Research Protocol

Title: Investigation of the effect of environmental temperatures on non-contact thermal imaging for core body temperature measurement

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A. Introduction

The purpose of this study is to examine the effect of the local environment and the physiology of the human body on the relationship between core body temperature and inner canthus (region near tear duct) skin temperature measured using non-contact thermal imaging. The overall goal of this research study is to validate and improve the science of non-contact core body temperature measurement. The present inquiry is of minimal or no risk, is not focused on a vulnerable population, will include study participants who are not current members of the St. Olaf community and findings will be shared outside St. Olaf, thus this is a Type 2 project.

Core body temperature is one of the vital signs, being used to diagnose conditions associated with abnormally high or low temperatures. Normal body temperature can vary with gender, recent activity, food and fluid consumption, mental and physical stress, time of day, and, in women, the stage of the menstrual cycle[1]. Clinical studies of oral temperatures acquired using thermometers having a measurement accuracy of 0.1C (0.18F) in healthy adult humans have found a distribution with a standard deviation of approximately 1F (0.6C) and averages ranging from 97.9F to 98.6F[2]. Oral thermometry is sensitive to probe placement, recent speaking or mouth-breathing, recent fluid or food consumption and even air temperature. In-ear thermometry is an oft-used alternative but is affected by ear geometry and debris, often requiring re-measurement attempts. These thermometry methods can be inconvenient in some clinical practices due to the time required, and thus, non-contact or other surface-based thermometry methods are desired.

The use of non-contact core temperature screening has become widespread in society due to the COVID-19 pandemic. Past clinical trials have demonstrated the sensitivity and accuracy of thermographic (image-based) non-contact body temperature measurement. A comprehensive

[1] Normal physiologic variability in core temperature is well established, with the time-of-day and menstrual cycle generally accepted as contributing the largest sources of variability, each ranging from 0.3 to 1F in magnitude.

[2] The idea of an adjusted “average” body temperature, lower than the value of 37C or 98.6F arrived at in the 19th century, is still of considerable debate, with some studies confirming lower values and others suggesting the findings are caused by confounds in the populations being studied. Several possible causes or confounds are being investigated, such as increases in medication usage, changes in diet and lifestyle or decreases in latent infectious disease.

online reference can be found in Hinnerichs 2011 (https://scholarworks.waldenu.edu/cgi/viewcontent.cgi?article=1018&context=hodgkinson), which discusses past studies and demonstrates a clinical study of thermographic febrile screening used during a swine flu epidemic on board a Navy vessel. All surface-based body thermometry methods rely on a skin surface temperature measurement and calibrated extrapolation to one of the core body temperature sites, most often the oral site. In order for the measurement to have diagnostic power, it must have sufficient accuracy, and while the surface temperature accuracy can be evaluated using calibration reference sources, the impacts of the local environment and physiology are not as simple to evaluate yet are essential elements that do not seem to be accounted for by the majority of non-contact core temperature measurement systems (see Addendum - Performance Standard for Non-Contact Core Body Temperature Measurement).

Surprisingly, while there is literature documenting the dependence of the skin temperature on air temperature, this was somehow forgotten in the first implementations of thermographic fever screening systems and subsequently the international standard developed and promulgated for this purpose. It is unclear how a thermographic system that does not account for environmental air temperature changes could produce accurate core body temperature measurements. Further, there is very little literature on the impact of these potential confounds on thermographic body temperature measurement methods (e.g. see Fig 2 in Obermeyer et al for correlates between oral core body temperature and pulse, blood pressure and weight/BMI). This is relevant for public health, since at this time, non-contact body temperature measurement is used widely not only by some clinical practices but also by public and private organizations for assessing individuals for the presence of possible fever. Early in 2020, retrospective studies on hospital admissions in China showed fever to be the single most common initial indication of infection with SARS-nCov-2 (Guan et al). Later studies revealed the presence of considerable asymptomatic and presymptomatic transmission, lowering the risk reduction possible for COVID-19 using temperature screening. The lack of research on the science of non-contact body temperature measurement and more importantly the lack of a method to assess the real-world sensitivity and specificity of such systems provides credence to the claim that much, if not all, of non-contact body temperature measurement for COVID-19 is mere “safety theater”, implemented with less regard to actual utility in detecting febrile individuals than to the appearance of providing safety.

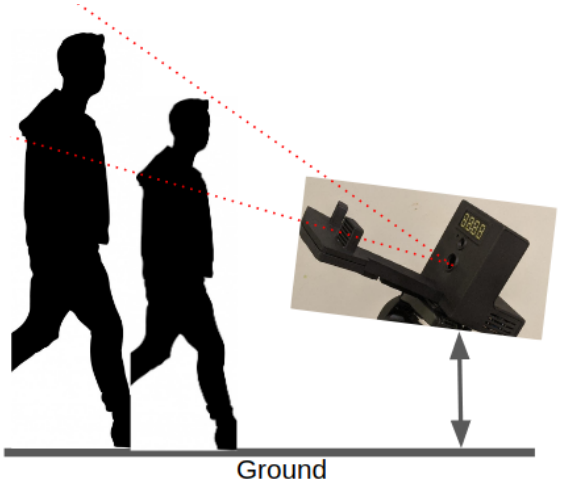
Beyond non-contact thermographic screening, deeper concerns for public health have arisen with a related non-contact technology. Specifically, the concern is with an existing FDA-approved class of non-contact single pixel (single pixel meaning non-thermographic, or non-image-based) infrared (IR) scanning systems configured to perform IR temperature measurements of the forehead and report an extrapolated core body temperature. FDA-approved devices within this class have been observed to report healthy body temperatures in conditions that should preclude an accurate measurement (e.g. being operated outdoors in inclement conditions), which has led to many clinicians being wary of trusting these devices. Furthermore these devices have also been observed to report temperatures all within a

normal range between 97 and 99F when operated on an IR calibration source having simulated body temperatures covering the range from 95F to 103F, which is a clear cause for concern. This specific observation has led to published reports documenting the use of “bias-to-normal” algorithms that take a range of input temperature measurements and output a smaller range of temperatures closer to the normal body temperature. This is difficult to detect due to the limited spread in normal core body temperatures in the healthy population, and in fact, by generating a made-up temperature from 98.6 plus or minus a small random fraction less than 1, one can produce an apparently-functional body temperature measurement system that is difficult to distinguish from the oral temperature measurement. Due to the presence of documented bias-to-normal algorithms, it is clear that improvements in test methods are desperately needed. Until such time, any evaluation must include a range of actual core body temperatures extending into diagnostically-relevant high temperatures (individuals having real fevers) or it will be difficult to detect a bias-to-normal algorithm.

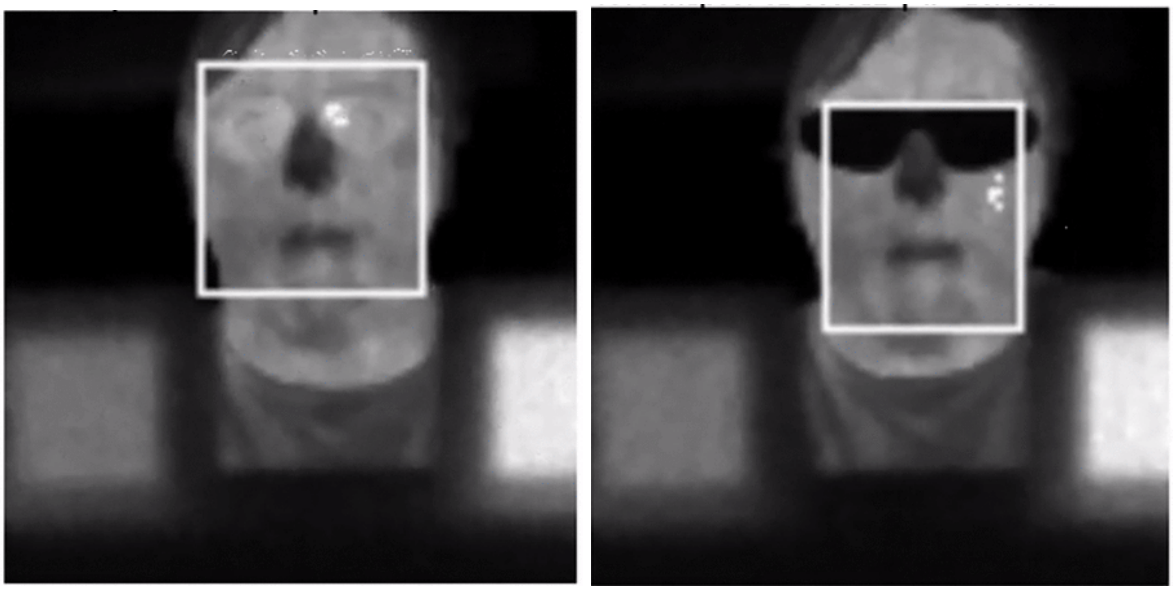
The gold standard for evaluating a diagnostic is a clinical trial, but obtaining measurements of actual febrile individuals is highly challenging and associated with added risks to the operator and potentially to the febrile participant. Large studies recruiting directly from participants seeking care in emergency departments in three major cities (Nguyen et al) recruited over 2,000 participants in *each* city yet only uncovered less than 100 fevers in each group of between 2,000 and 2,500. A major issue with the aforementioned study and other past thermographic studies (e.g. Ng et al and Chiang et al) has been the use of a post-hoc fever threshold, which makes the determined sensitivity completely meaningless, since the threshold was determined after the data was examined (see Table 1, “Optimal Fever Threshold” in Nguyen et al in particular). A detailed discussion of thresholds and their sensitivity to daily changes can be found in Hinnerichs et al 2011. The threshold is referred to in the ISO standard but no guidance is given on how this should be determined, nor is the science of how the ideal threshold will actually vary over time based on the ambient air temperature. It should be pointed out that a typical analysis presented in past thermographic studies is the linear correlation coefficient between the oral and thermographic temperature. However, a bias-to-normal algorithm does not preclude a strong correlation even if the system’s actual sensitivity is very low. When studying biological variables that do not vary widely, the use of linear correlation can be misleading.

Given the difficulty of obtaining sufficient febrile participants for assessing these systems, it would be ideal if there were a way of objectively manipulating face temperatures, however until now simple methods such as heated water bottles have had accuracy of at best 5 degrees C, which is too poor for the assessment of these systems in the way they are intended to be used. As a consequence, regulatory agencies and users have not had a way to assess these systems. Based on recent findings, it is possible that nearly all or even all body temperature measurement systems used to-date have relied on bias-to-normal methods due to major confounds. If there were a source of faces with varying temperatures corresponding to mild, moderate and severe fevers as well as healthy temperatures, it would become possible to detect biasing methods. A new method, used in this study, allows the objective manipulation of face temperatures with sufficient accuracy for assessing real-world sensitivity and specificity.

Furthermore, this method requires no special equipment beyond a clinical oral thermometer and control over air temperatures in closed spaces (rooms, large tents having sufficient dimensions for multiple persons to stand, or other controllable spaces, hereafter "***rooms***") to within 1C and allows the control of simulated body temperatures with 0.25C accuracy.



The image on the left shows a thermographic core body measurement system that incorporates dual IR calibration sources in the imaging field of view. The image on the right shows general positioning and usage for different height individuals. Once a face is detected within the field of view, the camera collects thermal images which have been corrected for luminance artifact and linearized to the IR calibration sources, and typically reports a core temperature estimate within a second, reporting the result on the display.



The images above show a typical thermal face image as captured by the system, with the results of an automatic thermal face detection system overlain on the subject's face. Below the subject's face and to the sides are the two IR reference targets. It is important to point out that thermal light does not penetrate clothing or common objects such as glass and plastic that is

transparent to visible light. Also note the subject's left inner canthus is delineated on the image to the left with white specks (the hottest subset of pixels is replaced by white to provide feedback on device operation). The inner canthus is not the eye nor the tear duct, but rather a space on the nasal bridge midway between the eye and the nasion, very close to where eyeglasses with metal wire bridges terminating in a flat soft pad would contact the nasal bridge.

The overall goal of this study is to improve the IR thermometry science by 1) contributing a method for the objective manipulation of face temperatures using environmental air temperature changes and 2) developing a schema to use this method to assess the real-world sensitivity and specificity of non-contact IR core temperature measurement systems in normal, mild, moderate and severe fever groups, corresponding to core temperatures below 38C (100.4F), 38-39C (100.4-102.2F), 39-40C (102.2-104F) and above 40C (104F). This study is relevant for public health risk, because at present, there is no real-world objective test for thermographic febrile temperature screening devices, which significantly hampers the ability of regulatory authorities to identify improperly operating devices. A secondary goal is to determine the impact of potential confounds on non-contact thermographic temperature measurement. This translates to clinical utility, as any confounds could influence the decisions to prioritize the use of such systems. This is also related to public health risk, because the non-contact core body measurement systems the public is now relying on may have unacceptable biases in their determination of core temperature and it is possible they may even induce harm by altering behavior. Additional documentation is provided as a supplement for the review of this study detailing methods for the evaluation of thermographic systems.

B. Research Design and Methods

Study Population

Participants will be recruited from the population of summer students, faculty and staff at St Olaf college and responders to the St Olaf-affiliated email list during the summer of 2021. The research study will be advertised in three ways: 1) via selected campus email lists created for summer research students, students working on campus over summer and international students living on campus or nearby over summer, 2) via faculty and staff email lists, the St Olaf-affiliated list stolaf-extra and the Psychology 125 Moodle site and 3) via posted advertisements in up to two areas allowing physical postings each in Buntrock Commons, the Athletic Center, the Science Center and residence halls, e.g. outside the Caf in Buntrock Commons, near the main entry to the Athletic Center. The exact advertisements are included as supplementary materials to the protocol along with an advertisement protocol denoting the timing and duration of each advertisement.

Participants responding to the advertisement will be briefly interviewed to determine their potential status regarding the inclusion and exclusion criteria and timing available for the study completion. Participants will be in common areas, in sufficiently close proximity to each other (respecting COVID-19 social distancing) to enable conversation and potentially revealing information to each other, which the study personnel will have little to no control over. The participants will be made aware of this possibility and told to refrain from disclosing personal

information in the consent document. Participants will be informed of the requirement to wear masks at all times during the study, except during oral temperature measurements or during a 15-minute break period in the middle of the study.

Population Size

The number of samples required to understand the impact of environmental or physiological confounds on surface temperature is dependent on the variability in the core-to-surface temperature physiologic offset. The variability in core body temperature has been found to be close to 1F but note the research design proposed here is not dependent on normal person-to-person variability in core temperature because the temperatures obtained are all referenced to each individual's core temperature. To estimate the likely physiologic variability in the population, we can extrapolate based on surface temperature data taken by the primary thermographic system obtained over the past six months because this should be approximately the vector sum of variability in core temperature, measurement accuracy, and the physiologic variability. This data must be interpreted with caution, because these have been obtained with less control over environmental conditions and furthermore we do not know the core body temperature variability in the preliminary data population, but it can provide a reasonable error bound. This data shows a standard deviation of 1.11F (note, this value is obtained without *any* bias-to-normal algorithm, which appears to be a novel feature in this research), which would suggest the physiologic variability component is at most 0.48F, or half a degree. Therefore, in order to determine the sensitivity and specificity at detecting elevated temperatures of 1.8F (100.4F threshold) to within 20% (meaning, can we significantly distinguish 100.40 from 100.04F with the aforementioned standard deviation in a one-sided paired t-test), we require 28 participants. To account for possible data collection failures, we intend to recruit as many as 45 participants.

Data Collection

- Demographic and clinical data: minimal demographic and clinical data will be collected by interview with the participant at the time of the imaging studies including age, gender, any disease- or autonomic-modulating treatment, height, weight and any antipyretic medications in past 12 hours in order to allow adjustment for confounding factors. We do not intend to collect data on menstrual cycle due to the additional potential privacy concerns this will place on participants worried about this data which is significantly more sensitive than other data being collected.
- NFC identification: the data collected will not be associated with any identifying information, instead being collected on a single printed sheet of paper having a near-field communication (NFC) sticker placed upon it. This NFC sticker will be used to activate the scanner as well as indicate which room a participant is equilibrating within. This is intended to reduce data collection errors as well as to reduce the possibility of personally identifiable information being exposed.
- Temperature measurements: Study participants will undergo non-contact body temperature measurements from several devices as well as an oral thermometry measurement. The non-contact thermal imaging temperature measurements must be

acquired while any eyeglasses are removed and the eyes must remain visible to the thermal imaging system during each measurement. The participant may be seated or standing for the non-contact thermal imaging temperature measurement, and the distance between the measurement system and the participant may be anywhere between 0.45 and 1.5 meters (1.5 to 5 feet). Masks can be worn during thermal imaging without interfering with the measurement.

- Imaging temperature measurements with glasses: Study participants will be asked to try to bring personal sunglasses and/or eyeglasses with them to the study for use in collecting thermal images of their faces while wearing these. Occluding the inner canthus is generally considered a major confound to acquiring an accurate imaging temperature with thermal imaging, and this data will be used to assess the impact of various eyewear on the output.
- Associated data: the ambient air temperatures at the time of each scan, the distance to participant's face, internal system parameters and the thermographs used to measure the imaging-based core body temperature will be stored, associated with the NFC UUID scanned prior to a scan. These thermographs will be encrypted with the public portion of a private/public key pair, the private portion being stored only on a separate password-protected and filesystem-encrypted computer used for analysis of the images. The thermal imaging system's filesystem is also encrypted and protected by a device-specific 160-bit key that is not practically recoverable from the device. System access is restricted by an RSA key and the system's network is protected by an on-device firewall.

Inclusion Criteria

1. Age > 18.
2. Have received a clinical oral thermometry measurement in the past.

Exclusion criteria

1. Contraindication to oral temperature measurement.
2. Inability to follow instructions.
3. Any diagnosis associated with abnormal core thermoregulation, e.g. autonomic dysfunction.
4. Obvious signs of tissue damage present in either inner canthus.
5. Facial artery abnormality if previously diagnosed.
6. Experienced discomfort while receiving most recent clinical oral thermometry measurement.

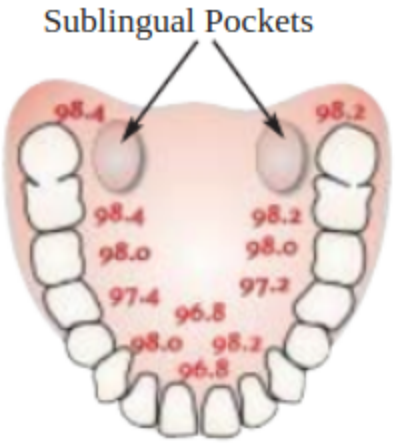
Study Procedures

After a detailed explanation of the study and its potential risks and benefits and informed consent will be obtained by the principal investigator or one of the co-investigators. Participants will then receive a single printed sheet containing places to enter the demographic and clinical information outlined above, as well as an NFC sticker uniquely linking the information on the sheet to all temperature measurements (Data Collection Sheet included in protocol materials).

The total time involved for participants will be approximately 120 minutes, with 100 minutes being spent in actual study procedures. The oral and thermal imaging evaluations will be performed in rooms identified as suitable for the purposes below. There are two separable phases to the study, the first (***blinded temperature phase***) involves isolated non-contact measurements and oral thermometry in a building-temperature room after spending ten minutes in each of three blinded elevated-temperature rooms and the second (***equilibration phase***) involves serial non-contact measurements of the inner canthi of seated participants over ten minutes and an oral thermometry measurement in one elevated temperature room and one reduced temperature room. All study procedures will be performed in groups sized no larger than allowed by St. Olaf College's COVID-19 restrictions on social distancing within the selected rooms. Participants will receive a $20 gift card in compensation for their time and effort involved in participation in this study.

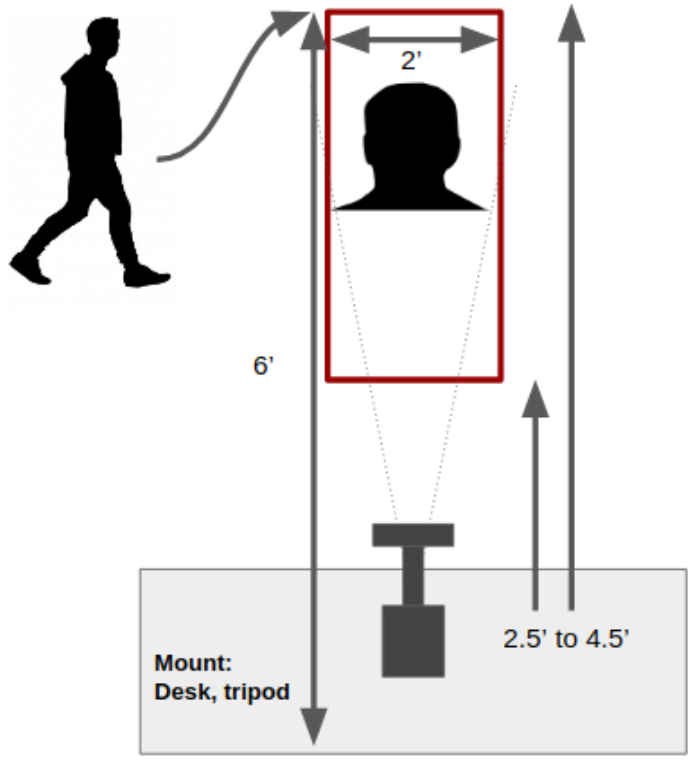
<u>Oral Thermometry</u>

Oral thermometry will be performed by a trained study personnel using a clinical FDA-approved oral thermometer (Welch-Allyn SureTemp Plus 960, see figure below right) with disposable probe covers. The operator will wear a N-95 or KN-95 face mask and disposable gloves for the duration of the measurement. The participant will be directed to remove their face mask from now until the oral temperature measurement is completed. The operator will place the probe tip inside a new probe cover, then place this covered probe tip under the sublingual pocket (see figure below left) of the participant's tongue on either side, whereupon the participant is directed to close their mouth. The device will report a lower-accuracy "Quick mode" reading within approximately 10 seconds and the operator of the device will place the thermometer into a higher-accuracy "Monitor mode", which will require up to two minutes until the device reports a stable reading. Once the stable reading has been reported, the probe will be removed from the participants mouth and the probe cover discarded. Prior to the oral thermometry, the participant will be instructed to refrain from excessive breathing with an opened mouth, consuming food or drink, placing gum or other objects inside their mouth, and excessive talking for the 10 minutes before the oral thermometry measurement is completed. Oral temperatures will be obtained after each set of non-contact measurements.



Primary Thermographic Camera

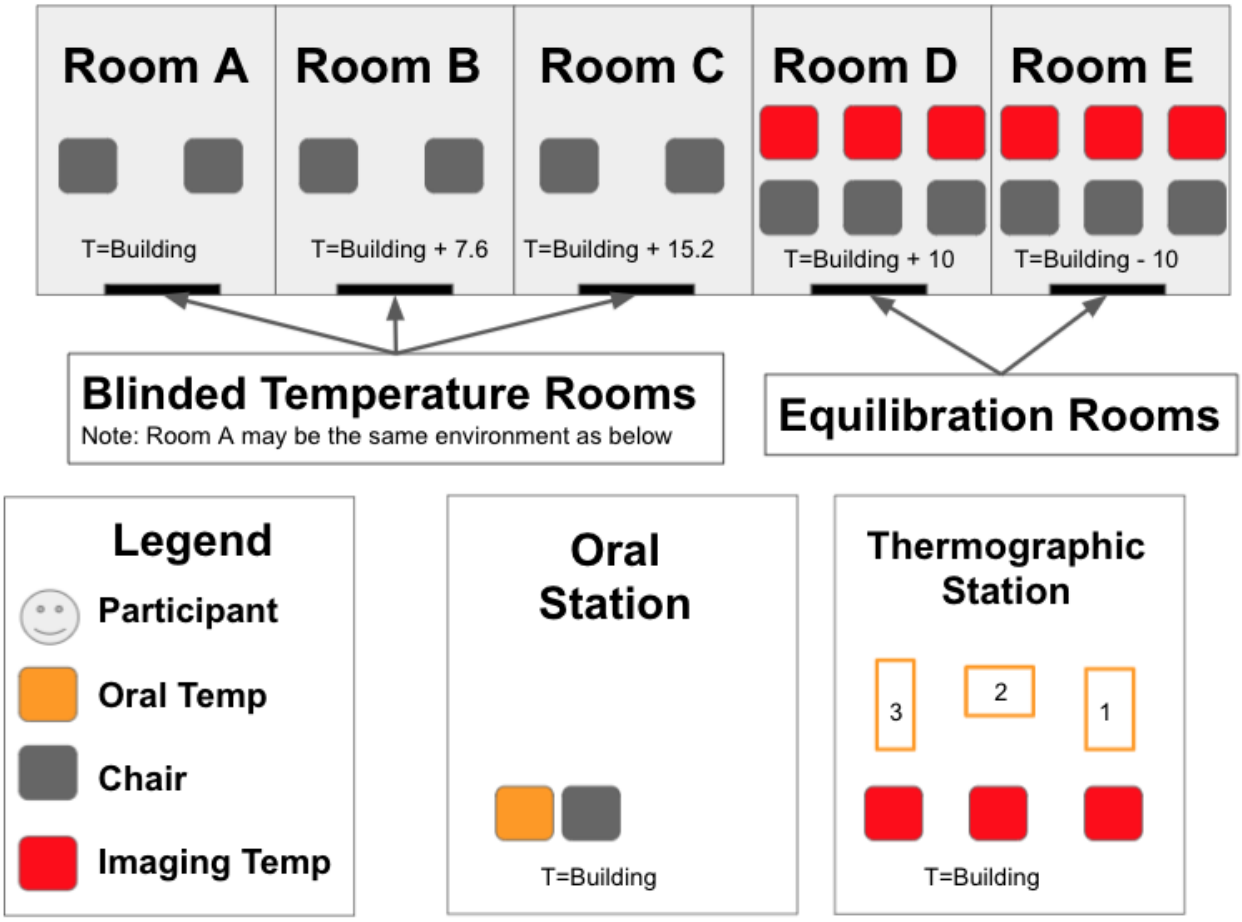
The thermographic camera (non-contact thermal imaging temperature scanning system) used in this study is the Thermal Diagnostics FIP-S system, referred to hereafter as the ***primary*** non-contact system. This system must be located in an area free of noticeable drafts and without large heat sources within two meters of the camera, such as a space heater, oven or other device that may provide more than a square meter of surface area heated above 160F. The camera will be mounted on an adjustable height microphone stand near a standard source of building power (100-240VAC, 0.6A). The scanning area may be denoted by tape markings on the floor or indications posted on the wall or otherwise provided to the scanner operator (investigator or research assistant performing the scan). As shown in the image to the left below, the camera is mounted at 4 feet from the ground and angled upwards at 45 degrees or more. For very short or very tall individuals, the operator may adjust the height or angle of the camera or alternatively provide a stepstool or ask the volunteer to stoop slightly. The volunteer's face must be at least 1 ½ feet away from the camera and no more than 4 ½ feet away from the camera. When a face is detected for a person standing within an approximately 2 foot by 2 foot area, the camera will begin collecting measurements and typically will report a result in approximately one second, completing a scan. The camera requires five minutes to power on and stabilize in standby mode, ready for scanning, before first use. The camera is placed in scanning mode by placing an NFC sticker or card on the attached NFC reader, whereupon the camera transitions to scanning mode for up to 30 seconds, collecting 3 face scans in sequence, typically taking 10 seconds to complete and displaying a unique 4-digit hexadecimal number and a yellow light, before returning to standby and clearing the display after 4 seconds.



Secondary Non-Contact Equipment

Several other non-contact thermographic and single-pixel NCIT systems are available for use in this study. These are referred to as the ***secondary*** non-contact systems and each measurement will be denoted by the system or manufacturer name. Each system will be set up following the manufacturer's operating instructions, similarly to the primary non-contact system and immediately adjacent to said primary system. Each secondary system will be configured in logging mode, if a mode that records the estimated core temperature with a timestamp is available. If such mode is not available on a particular system, said system will be associated with a clipboard for manually logging the system's output along with the unique number outputted by the primary system upon scanning the participant.

Controlled Temperature Rooms



Please refer to the image above, which is reproduced from page 3 of the Study Schema document. This study requires four rooms having independent control of air temperature to gradients above or below the primary setpoint of the building and a main area at the primary setpoint of the building. This main area may consist of two rooms (e.g. Room A and the room containing both Oral and IR thermometry stations above), one for acquiring IR thermometry and oral temperatures and a second for blinded ambient temperature or a single room

encompassing both areas. The desired target temperatures for the equilibration phase (Rooms D and E above) are 60F and 80F (or 10F lesser than and 10F greater than the building's setpoint), while the desired target temperatures for the blinded temperature phase (Rooms A, B and C) are 68, 75.6 and 83.2F, if the building's target temperature is 68F, otherwise these should be offset with the difference. To obtain these temperatures, three rooms require heating and one room requires cooling. Each of the heated rooms will have a 1500W space heater and the cooled room will have a flexible temporary doorway installed with ductwork to a portable air conditioning unit. A wall-powered thermostat directed to switch by a rectified PID controller is then used to regulate the on/off cycle of each system. The building's airflow via the ductwork into the room may be damped with assistance from building maintenance. An air temperature logging system is set up in each room and in a preliminary study, is used to obtain the time constant and thermal stability of the room with the associated heating and cooling equipment. The key requirement for a suitable room is that the thermal stability must remain within 1C (1.8F) of a single value near the desired setpoint temperature for 10 minutes. Note, during both phases, it is unlikely these exact setpoints will be achieved at all times due to repeated opening and closing of doors, but fortunately this is not essential because ultimately the analysis is dependent on induced surface temperatures and the resulting induced core temperatures will be calculated for each subject based on the actual blinded temperature and the temperature of the room the IR thermometry is done within.

The rooms will each consist of a portable tent with dimensions of at least 5x5ft base and height of 6ft. The critical requirement of said tent is sufficient thermal isolation from ambient temperatures to allow the maintenance of the required elevated or cooled temperature setpoints to within 1.8F. At present time, the most suitable tent is the THUNDERBAY Ice Cube 3 Man Portable Ice Shelter https://www.amazon.com/gp/product/B019CU59VI. This tent is surprisingly large, and has sufficient space to allow four adults to stand with 2 feet between adjacent people or two people with over 3 feet between them. The thermal radiant intensity of the walls of this tent do not match that of the elevated or cooled air temperature, because these walls directly contact and conduct to the ambient air and equilibrate between the ambient and internal temperatures, thus they radiate closer to the ambient temperature. Therefore, additional radiating membranes are used, consisting of sheets of fabric or paper hung from the ceiling or otherwise mounted with at least several inches displacement from the walls and having sufficient but low level of air flow to equilibrate the majority of the membrane to the internal air temperature. A GFCI-protected extension cord and powerstrip will be used to provide power to each tent.

The formula relied upon to obtain the ideal elevated temperatures is as follows, given as a lambda expression, which incorporates a first lambda (Python):
*- core2surf = lambda core, air: core - (core-air)*0.191*
- get_needed_room_air = lambda air, febrile: core2surf(febrile, air)- ((98.6 - core2surf(febrile, air))/0.236)

This gives us the needed heating temperature to get a desired change in body temperature, e.g. *get_needed_room_air(68, 100.4)* returns 75.6F, meaning, in order to simulate a 100.4F core

temperature, a person must equilibrate to 75.6F air temperature before returning to receive a scan from the primary scanner located in 68F air temperature. This can be summarized more simply as, for every 1C (1.8F) elevation desired, the heated room must be that multiple of 4.23C (7.62F) above the scanning area's air temperature. Note, the exact coefficient was determined in a pilot study performed in June 2020, and may be refined by this study, which could alter the expected induced core temperatures.

Detailed Procedure - Blinded Temperature Study

Each participant is given a random room letter provided by a display configured to output a letter randomly pulled from a uniform distribution of the room numbers A, B and C. The participant is to go to said room and locate the NFC scanner inside and scan their data collection form to obtain their ***nfc-room-scan*** (to be used in later identifying which temperature group their body is simulating). Once the participant has entered a room, the door to the room is closed and the participant is instructed to wait while remaining relatively still for ten minutes while avoiding touching their faces and avoiding stressful content (e.g. avoid browsing the internet). At the conclusion of the ten minutes, determined by study personnel, the door will be opened and the subjects will exit the room and walk to the scanning area to scan their data collection form to obtain their ***nfc-temperature-scan*** and receive three consecutive face scans. After these scans are complete, participants will proceed to additional thermographic face scanning equipment to receive additional scans within one minute of exiting the equilibration room. Study personnel will record the results of any additional equipment scans along with a unique number displayed on the primary thermographic system display at the conclusion of their primary temperature scan. Study personnel will then obtain an oral thermometry measurement. After all oral and IR thermometry measurements are complete, participants will proceed to the next blinded temperature room and the above process is repeated. This is repeated until all participants have received scans after spending ten minutes in all three blinded temperature rooms, at which point they proceed to one of the equilibration rooms, described below.

Detailed Procedure - Equilibration Study

Each participant is directed to go to one of two rooms (labelled D or E, used for *heating* or *cooling*), enter as directed by a study personnel, scan their NFC sticker to enable their ***nfc-equilibration-scan***, and subsequently sit in front of the primary thermographic system for 10 minutes. The subject may freely close their eyes and move around as long as their eye locations are visible by the camera system, which is aided by instructions provided by the operator to "ensure that at nearly all times you can see the lens of the thermal camera", with a picture as below posted nearby. At the conclusion of the serial measurement, study personnel will obtain an oral thermometry measurement. This process is repeated in the second room.

You may move around and close your eyes freely but please make sure both eyes are in view of the thermal image lens (see arrow) at all times.
Periodically check that you can see the entire ring (red circle) with both eyes.

Timing of Study Procedures

By appointing five rooms and interleaving equilibration times with scan times, it is possible to complete all measurements above on 9 subjects in 94 minutes, plus up to a 15-minute break in the middle of procedures. Briefly, every two minutes, one of the nine subjects is given a letter, whereupon they proceed to said lettered room to wait for 10 minutes to equilibrate for the blinded portion. The random letter drawing process is balanced so at most times, there are no more than 2 subjects in the room at a time. After the ten minutes is complete for a participant, study personnel will direct the participant to the scanning area. A third of the time, a new participant will be entering about the same time as a participant is leaving the room. The participant obtaining a scan will walk to the scan area, receive their primary scan, then any secondary scans, requiring a total of two minutes. Then the participant will receive a monitor-mode oral temperature, requiring up to two minutes. There will be approximately 4 minutes between this time and when the participant should go to the next lettered room for a ten minute equilibration time. This process repeats until all three rooms are complete, at which point the subjects are given an opportunity to have a break for up to 15 minutes. Note, we will interview subjects at the start of their break time and if they wish to begin sooner than 15 minutes and if the sequencing permits, the subject may proceed with less than a 15 minute break.

Once the break time is concluded for each subject, the process switches to the equilibration time measurement. Participants will wait an extra six minutes before proceeding to one of the rooms, in alternating order, so after ten minutes, the participant simply switches to the other equilibration room. A spreadsheet demonstrating the sequencing is included in the protocol materials, showing the time (10:00AM is selected as the start time for demonstrative purposes) in two-minute increments for 100 minutes, the participant (out of nine) who is currently switching rooms, the room they are being sent to (lettered A-E), which person is receiving the

thermographic scan, which person is receiving an oral measurement and the number of people at any given time in each room.

C. Safety

The risk to the participants participating in this study is low. Thermal imaging is a non-invasive, completely passive procedure. We do not expect any discomfort associated with thermal imaging. Oral thermometry is considered to have no risk, but it is possible participants could experience discomfort with oral thermometry. If participants indicate severe discomfort, the operator will immediately discontinue the procedure. The majority of the population has received a clinical oral thermometry procedure and participants are only eligible if they have received a clinical oral thermometry procedure in the past.

D. Analyses

It is foreseen that the two types of data will be analyzed separately and in two ways each. The equilibration data will be analyzed to determine the physiologic time constant in each dataset and grouped by direction of equilibration (heating, cooling). The groups of time constants will be assessed for significant differences between heating and cooling by two-sample t-test and a 95% confidence threshold. The average and standard deviation time constant (and if these are significantly different, this will be performed separately for heating and cooling) will be recorded and reported in an open-access publication with the rest of the results. The endpoint of each equilibration dataset will also be used to determine a linear physiologic offset (note, the existing parametric physiologic offset was previously determined in a 32-subject sample in June 2020 but for the purposes of this study, we intend to re-evaluate this equation) and the resulting equation and coefficients published along with the equilibration results.

In a second analysis, the equilibration time constants will be evaluated for possible linear correlations with the demographic data, although it is possible the small sample size and variability will preclude the detection of any significant correlations. In case there are nonlinear relations, scatter plots will be examined to determine if a low-order polynomial or other reasonable fit could explain a relation, while keeping in mind the fact each additional test is a multiple comparison, thus increasing the required p-value multiplicatively. Scatter-plots, trends and r-values will be reported, and this data may be collated with future collections of independent datasets.

The controlled face temperature data will be analyzed for sensitivity and specificity of each non-contact system used, first in a blinded analysis and then in an open-label analysis. First, the blinded face temperature data will be used to assign each recorded datapoint into normal, mild and moderate and severe fever groups, corresponding to below 38C (100.4F), 38-39C (100.4-102.2F), 39-40C (102.2-104F) and above 40C (104F). Note, the heated rooms' air temperatures were selected to produce simulated core temperatures that straddle the mild and moderate thresholds (hence, a well-performing system should place 50% of the measurements above the threshold and 50% below while a system relying on a bias-to-normal method might place only 10% above the selected threshold), therefore the severe fevers group

should likewise have few subjects placed within it. The sensitivity and specificity for assessing each of a mild and a moderate fever temperature will be assessed in a straightforward manner by revealing the labels and determining the fractions of correctly- and incorrectly-labelled datasets. These labels are generated by first matching the NFC UUID associated with an ***nfc-temperature-scan*** to the previous closest in time ***nfc-room-scan*** of this same NFC UUID and taking that room's air temperature difference to the temperature scanner's air temperature and converting to simulated core body temperature. Next, this now open-label data will be used to determine the mean and standard deviation across the core temperature scans of each of these four groups. The standard deviation of oral temperatures below the 38C threshold will be used to determine the false positive rate, using an assumed normal distribution or a low-dimensional parametric fit to the actual oral distribution. A parametric fit to the distribution above 38C will be used to determine the sensitivity and specificity for mild, moderate and severe fever thresholds, corresponding to 38-39C, 39-40C and 40C and above, respectively, using the sum of the area under the curve above the appropriate threshold. The linear correlation between oral and imaging temperatures in the below-threshold range will be tested for significance. A subset of the data consisting of equal parts of over-threshold (fevers, by oral temperatures) and under-threshold participants will be tested for significance, and this significance level compared with that of the whole set.

In a second analysis, the controlled face temperature data will be analyzed for effect of confounds with the primary non-contact thermographic system. In this case, the physiologic correction parameters obtained from each individual will be examined for linear correlates or nonlinear relationships with the demographic data. As with the equilibration data, scatter-plots, trends and r-values will be reported, and this data may be collated with future collections of independent datasets.

Quality control and data management

At the conclusion of data collection, the demographic, clinical and thermographic data will be entered into a database. This data will be stored on a password protected PC with access available only to the principal investigator and co-investigators. Raw imaging data will be stored using a unique identifier number for each participant that will be stored in the database. As no identifiers are collected, results will be reported with no individual identifying demographic information.

Timetable

It is anticipated that the study will last between one and two weeks, depending on rate of participant recruitment.

Adverse Events and Data Monitoring Committee (DMC)

Given the minimal risk of the procedures involved in the study the likelihood of adverse events is very low. Overall risk to participants should be no different from that of oral thermometry. Given the very low risk involved no data monitoring committee will be employed for the study. The thermal imaging temperature will not be entered into the participant's clinical report because the

imaging performed does not constitute a complete diagnostic imaging study and should not be considered by the participants as a substitute for the oral thermometry.

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Appendix - Physiologic Model

There is considerable published research on the heat transfer properties of human skin, with the original bioheat transfer equation (Pennes 1948) based on thermal conductivity of tissue, perfusion and blood density. Over the years, modifications were proposed incorporating fluid flow, viscosity and radiative effects (Wulff, Liu) primarily to better model dynamic effects. However, in static equilibrium the theoretical model is approximated sufficiently well by the Fourier heat equation. The model assumes that due to the anatomy of the angular artery, the tissue located a few mm beneath the skin of the inner canthus is at core body temperature. At the surface of the skin, the surface temperature is set by the heat flow through this thin layer of skin and then emitted to the ambient by radiative and convective routes to the air. The conduction through skin can be approximated to be proportional to the delta between core and surface skin temperature divided by a thermal resistance we do not need to know if we know the skin temperature and ambient temperature because the heat flow from core to skin is equal to the heat flow from skin to ambient air.

Radiative dissipation for typical body and ambient temperatures can be linearly approximated to good accuracy as 6 Watts per square meter times the delta in temperature between skin and ambient (C), and radiative dissipation is within an order of magnitude of the conductive plus convective pathway which is also proportional to the delta between skin and ambient temperatures. Because these are proportional to the delta, and if the air conditions are still and not excessively humid, the effect is linearly dependent on the delta and can be measured and used to perform a physiologic correction on the measured surface temperature in order to determine core body temperature to sufficiently good accuracy (0.5C). The primary sources of error in the physiologic correction are the air conditions, which can alter the

convective dissipation to ambient by a factor of two or more, and the thickness and other properties of the skin layer between core and inner canthus skin. Nevertheless, these have been observed by clinical study to be sufficiently consistent from person to person to serve as a modality for obtaining core body temperature. This model is used to perform a physiologic correction taking ambient air temperature to convert an inner canthus skin temperature to a core body temperature.