**Title**

# Effects on muscle strength after blood flow restriction resistance exercise (BFR-RE) in early in-patient rehabilitation of chronic obstructive pulmonary disease acute exacerbation (COPDAE), a single blinded, randomized controlled study

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## Introduction

Chronic obstructive pulmonary disease (COPD) is a prevalent disease around the world particularly in developed countries. COPD often has frequent admissions for acute exacerbation which increase the risks of mortality. Muscular dysfunction is one of extra-pulmonary morbidity of COPD (Jaitovich, 2018).

Reduced muscle strength is associated with increased mortality in moderate to severe COPD (Swallow, 2007). However, at least 70% of 1-repetiative maximum of weight is needed to achieve muscle growth in resistance training (ACSM, 2009). This might not be feasible particularly to the patients admitted for COPD acute exacerbation (COPDAE).

Blood flow restriction resistance training (BFR-RE), Kaatsu training, was developed by Dr. Yoshiaki Sato more than 40 years ago (Sato, 2005). The basic physiological mechanism of BFR-RE to increase muscle mass and strength is by metabolite accumulation, e.g. lactate. The metabolites lead to increase of serum growth hormone (GH) which promotes the collagen synthesis for tissue repair and recovery. The surge of GH leads to release of insulin-like growth factor (IGF-1) which is a protein related to muscle growth. IGF-1 contributes the muscle gain, which is a muscular anabolic process, by enhancing satellite cell proliferation. (Manini, 2009)

Concerning growth of muscle mass, BFR-RE leads to a comparable increase when compared to high load resistance exercise (HL-RE) (Lixandrão, 2017). However, concerning increase of muscle strength, BFR-RE is less effective in gain than that in HL-RE but more effective than that in low load resistance exercise (LL-RE) alone. Therefore, BFR-RE can be considered when HL-RE is not advisable. (e.g. frail elderly, post-operative rehabilitation, etc.)

BFR-RE is well studied among healthy adult (Lixandrão, 2017), elderly (Centner, 2019) and musculoskeletal rehabilitation patients (Hughes, 2017), but not in COPDAE patients.
Standardized isotonic knee extension resistance training on alternate day with a load of 15-30% of 1-repetition maximum (1-RM) with “BFR-device” will be compared with the control arm having same set of training without the device in COPDAE patient during 2-week of inpatient stay.

Though there no adverse risk responses were reported in published

randomized controlled trials in clinical populations in the literature, there are some expected transient perceptual type responses, e.g. dizziness, limb numbness, perceived exertion, delayed onset muscle soreness. There are no significant risks of complications if BFR-RE is prescribed by certified trainers who have knowledge of appropriate protocols and contraindications to the use of occlusive stimuli. (Brandner, 2018)

The effect on muscle strength in COPDAE inpatients, which is not well studied in the literature, will be the primary outcome of this study. The effect on mobility functions, systemic muscle strength reflected by hand grip strength, health related quality of life and unplanned readmission rate within 1 month of discharge for COPDAE will be evaluated as secondary outcomes. Since BFR-RE is newly introduced to Haven of Hope Hospital and not widely used in Hospital Authority, acceptability and feasibility of this training will be explored as secondary outcomes.

**Subjects**

Patients with COPD acute exacerbation (COPDAE) will be recruited to find out the effect of blood flow restriction resistance exercise (BFR-RE). There will be a control group without BFR-RE for comparison. Principal investigator will screen the medical fitness of the subjects before recruiting to the study.

**Inclusion criteria**

1. COPD acute exacerbation (COPDAE) as the primary diagnosis for hospitalization or transfer to pulmonary wards of the Haven of Hope Hospital
2. Able to walk under supervision
3. Understand instruction in Cantonese and can give informed consent.

**Exclusive criteria** (Hick, 2013)

Subjects will be excluded if they have any of the following conditions:

1. Concomitant acute cardiac event
2. Severe hypertension (BP > 180/100)
7. History of lymphectomies
8. Extremities with dialysis access
9. Vascular grafting

3. History of venous thromboembolism
4. History of peripheral vascular disease
5. Absence of posterior tibial or dorsalis pedal pulse
6. History of revascularization of the extremity
10. Current extremity infection
11. Active malignancy*
12. Open fracture / soft tissue injuries
13. Amputation to the lower extremity
14. Expected hospitalization less than 2 weeks on admission
15. Medications known to increase clotting risks
16. Isolation / Contact precaution requirement (e.g. MRSA status, CD toxin +ve status, etc.)

*Active malignancy (Kearon,2016) is defined as follow:

(1) not received potentially curative treatment; or

(2) there is evidence that the treatment has not been curative (e.g. recurrent or progressive disease); or

- A treated cancer is cured should be made by an experienced clinician, with the decision requiring a disease-free interval of follow-up.

(3) treatment is ongoing.

**Standardized 2-week in-patient rehabilitation**

- Breathing exercises,
- Bronchial hygiene,
- Health education,
- Bike exercise for 20 minutes (excluding history of hip operation done)
- Walking exercise at least 50m or as tolerated
- Activity of daily living training by Occupational Therapists
- Dietitian referral if needed, to ensure adequate nutrient intake.

**A standardized resistance training (Patterson, 2019)**

- Exercise: Isotonic knee extension
- Sessions per week: 6 (Except Sunday and public holiday)
- Duration of intervention: 2 weeks
- Total number of sessions during hospitalization: 12 sessions
- Sets per session: 4 (Total Repetitions: 75reps in total across 4 sets)
- Rest between sets: 30s
- Execution speed: 1-2s
- Load: 15-30% of 1 repetition maximum(1-RM) (Loenneke, 2012)

- Involvement of limb per session: Alternate limb training on alternate day
- Execution: until planned rep scheme is completed or contraction failure
- Remarks: If at any time the patient becomes dizzy, severe discomfort (e.g. pain, numbness), training will be stopped.

**The BFR-RE intervention group (Patterson, 2019)**

The participants will have the above-mentioned resistance training with "BFR-device" with details as follows:

- Cuff size: medium
- Restriction time: 5- 10 mins (stop after finishing 4 sets of training or terminating by Physiotherapists)
- Applied location: alternate quadriceps in consecutive day
- Applied pressure: 80% limb occlusion pressure (LOP)

**Control group**

Same standardized 2-week in-patient rehabilitation and same amount of the above-mentioned resistance training without the "BFR device".

**Determination of maximal voluntary isometric contraction (MVIC) (Hul, 2004)**

- Maximal voluntary isometric contraction (MVIC) is the simplest way to measure the force-producing capabilities of a muscle group objectively during its isometric contraction condition which means muscle group under contraction with a constant velocity of joint motion and muscle length. (The National Isometric Muscle Strength (NIMS) Database Consortium, 1996)
- Computer dynamometer will be used to measure the MVIC of the isometric knee extension of the dominant leg.
- Patient will be seated in hip flexion of 90°, knee flexion of 90°, and the padded force transducer set around malleolus. The lever arm (distance between the force transducer and the point of rotation) will be recorded for calculation of force produced by the computer dynamometer.
- Upper body will be stabilized and verbal encouragement will be given to the participants in a standardized way.
- 3 submaximal warm-up contractions trials will be given with 1-minute rest afterwards.

- 3 trials of MVIC with 1 min of rest between each trial will be instructed. After a build-up phase of 2 s, an MVIC needs to be in a steady, maximal contraction, with a plateau phase of 3 s.
- During measurements, the Physiotherapists can have visual feedback of the force signal, monitoring the quality of the shape of each contraction.
- The highest value for MVIC will be captured for future analysis.

**Determination of 1-repetition maximum (1-RM) (Kanada, 2017; Takeichi, 2012)**

1RM (kg)=0.188 + 0.187 × maximal isometric muscle strength. This formula was devised based on examination of 176 in-patient elderlies in Japan (352 legs).

**Determination of Hand grip strength (HGS) (Jeong, 2017; Yu, 2017)**

- In sitting position with elbow in 90-degree flexion
- Hold dynamometer by the testing hand with the grip meter indicator facing outward, and away from any part of the body.
- Allow 1 practice trial for dominant hand.
- Squeeze the grip with full force and continuously for at least 2 seconds.
- Two trials for handgrip strength test for the dominant hand
- Not to swing the grip dynamometer during the test and not to hold their breaths.
- The time between each trial: ~30s;
- The time interval between trials of the same hand: ~1min
- Verbal encouragement by Physiotherapists.
- HGS will be the average of the reading displayed on the dynamometer in the 2 trials

**Determination of limb occlusion pressure (LOP)**

- Limb Occlusion Pressure (LOP) is the minimum pressure required, at a specific time in a specific tourniquet cuff applied to a specific patient's limb at a specific location, to stop the flow of arterial blood into the limb distal to the cuff. (Noordin, 2009)
- The 3rd generation tourniquet system features a built-in LOP measurement capability. This allows a personalized tourniquet pressure for each individual patient and eliminated the need to account for cuff width, limb size or blood pressure.

**Determination of Leg dominance (Melick, 2017)**

Since mobility is a bilateral mobilizing task, the leg dominance will be defined by the participant's preferred leg to shoot a ball when being asked the following question: "If you would shoot a ball on a target, which leg would you use to shoot the ball?"

**Determination of completeness of training**

80% of the whole course of in-patient additional muscle strength training (i.e.10 out of 12 sessions)

**Determination of acceptance of program**

5-point Likert scale will be given to participants after the additional muscle strength training (i.e. very like, like, no comment, dislike, very dislike)

**Data collection timepoint**

- Baseline
- After completeness of training (i.e. at least 10 sessions of training)

**Clinical investigations**

- Laboratory tests at baseline and post training program
  - Clotting profile, Complete blood count (CBC), liver function test (LFT), renal function test (RFT), serum creatinine kinase level (CK), serum lactic acid level, C-reactive protein (CRP)
  - Estimated 32ml of venous blood in total will be needed for both pre and post training blood tests.
  - Myoglobulin in urine
- Spirometry before discharge of current admission

**Primary outcome:**

**Localized Muscle Strength** (Robles, 2011; Hul ,2004)

- Muscle strength is operationally defined as subject's capability for the exertion of force or torque to an external dynamometer over a specified period of time. (Kroemer, 1980)
- Maximal voluntary isometric contraction (MVIC) of knee extension of the dominant leg, with a unit Newton (N), will be assessed by computer dynamometry.

**Secondary outcomes:**

- **Functional test**
  - ✧ Short physical performance battery (SPPB) (Mora, 2015)
    Gait speed with 4m distance, Balance test & repeated chair stands test
  - ✧ 6-minute walk test (Holland, 2010)
- **Systemic muscle strength** (Jeong, 2017; Yu, 2017)
  - ✧ Hand grip strength, a non-invasive marker of systemic skeletal muscle strength and function, is assessed by handheld grip dynamometer of dominant hand
- **Health related quality of life**
  - ✧ Self-administered Chinese version of COPD assessment test (CAT) (Karloh,2016)
- **Acceptability of BFR-RE**
  - ✧ Pain by visual analog scale (0-10) before, immediate and 5-min post exercise
  - ✧ Participant's acceptance by a Likert 5-point categorical scale after the whole program
- **Feasibility of BFR-RE**
  - ✧ Examination of drop-out rate and reasons of drop-out in those discontinuing the training
- **Unplanned readmission rate within 1 month of discharge for COPDAE**

**Data analysis**

SPSS version 17.0 will be used for statistical analysis.

The comparison of baseline characteristics of subjects across the 2 groups will be tested by independent t-test for continuous variables (e.g. age, anthropologic data, maximum voluntary isometric contraction of knee extension of dominant leg, hand grip strength of dominant hand, laboratory test results, spirometry data, 6-minute walk test, COPD Assessment test (CAT), etc.), Chi-square test for nominal variables (e.g. presence of myoglobulin in urine, etc.).
For testing between-group and within-group changes after Blood flow restriction resistance exercise (BFR-RE), multivariate repeated measures ANOVA will be used.
All continuous variables are presented as mean ± SD (standard deviation). The level of statistical significance was set at $p < 0.05$.

**Sample size calculation**

A priori power analysis (calculated by G*Power 3.1.9.5) showed that in order to have a power of 80% to detect a difference of medium effect (f squared: 0.22) of muscle strength gain (Cook, 2017) at the 0.05 level of significance, 18 patients is needed in each group. If a dropout rate of 30% is estimated, 48 patients in total will be needed for the study.

**Randomization**

Participants are randomized into one of the two treatment groups. A computer compiles randomization list. Based on randomization, envelopes are made with participant number, including allocation of patients to BFR-RE vs. without BFR-RE. The envelopes are opened after inclusion for the individual participant only. The randomization list is kept in a sealed envelope.
Stratification of participants into two groups by maximum voluntary isometric contraction (MVIC) at baseline before randomization will be done. The cutoff for the stratification will be determined from the data in the recent service.

**Blinding**

Participants, doctors, nurses and involved Physiotherapists are for obvious reasons not blinded, but assessments at recruitment and on discharge will be carried out by blinded Physiotherapists without knowledge of treatment group.

**Interruption**

The individual participant can withdraw from the study at any time. Participants

may also be excluded from the study at any time based on the investigator's evaluation.

**Data registration**

All data relevant for the study are recorded in a specific form.
Data of each enrolled participant are listed in a personal form.

**Recruitment**

Consecutive patients will be recruited in the three pulmonary wards in Haven of Hope Hospital between 10.6.2020 – 28.2.2021. The study will be expected to finish within 9 months or earlier if the expected recruitment achieved.

**Expected Benefits**

BFR-RE may improve the muscle strength of the knee extension and muscle size of quadriceps in the patients undergoing early rehabilitation for COPDAE. This may allow patients to actively participate the resistance training to improve the mobility function, subsequently health-related quality of life.

**Adverse events**

In this context, adverse events are defined as any unintended, unfavorable finding, symptom or disease that can be connected to the strength training, whether it is deemed to have a correlation with this or not. Adverse events are recorded by spontaneous registration as well as by open questioning.

**Concerns on patient's safety**

**Delayed onset of muscle soreness (DOMS)**

DOMS is normal after exercise, including after LL-BFR training. It was reported in 40% of participants in a survey before but this will subside within 24-72 hours (Patterson, 2018).

**Numbness**

Incidence of transient numbness is between <2% (Nakajima, 2006) to 18.5% (Patterson, 2018). This is related to the tourniquet pressure causing peripheral nerve compression.

**Central vascular response**

Continuous BFR-RE (keep restriction during rest period between sets) will

increase the heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), or double product (HR x SBP) compared with same exercise in free flow conditions.

Cardiac output is not affected by BFR during exercise since HR increases and stroke volume decreases proportionally compared to non-BFR groups. Changes in central hemodynamic response are blunted after BFR-RE when compared to HL-RE. However, there was reported to be 14.6% of fainting / dizziness related to BFR-RE (Patterson, 2018). The study is not blinded to the physical therapists; thus, the identification of any safety issues will be easy.

**Venous thromboembolism (VTE)**

The incidence rate of VTE in general population in Asia was 0.2-0.26% (Klatsky, 2000). However, there are minimal adverse events related to this possible complication reported in BFR-RE literature. Most studies use blood markers to assess the risks of VTE BFR-RE. There is no rise in D-dimers, prothrombin fragment, thrombin-antithrombin III complex, C-reactive protein immediately after BFR-RE training or weeks after training (Madarame, 2013). The reported incidence rate of venous thrombus in a large epidemiologic questionnaire (Nakajima, 2006) in Japan was 0.055% and pulmonary embolism was 0.008%.

Moreover, BFR-RE demonstrated a stimulation of fibrinolytic system by increased tissue plasminogen activator (t-PA), a thrombus-degrading protein in the epithelial cells in healthy participants (Nakajima, 2007).

**Other vascular concerns** (Patterson, 2018)

There are reported superficial thrombophlebitis (0.8%) and subcutaneous hemorrhage (0.8%). Bruising was reported to be 13.1% (Nakajima, 2006).

**Rhabdomyolysis**

It is a clinical syndrome due to skeletal muscle damage and the release of potentially toxic substances into the circulation. The reported risk was between 0.07-0.2% (Thompson, 2018). The survey (Nakajima, 2006) in Japan revealed the low incidence of 0.008%. However, this risk was not extraordinarily higher than traditional HL-RE training.

**Education**

Observations and measurements are carried out by physiotherapists,

occupational therapists, doctors associated with the project.

**Serious adverse events**

In this context, serious adverse events are defined as events or reactions that cause:

- Death
- Life-threatening situations
- Urgent transferal to acute hospital or prolongation of existing hospitalization
- Permanent or severe disability/incapacity

Serious adverse events must be evaluated by the investigator for possible correlations with treatment in the intervention group, to consider whether there is a reasonable possibility that the adverse event has been caused by that. The following factors are included in the evaluation:

- Consistency of time.
- Conformity with known effects of the treatment.
- Alternative reasons.

If a serious adverse event is considered to have a causal correlation with the treatment, the investigator must consider the study to be terminated ahead of time.

**Ethics**

The study will be conducted in accordance with the principles of the Helsinki Declaration.

The protocol including patient information and consent forms for the randomized study is approved by the Research Ethics Committee.

The investigator is responsible for informing the Research Ethics Committee of any serious adverse event and/or major changes in the protocol. The coordinating investigator files all correspondence.

During the study period, data will be disclosed to the investigator of the study only. The research data of subjects will be masked with a set of project codes assigned to the subjects. A matching list with subjects' information will be kept away from the project files physically and electronically. Data will be well covered and stored in a locked room when it is not in used or after the study. Electronic data will be encrypted. All study data will be locked in cabinets where the department keeps patient/confidential information. Electronic data will be saved in secured computer of the hospital with restricted access. The

principal investigator will be responsible for its safe keeping. The data will be kept for three years and then discarded following the guideline of HA after completion of storage period.

~ THE END ~

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Participant Reference No.:
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# Department of Medicine, Haven of Hope Hospital
# Subject Informed Consent Form

**Project Title**

Effects on muscle strength after blood flow restriction resistance exercise (BFR-RE) in early in-patient rehabilitation of chronic obstructive pulmonary disease acute exacerbation (COPDAE), a single blinded, randomized controlled study

**Introduction**

You are invited to participate in the randomized controlled trial of the blood flow restriction resistance training (BFR-RE) in early rehabilitation of chronic obstructive pulmonary disease acute exacerbation (COPDAE) in the Haven of Hope Hospital.

BFR-RE was invented by Dr. Yoshiaki Sato in Japan 40 years ago. This exercise makes use of a pneumatic band to reduce the blood flow of the distal limb. This can accumulate the metabolites generated during exercise in order to promote muscle growth and increase muscle strength.

BFR-RE is newly introduced to Physiotherapy Department of Haven of Hope Hospital in March, 2020 though it is not a common practice in Hospital Authority. However, the "BFR-device" is in its 3rd generation currently with tremendous research showing promising results. Under the guidance of a certified physiotherapist, a "low load intensity" can be used for resistance training to build up muscle mass and strength by applying the device over the thigh to partially limit the blood flow to the distal limb.

BFR-RE is well studied in athletes, elderlies and patients for rehabilitation after orthopaedics surgeries. A large amount of literature reveals BFR-RE with "low load intensity" shows comparable increase of muscle mass as "high load intensity" resistance training and more increase of muscle strength than those only undergoing "low load intensity" resistance training.

The objective of this study is to investigate the additional effects of 2-week BFR-RE in patients with COPDAE on top of the conventional in-patient rehabilitation training.

**Study Participants**

48 in-patients with COPDAE will be recruited in order to find out the effect of BFR-RE. They will be randomly allocated into two groups by drawing enclosed envelope containing the assigned groups. One is BFR-RE, the other is control group for comparison. All the patients will be medically screened by doctors in the Department of Medicine, Haven of Hope Hospital (HHH) before participating in this study.

**Assessment procedures**

Both group of participants will undergo the following baseline and post training assessments:

1. To test the muscle strength of knee extension by computer dynamometer
2. 'Short physical performance battery' (SPPB) under the instruction of physiotherapists.
    - Balance study, 4m gait speed assessment, 5 times sit-to-stand test
3. 6-minute walking test (6 MWT)
4. Hand grip strength by hand grip dynamometer
5. A self-administered Chinese version of COPD assessment test (CAT)
6. Discomfort assessment before and post training
7. Blood and urine specimens will be collected to investigate the metabolic change with this exercise.
    - Pre-exercise blood taking will be done in the same setting with other routine admission blood specimen collection ensuring no additional needle pricking
    - Post-exercise blood taking will be taken place after finished the whole course.
    - The estimated amount of blood will be 32ml in total of pre and post exercise tests.

The estimated time required to complete the questionnaire and assessment is 1 hour.

**Standard Treatment**

Standardized 2-week in-patient rehabilitation consists of

- Breathing exercises,
- Bronchial hygiene,
- Health education,
- Bike exercise for 20 minutes (excluding history of hip operation done)
- Walking exercise at least 50m or as tolerated
- Activity of daily living training by Occupational Therapists
- Dietitian referral if needed, to ensure adequate nutrient intake

**Standardized Muscle Strength Training**

- Exercise: knee extension

- Sessions per week: 6 (Except Sunday and public holiday)
- Duration of intervention: 2 weeks
- Total number of sessions during hospitalization: 12 sessions
- Sets per session: 4 (Total Repetitions: 75 reps in total across 4 sets)
- Rest between sets: 30 seconds
- Execution speed: 1-2 seconds
- Load: 15-30% of 1 repetition maximum(1-RM) (Loenneke, 2012)
- Involvement of limb per session: Alternate limb training on alternate day
- Execution: until planned rep scheme is completed or contraction failure
- Maximum time for training: 8 minutes (preset safety time limit for the BFR device)
- Remarks: If at any time the patient becomes dizzy, severe discomfort (e.g. pain, numbness), training will be stopped.

**BFR-RE intervention group**

The patient will have the above-mentioned muscle strength training with "BFR-device" with details as follows:

- Cuff size: medium
- Restriction time: 8 mins (stop after finishing 4 sets of training or terminating by Physiotherapists or maximum restriction safety time limit preset by the BFR device)
- Applied location: alternate quadriceps in consecutive day
- Applied pressure: 80% limb occlusion pressure (LOP).
- All the instructors of the exercise are certified Physiotherapists who have attended the official training session of the device.

**Control group**

Same standardized 2-week in-patient rehabilitation and same amount of above-mentioned muscle strength training without the "BFR device"

If the participant is allocated to the control group, the one will not receive BFR-RE afterwards since a prolonged hospitalization may be required to complete another 2-week course of training.

**Alternative Procedures or Treatments**

If the participant decides not to join this study, the one will proceed to undergo the routine in-patient rehabilitation as usual since the current standardized muscle strength training is a usual practice without the BFR device. All follow-ups and examinations subsequently will be conducted in the same manner whether you opt to join the study or not.

**Expected Benefits**

BFR-RE may improve the muscle strength of the knee extension and muscle size of quadriceps in the patients undergoing early rehabilitation for COPDAE. This may allow patients to actively participate the resistance training to improve the mobility function, subsequently health quality of life.

**Foreseeable Risks or Discomforts**

- Delayed onset of muscle soreness (DOMS) which will subside within 24-72 hours (40%)
- Numbness which is transient (2% - 18.5%)
- Dizziness (<15%)
- Bruising (<15%)
- Superficial thrombophlebitis (<1%)
- Subcutaneous hemorrhage (<1%)
- Rhabdomyolysis (<0.3%)
- Deep vein thrombosis (<0.06%)
- Pulmonary embolism (<0.01%)

**Expected Duration of Research** Within 3 weeks

**Study Termination**

Your participation in this study can be terminated when you withdraw from the study at any time or you cannot adhere to the protocol. If the participant attends less than 80% of the training sessions (i.e. less than 10 out of 12 sessions), the one will be counted as a drop out group.

**Cost and Payment of the Study**

Apart from paying standard hospital fees, you are not required to pay additional fees and will not receive any remuneration.

**New Information**

You will be informed if any new information about this study becomes available that may affect your decision to continue participation in the study.

**Compensation and treatment for study related injury**

If the result of your participation in this study caused any physical injury, the investigator will treat you or refer you for treatment. You are not giving up any of your legal rights by signing this form.

**Voluntary participation/ Withdrawal**

Participation in the study is voluntary. Your decision to participate or not will be respected. You have the right to terminate your participation at any time and without giving any reason during the study, and this will not affect your present or future medical care. If you feel uncomfortable in any way during the session, you may not continue to participate in the study. If you withdraw from the study, the data collected up to your withdrawal will not be used unless with your consent. You may also express your consent to research team through Subject Informed Consent Form to allow research team to continuously use data collected before your withdrawal for research purpose. You can take time to decide whether or not you wish to take part. By signing a written consent form, you will be given a study information sheet and a signed informed consent form for record.

**Confidentiality**

Your confidentiality will be the highest priority. If the information you provide is reported or published, this will be done in a way that does not identify you as its source. To ensure the highest form of confidentiality, we do not fill in your name on the questionnaire. Your signed consent form will be stored separately from your personal data to further protect your confidentiality. Access to the data will be restricted to the researchers of this study. Along with this, the research documents as well as personal data will be stored in the computers which are only accessible by the researchers. Data can be withdrawn and destroyed if requested by you and all data will be destroyed three years after the completion of the study.

Under the laws of Hong Kong (in particular the Personal Data (Privacy) Ordinance, Cap 486), you enjoy or may enjoy rights for the protection of the confidentiality of your personal data, such as those regarding the collection, custody, retention, management, control, use (including analysis or comparison), transfer in or out of Hong Kong, non-disclosure, erasure and/or in any way dealing with or disposing of any of your personal data in or for this study. For any query, you should consult the Privacy Commissioner for Personal Data or his officer (Tel no.: 2827 2827) as to the proper monitoring or supervision of your personal data protection so that your full awareness and understanding of the significance of compliance with the law governing privacy data is assured.

By signing a written consent form, you are authorizing the Research Ethics Committee (REC) and the regulatory authority(ies) will be granted direct access to your study data for data verification.

**Enquiry**

If you have any questions related to this project can be addressed to the principal investigator

Dr. LAU Chung Wai, Resident, Department of Medicine, Haven of Hope Hospital at 2703 8888.

If you have questions related to your rights as a research participant, please contact Research Ethics Committee (Kowloon Central / Kowloon East) at 3506 8888.

**Project Title**

Effects on muscle strength after blood flow restriction resistance exercise (BFR-RE) in early in-patient rehabilitation of chronic obstructive pulmonary disease acute exacerbation (COPDAE), a single blinded, randomized controlled study

I (full name) _____ agree to participate in the randomized controlled trial of the blood flow restriction resistance training (BFR-RE) in early rehabilitation of chronic obstructive pulmonary disease acute exacerbation (COPDAE) in the Haven of Hope Hospital.

The purpose of this research is to investigate the additional effects of a 2-week BFR-RE in patients with CODPAE on top of conventional in-patient rehabilitation training.

I understand that participation in this project will involve me participating a 2-week of standardized muscle strength training with or without "BFR-device" according to study protocol in the Haven of Hope Hospital on top of the conventional in-patient rehabilitation training and taking part in the outcome assessment before and after the additional training.

I further understand that any information obtained in this study will remain very strictly confidential and will be used for research purposes only.

My participation is voluntary. I am free to withdraw from this study at any time with no adverse consequences.

If I request to withdraw from this study, I ☐ agree / ☐ disagree my research data provided before my withdrawal will be continuously used by the investigator.

I understand that my identity will be kept confidential. I agree to authorize the Research Ethics Committee (REC) and the regulatory authority(ies) a direct access to my research data for verification of clinical trial data, without violating my confidentiality, to the extent permitted by the applicable laws and regulations.

| _____ | _____ | _____ |
|---|---|---|
| Name of Participant (Block Letters) | Signature of Participant | Date |

| Name of Impartial Witness If Applicable (Block Letters) | Signature of Impartial Witness | Date |
|---|---|---|

An impartial witness's signature should be included if the participant is unable to read or write.

| Name of Investigator (Block Letters) | Signature of Investigator | Date |
|---|---|---|

I will be given a signed copy of subject informed consent form for reference.