Participant Information and Consent Form

Title of Study:	Salbutamol reversal of methacholine induced bronchoconstriction: vibrating mesh nebulizer versus pressurized metered dose inhaler
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24-Hour Emergency Contact	Beth Davis (306-229-8709 call/text) or email beth.davis@usask.ca.

Introduction: You are invited to participate in this research study, as your age (i.e. at least 18 years of age) and health status (i.e. asthma, airway hyperresponsiveness) make you a suitable representative of the population of interest.

Your participation is entirely voluntary. You may also withdraw from the study at any time without providing a reason and without negative consequence. If you do not wish to participate or if you choose to withdraw from the study, your current health care and/or academic status (if you are a student at the U of S) will not be impacted.

Please take time to read the following information carefully. You may direct any questions or concerns to the study staff prior to and at any time during the study. Please feel free to discuss the study and your potential participation with friends, family, and/or your personal healthcare provider.

Agencies Contributing Funds and Resources to the Study: The Asthma Research Lab will be managing the cost of the study. Product supply and/or financial compensation to offset the cost of the study will be supplied by the manufacturer of the Solo vibrating mesh nebulizer. The researchers will not receive any personal financial benefit for conducting the study. The University of Saskatchewan will receive some financial compensation to offset research associated costs.

Purpose of Study: As an individual with asthma, you are probably aware that bronchoconstriction (i.e. the feeling of chest tightness and shortness of breath) can be relieved with bronchodilator (e.g. salbutamol). We call this reversible airflow obstruction and we can test for this by performing bronchodilator responsiveness testing (BRT). Although guidelines for BRT exist, a standardized,

validated method is lacking. Common approaches to BRT involve measuring lung function, administering 200mcg or 400mcg of salbutamol using a pressurized metered dose inhaler (pMDI) with a valved holding chamber (VHC or "spacer") or using a jet nebulizer and a mouthpiece or mask. A waiting period of 15 minutes follows and then lung function measurements are repeated. For BRT to be positive, the improvement in the amount of air you can forcefully exhale in one second (FEV_1) and/or the total amount of air you can forcefully exhale (FVC) must be at least 12% and 200mL from baseline values after receiving salbutamol. There are two problems with the current approach. First, the amount your airways can "open-up" is limited by the anatomy of your lungs. Second, BRT may not coincide with your symptoms. In other words, the day of your BRT test is not the same day as you are experiencing bronchoconstriction (i.e. asthma symptoms).

The methacholine challenge test (MCT) is another test used to guide a diagnosis of asthma. Methacholine challenge testing tends to cause bronchoconstriction in individuals who have asthma. Current guidelines for MCT also lack specific details with respect to relieving the constriction caused by inhaling methacholine. The constriction will gradually disappear without treatment however the administration of salbutamol may relieve the constriction quicker. A common approach in our lab is to administer salbutamol (200mcg) using only a pMDI. A common approach used in clinical MCT is to use a pMDI with a VHC with either 200mcg or 400mcg salbutamol.

The purpose of this study is to compare BRT after MCT using two methods of salbutamol administration. One method will involve administering salbutamol after MCT using a Solo vibrating mesh nebulizer (VMN) with the Ultra accessory (i.e. the Ultra accessory will serve as the spacer), and the other method will involve administering salbutamol after MCT using the common BRT approach of pMDI with a VHC. These data will be useful to guide the method for performing BRT in both clinical and research settings.

Eligible Participants: To be eligible to participate in this study, you must be 18 years of age or older and in general good health. You must not be pregnant or breastfeeding. You must be a non-smoker and you must be free from respiratory infection (e.g. common cold) for at least 4 weeks. The amount of air you can forcefully exhale during the first second of exhalation (FEV_1) must be at least 65% of what is predicted for your age, sex and height. In addition, your current methacholine PD_{20} (dose of methacholine causing a 20% reduction in your FEV_1) must be 800µg or less.

You may not participate in this study if you are currently taking long-acting bronchodilators (e.g. formoterol, salmeterol), including combination therapies (e.g. Symbicort®). If you are taking inhaled corticosteroids (e.g. budesonide, fluticasone) on a daily basis, you may participate in this study provided that you continue to take your usual dose. Short-acting bronchodilator therapy (e.g. Ventolin®, bricanyl) is allowed but must be withheld for at least six hours prior to all lab visits. You must also avoid strenuous exercise on study visit days. (e.g. doing a workout before coming to lab, biking or jogging/running to the lab).

Study Overview/Visit Schedule (Table 1): You will be required to attend the laboratory on three occasions; Visits 1, 2 and 3. Each visit will last approximately 2 hours. The time between visits will be at least one week. At Visit 1, staff will discuss the study with you, answer any questions you may have and if you agree to participate, this document will be signed and dated by you and the individual discussing the study with you. Demographic information (e.g. date of birth, height, weight, ethnicity) and information about your general health and your respiratory health, including any medication use will then be collected. Next, you will undergo spirometry and a methacholine challenge. If you meet the spirometry and methacholine entrance criteria, your pulse will be measured. You will then be asked to inhale both salbutamol, a bronchodilator medication that relaxes airway smooth muscle and improves breathing, and placebo (normal saline; does not contain bronchodilator). The details of inhaling bronchodilator are described below under the heading Bronchodilator Inhalation. After inhaling bronchodilator, your pulse and lung function (i.e. spirometry) will be assessed at various timepoints.

Table 1: Study overview/visit schedule

	Visit 1	Visit 2	Visit 3
Study discussion and consent	x		
Spirometry	x	x	x
Methacholine challenge	x	x	x
Pulse	x	x	x
Bronchodilator administration	x	x	x
Spirometry @ 5, 10, 15, 30, 45 and 60 minutes after administration of bronchodilator	x	x	x
Pulse @ 5, 10, 15, 30, 45 and 60 minutes after administration of bronchodilator	x	x	x

Study Procedures:

Spirometry: This procedure involves you taking a full breath in and exhaling as hard as you can for as long as you can through a mouthpiece that is attached to a nSpire KoKo® spirometer (a handheld device that is connected to a computer). You will be required to wear noseclips. This process will be repeated at least 3 times.

Methacholine Challenge: Methacholine challenge testing involves the inhalation of aerosolized methacholine, a known bronchoconstrictor that may cause your airway to narrow. After completing initial spirometry as described above, you will inhale 0.5mL aerosolized saline (i.e. salt water) using normal breathing through a mouthpiece connected to a vibrating mesh nebulizer.

You will be required to wear nose clips during the inhalations. You will inhale for approximately 2 minutes, until the nebulizer is empty, followed by spirometry at 30 and 90 seconds post-inhalation. Five minutes after the start of the previous inhalation cycle, you will begin to inhale your first dose of methacholine until the nebulizer is empty. The process will repeat with increasing doubling doses of methacholine until your FEV_1 is reduced by at least 20%.

Pulse Measurement

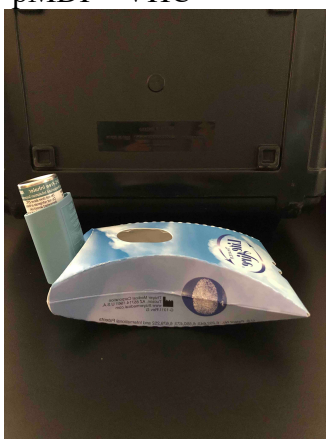
Your pulse will be measured at various timepoints at all visits. Your pulse will be measured using a commercially available vital sign monitor. The measurement of your pulse will involve the placement of a small device on your index finger.

Bronchodilator Inhalation: There are two methods being used to administer bronchodilator. One method will use a pressurized metered dose inhaler with a valved holding chamber, often referred to as a spacer (pMDI+VHC), and the other will use the Solo vibrating mesh nebulizer with the Ultra accessory (VMN+Ultra). Both methods will be used at each administration because the device being used to administer the salbutamol cannot be concealed. This will remove any bias that may be present by knowing which method you are using. One method will therefore contain the salbutamol and one method will contain normal saline. This is referred to as "double dummy". At one of the visits, both methods will contain a placebo (i.e. no salbutamol will be administered). This indicates the study is placebo controlled. The study is also randomized which means the three possible methods of salbutamol and placebo administrations will be performed by each study participant in random order. The three possibilities are:

1. salbutamol (200mcg) using pMDI+VHC and placebo using VMN + Ultra
2. placebo using pMDI+VHC and salbutamol (200mcg) using VMN + Ultra
3. placebo using pMDI+VHC and placebo using VMN + Ultra

Images of the two bronchodilator delivery methods being used are shown below.

pMDI + VHC



VMN + Ultra

Responsibilities of The Participant: As a participant of this study, you will be expected to (1) follow the directions of the investigators and researchers, and (2) report all medications (prescribed, over-the-counter, and herbal products) being used. These steps are important both for your own safety as well as for accurate interpretation of the test results. The study investigator may remove you from the study early in the event of non-compliance with the above responsibilities.

Benefits of Participating in This Study: If you choose to participate in this study, there will be no benefit for you personally. It is hoped that the information gained from this study can be used to guide the way bronchodilator is administered in clinical and research settings.

Honorarium: If you choose to participate in this study, you will not be charged for any research-related materials or procedures. If you are eligible and you complete the study, an honorarium in the amount of $100 will be provided to you to cover your time and out-of-pocket expenses (e.g. parking, transportation, meal). If you enroll but do not qualify after initial testing (i.e. spirometry and MCT), an honorarium of $25 will be provided to you. If you qualify but do not complete all visits, the honorarium will be pro-rated ($33.33 for each completed visit).

Potential Risks and Discomforts: MCT may cause the following symptoms: wheezing (10%), coughing (25%), shortness of breath (21%), dizziness (6%), and/or headaches (2%). These effects are short-lasting and should subside untreated. Bronchodilator administration (i.e. salbutamol) is the standard treatment following MCT. The study requires that bronchodilator be administered after two of the three MCT. After one of the tests however, bronchodilator will not be administered immediately following the test but will be administered one hour after the test if necessary (i.e. recovery has not occurred). Bronchodilator may be administered at any time as medically necessary.

High doses of salbutamol may lead to an increased heart rate or a feeling of shakiness. We do not anticipate this to occur with the dose being used in this study (i.e. 200mcg) but we will monitor for this by measuring your pulse. These effects, should they occur, will resolve quickly without treatment.

Voluntary Withdrawal: Your participation in this study is voluntary and as such, you may withdraw from the study at any time. No reason needs to be given for your withdrawal, and your current health care and/or academic status (if you are a student at the U of S) will not be impacted in any way. The data collected about you until the point of withdrawal may be retained for analysis. You will be notified if new information regarding the procedure involved becomes available during the course of the study that may affect your willingness to participate. Early withdrawal from the study poses no safety concerns.

Study-Related Injury: In the unlikely event of an adverse effect arising related to the study procedures, trained staff will be available throughout the conduct of the study who can respond immediately. Necessary medical treatment will be made available at no additional cost to you. By signing this document, you do not waive any of your legal rights against the investigators or anyone else.

Confidentiality: In Saskatchewan, the Health Information Protection Act (HIPA) defines how the privacy of your personal health information must be maintained so that your privacy will be respected. Your name will not be attached to any information, nor mentioned in any study report, nor be made available to anyone except the research team (i.e. non-identifying codes will be used for identifying your study data. For example, if you are participant 1, your data/documentation will be coded with SBDR01; SBDR stands for **s**albutamol **b**ronchho**d**ilator **r**eversibility, a code we created specifically for this study). Your de-identified information will remain under lock and key at the lab for a minimum of 5 years after which time it will be shredded in a confidential manner. Note that no guarantee can be made for complete confidentiality. For quality assurance and/or monitoring purposes, the University of Saskatchewan Biomedical Research Ethics Board reserves the right to inspect research records and medical records that may identify you in the presence of the investigator or his or her designate. It is the intention of the research team to publish results of this research in scientific journals and to present the results of the study at related conferences and workshops however, your identity will not be revealed in any publication or presentation.

Study Results:

Study staff will be able to discuss your own study results with you at each visit. Once all participants have completed the study and the data are analyzed publication of the study results will be sought. If the study data are published, you can request a copy of the publication by contacting study staff.

Contact Regarding Any Questions/Concerns About The Study: If you have any questions or concerns regarding this study before or during participation, you may contact Dr. Davis at beth.davis@usask.ca or 306-229-8709 or Dr. Cockcroft at 306-844-1446 or don.cockcroft@usask.ca.

If you have any concerns about your rights as a research participant and/or your experiences while participating in this study, contact the Chair of the University of Saskatchewan Research Ethics Board, at 306-966-2975 (out of town calls 1-888-966-2975). The Research Ethics Board is a group of individuals (scientists, physicians, ethicists, lawyers and members of the community) that provide an independent review of human research studies. This study has been reviewed and approved on ethical grounds by the University of Saskatchewan Research Ethics Board.

Consent:

Study: Salbutamol reversal of methacholine induced bronchoconstriction: pressurized metered dose inhaler with valved holding chamber versus vibrating mesh nebulizer

- I have read the information in this consent form.
- I understand the purpose, procedure and possible risks of the study.
- I was given sufficient time to think about it.
- I have had the opportunity to ask questions and have received satisfactory answers.
- I am free to withdraw from this study at any time for any reason and the decision to stop taking part will not affect my future medical care or academic status.
- I agree to follow the study staff's instructions and will tell the study staff at once if I feel I have had any unexpected or unusual symptoms.
- I give permission for the use and disclosure of my de-identified personal health information collected for the research purposes described in this form.
- I understand that by signing this document, I do not waive any of my legal rights.
- I will be given a signed and dated copy of this consent form.

I agree to participate in this study:

Printed name of participant	Date
Signature of participant	Phone number
Printed name of person obtaining consent	Date
Signature of person obtaining consent	