Wingate-type Exercise Test to evaluate the effect of High Velocity Therapy on Recovery Sensation and Blood Lactate Decline

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Protocol Title:	**Wingate-type Exercise Test to evaluate the effect of High Velocity Therapy on Recovery Sensation and Blood Lactate Decline**
Protocol Number:	RP-VTPF2022001Sci
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Principal Investigator:	Dr. L. Bruce Gladden
Co-Investigators:	Dr. Michael Roberts Dr. Jessica Whittle
Sponsor:	Vapotherm, Inc 100 Domain Drive Exeter, NH 03833 1 (603) 658-0011 http://www.vtherm.com

Confidential

Study site should keep protocol, all contents and related information confidential.

Protocol Approval

Investigator Statement

As Investigator of the study titled **Wingate-type Exercise Test to evaluate the effect of High Velocity Therapy on Recovery Sensation and Blood Lactate Decline** (the "Study"), I agree to:

(i) conduct the Study in accordance with: this Investigator Agreement; the Study's Protocol as approved by the IRB (the "Protocol"); all applicable laws and regulations; and any IRB or FDA conditions of approval;
(ii) await IRB approval for the Protocol before obtaining informed consents (if applicable);
(iii) ensure that all requirements for informed consent are met and not allow any participant to participate in the Study before obtaining that participant's informed consent (if applicable);
(iv) not make modifications to the Protocol without first obtaining consensus from the Vapotherm Science and Innovation team and necessary IRB approval;
(v) maintain Study documentation for the period of time as required by appropriate regulations; and
(vi) supply to the Sponsor, as part of this Investigator Agreement, my curriculum vitae.

INVESTIGATOR

Signature: _____

Printed Name: L. Bruce Gladden_____

Date: _____

Glossary of Definitions and Terms

High Velocity Therapy (HVT): The use of a medical device to deliver ideally humidified, heated gas through a small bore nasal cannula to augment ventilation and breathing.

Work of Breathing (WOB)/Recovery Sensation: The physical, physiologic muscular demands of breathing and exercise recovery manifested through the sign and symptoms of increased physical exertion.

Respiratory Rate (RR): The number of breaths a participant takes per minute (breaths·min^{-1}).

Heart Rate (HR): The number of heart beats per minute (beats·min^{-1}).

BORG Score: a rating scale (1-10) for perceived level of exertion

I. Background and Significance

Vapotherm high velocity therapy (HVT) creates ideally conditioned respiratory gas and delivers it nasally, supporting spontaneous ventilation. This differs from simple oxygen therapy in that the gas is heated, humidified, an exchange of all gasses, including CO_2, is enhanced. [1,2]. Vapotherm technology is unique in its ability to provide this conditioned gas through a small-prong nasal cannula resulting in a high velocity without the well-known adverse effects related to drying and cooling of the nasal mucosa [3]. This high velocity nasal flow facilitates a well described mechanism of improving ventilatory efficiency by way of eliminating anatomical dead space of the upper airway [2].

The purging of the nasal cavity is important to alveolar gas exchange because the gas that is drawn to the respiratory regions of the lungs comes from the anatomical reservoir created by the flush, in the same way that oxygen conservation masks can incorporate reservoir bags to reduce the bulk flow requirements from the oxygen source to achieve the same oxygenation effect [2,4]. Based on mathematical modeling, physiologic studies and clinical observations flow rates of 25 to 35 L·min^{-1} through Vapotherm's adult cannula purges the anatomical reservoir of the upper airway in the window of time between breaths. Vapotherm's humidification systems are specifically designed to tolerate a high back pressure in the humidification cartridge that is generated by passing these flow rates through small bore cannula resulting in the appropriate flow velocities (turbulent energy) [4].

Since 2000, HVT has been used extensively and has been well studied. [2-6] This study is intended as a pilot study utilizing a Wingate-type Exercise Test[18] to evaluate the impact of HVT on reduction of work of breathing and improvement of lactate clearance rate during exercise and the recovery interval. This work may provide foundational data for a larger study and may identify the appropriate parameters for evaluation of physical rehab patients.

II. Overall Study Objective

The **overall objective** of this study is to evaluate the impact of HVT on reduction of work of breathing and change in lactate clearance rate during exercise and recovery during a Wingate-type Exercise test. The study will include four study segments, corresponding to four therapy settings

being tested: (1) FiO2=100% with Flow=5LPM, (2) FiO2=21% with Flow=25-30LPM, (3) FiO2=100% with Flow=25-30LPM, (4) FiO2=21% with Flow=5LPM.

The **hypothesis** is that HVT, regardless of the oxygen concentration (i.e., FiO2), will reduce the work of breathing and increase the lactate clearance rate during exercise and recovery intervals.

To test this hypothesis, the study will be conducted with the following specific aims:

Aim #1: Primary Outcome.
The primary endpoint is change in blood lactate from before the exercise test to recovery over a period of 30-60 minutes post-exercise.

Aim #2: Secondary Outcomes.
The secondary endpoints evaluate additional data that may be clinically meaningful. Data will include vital signs (SpO2, heart rate [HR], respiratory rate [RR], blood pressure [BP]), and perceived level of exertion (BORG [score 0-10]), as measured during the exercise and recovery intervals. Work performance will be computed during test period only, including peak power output, mean power output over 30second intervals, and decrease in power.

Aim #3: Tertiary Outcomes.
The tertiary endpoints will evaluate the participant perceptions of the therapy impact during study procedures: (1) Level of Exertion at Exercise End, (2) Relief of Exertion Recovery End, (3) Comfort/Tolerance of Therapy at Study End [exercise and recovery], as measured on a 1-10 Likert scale.

1. Level of Exertion at Exercise End: "How tired do you feel?"
2. Relief of Exertion at Recovery End: "How fast do you feel you recovered?"
3. Comfort/Tolerance of Therapy at Therapy Segment End: "How comfortable was the therapy while you had it on during exercise? How comfortable was the therapy while you had it on during recovery?

These **endpoints** will establish the effect of Vapotherm HVNI on lactate clearance, work of breathing, and perceived exertion during exercise and recovery intervals.

III. Participant Selection

Participants will be identified and recruited by study investigators. The study will take place in an appropriate educational forum (e.g., hospital, academic center, laboratory setting, etc.) where kinesiology testing can be accomplished. Initial contact will be made by study investigators, and volunteers may include any interested participants. Participants will be compensated for their time at a rate of approximately $50 per hour.

Inclusion Criteria

1. Adults over 18 years old, in a general state of good health, of either sex
2. No known contraindication to performing a maximal exercise test, i.e., Wingate-type Anaerobic exercise test
3. Participants must consider themselves able to perform "regular moderate" or "regular strenuous" exercise.

a. "Regular moderate" exercise includes less than 30 minutes every day or 30 minutes every other day, of some form of deliberate exercise, that does not include walking. [7]
b. "Regular strenuous" exercise is 30+ minutes per day, of some form of deliberate exercise, that does not include walking. [7]

Exclusion Criteria

1. Not considered a 'high-performance athlete'
2. Known active cardiovascular, metabolic, liver, or renal disease [8,9]
3. Orthopedic limitations to exercise [10]
4. Pregnancy [10]
5. Use of beta-blockers or beta-agonist asthma medications [10]
7. Exercise induced asthma
8. Any other health-related issue that would involve the participant's fitness capability
9. Inability to complete all of the study procedures

IV. Study Design

The feasibility/pilot study will be performed as a prospective, unblinded clinical trial of a Wingate-type Anaerobic exercise test. Submaximal cycle ergometry tests are routinely used in exercise, kinesiology, and rehabilitation facilities, typically without physician supervision, to assess fitness level and/or physiologic response to exercise and pose minimal risk. The study will take place in an exercise kinesiology and rehabilitation laboratory facility setting.

The study is a repeated measures model that will collect data on the participants with the designated HVT at four specified settings (Flow/FiO2) during the Wingate exercise test and during the recovery interval. The Wingate exercise test configuration, equipment and procedures will be repeated for each HVT setting for a matched dataset. Participants who fit criteria will be asked to consent to enroll in the study.

The study will include four study arms, corresponding to four therapy settings being tested: (1) FiO2=100% with Flow=5LPM, (2) FiO2=21% with Flow=25-30LPM, (3) FiO2=100% with Flow=25-30LPM, (4) FiO2=21% with Flow=5LPM. The participants will wear the appropriately sized nasal cannula interface during the exercise and recovery.

V. Participant Enrollment

Participants will be solicited by investigators and consented prior to participation. Once consented, participants will be scheduled for their testing session(s) per protocol procedures. If enrolled, participants will be randomized to the order of the different settings on the HVT 2.0 device in different test sessions. Each participant will present on 4 different days for testing. This is to avoid fatigue related changes in sequential tests. Additional testing sessions may be scheduled to complete data collection if needed.

Sample Size:

Because no data exist for variance around these parameters, we will plan to enroll 15 participants, each to perform 4 test sessions.

Data Safety Monitoring:

Given that this protocol is a conventional exercise test protocol and therefore very low risk and routinely performed without physician oversight, there is no plan for a Data Safety Monitoring Board. Any adverse events (AE) will be promptly reported to the IRB for consideration.

VI. Study Procedures

Screening, Enrollment, & Management

During screening, participants will be asked to participate in this study, and if so, they will provide informed consent prior to enrollment. Participants will be instructed that if at any time during the study that they wish to discontinue the study, they are free to stop the testing and discontinue study participation at any time. All study procedures will be explained to the participant prior to starting any procedures, and all participants will be given a copy of the informed consent form.

Participants will be scheduled for test sessions to complete the objectives of the study and instructed to wear exercise appropriate clothing. Participants will be informed that prior to each test session, they should abstain from caffeine or tobacco products for a minimum of 4-hours, and alcohol and strenuous exercise for 10-hours [10]. Participants are instructed that if at any time during the study he/she feels faint, dizzy, short of breath, or for any reason, they should stop the test.

Data collection during enrollment will include participant demographics (e.g., age, sex, height, weight). At each session, participant vital signs, lactate levels, dyspnea scores, work performance indices, and perception scores will be collected. The study will include four sessions, corresponding to four therapy settings being tested: (1) FiO2=100% with Flow=5LPM, (2) FiO2=21% with Flow=25-30LPM, (3) FiO2=100% with Flow=25-30LPM, (4) FiO2=21% with Flow=5LPM.

For each **test session** of the four HVT Settings, the following procedures will be followed.

Pre-Test Preparations:

Prior to starting the test, the participant will perform 2-3 second warm up sprints to acclimate to the ergometer. The cycle ergometer seating settings will be maintained consistent across all four therapy settings. Participants will be instrumented appropriately and initial data (e.g., vital signs, lactate, dyspnea) will be collected for baseline.

Wingate-type Exercise Test Procedures:

The exercise test model is called the Wingate anaerobic test. In a pre-test, the participants will Wingate test consists of pedaling with maximal effort for a series of short 8-second intervals against different loads, separated by 5 min of rest. This pre-testing is done to determine the load required for maximal power output. For the actual Wingate-type test, the participant will pedal as rapidly as possible for 60 sec against the load determined for maximal power output. Three indices of performance will be computed during the test period – peak power output, mean power output over the 60 seconds, and decrease in power (fatigue index).

At end of exercise interval, participant will be asked their perception of their level of exertion.

Recovery Interval:

Recovery interval will take place after exercise period up to 1 hour, or until participant is fully recovered and lactate levels approach baseline. A minimum of 15 samples during the recovery interval will be performed to complete lactate recovery data evaluation.

At end of recovery interval, participant perception of (1) Relief of Exertion at Recovery End, and (2) Comfort/Tolerance of Therapy will be recorded.

Sessions will be repeated on separate days, scheduled at the convenience of participant and laboratory, until a participant has completed a session at each of the HVT setting levels.

VII. Data Collection

Table 1. Key study data and collection points for each Phase of the Study.

	Study Start	After Warm-Up	Exercise Period q60sec	Recovery Period q5min	Study End
Participant pertinent Medical History	X				
Participant Vitals * (HR, RR, SpO2, BP)	X	X	X	X	
Lactate [La^-]	X	X	X	X	
Dyspnea (Borg scale)	X	X	X	X	
Perception Scores (1-10 scale)					X
Work Performance			X		

*Vitals only measured prior to start of exercise, after exercise period ends, and after recovery interval. If practical, may record real-time the HR, RR, and SpO2 with digital sensors. This will be completed for each Therapy Settings designated in the Study Protocol.

Data collection during enrollment will include participant demographics (e.g., age, gender, height, weight). Each Therapy Settings will collect the relevant participant vitals, lactate levels, dyspnea scores, and perception scores.

Primary Endpoint

- Change in lactate over (1) the exercise test interval, and (2) the recovery interval

Secondary Endpoints

- Participant Vitals: HR, RR, SpO2, BP
- Dyspnea Score: modified BORG score, 1-10 scale
- Exercise Test Work Performance: peak power output, mean power output over 60 seconds, and decrease in power (fatigue index)

Tertiary Endpoint

Participant Perception of Performance/Recovery [1-10 scale]

- Level of Exertion at Exercise End: "How tired do you feel?"
- Relief of Exertion at Recovery End: "How fast do you feel you recovered?"

- Comfort/Tolerance of Therapy at Therapy Segment End: "How comfortable was the therapy while you had it on during exercise? How comfortable was the therapy while you had it on during recovery?

VIII. Statistical Analysis

Participant demographics and characteristics will be summarized, compared, and appropriate statistical testing will be performed for the continuous and categorical variables. Descriptive analyses of the primary endpoints, supporting data/variables, and secondary outcome data will be performed. Assuming a non-normal data distribution for this study, a non-parametric test (e.g., Wilcoxon Signed Rank Sum test) will be performed with significance interval of 0.05 on all applicable variables. If continuous variables present a normal distribution, between-trial comparisons will be performed using two-way (within-within; trial* post-exercise sampling times) repeated measures ANOVAs. Otherwise, for the categorical variables, the Fisher's Exact test will be performed. Further analyses may be performed on the collected data based on ongoing analyses at time of study completion to identify additional relevant results.

IX. Risks and Discomforts

There are minimal or no known risks to the Wingate Anaerobic Exercise Test.[12,13] Use of the high flow nasal cannula therapy by healthy persons has no known risks and has been used in the clinical setting for approximately seventeen years without known reports of adverse events related to the administration of high nasal flows when used according to manufacturer's recommendations. Prior work indicates that approximately ≤ 4 cmH_2O of distending pressure may be generated in the upper airway [14,15] which is well below any known threshold for injury. In addition, it has been demonstrated that delivery of high flows of conditioned gas from a nasal cannula has a positive effect on airway mucosal function [16,17]. Blood lactate measurements will be made using 1-2cc of whole blood from finger sticks (similar to blood glucose measurements using a glucometer). Fingers will be wiped with alcohol pads prior to sticking and sterile capillary tubes will be used for each sample. Alternatively, blood samples will be collected from a venous catheter in a prominent arm vein for enzymatic and/or lactate meter measurement of blood lactate concentration.

For these reasons, we have determined that this study represents a minimal risk and discomfort to the participants. The is the expected discomfort related to standard exercise and performance testing in exercise physiology laboratories.

X. Potential Benefits

Participants will receive no direct health benefit from participation. The trial may result in knowledge that leads to improvements in the quality of care, participant experience and ultimately cost of care associated with the care for participant with respiratory disease or those needed physical rehabilitation. Participants may receive up to $50 per hour for participation, paid at the end of their participation.

XI. Monitoring and Quality Assurance

The clinical trial site will be monitored in accordance with policies at Vapotherm and those federal regulations that pertain to clinical research, namely 21 CFR Parts 50, 54, 56 and 812 and others as applicable. Monitoring will occur at regular frequency by the PI or designee, such as to allow ongoing review of data collected, site qualifications and compliance with the protocol. All investigators and study staff will be appropriately trained to ensure compliance with the protocol.

XII. Protocol Deviations

Any deviations from the Data Collection plan identified during monitoring or through other means will be documented on appropriate case report forms. These deviations include, but are not limited to items such as the following:

- Deviation from procedural sequencing, per protocol
- Failure to complete initial participant data collection
- Failure to capture/record physiologic readings at required/prescribed intervals

If the study site demonstrates a pattern of consistent and frequent deviations, the Sponsor will undertake appropriate activities (e.g., re-training) to attempt to bring the site into compliance with the protocol. A pattern of repeated serious deviations from the protocol may result in site termination from the study.

XIII. Adverse Event Reporting

During the course of the participant's participation in the study, the investigator will determine whether any adverse events have occurred. For the purposes of this protocol, an adverse event is any undesirable clinical/medical occurrence in a participant that is or is not attributed to the device or procedure required by this protocol. If any adverse event occurs, either anticipated or unanticipated, the investigators will immediately contact the sponsor's representative (site monitor) indicated on page 1.

XIV. Confidentiality

Rigorous procedures will be followed to maintain confidentiality of participant identification and test-related information and to adhere to government regulations concerning privacy. The privacy rules and requirements according to governing regulations will be adhered to. Participants will be assigned a study ID number. Only the data collection form and medical history form will link the participant's name to their ID number. These forms, along with consent forms, will be locked in Dr. Gladden's office and will only be accessed by him or involved study personnel. Assigning participant ID numbers and aliases to participant names on data collection and medical history forms will be performed in order to facilitate testing procedures.

When data collection is complete, all linking information to participant identity will be destroyed.

All Vapotherm representatives involved in this study will only have access to the participants' unique identification number throughout the study.

Confidentiality will be protected and maintained to the extent allowed by law.

XV. References

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