The Efficacy of Diaphragmatic Contract-and-Release in the Physical Therapy Management of Postoperative Diaphragmatic Paresis Following Open-Heart Surgery.
COREDIA

INTERVENTIONAL RESEARCH PROTOCOL
WITH MINIMAL RISKS AND LIMITATIONS

GENERAL INFORMATION

PROTOCOL REFERENCES

Protocol code number assigned by the sponsor: 2021/01
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PROTOCOL SIGNATURE PAGE

Study Title: Efficacy of Diaphragmatic Contract-Relaxation in the Physical Therapy Management of Postoperative Diaphragmatic Paresis Following Open-Heart Surgery.
Protocol code: 2021/01
Version: V2.0 dated 09/29/2021

This protocol was read and approved on the date noted below.
The parties agree to conduct the research in accordance with the protocol, good clinical practices, and applicable laws and regulations.

FOR THE SPONSOR

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President

Date: _ _ / _ _ / _ _ _ _

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PRINCIPAL INVESTIGATOR

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Date: _ _ / _ _ / _ _ _ _

Signature:

TABLE OF CONTENTS

1. ABBREVIATIONS

AFE: Acceleration of Expiratory Flow
ANSM: French National Agency for Medicines and Health Products Safety
ARC: Clinical Research Associate
GCP: Good Clinical Practice
COPD: Chronic Obstructive Pulmonary Disease
ECC: Extracorporeal Circulation
CMC: Medical-Surgical Center
CNIL: National Commission for Information Technology and Civil Liberties
CPAP: Continuous Positive Airway Pressure
CPP: Committee for the Protection of Persons
CR: Contract-Relax
eCRF: Electronic Case Report Form
AE: Adverse Event
EN: Numerical Scale
IEM: Maximum Inhalation-Exhalation
BMI: Body Mass Index
ITT: Intent to Treat
RM: Reference Methodology
PEP: Positive End-Expiratory Pressure
GDPR: General Data Protection Regulation
CT: Clinical Research Technician
TM: Time-Movement
CCU: Continuous Care Unit
NIV: Non-Invasive Ventilation

2. SCIENTIFIC RATIONALE AND GENERAL DESCRIPTION OF THE RESEARCH

2.1. Study Context

Open-heart surgery is a traumatic procedure for the body. Postoperative respiratory complications can worsen the patient's prognosis. Diaphragmatic dysfunction accounts for between 2% and 15% of these complications [1,2]. Diaphragmatic paresis is one such dysfunction. Injury to the phrenic nerve or the harvesting of a mammary artery leading to diaphragmatic devascularization during surgery may be causes of this dysfunction [3, 4]. It alters ventilatory mechanics and causes acute respiratory distress, often requiring the initiation of mechanical ventilation. This dysfunction can be diagnosed by thoracic ultrasound to assess the range of diaphragmatic movement [5]. Paresis is considered present when, after a deep breath, the range of diaphragmatic movement is less than 25 mm for at least one of the two hemidiaphragms [6]. This dysfunction is most often transient in the postoperative period [7], but it can also lead to a worsened prognosis for a patient.
Contract-Relax (CR) is a physical therapy technique applicable to any muscle, enabling muscle strengthening, neuromotor stimulation, and increased joint range of motion [8, 9, 10] .
To date, the post-cardiac surgery respiratory physical therapy protocol is the same for patients with or without paresis. Furthermore, CR of the diaphragm is not part of this "standard" rehabilitation.

2.2. The objective of the research

The objective of this study is to determine whether the diaphragmatic CR technique, when added to the current management protocol, enables early rehabilitation of patients with diaphragmatic paresis following cardiac surgery.

2.3. Summary of the benefits, if any, and the foreseeable and known risks for research participants

2.3.1. Expected benefits for the patient

The expected benefits include enhanced diaphragmatic function, more effective ventilation, more appropriate treatment, early rehabilitation, and close monitoring.

2.3.2. Predictable and known risks

The only additional risk posed by the study is pain sensitivity during the CR technique. However, this risk is minimized because CR is performed away from the sternotomy site, at the level of the lower ribs. Additionally, during their hospitalization, patients receive regular pain medication. RC is a common physical therapy practice that has already demonstrated its effectiveness in patients. It will be performed by experienced physical therapists accustomed to working in intensive care. The onset of excessive pain during or after the respiratory physical therapy session may lead to the postponement or termination of the session.

2.4. Description of the study population

Patients who have undergone cardiac surgery via sternotomy and present with postoperative diaphragmatic paresis.

3. RESEARCH OBJECTIVES

3.1. Primary objective

To evaluate the effectiveness of adding diaphragmatic CR to the physical therapy regimen for patients with post-cardiac surgery diaphragmatic paresis, as measured by diaphragmatic excursion during maximum inspiration.

3.2. Secondary objectives

1. To evaluate the effect of CR on diaphragmatic excursion at rest.
2. To evaluate the effect of CR on changes in oxygen saturation.
3. To evaluate the effect of CR on the need for noninvasive ventilation.
4. To evaluate the effect of CR on the duration of oxygenation.
5. To evaluate the effect of CR on the incidence of respiratory complications.

6. Assess the effect of CR on the length of stay in the ICU/continuous care unit.
7. Assess the effect of CR on length of hospital stay.
8. Assess the tolerability of the CR technique compared to standard care.

4. OUTCOME MEASURES

4.1. Primary outcome measure

Ratio of diaphragm amplitude measurements at maximum inspiration on Day 3 and Day 5. These measurements are determined by TM-mode ultrasound on Day 3 before the first rehabilitation session of the day ($M1_{max}$) and on Day 5 before the first rehabilitation session of the day ($M2_{max}$).

4.2. Secondary endpoints

1. Ratio of diaphragm amplitude measurements at rest on Day 3 and Day 5. These measurements are determined by TM-mode ultrasound on Day 3 before the first rehabilitation session of the day ($M1_{rest}$) and on Day 5 before the first rehabilitation session of the day ($M2_{rest}$).
2. Recording of the patient's oxygen saturation (SpO2) before and after each physical therapy session on Day 3 and Day 4, then on Day 5 before the first rehabilitation session of the day.
3. Need (Yes/No) and duration of noninvasive ventilation (NIV, Optiflow, CPAP).
4. Time (in hours) to wean from oxygenation (the reference time $t_0$will be the time of postoperative extubation).
5. Recording of respiratory complications (Yes/No): reintubation, pneumonia, atelectasis, bronchoscopy, bronchospasm, pleural effusion, pneumothorax.
6. Number of days in the ICU/continuous care unit.
7. Number of days hospitalized.
8. Patient self-assessment of pain using a Numerical Rating Scale (NRS) ranging from 0 (no pain) to 10 (unbearable pain) after each respiratory physical therapy session on Day 3 and Day 4.

5. SELECTION OF RESEARCH PARTICIPANTS

5.1. Inclusion criteria

- Patients aged 18 years or older,
- Who have undergone cardiac surgery with cardiopulmonary bypass (CPB),
- Presenting with postoperative diaphragmatic paresis (diaphragmatic excursion during maximum inspiration, as determined by transabdominal ultrasound, < 25 mm),
- Having given informed consent to participate in accordance with regulations,
- Covered by social security or eligible for coverage.

5.2. Exclusion criteria

- History of respiratory diseases (COPD, asthma, etc.),
- History of neurological conditions,
- Postoperative cardiac and circulatory complications,
- Pregnant or breastfeeding women,
- Inability to understand,
- Under guardianship, conservatorship, or judicial protection.

5.3. Exclusion criteria

- Occurrence of a cardiac or circulatory complication after enrollment
- Reintubation
- Pneumothorax
- Rib fracture
- Poor thoracic echogenicity

5.4. Recruitment criteria

All patients who have undergone cardiac surgery, present with diaphragmatic paresis, and meet the eligibility criteria will be offered the opportunity to participate in the study. They will be informed by an investigator during the postoperative cardiology consultation following the diagnosis of diaphragmatic paresis.

5.5. Simultaneous participation in another study, exclusion period

Patients may participate in another study concurrently provided that the inclusion and exclusion criteria are met. There is no exclusion period for participants in this study.

6. RESEARCH METHODOLOGY

6.1. Study Type

Single-center, prospective, comparative, randomized, controlled, two-arm, parallel-group, single-blind study (investigators and assessors are blinded to the patient's arm).
The study compares two groups (1:1):

- **"T-" group (control group):** Standard physical therapy management of diaphragmatic paresis by experienced physical therapists dedicated to the care of patients in the post-cardiac surgery intensive care unit.
- **"T+" group (intervention group)**: Standard physical therapy care supplemented with three diaphragmatic Contract-Relax (CR) exercises performed by the same physical therapists as in the control group, who are also trained in the CR technique.

6.2. Study Protocol

Inclusion:

- Information regarding the protocol provided by a cardiologist-intensivist-investigator during the postoperative visit confirming a diagnosis of diaphragmatic paresis.
- Verification of inclusion and exclusion criteria.
- Obtaining consent after a reflection period deemed sufficient by the patient (minimum 2 hours).

Randomization:

Patients will be randomized into 2 groups (1:1):

- Control group "T-": Standard rehabilitation technique.
- Intervention group "T+": Standard rehabilitation technique + 3 CR exercises.

Randomization will be performed electronically via the eCRF.
Randomization stratification is planned based on diaphragmatic involvement (unilateral vs. bilateral).

Procedure:

- **Physical therapy management:**

Physical therapy for diaphragmatic paresis will begin on postoperative day 3 and continue until the end of hospitalization. Care for patients with diaphragmatic paresis will remain unchanged. The only difference will be the addition of 3 CR exercises in the intervention group. The patient will undergo 4 sessions of respiratory physical therapy spread throughout the day in the ICU, followed by 2 sessions in the cardiac surgery ward.

Standard rehabilitation technique ("T-" and "T+" groups):

- AFE (Accelerated Expiratory Flow) at the upper thoracic level.
- PEEP (Positive End-Expiratory Pressure) [11] .
- Coughing and expectoration as needed.

Diaphragmatic Contract-Relax Technique (only "T+" group):

Diaphragmatic CR is performed in a semi-sitting position, with the bed backrest at approximately 45°.
The CR can be broken down into four distinct stages:

- First MIE (Maximal Inhalation-Exhalation) with the physical therapist's hands positioned on the lower ribs and without resistance (Goal: establishing a rhythm).
- Second MIE: Free inhalation, followed by exhalation accompanied by pressure on the patient's lower ribs to bring the diaphragm into internal movement.
- Maximal inhalation against resistance, followed by maximal exhalation with increased pressure.
- Maximal inhalation with dynamic release of resistance (Goal: hyper-extension of the diaphragm) followed by maximal exhalation with resistance to allow for an increase in expiratory flow.

- **Ultrasound measurements:**

Four ultrasound measurements of diaphragmatic amplitude in TM mode will be performed. The $M1_{max}$and $M1_{rest}$measurements will be taken before the very first rehabilitation session on Day 3, followed by the $M2_{max}$and $M2_{rest}$measurements before the first daily rehabilitation session on Day 5.

Ultrasound measurement of diaphragmatic excursion in TM mode:

The measurement is taken on the midclavicular line below the costal margin with the probe oriented at 90° toward the diaphragmatic domes. The goal is to visualize the diaphragm through an acoustic window formed by the liver on the right and the spleen on the left. The diaphragm appears as a hyperechoic line on the screen; the amplitude of movement is therefore assessed using a TM scan. The TM scan is a mode that allows the recording of a structure's movements over time.

Activate the TM mode, then perform:

- A maximum exhalation followed by a maximum inhalation to calculate $M1_{max}$and $M2_{max}$
- A normal exhalation followed by a normal inhalation to calculate $M1_{rest}$and $M2_{rest}$

The range of motion of the diaphragm is measured using the "caliper" tool.

- **Saturation measurement:**

Oxygen saturation SpO_2 will be recorded before and after each respiratory physical therapy session on Days 3 and 4 using the scope, 15 minutes after the last exercise of the session. A final measurement will be taken on Day 5 before the first rehabilitation session of the day.

- **Pain assessment:**

A self-assessment of the pain experienced by the patient will be conducted using a numerical scale at each physical therapy session, in accordance with standard practice. Only data from Day 3 and Day 4 will be collected for the purposes of this study.

Follow-up and end of the study:

Recording of respiratory complications throughout the hospital stay.

The follow-up period ends upon the patient's discharge from the hospital or after a maximum of 30 days.

6.3. Study design

Actions	**Inclusion (postoperative consultation in the ICU)**	**In the ICU/CCU**	**On the ward**
Information	R		
Consent	R		
Verification of eligibility criteria	R		
Randomization	R		
Chest ultrasound		S	S
Respiratory physical therapy		S *(4 times a day)*	S *(twice a day)*

3 CR per physical therapy session		R	R
O_2saturation		S	S
Numerical pain scale		S	S
Complications Registry		S	S

Distinction: Care (C) – Research (R)

6.4. Expected duration of participant involvement, description of the timeline and duration of the study

Enrollment period: 23 months
Duration of participation per patient: Length of hospital stay (maximum 30 days)
Total duration of the study: 24 months

6.5. Subject identification

For the purposes of this study, participants will be identified as follows: upon signing the consent form, the patient will be assigned an alphanumeric "patient identifier" enrollment number. It consists of the center number followed by a sequential enrollment number and the patient's initials (first letter of the last name and first letter of the first name). This unique identifier will be retained for the entire duration of the study.

The principal investigator will create and maintain a list of patients enrolled in the study. This list allows for the unambiguous association of the patient's identity with their enrollment number.

6.6. Description of measures taken to reduce or avoid bias

6.6.1. Patient selection

To avoid any selection bias, this study will be offered to all eligible patients in the ICU following cardiac surgery with CPB who present with diaphragmatic paresis. For eligible patients who are not included, the reason for exclusion will be noted.

6.6.2. Randomization

Randomization (1:1) will be centralized and conducted in random-sized blocks to minimize recruitment bias and ensure comparability between the two groups. The investigator will not know the randomization arm. Randomization will be performed by the physical therapist in charge of the patient after enrollment by logging into the eCRF.
Randomization stratification is planned based on diaphragmatic involvement (unilateral versus bilateral).

6.6.3. Assessment of Endpoints

To minimize assessment bias, the primary outcome measure (thoracic ultrasound) will be performed by an assessor (investigator or qualified person) who is blinded to the patient's arm.

6.6.4. Blinding procedures, measures implemented to maintain blinding, and procedures for unblinding, if necessary t

In this single-blind study, only the physical therapist and the patient will know the randomization arm and may disclose it to the physician if necessary for medical care.

6.7. Description of the rules for permanent or temporary withdrawal of a person's participation in the research, procedures for follow-up of these individuals, and procedures for replacing these subjects, if applicable

Any subject included in the study may decide at any time to withdraw their consent to participate, for any reason, without having to provide explanations or justifications and without this affecting the care they are receiving or will receive. The investigator must indicate in the patient's eCRF the date and, if applicable, the reason for discontinuation of participation in the research. Withdrawal of consent prohibits the use of medical data obtained after the withdrawal of consent. Data already collected regarding the subject may be used, unless the patient objects.

The investigator may temporarily or permanently discontinue a subject's participation in the study for any reason that affects the subject's safety and in the best interests of the patient. Data already collected regarding the subject may be used in the analysis of the study results.

A subject's withdrawal from the study will not affect their usual care.

Once the protocol-specified enrollment target is reached, the investigator must halt recruitment for the study. However, patients who have already signed a consent form may still be included in the study.

7. SAFETY ASSESSMENT

In the context of interventional research involving minimal risk and minimal burden, the medical procedures or strategies that are the subject of the research are part of standard practice and are used in accordance with their indications. Potential adverse events or incidents are therefore those related to the patient's standard care (care-related) and do not require specific reporting by the research manager.

These events must follow the standard reporting procedure established by current regulations and implemented at the facility:

• Adverse effects that may be related to a medication, to be reported to the Regional Pharmacovigilance Center,

• Incidents or potential incidents resulting from the use of a medical device to be reported to the local medical device vigilance liaison,

• Others (reporting of nosocomial infections).

These reports are mandatory for all physicians (or other relevant healthcare professionals), both within the context of this research and outside of it.

In accordance with the provisions of the Public Health Code for a RIPH2, new developments, as defined in paragraph 12 of Article R1123-46, must be reported to the Committee for the Protection of Persons (CPP) in accordance with the procedures described in Article R1123-59 of the same code.

8. STATISTICS

8.1. Description of the planned statistical methods

Analyses will be performed on the intention-to-treat (ITT) population, which is defined as all patients included (regardless of their eligibility criteria) and randomized.

The number and percentage of patients approached, enrolled, randomized, analyzed, withdrawn prematurely, and who completed the entire trial will be provided. A CONSORT diagram will be prepared.

- **Descriptive Analysis**

An initial data analysis will allow for the description of the total population and by group. The normality of the distribution of quantitative variables will be assessed using the Shapiro-Wilk normality test. The following will be determined: 1) for categorical variables, the total and category-specific counts, as well as the corresponding proportions and their confidence intervals; 2) for normally distributed continuous variables, the available count, the mean, and its standard deviation; 3) for non-normally distributed continuous variables, the available count, the median, and the first and last quartile limits.

- **Inferential statistics**

Comparisons between the two randomized groups will be based, for qualitative variables, on the chi-square test or, if the conditions for performing this test are not met, on Fisher's exact test; for quantitative variables, on Student's t-test for Gaussian variables and on the Wilcoxon-Mann-Whitney test for non-Gaussian variables. Censored data (duration) will be represented by Kaplan-Meier survival curves and analyzed using the log-rank test.

Throughout the study, adverse events (AEs) will be monitored (secondary endpoint 6). At the end of the study, AEs will be grouped, and the following derived variables will be calculated: percentage of patients

experiencing an AE, number of AEs per patient, and calculation of odds ratios and their 95% confidence intervals.

A difference will be considered statistically significant when the p-value is less than or equal to 0.05.

- **Exploratory analysis**

If the study statistician or investigators determine that it could help clarify the results obtained, an exploratory phase may be conducted using bivariate tests (correlation coefficients) or multivariate tests (multiple regression, logistic regression, or correspondence analysis) to determine the relationships between the variables. This phase will be the subject of a written description to be appended to the study's statistical analysis plan. In the analysis report, the tests conducted will be clearly identified as post-hoc tests. Consequently, the probabilities obtained will be for guidance only.

8.2. Planned number of participants to be included in the study with statistical justification

Based on the study center's experience, the gain factor for diaphragm amplitude at maximum inspiration between Day 3 and Day 5 with standard respiratory physical therapy is approximately 1.10 ± 0.25. Assuming a gain factor of 1.40 ± 0.25 in the "T+" experimental group, the number of subjects required for the study corresponds to a total sample size of 26 patients, or 13 per group, for 80% power with a 5% Type I error rate. Taking into account the attrition rate (patients with post-cardiac surgery complications or insufficient echogenicity), the total number of patients will be 30, or 15 patients per group.

8.3. Statistical criteria for study termination

No interim analysis is planned that could lead to the study being discontinued.

8.4. Method for handling missing, unused, or invalid data

No specific method for imputing missing data is planned.

8.5. Principal Investigator

Dr. Pierre Squara, CMC Ambroise Paré

9. DATA MANAGEMENT

9.1. Data entry

The information required by the protocol will be recorded in a standardized electronic case report form (eCRF), with data hosted on a secure central server at the CMC Ambroise Paré. Data will be collected as it is obtained by the investigator and/or CMC Ambroise Paré staff designated by the investigator. Missing data must be coded. An investigator will validate the eCRF with an electronic signature to certify the authenticity of the collected data.

The eCRF used will comply with current regulations imposed by the CNIL (MR001). Access to the eCRF will be limited to authorized individuals (sponsor, investigators, clinical research associates, clinical trial technicians, etc.), and permissions (viewing, data entry, access to specific CRF pages, access to patients at a single site or all patients, etc.) may be granted based on their role in the study and their site. Access to the eCRF will be protected by a personalized username and password for each user. Logins to the eCRF will be recorded in the audit trail.

9.2. Description of data to be collected

Preoperative data:

- Demographic data: Date of birth (month and year), gender, height, weight, BMI, overweight status.
- Medical and surgical history and risk factors.

Intraoperative data:

- Data regarding the procedure: date of surgery, type of surgery, number of bypass grafts, duration of CPB (in minutes), duration of clamping (in minutes), intraoperative complications.

Postoperative data:
- Number and type of Redon drains.
- Data regarding chest ultrasounds: diaphragmatic excursion (TM mode) during maximum inspiration and at rest (in cm) on Day 3 and Day 5.
- Oxygen saturation ($_{SpO_2}$) before and after each respiratory physical therapy session on Day 3 and Day 4, and on Day 5 before the first rehabilitation session.
- Patient-reported pain assessment (EN) after each respiratory physical therapy session on Day 3 and Day 4.
- Duration of intubation (in hours), duration of non-invasive ventilation (in hours).
- Time to wean from oxygen: time of extubation, time of weaning from oxygen.
- Postoperative respiratory complications (Yes/No): reintubation, pneumonia, atelectasis, bronchoscopy, bronchospasm, pleural effusion, pneumothorax.
- Death.
- Length of stay in the ICU/CCU (in days), length of hospital stay (in days)
- Laboratory tests: Troponin, CPK, blood gases (pH, paO2, paCO2, HCO3-)

9.3. Identification of data to be collected directly in the eCRF and considered as source data

NA

9.4. Access rights to source data and documents

9.4.1. Source documents

Source documents are defined as any original document or item that serves to prove the existence or accuracy of data or facts recorded during the research. They will be retained for 15 years by the healthcare facility where the research was conducted, in accordance with regulations.

9.4.2. Access to data

The sponsor has obtained the consent of all parties involved in the research to ensure direct access to all research sites, source data, source documents, and reports for the purpose of quality control and auditing by the sponsor and/or the competent authorities.

The sponsor will ensure that each person participating in the research has provided written consent for access to and use of their individual data that is strictly necessary for the quality control of the research.

The investigators shall make the documents and individual data strictly necessary for the monitoring, quality control, and audit of the research available to persons authorized by the sponsor in accordance with applicable laws and regulations (Articles L.1121-3 and R.5121-13 of the Public Health Code).

9.4.3. Data Confidentiality

In accordance with the provisions regarding the confidentiality of data to which persons responsible for quality control in research involving human subjects have access (Article L.1121-3 of the Public Health Code), and in accordance with the provisions regarding the confidentiality of information concerning, in particular, the nature of investigational drugs, trials, the participants, and the results obtained (Article R. 5121-13 of the Public Health Code), individuals with direct access to such data shall take all necessary precautions to ensure the confidentiality of information regarding the participants, particularly with respect to their identity, as well as the results obtained. Those responsible for quality control, just like the investigators themselves, are bound by professional secrecy (under the conditions defined by Articles 226-13 and 226-14 of the Penal Code).

During the course of the research or upon its completion, the data collected on the participants and transmitted to the sponsor by the investigators (or any other specialized personnel) will be anonymized. Patients will be identified only by an identification number containing the center number, their study entry number, and their initials. These details are recorded in the observation log. The collected data are strictly confidential. They are accessed only by the medical team, persons duly authorized by the study sponsor, and, if necessary, by representatives of the competent health and judicial authorities. The identity of participants will not be disclosed in any report or publication resulting from this study.

9.5. Data Processing and Storage

9.5.1. Data protection

The processing of personal data for this research falls within the scope of Articles 53 through 61 of Law No. 78-17 of January 6, 1978, as amended, relating to information technology, files, and civil liberties; and the General Data Protection Regulation (EU) 2016/679 of the European Parliament and of the Council of April 27, 2016, on the protection of individuals.

In accordance with the requirements of the CNIL (Law on Information Technology, Data Files, and Civil Liberties) and the European General Data Protection Regulation (GDPR), participants in this research will be informed, via the information sheet and the consent form, of the following rights:

- the nature and purpose of the data collected as part of the research, as well as the retention period for such data.
- the possibility of withdrawing from the study at any time and the retention, by the sponsor, of the information collected (unless otherwise indicated by the data subject).
- their rights of access, rectification, objection, restriction, and erasure of the data collected as part of the research. These rights may be exercised at any time during the research either by submitting a request to the physician overseeing the participants in the research (who will contact the sponsor) or by submitting a request to the sponsor's Data Protection Officer.
- the option, in the event of a problem or disagreement, to file a complaint with the CNIL.

The sponsor (through the TEC or the investigators) undertakes to respond to any request for access to data within a maximum of one month. Furthermore, only personnel authorized by the sponsor (investigators, ARC, TEC) and representatives of health authorities may have access to this information.

9.5.2. Data Retention Period

In accordance with the decree of August 11, 2008, establishing the retention period by the sponsor and the investigator for documents and data relating to biomedical research other than that involving medicinal products for human use, upon completion of the research:

- all documents (different versions of the protocol, case report forms, investigator's file, consent forms, correspondence, etc.) in paper form shall be archived at the center and at the sponsor's premises for 15 years.
- Data in electronic format will be retained until the final report is completed or the research is published, and then archived for 15 years.

9.6. Data Ownership

The CMC Ambroise Paré is the owner of the data, and no use or transfer to a third party may be made without its prior written consent.

10. QUALITY CONTROL AND ASSURANCE

10.1. Monitoring Procedures

The sponsor appoints a Clinical Research Associate (CRA) to conduct monitoring visits, who will ensure that:

- the rights, safety, and protection of the individuals participating in the research are upheld,
- the information needed to analyze the primary and secondary objectives is included,
- the reported data are accurate, complete, and consistent with the source documents,
- the study is conducted in accordance with the protocol, the Sponsor's Standard Operating Procedures, Good Clinical Practice (GCP), and applicable laws and regulations.

Quality control of the trial is carried out under the sponsor's responsibility in accordance with its Standard Operating Procedures and in compliance with GCP, the latest revision of the Declaration of Helsinki, and applicable laws and regulations.

The investigator and members of his or her team agree to make themselves available during visits conducted by the ARC.

During these visits, the following items will be reviewed:

- Written informed consent;
- Adherence to the research protocol and the technical procedures defined therein;
- Quality of data recorded in the observation log: accuracy, missing data, consistency of data with "source" documents (medical records, appointment logs, original laboratory results, etc.).

10.2. Audits/Inspections

Quality control of the trial is carried out under the responsibility of the Ambroise Paré Clinical Research Center (CMC). An audit may be conducted at any time by individuals appointed by the sponsor and independent of the research leaders. Except in special cases, the investigator is informed well in advance of the planned audit. The same applies to an inspection conducted by the Competent Authority. The purpose of these procedures is to ensure the quality of the research, the validity of its results, and compliance with applicable laws and regulations. Those who direct and oversee the research agree to comply with the requirements of the sponsor and the Competent Authority regarding an audit or inspection of the research.

11. ETHICAL CONSIDERATIONS

11.1. Statement indicating that the research will be conducted in accordance with the protocol, good clinical practice, and applicable laws and regulations

The protocol complies with the ethical principles established by the 18th World Medical Assembly (Helsinki 1964) and by the amendments established at the 29th (Tokyo 1975), 35th (Venice 1983), 41st (Hong Kong 1989), 48th (Somerset West 1996), 52nd (Edinburgh 2000), 53rd (Washington 2002), 55th (Tokyo) 59th (Seoul), and revised at the 64th th World Medical Assembly (Fortaleza, Brazil, October 2013). It will be conducted in accordance with the ICH guidelines on Good Clinical Practice.

11.2. Procedures for informing and obtaining consent from research participants

No interventional research may be conducted on a person without their free and informed consent, obtained in writing after all relevant information has been provided to them orally and in writing and prior to any procedure specified in the protocol and related to the research.

The research is presented orally to the patient by an investigator. During this visit, patients receive information in understandable terms regarding the study's objectives and constraints, potential risks involved, necessary monitoring and safety measures, their right to refuse to participate in the study, and the possibility of withdrawing at any time without this affecting the care they receive. An information sheet corresponding to the information provided to the patient is given to the patient. After answering any questions the patient may have, and after ensuring that the patient has had sufficient time to reflect, the investigator obtains the patient's consent before enrolling the patient in the study.

A copy of the consent form, dated and signed by the person participating in the research as well as by the investigator, is provided to the person prior to their participation in the research. The investigator retains the original copy of the person's dated and signed consent form.

Changes to the protocol that result in an amendment shall be reflected by corresponding changes in the informed consent form and the information provided verbally to the patient.

11.3. Compensation for Participants

No compensation is provided for patients in this study.

11.4. Registration in the national registry of individuals participating in human research

Registration is not required for this study.

11.5. Legal obligations

11.5.1. Role of the sponsor

The CMC Ambroise Paré is the sponsor of this research and carries out its duties in accordance with Article L.1121.1 of the Public Health Code. The sponsor reserves the right to suspend the research at any time for medical or administrative reasons; except in cases of force majeure, the investigator's opinion on this decision will be obtained and recorded in the trial documentation.

11.5.2. Approval of the Protocol and Amendments

Prior to the start of the study, the protocol, the information sheet, the informed consent form, and any other relevant documents shall be submitted for review to the Institutional Review Board (IRB). Notification of the HPC's favorable opinion will be forwarded to the study sponsor. This document must include a list of the HPC members who were present on the day the opinion was issued, along with their positions and qualifications.
The sponsor shall notify the French National Agency for Medicines and Health Products Safety (ANSM) of the study.
The study may only be initiated after the sponsor has received all documents required from an ethical and regulatory standpoint, and in particular the CPP's favorable opinion.
Any substantial modification to the protocol concerning the study's objectives, design, study population, or significant administrative aspects will require the approval of the coordinating investigator and the sponsor, as well as a favorable opinion from the CPP.

11.5.3. Commitment to Compliance with "Reference Methodology" MR-001

This study falls within the scope of the CNIL's Reference Methodology MR-001 for the following reasons:
- the collection of health data for research purposes
- obtaining the opinion of an Ethics Committee (CPP) before beginning the research
- the use of anonymized data (identification by enrollment number)
- providing information and obtaining individual consent from the participants
- Access to data is restricted to healthcare and research professionals involved in the study under the responsibility of the investigators or the sponsor.

The CMC Ambroise Paré, the study sponsor, has signed a commitment to comply with the "Reference Methodology" MR-001.

Patient data confidentiality will be ensured by using the enrollment number and initials on documents necessary for the research, or by appropriately redacting personally identifiable information from copies of source documents required for research documentation. Only coded data will be accessible to the Sponsor.

The identity of participants will not be disclosed in any report or publication resulting from this study.

In accordance with the Law of March 4, 2004, on patients' rights, and if they express this wish to their investigator, participants in this research may be informed of the study's results once it is completed.

11.5.4. Declaration of the End of the Study

The sponsor declares the end of the trial within 90 days of the trial's completion (the date of the last visit by the last patient) when the research has reached its planned end (planned termination) or within 15 days when the research is terminated prematurely (early termination).

11.5.5. Final research report

The final research report is prepared and signed by the sponsor, the coordinating investigator, and the principal investigator. A summary of the report, drafted in accordance with the Competent Authority's reference template, must be submitted to the Competent Authority and the CPP within one year of the end of the research, corresponding to the end of the last participant's involvement in the study.

12.FUNDING AND INSURANCE

12.1. Study Funding

The costs associated with conducting this research are the responsibility of the sponsor.

12.2. Insurance

The Sponsor shall take out insurance for the entire duration of the research covering its own civil liability as well as that of the investigators responsible for directing and supervising the conduct of the research on behalf of the Insured, and of any other person involved in this research on behalf of the Insured. This insurance policy, in accordance with Article L.1121-10 of the Public Health Code, is taken out with **Lloyd's,** 8/10 rue Lamennais, 75008 Paris, France.

13. PUBLICATION POLICY

The study will be registered on the open-access website (Clinicaltrials.gov) prior to the inclusion of the[first]patient.
This study will be the subject of a final thesis for the state-certified physical therapy degree, as well as publications in the form of presentations and original articles. The order of authorship will be determined by Dr. Philippe Estagnasié (Principal Investigator) and Maxence Burelle (Scientific Director).
The CMC Ambroise Paré must be cited as the research sponsor and as a source of financial support, if applicable.

14. REFERENCES

1) Aksakal, E., Erol, M. K., Gündoğdu, F., & Çinici, O., 2009. An important cause of dyspnea after coronary artery bypass grafting: phrenic nerve paralysis. Turk Kardiyol Dern Ars., 37(2), 132-135.

2) Merino-Ramirez, M. A., Juan, G., Ramon, M., Cortijo, J., Rubio, E., Montero, A., & Morcillo, E. J., 2006. Electrophysiologic evaluation of phrenic nerve and diaphragm function after coronary bypass surgery: prospective study of diabetes and other risk factors. The Journal of Thoracic and Cardiovascular Surgery, 132(3), 530-536.

3) Ricoy, J., Rodríguez-Núñez, N., Álvarez-Dobaño, J. M., Toubes, M. E., Riveiro, V., & Valdés, L., 2019. Diaphragmatic dysfunction. Pulmonology, 25(4), 223-235.

4) Curtis, J. J., Nawarawong, W., Walls, J. T., Schmaltz, A., Boley, T., Madsen, R., & Anderson, S. K., 1989. Elevated hemidiaphragm after cardiac operations: incidence, prognosis, and relationship to the use of topical ice slush. Ann. Thorac. Surg., 48(6), 764-768.

5) Boussuges, A., Brégeon, F., Blanc, P., Gil, J. M., & Poirette, L., 2018. Characteristics of the paralyzed diaphragm studied by M-mode ultrasonography. Clinical Physiology and Functional Imaging, 39(2), 143-149.

6) Lerolle, N., Guérot, E., Dimassi, S., Zegdi, R., Faisy, C., Fagon, J. Y., Diehl, J. L., 2009. Ultrasonographic diagnostic criteria for severe diaphragmatic dysfunction after cardiac surgery. Chest, 135(2), 401–407.

7) Tralhao, A., Cavaleiro, P., Arrigo, M., Lopes, J. P., & Lebrun, M., … & Cholley B., 2020. Early changes in diaphragmatic function evaluated using ultrasound in cardiac surgery patients: a cohort study. Journal of Clinical Monitoring and Computing, 34, 559-566.

8) Viel E., 1985. Implementation and use of the contract-relax maneuver. Ann. Kinésithér., 12(1-2), 59-61.

9) Dufour, M., Colné, P., & Barsi, S., 2020. The Kabat Method: A Technique Worth Discovering. Practical Massage Therapy and Manual Therapy, 1(9).

10) Hindle, K. B., Whitcomb, T. J., Briggs, W. O., & Hong, J., 2012. Proprioceptive neuromuscular facilitation (PNF): Its mechanisms and effects on range of motion and muscular function. Journal of Human Kinetics, 31(March), 105-113.

11) Olsé, M. F., Lannefors, L., & Westerdahl, E., 2015. Positive expiratory pressure - Common clinical applications and physiological effects. Respiratory Medicine, 109(3), 297-307.