STUDY PROTOCOL AND STATISTICAL ANALYSIS PLAN

Official title: Intranasal cocaine and temperature regulation during exercise

NCT number: NCT05809453

IRB Approved date: 02-07-2024

STU-2023-0094

PROTOCOL FORM / RESEARCH DESCRIPTION

If an item does not apply to your research project, indicate that the question is "**not applicable**" – do not leave sections blank

Click once on the highlighted entry in each box to provide your response. Click the item number/letter or word, if hyperlinked, for detailed instructions for that question. If your response requires inserting a table, picture, etc, you may need to first delete the box that surrounds the answer and then insert your table or other special document.

1. Purpose and objectives. *List the purpose and objectives:*

The objective of this study is to identify whether intranasal cocaine impairs temperature regulation during exercise in warm environmental conditions.

2. Background.

- Describe past experimental and/or clinical findings leading to the formulation of your study.
- For research involving investigational drugs, describe the previously conducted animal and human studies.
- For research that involves FDA approved drugs or devices, describe the FDA approved uses of this drug/device in relation to your protocol.
- Attach a copy of the approved labeling as a product package insert or from the Physician's Desk Reference.

You may reference sponsor's full protocol or grant application (section number and/or title) or if none, ensure background includes references.

Please respond to all components of this item, or clearly indicate which components are not applicable.

a. Background

Individuals who abuse cocaine for recreational purpose can have excessively elevated core temperatures (PMID: 9628710, 7484066, 8010552, 18823733, and 2728444). Using a passive heat stress approach, we previously showed that intranasal cocaine administration suppressed skin blood flow and sweating (PMID: 12044126). However, it remains unknown whether suppression of skin blood flow and sweating responses to cocaine are sufficient to cause excessive elevations in core temperature during exercise.

We propose that cocaine-induced reductions in sweating and skin blood flow will result in excessive elevations in core temperature during exercise in warm environmental conditions. Thus, the objective of this work is to test the hypothesis that intranasal cocaine impairs core temperature responses during mild to moderate intensity exercise while in warm environmental conditions.

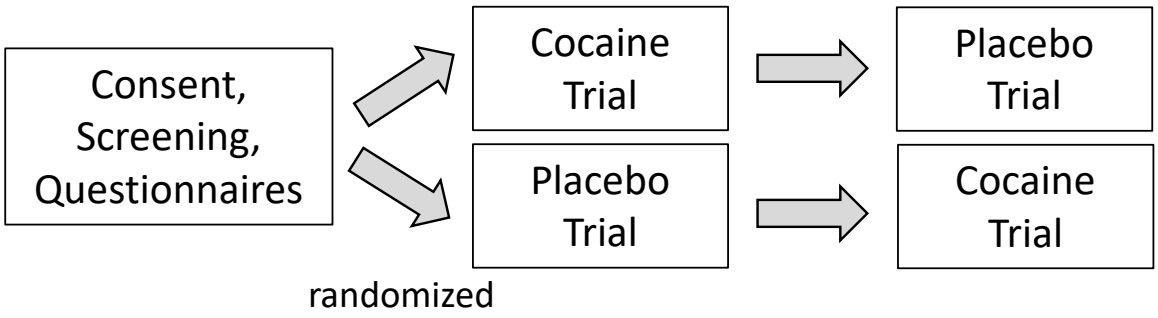
b. Current practice

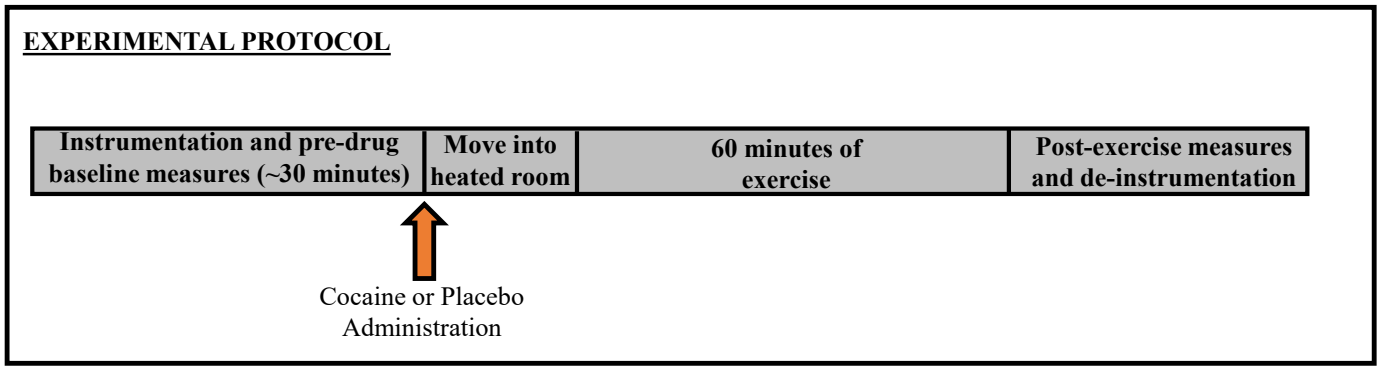
A cocaine solution, administered in each nostril to achieve analgesia and vasoconstriction, is commonly used in rhino-surgical procedures (PMID: 32730351, 16848922, and 26452438). According to the product insert, "The total dose for any one procedure or surgery should not exceed 3 mg/kg cocaine hydrochloride", which is the basis for our decision to not administer more than 3 mg/kg cocaine for any one procedure.

A lidocaine solution is also commonly used for related procedures (PMID: 26452438, 24980226, and 30017430) at doses similar to proposed with the present protocol.

3. Study Design.
Describe the study design (e.g., single/double blind, parallel, crossover, etc.) Consider inserting a scheme to visually present the study design.

We will conduct a double-blind, placebo-controlled, crossover study. Following informed consent and screening, eligible participants will be randomized to complete the cocaine or the placebo (lidocaine) trial first, with the other "agent" administered during the subsequent visit. After the administration of either of these drugs, the participate will perform mild to moderate intensity exercise in warm environmental conditions (no higher than 41 °C).





4. Research Plan / Description of the Research Methods:

4.a. Provide a **comprehensive narrative** describing the **research methods**.

1) Provide the **order in which tests/procedures will be performed**,

2) Provide the **setting** for these events and a description of the **methods used to protect privacy** during the study.

3) Provide the **plan for data analysis** (include as applicable the **sample size calculation)**

Please respond to all components of this item, or clearly indicate which components are not applicable.

Inclusion:

- 18-50 years of age
- Healthy
- Non-obese (body mass index less than 31 kg/m^2)
- Speak English
- Systolic blood pressure <140 mmHg
- Diastolic blood pressure <90 mmHg

Exclusion:

- Subjects not in the defined age range
- Subjects who have cardiac, respiratory, neurological and/or metabolic illnesses
- Any known history of renal or hepatic insufficiency/disease
- Pregnancy or breast feeding
- Current smokers, as well as individuals who regularly smoked within the past 3 years
- Subjects who cannot speak or read English
- History of drug above within the past 5 years
- Positive urine drug screen
- Currently taking pain modifying medication(s)

Although this study requires relatively uncomplicated procedures, inclusion of non-English speaking subjects would compromise subject safety. Consequently, it is imperative that the research and medical staff can communicate instantly and effectively with subjects, without the need of a translator. Therefore, the investigators feel that inclusion of non-English speakers would markedly and unnecessarily increase the risk to those participants.

Healthy adults will be recruited via online and paper flyers, emails to the Texas Health System (reaches over 18,000 people), local universities (inclusive of UTSW), and our institutional participant database. Participants must be free from underlying serious medical conditions (detailed via medical history, physical exam), non-smokers, have a body mass index less than 31 kg/m^2, and will be excluded if they have any current cardiometabolic diseases (e.g., diabetes, heart disease). Individuals who are pregnant, planning to become pregnant, or breastfeeding will be excluded. We will also exclude those with a history of drug abuse.

As described above, all participants will complete an informed consent and screening for eligibility. Participants will be randomized to complete either the cocaine or placebo trial first. During these experimental visits, participants will perform mild to moderate-intensity exercise in warm environmental conditions (no higher than 41 °C).

The setting for all visits will be the Institute for Exercise and Environmental Medicine. Trials will be conducted in controlled laboratory settings. A physician with a license to prescribe schedule II drugs (Noah Jouett DO, Satyam Sarma MD, or Tiffany Brazile MD), or a research nurse (with oversight from that physician) will administer cocaine (no higher than 3 mg/kg body mass) or placebo (lidocaine, no higher than 3 mg/kg body mass) during each experimental visit. We will assess core and skin temperatures, local and whole-body sweat rate, brachial blood pressure, heart rate via electrocardiogram, respiration rate (from metabolic cart), compensatory reserve via photoplethysmography, and plasma catecholamine concentrations from blood samples collected prior to and after exercise (~3 tablespoons per experimental visit). In addition, ratings of perceived exertion and thermal perception will be obtained.

Data analysis will be performed as done previously in Dr. Craig Crandall's laboratory in companion studies addressing the same questions but during passive heating rather than exercise (PMID: 12044126). Specifically, we will compare thermoregulatory and cardiovascular data (e.g., baseline and end-exercise)

between placebo and cocaine trials. All data will be analyzed while blind to condition and with proper co-variate analyses.

Personal health information (PHI) that is collected will be kept in a key-lock filing cabinet in a key-lock room only accessible to study team members within a numeric-padlocked laboratory. As described in the eIRB portal, a coded number system will be used in place of the participants name to de-identify their research information collected. A participant ID key, only accessible to study team members, will link the participants 'information with the coded number. Additionally, we follow all applicable University of Texas Southwestern IRB and Institute of Exercise and Environmental Medicine (i.e., where the research will take place) guidelines for protecting research participant privacy.

Up to 30 participants are anticipated to enroll in this study, with a goal of obtaining complete datasets on 20 individuals. No study has evaluated the effects of cocaine on core temperature responses during exercise in warm (or thermoneutral) environmental conditions. The power and sample size estimates are based on findings from Dr. Crandall's laboratory investigating core temperature responses to 60 min of exercise in burn survivors. Our rationale for using burn survivors is the expectation that the suppression in sweating in burn survivors with 20-40% body surface area burn may be similar to the suppression in sweating caused by cocaine. The power analysis was calculated using G*Power [Ttests – Means: Difference between two dependent means (matched pairs)] using a projected ~25% heightened increase in core body temperature following 60 minutes of exercise with cocaine relative to when participants received placebo (i.e., placebo: 0.82±0.36 °C, cocaine: 1.02±0.40 °C). These predictions resulted in an effect size of 0.60. With a study power=0.81 at an alpha=0.05, yielded an estimated subject size of 19 individuals. That value was inflated to 20 subjects (10 male and 10 female) to permit an exploratory comparison in the primary responses between sexes. Given the potential for subject dropouts, we propose to recruit up to 30 individuals to obtain complete datasets from 20 subjects. Since the effects of cocaine on thermoregulatory responses during exercise have never been assessed, the indicated values are estimates and thus interim power analyses will be performed, with the number of required subjects adjusted based upon the variance of the obtained data.

4.b. List of the study intervention(s) being tested or evaluated under this protocol			
☐	**N/A -** this study does not test or evaluate an intervention. Skip to item 4.d.		
#	**Study intervention(s) being tested or evaluated under the protocol** *Add or delete rows as needed*	**Affiliate** Place a check next to institution(s) where the intervention will be performed	**Local Standard Practice?** Indicate whether the intervention is considered acceptable practice locally for applicable institutions
1	**Cocaine/Placebo administration**	☐ UTSW	☐ Yes
		☐ PHHS	☐ Yes
		☐CMC	☐ Yes
		☒THR	☐ Yes
		☐TSRH	☐ Yes
		☐ Other: _____	☐ Yes

4.c. Risk:Benefit Analysis of study interventions being tested or evaluated under this protocol

For each study intervention identified in section 4b above, complete a risk:benefit analysis table.

(Two tables are provided, copy & paste additional tables as needed or delete both tables if this study does not test an intervention)

4.c.
Study Intervention #1
Cocaine /Placebo Trials

List each group exposed to this intervention on a separate line. (e.g., experimental, control, Arm A, Arm B, etc) **Or** state All Groups/Subjects	For each group, list the **benefits** of this intervention. (Benefits can be directly from the intervention or from a monitoring procedure likely to contribute to the subject's well being). If there are no benefits, state "none".
All subjects	Identify whether intranasal cocaine impairs temperature regulation during exercise in warm environmental conditions

If you are requesting a Waiver of Informed Consent, complete the table below.

If you have a consent form, **list the reasonably foreseeable risks in the consent form (and do not complete this section).**

List the risks according to the probability (likely, less likely or rare) and magnitude (serious or not serious). (include: 1) expected adverse events; 2) rare and serious adverse events; 3) all other psychological, social, legal harms)
Do not delete frequency. Frequency must be estimated because it will assist you with determining which adverse events will require prompt reporting.

	Not serious	**Serious**
Likely These risks are expected to occur in more than **20** out of **100** subjects.	• N/A	• N/A
	Not serious	**Serious**
Less likely These risks are expected to occur in **5-20** subjects or less out of **100** subjects.	• N/A	• N/A
		Serious
Rare These risks are expected to occur in less than **5** subjects out of **100**		• N/A

		4.d. List ALL other research procedures or components not listed in table 4.b. ***The combination of Tables 4b and 4d should account for all of the research procedures that will take place during this study.*** Consider grouping similar procedures under a single component (e.g., blood work, CT = safety assessments)		
#	**Research component** • **individual procedures** *example:* **Eligibility Assessments** • History and physical • Questionnaire • Laboratory tests *Add or delete rows as needed*	**Column A** **Local Standard Practice** Indicate the number of times each procedure will be performed as stipulated in the research plan **that would be performed if the participant were not participating in the study.**	**Column B** **Research Only** Indicate the number of times each procedure will be performed solely for research purposes *(meaning that the participant would not undergo the same number of procedures or would not undergo the procedure(s) at the same frequency if they were not participating in the study)*	**Column D** **Risks** **If you are requesting a Waiver of Informed Consent, complete the table below.** List the reasonably expected risks for each procedure or group of procedures under the following categories as appropriate: • Serious and likely; • Serious and less likely; • Serious and rare; • Not serious and likely; • Not serious and less likely
1	**Eligibility assessments**			
	Health history assessment	0	Once	
	Body height and mass	0	Once	
	Heart rate and rhythm via 12-lead ECG	0	Once	
	Brachial blood pressure	0	Approximately 3 times	
	Submaximal exercise	0	Once during the screening visit	
	Physical activity questionnaire (IPAQ)	0	Once	
2	**Other assessments**			
	Core temperatures	0	Continuously during the experimental visits	
	Skin temperatures	0	Continuously during the experimental visits	
	Regional sweat rate	0	Continuously during the experimental visits	
	Whole-body sweat rate	0	Once per experimental visit	

	Skin blood flow	0	Continuously during the experimental visits	
	Limb blood flow (Doppler ultrasound)	0	Approximately 3 times	
	60 minute of exercise in warm environmental conditions	0	Once per experimental visit	
	Assessments of perceived exertion and thermal perception	0	Approximately every 10 minutes during exercise	
3	**Blood sampling**			
	Blood sampling	0	Up to 6 draws (up to 3 draws per visit; baseline, post-drug/placebo administration, and post-exercise). Total blood withdrawn for the entire study: ~6 tablespoons.	
4	**Cardiovascular and other physiological measures**			
	Heart rate and rhythm via ECG	0	Continuously during the experimental visits	
	Brachial blood pressure	0	Before exercise, approximately every 10 minutes during exercise, and after exercise for each experimental visit	
	Compensatory reserve	0	Continuously during the experimental visits	
	Cardiac output	0	Approximately every 15 minutes during exercise for each experimental visit	
	Urine sample	0	Once each visit	
	Ventilation and oxygen uptake	0	Approximately every 15 minutes during exercise for each experimental visit	

5. Safety Precautions. *(Describe safeguards to address the serious risks listed above.)*

a. Describe the procedures for protecting against or minimizing any potential risks for each of the more than minimal risk research procedures listed above.

Cocaine and lidocaine administration: No greater than 3 mg/kg body mass of cocaine or lidocaine will be administered once during one each experimental visit. At the administered doses of cocaine or lidocaine (doses consistent with procedures performed by an ears, nose, and throat physician in a doctor's office setting) the risks to the participants are minimal. That said, the administered dose of cocaine has the potential to slightly elevate arterial blood pressure and heart rate. However, in our prior trial (PMID: 12044126) cocaine increased resting blood pressure less than 10 mmHg and increased resting heart rate

less than 10 bpm, both relative to the placebo (lidocaine) trial. Thus, we do not expect blood pressures or heart rates to be excessively elevated. Importantly, in the healthy cohort that will be assessed, such increases in arterial blood pressure and heart rate are inconsequential. Importantly, we will monitor the patient's vital signs continuously for both the cocaine and lidocaine experimental limbs. A physician licensed to precribe schedule II drugs (Noah Jouett DO, Satyam Sarma MD, or Tiffany Brazile MD) will be present whenever cocaine is administered to observe and intervene should the patient exhibit the slightest evidence distress. Standard “crash cart” equipment (inclusive of a defibrillator) will always be readily available. As mentioned above, we performed similar trials, using cocaine and lidocaine (PMID: 12044126) in young healthy adults without any complications.

Upon the conclusion of the protocol, subjects will not be permitted to leave the laboratory until all of the following discharge variables are met:

- The subject presents with an Aldrete score (post-anesthesia discharge scoring system) matching baseline,
- The subject demonstrates an awareness of time, person, and place and is able to answer questions appropriately
- The subject is able to stand up and walk for 5 minutes without assistance (supervised)
- The subject is able to drink water and eat crackers without reports of nausea
- The subject able to void

Sub-maximal exercise in thermoneutral conditions: There are no additional risks involved with performing a sub-maximal exercise test beyond that associated with light to moderate-intensity physical exertion. Every precaution will be taken to minimize the risk by closely monitoring vital signs (blood pressure, heart rate and rhythm) throughout the exercise. This test will be stopped if signs or symptoms of cardiac ischemia develop, if excessive hypertension or hypotension develop, or if arrhythmias occur during exercise. A research nurse will be present during the sub-maximal exercise test to interpret any danger signs and symptoms.

Exercise in warm environmental conditions: Internal body temperature will be monitored throughout each experiment. The protocol will stop, and the environmental temperature will be reduced, in the unlikely occurrence that internal body temperature exceeds 39.5°C or upon any indication of adverse cardiovascular or neurological symptoms (e.g., lightheadedness, hypotension, hypertension, nausea, etc). Our 20+ years of experiences reveals that healthy individuals are able to tolerate the exercise bout well. Upon completion of each trial, we will ensure that each subject is normothermic and adequately hydrated prior to being permitted to leave the laboratory. A research nurse will monitor the participant’s vital signs throughout exercise and will stop the exercise, and cool the environment, should any adverse signs or symptoms occur.

Internal temperature (temperature sensor pill): See comments above regarding the internal body temperature cut-off (39.5 °C) for all trials. This pill should not be taken if the subject weighs less than 80 pounds, nor should the subject take this pill if they have or have had any gastrointestinal disease or surgery. The research nurse will also check each subject’s medical history prior to the pill being swallowed. Should a subject have any contraindications in taking the pill, the pill will not be ingested. Rather, rectal temperature will be obtained.

Internal temperature (rectal sensor): If rectal temperature is used, the subject will self-insert a small single-use rectal temperature sensor to a pre-marked depth of 15 cm. The rectal thermocouple will not be inserted if they have or previously had inflammatory bowel or colon disease and/or rectal or anal surgery. They also may not use the probe if they currently have hemorrhoids (internal or external), rectal bleeding, diarrhea or fecal impaction in the rectum. Each subject’s medical history will be verified prior to self-insertion of the rectal probe by the research nurse.

Internal temperature (suppository pill): If a suppository temperature sensing pill is used, with a gloved hand the subject will self-insert a lubricated temperature sensor pill (like a suppository) into their rectum.

This pill will be discharged through normal defecation. This temperature sensing pill will not be used if the subject currently has hemorrhoids (internal or external), rectal bleeding, diarrhea or fecal impaction in the rectum. Each subject's medical history will be verified by the research nurse prior to self-insertion of this pill.

Blood draws: Blood draws will be obtained via a "butterfly" needle. No more than 6 tablespoons of blood will be withdrawn across all visits. There is a small risk of infection and a still smaller risk of a blood clot. The likelihood of these complications is remote (less than 1 in 10,000) when the procedure is carried out by trained personnel and proper equipment is used, as during this study. There is also a small risk of the needle perforating the vein or not being inserted into a blood vessel. The participant may have discomfort, bleeding, and/or bruising and on rare occasions, a person may feel dizzy or faint.

Health history assessment: Participants will fill out a survey related to their physical well-being. It is possible individuals may feel uncomfortable while completing this survey. We will ensure all participants are aware of this procedure during the informed consent visit. If a participant is uncomfortable completing all of the survey, they will be reminded that 1) their participation is entirely voluntary, 2) that only study investigators will have access to the surveys and their results, and 3) only de-identified results will be shared in scientific meetings and/or in future scientific manuscripts.

b. Where appropriate, discuss provisions for ensuring necessary medical or professional intervention in the event of adverse events, or unanticipated problems involving subjects.

When the participant is undergoing any testing, they will be supervised by an ACLS trained nurse and/or physician. In addition, physicians and nurses at the Institute for Exercise and Environmental Medicine will assist as needed. A physician licensed to prescribe schedule II drugs (Noah Jouett DO, Satyam Sarma MD, or Tiffany Brazile MD) will be present when cocaine is administered. There is a fully stocked "crash cart" with a defibrillator and medications within 50 feet of the laboratory. Anti-arrhythmic medications are rapidly available if a sustained but not life-threatening arrhythmia were to occur. Airway management equipment is also stocked in that cart. Furthermore, the Texas Health Resource Emergency Room is minutes away if an escalation of care is required.

Upon screening, participants will be given contact information for a nurse to contact in case any adverse event occurs following discharge from experimental days. However, this is unlikely to occur given the short-acting effects of cocaine and the fact that participants are not discharged until vital signs are similar to that of baseline values.

c. Will the safeguards be different between/among groups?

☐ Yes ☑ No