables: 1) ISV-matrix describing the interrelationship between ventilator in pressure-controlled mode, the ISV-circuit, and the test lungs. 2) Pre-clinical protocol enabling the testing of different clinical situations in bench for the management of various types of lung injury. 3) Clinical protocol V1.0 based on the pre-clinical protocol tests, ready for in vivo transition. • Work package 4 (WP 4): In vivo transition and clinical protocol validation. Goals: 1) Individualize tidal volumes, PEEP, and oxygen with our optimized ISV-circuit in a large animal model and obtain stable ventilation parameters for twelve hours of ventilation. 2) Indicate the severity of ARDS (mild, moderate, and severe) our ISV-protocol can manage. Deliverable: a clinical protocol V2.0 ready for first in human transition, stating the indications, the limitations and how to set the ventilator and the ISV-circuit to manage different patients. Challenges and fallback options: As our research group already completed an in vitro and in vivo experiment and developed a proof of concept, we have an enormous expertise advantage. The transition from in vitro bench to an in vivo large animal model is a critical step within the project. To minimize the risk of animal mortality we will work with an increasing level of ARDS severity and quantify the level of ARDS the ISV technology can manage.
Institution: KU Leuven

1. GENERAL INFORMATION

Name of the project lead (PI)
Prof. dr. Marc Sabbe

Internal Funds Project number & title
IOF C3: C3/21/074
RESCIUS-project:
Responding to the ventilator surge capacity problem raised during the COVID-19 crisis by designing Individualized Shared Ventilation

2. DATA DESCRIPTION

2.1. Will you generate/collect new data and/or make use of existing data?

- Generate new data

2.2. What data will you collect, generate or reuse? Describe the origin, type and format of the data (per dataset) and its (estimated) volume. This may be easiest in a numbered list or table and per objective of the project.

In vitro			
Type of data	Format	Volume	How

			created
Ventilation parameters	.csv	500 GB	Citrix H5
Metadata	.csv	150 GB	Google forms
In vivo			
Type of data	Format	Volume	How created
Ventilation parameters	.csv	100 GB	FluxMed
Metadata	.csv	100 GB	Google forms
Animal in vivo parameters	.csv	75 GB	FluxMed, arterial blood gas analysis.

3. ETHICAL AND LEGAL ISSUES

3.1. Will you use personal data? If so, shortly describe the kind of personal data you will use. Add the reference to the file in KU Leuven's Record of Processing Activities. Be aware that registering the fact that you process personal data is a legal obligation.

Not applicable.

3.2. Are there any ethical issues concerning the creation and/or use of the data (e.g. experiments on humans or animals, dual use)? If so, add the reference to the formal approval by the relevant ethical review committee(s).

The project is in cooperation with the Royal Military Academy and there is a dual-use aspect being for humanitarian purposes in disaster situations. This has already been reported through the LRD colleagues and is being looked into further by them.

The in vitro trials do not require any applications to the ethics committee. As soon as these in vitro tests are completed, we can switch to in vivo and these applications will be added to the DMP.

3.3. Does your research possibly result in research data with potential for tech transfer and valorisation? Will IP restrictions be claimed for the data you created? If so, for what data and which restrictions will be asserted?

The RESCIUS-project benefits from C3 funding and is by definition focused on valorisation. On the one hand, there is an optimisation of the ISV circuit with the development of the flow modulator in cooperation with the RMA. On the other hand, there is the development of the clinical protocol, which will increase clinical uptake and utilisation of the ISV technology.

The valorisation component is monitored in close cooperation with LRD and our consultants Qserve and InnovHealth. The research team is also following an MBA bootcamp at the Flanders Business School to write a business proposition.

No results are published without the express consent of LRD after a review process. If it is decided, as described above, to make the data publicly available, we will make use of the Research Data Repository (RDR) from KU Leuven.

The flow modulator is currently under patent evaluation.

As soon as there is clarity in the business strategy and the valorisation track, we strive to make the database as publicly accessible as possible, without prejudice to the valorisation track.

3.4. Do existing 3rd party agreements restrict dissemination or exploitation of the data you (re)use? If so, to what data do they relate and what restrictions regarding reuse and sharing are in place?

The RESCIUS-project is an interdisciplinary and interuniversity collaboration in which KU Leuven, the research unit of emergency medicine, has the lead.

In the event that an additional party joins the RESCIUS group as part of the valorisation process, this will always be covered by the above-mentioned approach. All other parties will be appointed as subcontractors and will not be able to prevent the RESCIUS group from data sharing or publication, once it has decided to do so.

4. DOCUMENTATION AND METADATA

4.1. What documentation will be provided to enable understanding and reuse of the data collected/generated in this project?

- ISV-matrix
- Ventilation parameters
- Measured parameters: flow and airway pressure
- Calculated parameters: VT, Pplat, I:E, MV, PEEP, PIP, Ti, Cdyn
- Curves: Volume, Pressure, Flow-Time curves
- Measured parameters: flow and airway pressure, esophageal pressure and oxygen saturation level in blood.
- Calculated parameters: VT, RR, RSBI, Pplat, I:E, MV, NIP, PEEP, PEF, PIF, PIP, PEP, Te, Ti, VTi, VTe, Cdyn, Cstat, MAP, Raw, Ti/Tot,

- Curves: Flow-Volume, Pressure-Volume, Pressure-Time, Volume-Time, Flow-Time, Esophageal pressure-Time, Esophageal Pressure-Volume, Transpulmonary pressure
- Animal in vivo parameters

- ISV-matrix
- Ventilation parameters
- Measured parameters: flow and airway pressure
- Calculated parameters: VT, Pplat, I:E, MV, PEEP, PIP, Ti, Cdyn
- Curves: Volume, Pressure, Flow-Time curves
- Measured parameters: flow and airway pressure, esophageal pressure and oxygen saturation level in blood.
- Calculated parameters: VT, RR, RSBI, Pplat, I:E, MV, NIP, PEEP, PEF, PIF, PIP, PEP, Te, Ti, VTi, VTe, Cdyn, Cstat, MAP, Raw, Ti/Tot,
- Curves: Flow-Volume, Pressure-Volume, Pressure-Time, Volume-Time, Flow-Time, Esophageal pressure-Time, Esophageal Pressure-Volume, Transpulmonary pressure
- Animal in vivo parameters

The ventilation parameters are collected via the Citrix H5 in the bench set-up and via the FluxMed device in the animal studies.

We will measure and register the following ventilation parameters at a sampling rate of 256 samples per seconde via the CitrixH5 with subsequent data collection via LabVIEW.

- ISV-matrix
- Ventilation parameters
- Measured parameters: flow and airway pressure
- Calculated parameters: VT, Pplat, I:E, MV, PEEP, PIP, Ti, Cdyn
- Curves: Volume, Pressure, Flow-Time curves
- Measured parameters: flow and airway pressure, esophageal pressure and oxygen saturation level in blood.
- Calculated parameters: VT, RR, RSBI, Pplat, I:E, MV, NIP, PEEP, PEF, PIF, PIP, PEP, Te, Ti, VTi, VTe, Cdyn, Cstat, MAP, Raw, Ti/Tot,
- Curves: Flow-Volume, Pressure-Volume, Pressure-Time, Volume-Time, Flow-Time, Esophageal pressure-Time, Esophageal Pressure-Volume, Transpulmonary pressure
- Animal in vivo parameters

We will measure and register the following ventilation parameters at a sampling rate of 256 samples per seconde via the FluxMed GrE with subsequent data collection via LabVIEW.

- ISV-matrix
- Ventilation parameters
- Measured parameters: flow and airway pressure
- Calculated parameters: VT, Pplat, I:E, MV, PEEP, PIP, Ti, Cdyn
- Curves: Volume, Pressure, Flow-Time curves

- Measured parameters: flow and airway pressure, esophageal pressure and oxygen saturation level in blood.
- Calculated parameters: VT, RR, RSBI, Pplat, I:E, MV, NIP, PEEP, PEF, PIF, PIP, PEP, Te, Ti, VTi, VTe, Cdyn, Cstat, MAP, Raw, Ti/Tot,
- Curves: Flow-Volume, Pressure-Volume, Pressure-Time, Volume-Time, Flow-Time, Esophageal pressure-Time, Esophageal Pressure-Volume, Transpulmonary pressure
- Animal in vivo parameters
- ISV-matrix
- Ventilation parameters
- Measured parameters: flow and airway pressure
- Calculated parameters: VT, Pplat, I:E, MV, PEEP, PIP, Ti, Cdyn
- Curves: Volume, Pressure, Flow-Time curves
- Measured parameters: flow and airway pressure, esophageal pressure and oxygen saturation level in blood.
- Calculated parameters: VT, RR, RSBI, Pplat, I:E, MV, NIP, PEEP, PEF, PIF, PIP, PEP, Te, Ti, VTi, VTe, Cdyn, Cstat, MAP, Raw, Ti/Tot,
- Curves: Flow-Volume, Pressure-Volume, Pressure-Time, Volume-Time, Flow-Time, Esophageal pressure-Time, Esophageal Pressure-Volume, Transpulmonary pressure
- Animal in vivo parameters

The in vivo animal parameters are measured via the clinical monitoring system from the animal lab and the FluxMed device, the data is synchronized via LabVIEW and stored in the ISV-matrix.
We will measure temperature, invasive blood pressure, central venous pressure and heart rate via the clinical monitoring system. The invasive blood pressure measurement will be used to perform blood gas analyses, the result of which will be printed out and then scanned and linked to the database.
The capnography and O saturation will be measured via the FluxMed device and will be processed like the other parameters.

4.2. Will a metadata standard be used? If so, describe in detail which standard will be used. If not, state in detail which metadata will be created to make the data easy/easier to find and reuse.

5. DATA STORAGE AND BACKUP DURING THE PROJECT

5.1. Where will the data be stored?

The time-stamped master copy of the data will be kept on the One Drive account in the safe KU Leuven environment. Copies can be made and kept on personal devices.
The planned 2 TB of One Drive space will be enough to store the data.

5.2. How will the data be backed up?

The data will be stored on the university's central servers with automatic daily back-up procedures.

5.3. Is there currently sufficient storage & backup capacity during the project? If yes, specify concisely. If no or insufficient storage or backup capacities are available, then explain how this will be taken care of.
The planned 2 TB of One Drive space will be enough to store the data.

5.4. What are the expected costs for data storage and backup during the project? How will these costs be covered?
The planned 2 TB of One Drive space will be enough to store the data.

5.5. Data security: how will you ensure that the data are securely stored and not accessed or modified by unauthorized persons?
The RESCIUS project does not work with personal data. The data will be stored and kept in the secure environment of the University One Drive account.

6. DATA PRESERVATION AFTER THE END OF THE PROJECT

6.1. Which data will be retained for the expected 10 year period after the end of the project? If only a selection of the data can/will be preserved, clearly state why this is the case (legal or contractual restrictions, physical preservation issues, ...).
The dataset and the ISV-matrix will be retained for at least 10 years. The constructed ISV matrix can also be useful for experimental research by the colleagues of Leuven.AI.

6.2. Where will these data be archived (= stored for the long term)?
The data will be stored on the university's central servers (with automatic back-up procedures) for at least 10 years, conform the KU Leuven RDM policy.

6.3. What are the expected costs for data preservation during these 10 years? How will the costs be covered?
The data of the RESCIUS project will not exceed the planned space of 2 TB.

7. DATA SHARING AND RE-USE

7.1. Are there any factors restricting or preventing the sharing of (some of) the data (e.g. as defined in an agreement with a 3rd party, legal restrictions or because of IP potential)?
In function of the valorisation process to be followed, certain data will probably not be published, see above.

7.2. Which data will be made available after the end of the project?
In function of the valorisation process to be followed, certain data will probably not be published, see above.

7.3. Where/how will the data be made available for reuse?

In function of the valorisation process to be followed, certain data will probably not be published, see above.

Preferentially, if the valorisation path allows it, we will ensure that low-income countries will have easy access to the data.

7.4. When will the data be made available?

- After an embargo period. Specify the length of the embargo and why this is necessary

In function of the valorisation process to be followed.

7.5. Who will be able to access the data and under what conditions?

In function of the valorisation process to be followed.

7.6. What are the expected costs for data sharing? How will these costs be covered?

In function of the valorisation process to be followed.

8. RESPONSIBILITIES

8.1. Who will be responsible for the data documentation & metadata?

Michiel Stiers, who is funded by the C3, is a PhD researcher and also a co-founder of the ISV technology.

8.2. Who will be responsible for data storage & back up during the project?

Michiel Stiers, who is funded by the C3, is a PhD researcher and also a co-founder of the ISV technology.

8.3. Who will be responsible for ensuring data preservation and sharing?

Michiel Stiers, who is funded by the C3, is a PhD researcher and also a co-founder of the ISV technology.

8.4. Who bears the end responsibility for updating & implementing this DMP?

The end responsibility for updating and implementing the DMP is with the supervisor (promotor), prof.dr. Marc Sabbe.