Effect of Masks on Cardiopulmonary Exercise Test and Lower Limb Muscle Performance for Evaluating the Safety of Wearing Surgical Masks During Aerobic Exercise in Normal Subjects: Study Protocol for A Randomized Cross-Over Trial

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Study protocol

Keywords: Cardiopulmonary exercise test, CPET, surface electromyography, EMG, surgical masks, aerobic exercise.

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Abstract

Background: Face masks are an important mitigation strategy against respiratory virus contact and community transmission. Sometimes, people must wear surgical mask at rest or during exercise to minimize the risk of cross-infection, but it is unclear whether wearing a surgical mask during exercise can impact cardiopulmonary health. Thus, we designed this study using the cardiopulmonary exercise test (CPET) with simultaneous surface electromyography (EMG) to objectively evaluate the impact of mask-wearing on ventilation, exercise intolerance, and aerobic functional capacity.

Methods: Healthy young subjects without professional sports experience will be recruited in this randomized cross-over clinical study. The recruited subjects will be randomly allocated into two groups: Group 1 will first receive an intervention protocol (CPET wearing surgical mask) followed by 2-7days of washout. This will be followed by a control protocol (CPET without wearing surgical mask). Group 2 will receive the opposite sequence of interventions. The surface EMG data will be simultaneously collected. The primary outcome is the maximum oxygen uptake (VO_2max) between the two CPETs (with or without a mask). The secondary outcomes are peak oxygen consumption (VO_2), volume of carbon dioxide released (VCO_2), tidal volume (VT), and EMG parameters including root mean square (RMS), and median frequency (MF). An ANOVA with a two-stage crossover will be used. Three factors will be considered for the experimental effect: the type of intervention (wearing masks or not wearing masks), the experimental periods (period I and period II), and individual differences in subjects. The paired t-test will be used to compare the differences of CPET parameters and surface EMG values between subjects with and without a mask.

Discussion: This study offers insight on the use of surgical mask during aerobic exercise by CPET in the normal subjects. The data expand on the use of CPET with surface EMG for insight into the pathophysiological relationship between cardiopulmonary function and muscular motor performance.

Trial registration: Chinese Clinical Trial Registry, ID: ChiCTR2000033449. Data of registration: June 1, 2020.

Introduction

Background and rationale {6a}

Respiratory viral infections may spread through respiratory droplets, and thus reducing exposure and discharge of infectious respiratory secretions has become a major infection control method during each epidemic [1]. The use of facemasks (commonly referred to as ‘surgical masks’) has been suggested to be an important mitigation strategy against respiratory virus contact and transmission [2]. Sometimes, people must wear surgical mask at rest or during exercise to minimize the risk of cross-infection [3]; however, it is unclear whether wearing a surgical mask during exercise impacts cardiopulmonary health. To the best of our knowledge, there is no literature documenting or quantifying this effect.

The cardiopulmonary exercise test (CPET) is a recognized and standard method for assessing cardiopulmonary health. It can provide assessment of integrative exercise responses involving the pulmonary, cardiovascular, and skeletal muscle systems [4]. It describes the maximal achievable level of oxidative metabolism involving large muscle groups. The exercise gas exchange analysis with CPET can comprehensively analyze the organ systems and pathways involved in damaged physiological response [5]. CPET is increasingly used to assess undiagnosed exercise tolerance, exercise-related symptoms, and is uniquely suited to objectively determine functional capacity and impairment [6].

Thus, we designed this study using CPET with simultaneous surface EMG to objectively evaluate the influence mediated by masks on abnormalities in ventilation, exercise intolerance, aerobic functional capacity, and even impairment. We hypothesized that masks decrease the oxygen uptake and thereby accelerate muscle fatigue and affect exercise performance during CPET on a cycle ergometer. Accordingly, we could assess the immediate effects of masks (here, “masks” refer to medical surgical masks) on the physiological and electromyographic response of CPET in healthy untrained adults. The results can measure the safety of wearing masks for aerobic exercise. This research will be particularly applicable to periods of pandemic respiratory disease.

Objectives {7}

We hypothesized that masks decrease the oxygen uptake and thereby accelerate muscle fatigue and affect exercise performance during CPET on a cycle ergometer. Accordingly, we could assess the immediate effects of masks (here, “masks” refer to medical surgical masks) on the physiological and electromyographic response of CPET in healthy untrained adults. The results can measure the safety of wearing masks for aerobic exercise. This research will be particularly applicable to periods of pandemic respiratory disease.

Trial design {8}

Healthy young subjects without professional sports experience will be recruited in this randomized cross-over clinical study. The recruited subjects will be randomly allocated into two groups: Group 1 will first receive an intervention protocol (CPET wearing surgical mask) followed by 2-7days of washout. This will be followed by a control protocol (CPET without wearing surgical mask). Group 2 will receive the opposite sequence of interventions. The surface EMG data will be simultaneously collected. The primary outcome is the maximum oxygen uptake (VO_2max) between the two CPETs (with or without a mask). The secondary outcomes are peak oxygen consumption (VO_2), volume of carbon dioxide released (VCO_2), tidal volume (VT), and EMG parameters including root mean square (RMS), and median frequency (MF). An ANOVA with a two-stage crossover will be used. Three factors will be considered for the experimental effect: the type of intervention (wearing masks or not wearing masks), the experimental periods (period I and period II), and individual differences in subjects. The paired t-test will be used to compare the differences of CPET parameters and surface EMG values between subjects with and without a mask.

Methods: Participants, Interventions And Outcomes

Study setting {9}

The potential subjects will be recruited among college students in the Department of Rehabilitation Therapy at the Fifth Affiliated Hospital of Guangzhou Medical University in China by flyers. All recruited subjects will be asked to sign an informed consent form. The lead author (HNO) has the final approval of a subject's eligibility. The subjects may choose to discontinue their participation at any time.

Eligibility criteria {10}

The inclusion criteria include subjects aged 18-26 years old in which the International Physical Activity Questionnaire (IPAQ) indicates good health. Subjects should have no professional sports experience, the ability to perform a CPET on a cycle ergometer and be willing to sign the informed consent. The exclusion criteria are a medical history of cardiovascular and respiratory diseases, subjects who fail to pass the IPAQ pre-exercise risk screening, and/or those who confirm that they cannot participate in high-intensity exercise.

Who will take informed consent? {26a}

The potential subjects will be recruited among college students in the Department of Rehabilitation Therapy at the Fifth Affiliated Hospital of Guangzhou Medical University in China by flyers. All recruited subjects will be asked to sign an informed consent form.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

Not applicable as no biological specimens were collected as part of this trial.

Interventions

Explanation for the choice of comparators {6b}

We used a surgical mask due to its ubiquitous use in both hospitals and the community in the context of respiratory infectious disease pandemic. Group 1 will receive an intervention protocol (CPET with surgical mask) followed by 2-7 days of washout period and then a control protocol (CPET without surgical mask). Group 2 will receive the opposite sequence of interventions. All the subjects will receive two CPETs with and without surgical mask.

Intervention description {11a}

Cardiopulmonary exercise test (CPET)

CPET will be performed in an electromagnetic braking cycle ergometer (Corival®, LODE BV Medical Technology, Groningen, Netherlands). Before the test, each subject will be familiarized with routine testing instructions; their age, height, and weight will also be collected.

Resting pulmonary function tests will be performed to determine parameters such as forced vital capacity (FVC), first second forced expiratory volume (FEV1), FEV1% (% of the expected value), FEV1/FVC, and maximum volume (MVV).

Subjects then will perform a ramp CPET on a cycle ergometer. The exercise protocol consists of the following stages[6]: 2 min for resting stage, 2 min for warm-up stage (unloaded cycling), 8-12 min cycling for testing stage (ramp exercise, 5-30 watts per min), 3 min cool-down stage (unload cycling), and 7 min rest for monitor stage. During the testing period, bicycle loading is constantly increased by 15-30 Watts per minute according to anticipated physical capacity, gender, age, body mass, and self-reported physical activity status. The heart rate (HR) and pulse oxyhemoglobin saturation (SpO_2) are continuously recorded. Blood pressure (BP) will be measured every two minutes of exercise. Dyspnea and lower limb fatigue scores will be assessed via the modified Borg scale when the patient is at rest and immediately after stopping the exercise session. Subjects are encouraged to exercise to their maximum endurance or until the practitioners ended the exercise due to symptoms like ischemic ECG changes, complex ectopy, second or third degree heart block, fall in systolic pressure > 20 mm Hg from the highest value during the test, hypertension (> 250 mm Hg systolic; > 120 mm Hg diastolic), severe desaturation ($SpO_2 \leqslant 80\%$), symptoms and signs of severe hypoxemia (sudden pallor, loss of coordination, mental confusion, dizziness, faintness), and signs of respiratory failure. The test will be terminated immediately if the subjects show extreme verbal or physical fatigue.

Simultaneous surface electromyography (EMG)

Surface EMG data are simultaneously collected using the BTS FREEEMG 1000 (BTS Bioengineering Spa, Italy) device with surface electrodes during the CPET. It has a 120 dB common mode rejection ratio (CMRR) and a 16-bit A/D resolution. The sampling rate is 1000 Hz per channel. Pre-gelled bipolar silver/silver chloride surface electrodes are fixed over the muscle bellies and aligned parallel to the underlying muscle fiber direction with an inter-electrode distance of 20 mm. The electrodes will be attached on the tibialis anterior (TA), lateral gastrocnemius (LG), medial gastrocnemius (MG), rectus femoris (RF), vastus medialis (VM), vastus lateralis (VL), semitendinosus, and biceps femoris (BF) in the dominant lower limb. Each electrode attachment region is identified using anatomical landmarks via a qualified physiotherapist. Fat and perspiration in the skin can make it difficult to paste electrodes and increase the impedance. The gauze dipped with alcohol is used to rub the skin at fixation sites after shaving the subject's skin to eliminate them and reduce impedance.

Criteria for discontinuing or modifying allocated interventions {11b}

Subjects are encouraged to exercise to their maximum endurance or until the practitioners ended the exercise due to symptoms like ischemic ECG changes, complex ectopy, second or third degree heart block, fall in systolic pressure > 20 mm Hg from the highest value during the test, hypertension (> 250 mm Hg systolic; > 120 mm Hg diastolic), severe desaturation ($SpO_2 \leqslant 80\%$), symptoms and signs of severe hypoxemia (sudden pallor, loss of coordination, mental confusion, dizziness, faintness), and signs of

respiratory failure. The test will be terminated immediately if the subjects show extreme verbal or physical fatigue.

Strategies to improve adherence to interventions {11c}

Not applicable as this study is just the immediate effect study and the assessment for normal subjects.

Relevant concomitant care permitted or prohibited during the trial {11d}

Not applicable as the potential participants are all normal healthy subjects.

Provisions for post-trial care {30}

Not applicable as this study is just focus on the comparison two times of CEPT assessments in normal young subjects and does not include any intervention with potential harm after the assessment.

Outcomes {12}

Primary outcome

Maximum oxygen uptake (VO_2 max) is the primary outcome from CPET and was performed on a cycle ergometer—this is the most important parameter associated with an individual's physical conditioning [7].

Secondary outcomes

- Parameters reflecting exercise tolerance and heart function: oxygen uptake, anaerobic valve, maximum oxygen pulse, heart rate reserve.
- Parameters reflecting ventilation function: respiration reserve, ventilation volume, tidal volume, breathing frequency.
- Parameters reflecting gas exchange: end-tidal oxygen and carbon dioxide partial pressure, oxygen equivalent, carbon dioxide equivalent, and the relationship between dead space and tidal volume.
- Parameters reflecting skeletal muscle function: oxygen uptake, anaerobic valve, work efficiency, and EMG parameters including root mean square (RMS), and median frequency (MF).

Participant timeline {13}

Summarized study schedule at each visit in the clinical trial including the enrolment, interventions, and assessments is shown in Figure 1.

Sample size {14}

We could not find in the literature any data on normal subjects wearing masks undergoing CPET in the literature. Thus, we did a ten-subject roughly preliminary experiment. We assumed an alpha risk of 0.05, a

beta risk of 0.95, and a mean difference in VO_2 max between the 2 CPETs (with and without wearing mask) of 11.7 (SD 13.27) mL/kg. The results suggest that 44 subjects are required (G*Power 3.1.92). Therefore, 50 subjects will be recruited considering a 10% drop-out rate.

Recruitment {15}

The potential subjects will be recruited among college students in the Department of Rehabilitation Therapy at the Fifth Affiliated Hospital of Guangzhou Medical University in China by flyers.

Assignment of interventions: allocation

Sequence generation {16a}

This study protocol followed the Standard Protocol Items for Randomized Trials (SPIRIT) [8]. The recruited subjects will be randomly allocated into two groups according to a sample randomization sequence generated via SPSS statistical software package (version 25.0).

Concealment mechanism {16b}

Not applicable as this study is cross-over designed with randomly of order with or without masks and blind methods are not involved.

Implementation {16c}

Not applicable as this study is cross-over designed with randomly of order with or without masks and blind methods are not involved.

Assignment of interventions: Blinding

Who will be blinded {17a}

Not applicable as this study is cross-over designed with randomly of order with or without masks and blind methods are not involved.

Procedure for unblinding if needed {17b}

Not applicable as this study is cross-over designed with randomly of order with or without masks and blind methods are not involved.

Data collection and management

Plans for assessment and collection of outcomes {18a}

All data are collected according to the participant timeline by two trained practitioners: one for cardiopulmonary data collection and the other for surface EMG data collection. The BTS EMG-Analyzer

(BTS engineering, version 2.9.37.0, Italy) will be used for data analysis of the surface EMG signals. First, all raw EMG signals will be filtered using a band-pass filter (10 -300 Hz) and RMS envelope with a window of 100 ms 9. Every muscle of every subject will be analysed for ten consecutive crank revolutions in each stage based on the CPET protocol including resting stage, warm-up stage (unloaded cycling), testing stage (ramp exercise), cool-down stage (unload cycling), and monitor stage (recovery and monitor). The RMS data will be normalized to the peak of the average RMS curves of ten consecutive crank revolutions for each muscle of every subject 10. RMS usually indicates the activity of muscles, and a high RMS corresponds to high muscle activity. Moreover, within applied EMG-frequency analysis, MF is calculated as the mathematical mean of the spectrum curve: this is indicating the level of muscle fatigue and therefore shows a decrease in MF from the initial status. The results will be used to indicate increased muscle fatigue during operation.

Plans to promote participant retention and complete follow-up {18b}

Not applicable as this study does not involve follow-up.

Data management {19}

Quality of data will be conducted by research personnel once data collection is complete.

Confidentiality {27}

We will store all data including the data with personal identifiers in a password-protected lab server only accessible to the researchers. The data could be downloaded for statistical analysis on a computing system maintained by the Guangzhou Medical University in China.

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

Not applicable as no biological specimens are collected as part of this trial.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

The data will be analyzed using SPSS software (version 25, IBM Crop., Armonk, NY, USA) and the methodology referenced our previous study[9]. Parametric data will be presented as means and standard deviation (SD) if normally distributed or median if not. An ANOVA with a two-stage crossover will be used. Three factors will be considered for the experimental effect: the type of intervention (wearing masks or not wearing masks), the experimental periods (period I and period II), and individual differences in subjects. The paired t-test will be used to compare the differences of CPET parameters and surface EMG values between subjects with and without a mask. The correlation between VO_2 max and median frequency of muscles will be analyzed with linear regression to explore the effect of VO_2 max on the

muscle fatigue during aerobic exercise based on the mask intervention. Statistical significance is $p < 0.05$. The results will be plotted with GraphPad Prism (version 8.4.2). We will not perform any interim analysis.

Interim analyses {21b}

Not applicable as this study does not involve interim analysis.

Methods for additional analyses (e.g. subgroup analyses) {20b}

Not applicable as this study does not involve additional analysis.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

We will exclude the subject who have missing data directly.

Plans to give access to the full protocol, participant level-data and statistical code {31c}

This document is the full protocol. Anyone interested in de-identified data or documentation should contact the corresponding author.

Oversight and monitoring

Composition of the coordinating center and trial steering committee {5d}

Not applicable this study does not involve coordinating center or trial steering committee.

Composition of the data monitoring committee, its role and reporting structure {21a}

Not applicable this study does not involve data monitoring committee.

Adverse event reporting and harms {22}

Not applicable as this study just plans to recruit the normal subjects and perform widely clinical used CEPT assessment.

Frequency and plans for auditing trial conduct {23}

Not applicable as this study is the cross-over designed and does not need auditing trial conduct.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees) {25}

Not applicable as this study is simple cross-over designed for CEPT assessment and does not need protocol amendments.

Dissemination plans {31a}

We will disseminate the study findings through journal publications and conference presentations.

Discussion

CPET provides valuable insights into the comprehensive functions of cardiovascular, ventilation, and skeletal muscle systems. During exercise, the heart and lungs primarily meet the increased demand for skeletal muscle metabolism by delivering oxygen and removing carbon dioxide [10]. Wearing a mask during exercise might interfere with gas exchange, and this may trigger a corresponding change in skeletal muscle metabolism that ultimately affects the performance of skeletal muscle. Thus, we designed to compare subjects with and without a mask via CPET plus simultaneously surface EMG data, which will be used to evaluate the impact and safety of wearing a surgical mask during aerobic exercise in normal subjects. The conclusions will be used to describe the impact of wearing surgical masks on the cardiopulmonary and skeletal muscle systems during aerobic exercise with implications for pandemics.

This research does have some limitations. First, the age of the potential subjects is 18-26 years old and fails to cover a wider age group. The main consideration is the significant difference in cardiopulmonary and motor function between different age groups. The probability of elderly people with cardiopulmonary diseases and skeletal muscle disease is higher than young people. Second, the masks are medical surgical masks, and they are more common than N95 masks. It is not feasible to wear N95 masks while performing aerobic exercise.

In conclusion, this study offers insight on the use of surgical mask during aerobic exercise by CPET in the normal subjects. It will expand the use of CPET with surface EMG to provide new insights into the pathophysiological relationship between cardiopulmonary function and muscular motor performance.

Trial status

Subject are been recruited at the time of submission. Protocol version is Version 1.0-20200610 (from June 16, 2020 to June 15,2021).

Abbreviations

BF: biceps femoris

BP: blood pressure

CMRR: common mode rejection ratio

CPET: cardiopulmonary exercise test

EMG: electromyography

FEV1: first second forced expiratory volume

FVC: forced vital capacity

HR: heart rate

IPAQ: International Physical Activity Questionnaire

LG: lateral gastrocnemius

MF: median frequency

MG: medial gastrocnemius

MVV, maximum volume

RF: rectus femoris

RMS: root mean square

SD: standard deviation

SPIRIT: Standard Protocol Items for Randomized Trials

SpO_2: pulse oxyhaemoglobin saturation

TA: tibialis anterior

VCO_2: volume of carbon dioxide released

VL: vastus lateralis

VM: vastus medialis

VO_2 max: maximal oxygen uptake

VO_2: peak oxygen consumption

VT: tidal volume

Declarations

Acknowledgements

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Authors' contributions {31b}

HJH and YXZ are joint first authors. QL and HNO obtained funding. QL, HNO, and HJH designed the study. QL, YXZ drafted the manuscript. LZZ, ML. SMX, YSL, SJL and MFZ collected the data. QL and HNO approved the final version of the manuscript. All authors have read and approved the final manuscript. LL and ZC are the study guarantors.

Funding {4}

This study is sponsored by the Key Clinical Specialist Fund of the Fifth Affiliated Hospital of Guangzhou Medical University. The management, analysis, and reporting of the study will be conducted independently by the study investigators.

Availability of data and materials {29}

Anyone interested in other data or documentation should contact the corresponding author.

Ethics approval and consent to participate {24}

The study was approved by the Medical Ethics Association of the Fifth Affiliated Hospital of Guangzhou Medical University (reference KY01-2020-06-06). The informed consent will be obtained from all study participants.

Consent for publication {32}

The informed consent forms will be obtained from all study participants.

Competing interests {28}

The authors declare that they have no competing interests.

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Figures

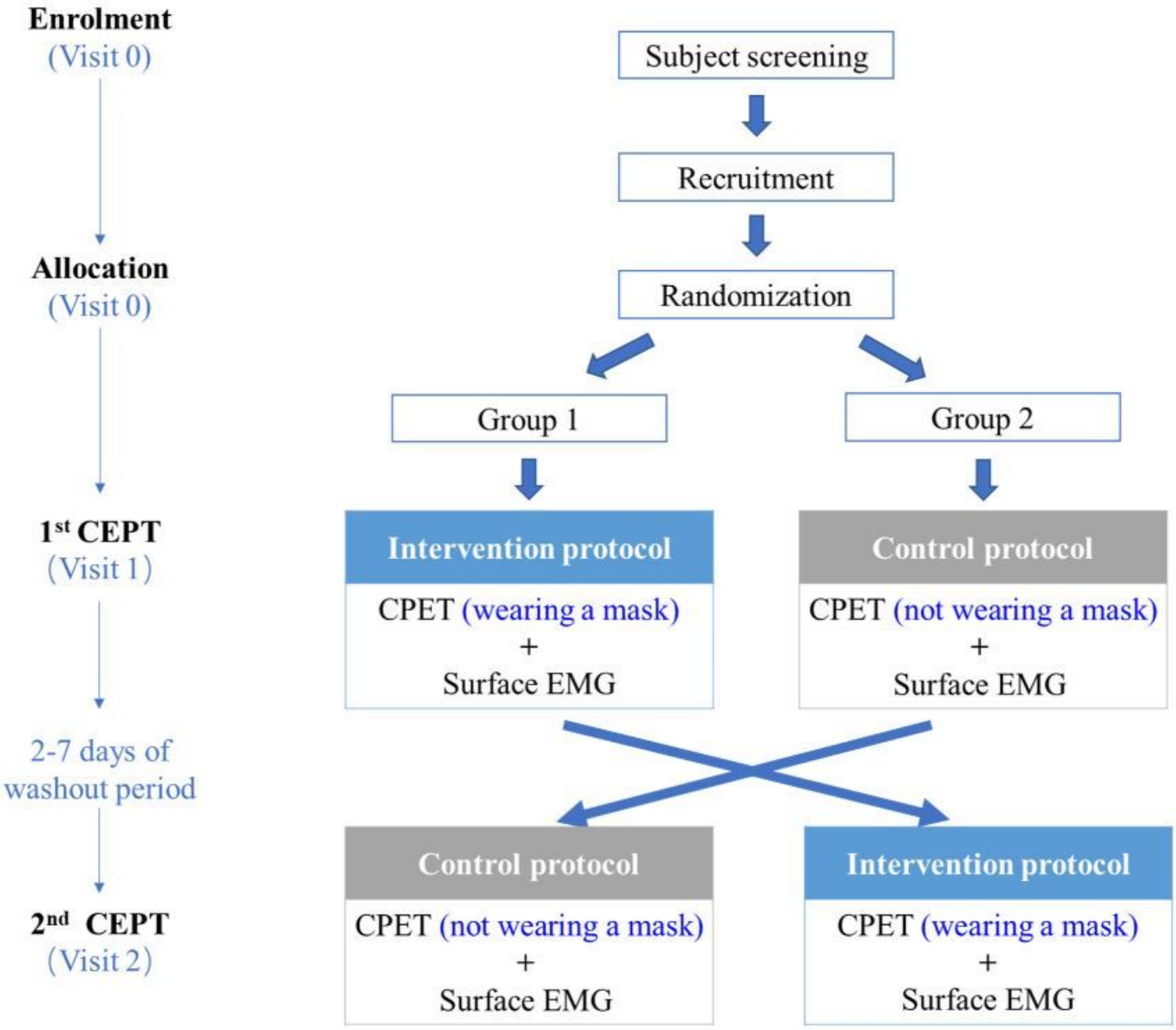

Figure 1

Summarized study schedule at each visit in the clinical trial including the enrolment, interventions, and assessments