CORE AND SKIN TEMPERATURES IN MEN WITH AND WITHOUT A PATENT FORAMEN OVALE AT REST AND DURING EXERCISE

by

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A THESIS

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Introduction: During exercise, core (Tc) and skin temperatures (Tsk) increase due to elevations in heat production (Hprod) from increased metabolism by exercising muscles. To maintain Tc and Tsk within a precise range, the body increases skin blood flow to facilitate heat loss primarily from radiation and sweating. Further, there is some additional heat released through breathing. Previous studies have shown that men with a patent foramen ovale (PFO) have a higher Tc at rest and during exercise, possibly due to alterations in thermoregulatory mechanisms (Davis et al, 2015, 2017). Purpose: The purpose of this study was to determine if the presence of a PFO was associated with higher Tc and Tsk at rest and during exercise in healthy adult men while controlling for Hprod. Methods: The study was completed in a thermoneutral environment (20° C, 39% rh). Twenty-one men (11 PFO+ and 10 PFO-), ages 18-35 y/o completed the study. Participants completed 3 study visits. On day 1 they performed non-invasive pulmonary function tests and a cardiac ultrasound to determine the presence or absence of a PFO. On day 2, participants performed a graded exercise protocol at 4 workloads to determine what workload would elicit a Hprod of 7 W/kg of body weight, followed by a VO_2 peak test. On visit 3, participants completed a 1 hour cycling protocol at the previously determined workload that

would elicit a Hprod of 7W/kg, which was confirmed using metabolic data during the 1-hour bout. Tc, measured by a telemetric pill, and Tsk, measured with skin thermistors on 4 sites of the body, were measured continuously. Results: Participants without a PFO (PFO-) had significantly higher ($p < 0.05$) Tc before and during exercise compared to participants with a PFO (PFO+) (rest PFO- $37.1℃ \pm 0.18$, rest PFO+ $36.9℃ \pm 0.19$) (exercise PFO- 37.6 ± 0.16, exercise PFO+ 37.4 ± 0.16). No significant differences were observed in Tsk between PFO+ and PFO- participants at any time point. Conclusions: Contrary to our previously published work, these data suggest that the presence of a PFO is associated with decreased Tc at rest and during exercise in young, healthy men. Reasons for these discrepancies are not yet understood.

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Introduction & Background

Humans are homeotherms, meaning that we maintain our core temperature (Tc) within a very narrow range despite fluctuations in the environment around us. To maintain Tc within the small range of 36.1° C – 37.2° C (in this study resting Tc ranged from 36.40° C – 37.46° C), the amount of heat produced within the body must equal the amount of heat removed or dissipated. Maintaining this range of temperatures, despite outside circumstances, is known as thermoregulation and is essential for the reactions within our body to run optimally. If Tc gets too high it is likely to cause destruction of proteins and enzymes within the body. Conversely, if Tc drops too low our metabolism may slow and we can experience arrhythmias of the heart. Thermoregulation is maintained through continuous negative feedback loops involving the hypothalamus, specifically the pre-optic anterior hypothalamus. Thermoreceptors located in the skin and viscera, sense the temperature of passing blood and send this information to the hypothalamus in addition to direct sensing of temperature by the hypothalamus. The hypothalamus then compares that temperature to the temperature set point, which is between 36.1° C – 37.2° C for humans. If Tc is too high then the hypothalamus sends signals to the body to activate cooling mechanisms and if Tc is too low then the hypothalamus sends signals to activate heat conservation and heat production mechanisms.

Metabolism is the sum of all the reactions that occur within our bodies and provide the body with energy. Heat production (Hprod) is occurring constantly within our bodies due to the energy releasing form of metabolism: cellular respiration. Cellular respiration is the process by which the cells in our body use oxygen and break down food molecules to obtain energy, generally in the form of ATP. While cellular respiration is constantly occurring, its rate can be altered by several factors. Epinephrine secreted from the adrenal medulla is released in response

to stress, triggering activation of the sympathetic nervous system. In turn, this increases ATP production and therefore Hprod. Eating food also increases Hprod as metabolism must increase to digest the food and produce ATP for peristalsis and synthesis of digestive enzymes. In addition, even at rest, our muscles are in a state of slight contraction called muscle tone. Muscle tone accounts for ~25% of total body heat at rest (Scanlon and Sanders, 2019). Another ~20% of heat at rest comes from activity in the liver (Scanlon and Sanders, 2019). To ensure these working organs don't get too warm, passing blood picks up heat from the skeletal muscles and the liver, and distributes it throughout the body.

When we exercise, our metabolic rate and Hprod increases, and we begin to feel warmer. The metabolic reactions that occur during exercise are extremely inefficient, with 80% of the energy produced being in the form of heat, causing Tc to rise (Balmain et al. 2018 & Bongers et al. 2015). These higher internal temperatures contribute to fatigue, thereby reducing our ability to continue exercising. If internal temperature gets too high, then individuals can experience hyperthermia, with symptoms including headache, dizziness, fainting, confusion, and even coma if it is severe enough. Increased temperature is sensed by the hypothalamus which sends signals to the body to engage mechanisms that aid in heat loss (Armstrong 2000). Our bodies have several mechanisms to keep our Tc in an optimal range so that we can continue to exercise without causing harm to ourselves. These methods include sweating, increasing skin blood flow, and respiratory system heat loss.

Sweating and increased skin blood flow are the primary mechanisms for maintaining temperature within a safe range, and account for 85-90% of heat dissipation (Lovering et al. 2022). Both mechanisms are monitored by the hypothalamus, commonly referred to as the thermostat of the body. Temperature sensitive neurons in the preoptic anterior hypothalamus

monitor temperature from passing blood in the brain and peripheral thermoreceptors around the body and use this information to elicit heat conservation or heat dissipation mechanisms (Yanovich et al. 2020).

Sweat originates in the secretory coil of the sweat glands and is produced by the sweat glands upon signal from the anterior hypothalamus that body temperature is increased. Sweat then moves to and wets the skin, with the heat from the skin turning the liquid sweat into a gas and causing it to evaporate: this is known as evaporative cooling (Armstrong 2000). Changing the phase of sweat from a liquid to a gas requires a significant amount of energy, which is quantified as the latent heat of evaporation of sweat. The latent heat of evaporation is the amount of heat over a given mass required to transform the liquid into a gas, without increasing the temperature. While different numbers have been calculated, and can be altered based on temperature, humidity, and sweat osmolality, the latent heat of evaporation of sweat is known to be ~2,430 J/g, meaning that a significant amount of heat is removed from the body to initiate the phase change (Havenith et al, 2013). Because sweat is being evaporated into the environment, a dry air environment is much more effective than a wet environment for evaporative cooling. The "wetness" of the air is determined by the relative humidity (rh), which is a measure of the amount of water in the air relative to the totally saturated volume of air (Armstrong 2000).

Skin blood flow is the other primary method of heat dissipation used and relies on dry heat loss mechanisms. From rest to maximal exercise, cardiac output can increase from ~5 L/min to as high as 25 L/min, with much of that blood being directed to the skin and working muscles, and not to the inner organs such as the liver, intestines, and kidneys. At rest our systemic blood vessels are in a state of tonic vasoconstriction due to norepinephrine binding to noradrenergic receptors. When Tc begins to rise, the brain sends efferent signals through the sympathetic

nervous system to the smooth muscle surrounding skin blood vessels. These signals tell the body to initiate passive vasodilation by reducing the release of norepinephrine and therefore reducing vasoconstriction. As exercise progresses and Tc continues to rise, we transition from passive to active vasodilation. There are two pathways that active vasodilation can occur through, and active vasodilation accounts for 80-95% of increased skin blood flow during heat stress (Kellogg, 2006). Acetylcholine is released from the varicosities of sympathetic cholinergic postganglionic neurons and travels to the muscarinic receptors present on the endothelial cells which causes vasodilation. The extent of this pathway is not fully understood. In addition, increased Tsk causes an increase in nitric oxide production. Nitric oxide diffuses from the endothelial cell into the smooth muscle where it causes a series of reactions which results in the detachment of actin-myosin filaments and the smooth muscle relaxes (Zhao et al. 2015). The smooth muscle surrounds the blood vessel, so when it relaxes, the blood vessel vasodilates and more blood is diverted away from the inner organs to the skin, bringing heat to the surface of the skin. During exercise ~30-40% less blood flow reaches the inner organs (Armstrong 2000). Once blood has reached the surface of the skin it dissipates heat through either radiation or convection, which causes the blood to cool down in the body before it returns to the heart.

The final method of heat dissipation that we utilize is respiratory system heat loss. We inhale air that is at the temperature of the ambient environment. That air enters the lungs and the alveoli and equilibrates with the passing blood, which is typically at a higher temperature than the ambient air. Heat from the body is used to warm the air in the lungs as we inhale and therefore when we exhale, we release carbon dioxide, water vapor and heat. Despite only ~10-15% of heat loss coming from respiration during exercise, this process may be disrupted or

affected in individuals that have a patent foramen ovale (PFO) for reasons discussed below (Lovering et al. 2022).

During fetal development there is a tunnel between the right and left atria of the heart called the foramen ovale. The foramen ovale allows fetal blood, oxygenated by the mother, to enter the fetus's right atrium and then bypass the developing lungs, going directly to the left side of the heart and then out through systemic circulation. When the baby is born and takes his or her first breaths, the pressure in the left atrium increases and the right atrial pressure decreases, causing a flap of tissue to cover this tunnel and eventually close it completely, after which it is known as a fossa ovalis (Cole-Jeffrey et al. 2012). Without the mother's blood supply to oxygenate the fetal blood, and a newly closed fossa ovalis, the baby's blood begins circulating through their own respiratory system where gas exchange and respiratory system heat loss occurs. However, in 25-40% of the population, the foramen ovale does not close, and the individual is left with a PFO (Hagen et al. 1984).

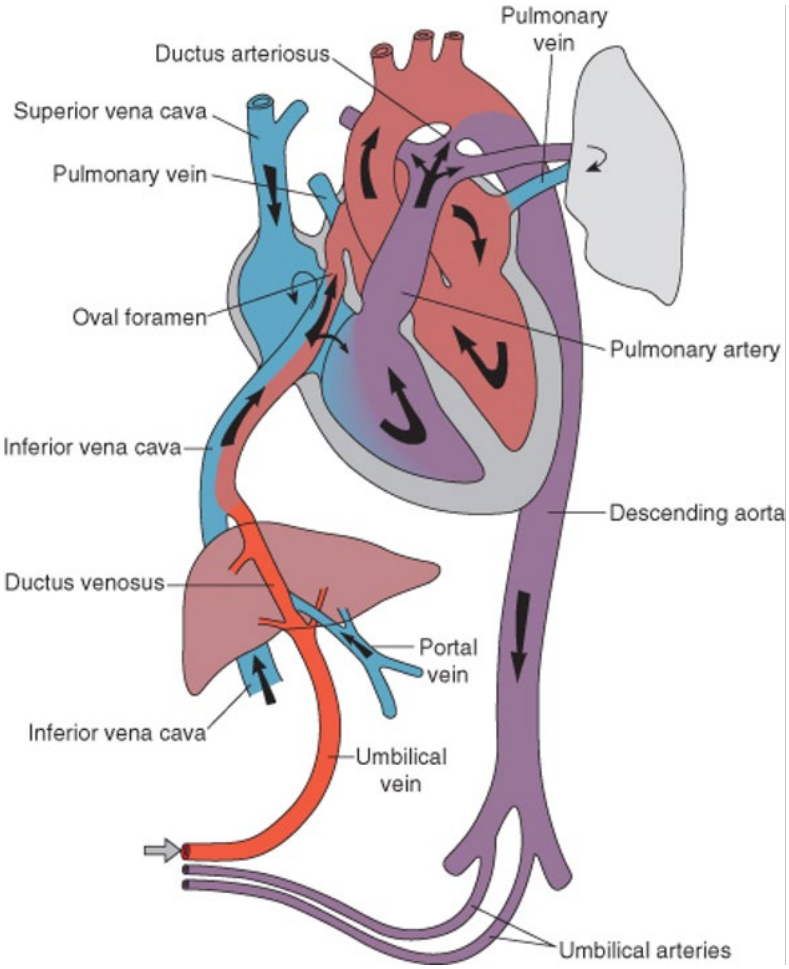

Figure 1: This is a diagram of fetal blood flow. Oxygen obtained from the mother's blood binds fetal hemoglobin and travels through the umbilical vein, through the vena cava to the developing right atrium. It then passes through the foramen ovale to the developing left atrium before going out into the body. (OBGYN Key, 2016)

Individuals with a PFO therefore continue to allow some blood to travel directly from the right to left atrium, bypassing the lungs. Depending on the size of the PFO up to 21% of cardiac output can be shunted through the PFO (Lovering et al. 2011), bypassing pulmonary circulation. This is important because when blood passes through the respiratory system, some metabolic heat is released through respiratory heat loss. This mechanism of heat loss accounts for ~10-15%

of heat dissipation in humans, and therefore may be important in regulating Tc (Lovering et al. 2022). With a fraction of blood bypassing the respiratory system and not participating in respiratory system heat loss in individuals with a PFO, they may rely more heavily on alternative mechanisms of heat dissipation to maintain Tc within an adequate range. During exercise our Hprod increases, with 80% of the energy that is produced being in the form of heat (Balmain et al. 2018 & Bongers et al. 2015). This means that our bodies need a way to release more heat while we exercise to maintain a stable Tc.

Figure 2: The image on the left shows normal blood circulation through the heart. The image on the right shows what occurs in a heart with a PFO; some blood in the right atrium will bypass the respiratory system and go straight to the left atrium.

It has been previously hypothesized that a PFO is associated with having a higher Tc compared to individuals without a PFO. This hypothesis was supported in a study of 30 men (15 PFO+ and 15 PFO-), in which it was found that the men with a PFO had significantly higher Tc (measured via esophageal probe) at rest and during exercise compared to the men without a PFO (Davis et al, 2015). It was further found that the size of the PFO affected Tc, with larger PFOs resulting in the highest Tc (Davis et al. 2015). The authors suggested that the higher Tc may be

in part because individuals with a PFO are not releasing as much heat through respiration (Davis et al. 2015). A potential limitation with this study was the fact that the researchers did not control for Hprod. Instead, subjects completed a VO_2 max test, which is an exercise test that measures the subject's maximal oxygen uptake, and the researchers used these data to have the subjects cycle at 25, 50, 75, and 90% of their maximum power output for the remaining trials. In subjects that are unmatched for VO_2 max, the same % VO_2 max could produce very different Hprod. When all subjects were working at 50% of their VO_2 max, a subject with a lower VO_2 max would likely be producing much more heat. Therefore, despite subjects all exercising at the same percentage of their maximal power, their Hprod may have been significantly different, contributing to differences in Tc.

In my current research I will be working to address this limitation by standardizing Hprod among all subjects. Research done to determine the best way to compare thermoregulatory responses has shown that when body mass and body surface area (BSA) are accounted for, but VO_2 peak is not matched, subjects must work at the same absolute Hprod (540 W) to elicit the same change in core temperature (ΔTc) (Jay et al. 2011). In subjects that are not matched for VO_2 peak, working at 540 W will be a different %VO_2 peak for each subject, but will elicit the same Hprod, allowing a thermoregulatory variable to be investigated without Hprod being a factor.

A further study questioned whether subjects unmatched for body mass and BSA should work at the same absolute Hprod (W) or the same relative Hprod (W/kg) (Cramer and Jay 2014). In this study, subjects cycled in 3 different trials: one absolute Hprod (500 W) and two relative Hprod (6.5 W/kg & 9.0 W/kg). The subjects were matched for age, sex, heat acclimation status, and onset threshold and thermosensitivities of sudomotor control, but were unmatched for VO_2

max. The researchers found that there was a significant difference in ΔTc when working at the absolute Hprod, but no difference between the groups when working at the relative Hprod. Therefore, in groups unmatched for VO_2 max, BSA and body mass, using a standardized relative Hprod in W/kg body weight appears to be the best method to investigate a thermoregulatory variable.

The purpose of this study was to determine if the presence of a PFO influenced Tc or Tsk in healthy, adult men, at rest and during exercise, when controlling for Hprod. I hypothesized that (1) due to a decrease in blood flow through the respiratory system in individuals with a PFO, Tc would be higher in subjects with a PFO compared to those without a PFO; (2) that the presence of a PFO would not influence Tsk; (3) that both PFO- and PFO+ groups would have a significant increase in Tc from rest to the end of exercise; (4) Tsk would not change throughout the duration of exercise because all subjects were exercising in a thermoneutral environment.

Methods

This study has received approval from the University of Oregon Research Compliance Services (IRB #: STUDY00000174). Informed consent was received from all the participants and all participants completed a brief medical history questionnaire. After obtaining informed consent, participants scheduled their next 3 visits. This study included men between the ages of 18 and 35 years old, who considered themselves to be recreationally active. Tc was measured using is an ingestible core temperature pill that measures gastrointestinal temperature and is the gold standard approach for long duration exercise. This pill is about 20 x 10mm and contains a telemetry system, a micro battery and a temperature sensor (Bongers et al. 2015). The temperature sensor vibrates at a particular frequency relative to the temperature of the substance around it, and then transmits those radio signals through the body. Those signals are read using an external recorder that can convert the radio signals into corresponding temperature readings (Bongers et al. 2015). The telemetric pill can record temperatures every 10 seconds with an accuracy of $\pm$0.1°C, making it a reliable method to measure Tc (Bongers et al. 2015). This pill will likely produce temperatures that are slightly higher than the temperature of blood leaving the heart because the tissue in the gastrointestinal region is much denser than the tissue at the level of the heart.

For the first study visit, subjects underwent anthropometric data collection, pulmonary function testing, and echocardiography. Anthropometric data included age, height, and weight. Pulmonary function tests consisted of forced vital capacity, slow vital capacity, forced expiratory volume in one second, and mid expiratory flow performed to American Thoracic Society / European Respiratory Society (ATS/ERS) standards (Table 1) (Miller el al, 2005). Each

subject's results were compared to Global Lung Initiative equations for lower limits of normal to ensure subject's had sufficient lung function (Quanjer et al. 2012).

Forced vital capacity	maximum amount of air that you can forcibly exhale after a full inhale
Slow vital capacity	maximum amount of air that you can exhale at a normal breathing pace, after a full inhale
Forced expiratory volume in one second	amount of air that can be forcibly exhaled in the first second of FVC
Mid expiratory flow	average expiratory flow between 25-75% of forced vital capacity

Table 1: The lung function tests performed in this study and what they are.

Echocardiography was used to determine if the subject had a PFO or not. Saline contrast, which is a manually mixed solution of sterile saline and air, was injected through an intravenous catheter (IV) in the arm. The saline contrast produces microbubbles, which are detected by ultrasound. The ultrasound machine shows the heart upside down and backwards, as shown in Figure 3. Subjects performed a Valsalva maneuver and upon release of this maneuver venous return was transiently increased which temporarily increased the pressure in the right heart. This facilitated blood flow through the PFO if one was present, making detection more reliable. The presence of bubbles in the left atrium and left ventricle in less than 3-5 cardiac cycles indicated a PFO. If a PFO was detected, we were able to further determine whether it was a large PFO or a small PFO by the number of bubbles that passed from the right to left atrium in any single frame

(Davis et al. 2017). Subjects with >13 bubbles were classified as having a large PFO and subjects with <12 bubbles were classified as having a small PFO (Davis et al. 1017).

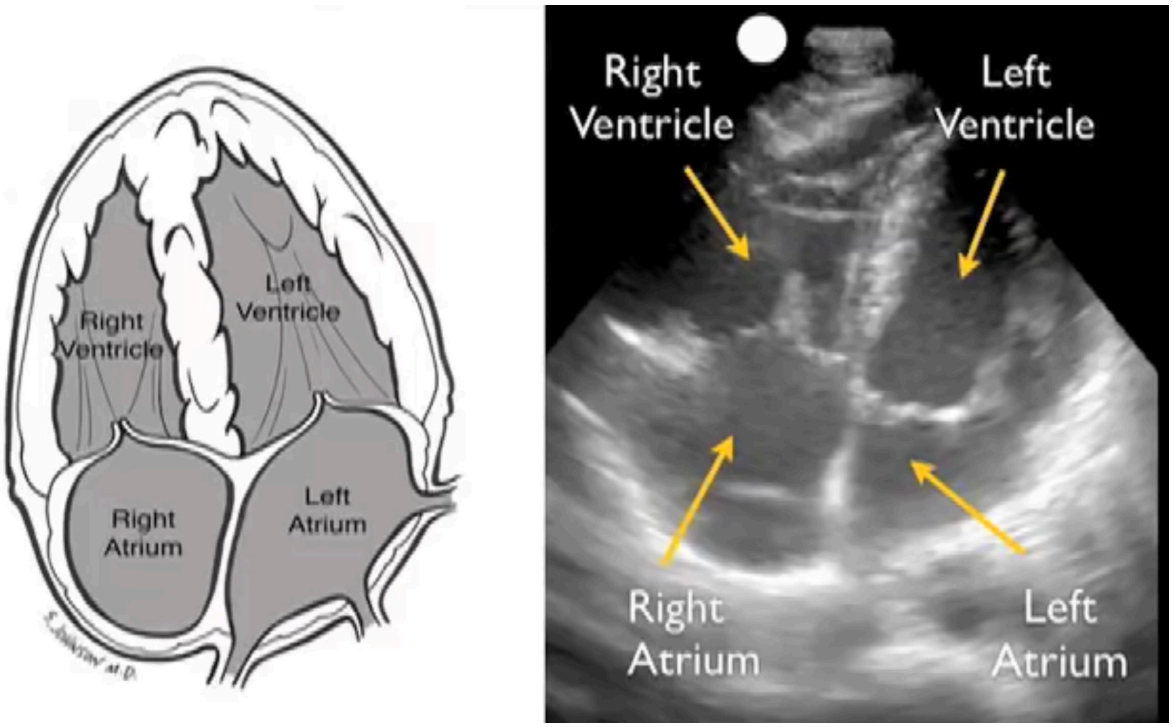

Figure 3: Orientation of the heart during the cardiac ultrasound. The heart is upside down and backwards, with the left atrium shown in the bottom right corner and the right atrium in the bottom left corner. (Sonosite, 2010).

The second day of testing included two different exercise protocols. The first was a graded exercise protocol, in which subjects exercised on a cycle ergometer at 4 increasing workloads for 5 minutes each. These workloads were estimated based on the subject's weight and comparisons to other subjects that had already completed the test. During this protocol, we continuously measured VO_2 (volume of oxygen consumed during exercise) and RER (respiratory exchange ratio—volume of CO_2 produced by the body / volume of O_2 consumed by the body.

These variables were measured by a metabolic analysis system while the participant breathed through an exercise mouthpiece connected to the metabolic system. We then used those measures to calculate absolute metabolic heat production, using the following equation:

$$H_{prod}(absolute) = \text{M (W)} - \text{W (W)} \quad (1)$$

In this equation M represents the mean energy expenditure, and is calculated using the equation below:

$$M = VO_2 \frac{\left(\frac{(RER-0.7)}{0.3}E_C\right)+\left(\frac{(1-RER)}{0.3}E_F\right)}{60} \cdot 1000\text{W}\,, \quad (2)$$

where VO_2= rate of oxygen consumption in L/min, RER is the respiratory exchange ratio (ratio of carbon dioxide production to oxygen consumption), E_C= caloric equivalent per liter of oxygen for the oxidation of carbohydrates, and E_F= caloric equivalent per liter of oxygen for the oxidation of lipids (Ravanelli et al. 2020). This gives M in kilojoules, so the value is multiplied by 1000 and then divided by 60 to give M in watts.

W in equation (1) refers to the rate of external work, measured in watts. Equation 1 gives an absolute Hprod measured in watts. We then took that absolute Hprod and divided it by the subject's body weight, using the following equation:

$$H_{prod}(relative) = \frac{H_{prod}(absolute)}{body\ weight}, \quad (3)$$

where relative Hprod is measured in W/kg, absolute Hprod is measured in W, and body weight is measured in kg.

A relative Hprod was calculated for each of the four workloads and then each Hprod was plotted against its corresponding external workload. From the graph we performed a linear regression analysis and used the target relative Hprod value of 7 W/kg to obtain the target

workload. While each subject was working at a different absolute Hprod and % VO_2 peak, they were all cycling at the same relative Hprod.

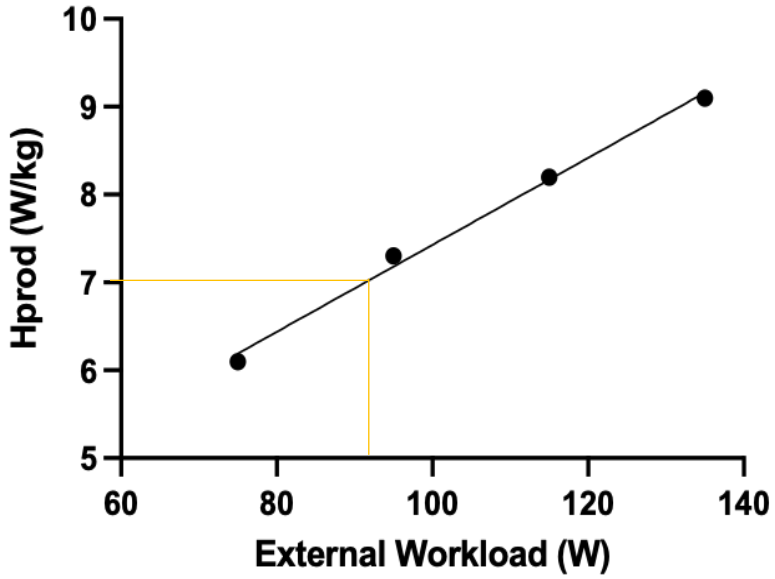

Figure 4: Graph of external workload and Hprod during the graded exercise protocol. This graph was used to determine what workload would elicit a Hprod of 7 W/kg body weight.

The second exercise protocol performed on the second day of testing was a VO_2 peak test. In this test, subjects exercised on the cycle ergometer beginning at 50 W of resistance. Each minute we increased the workload by 25 W, until the subject could no longer maintain a pedaling rate of 60 revolutions per minute or their VO_2 plateaued. We continuously measured heart rate, SpO_2 (oxygen saturation, a measure of the amount of oxygen carrying hemoglobin in the blood), VO_2 (rate of oxygen consumption) and ventilation. This test gave us information on the subject's overall fitness level and helped to determine if they would be able to complete the hour-long exercise protocol on day 3.

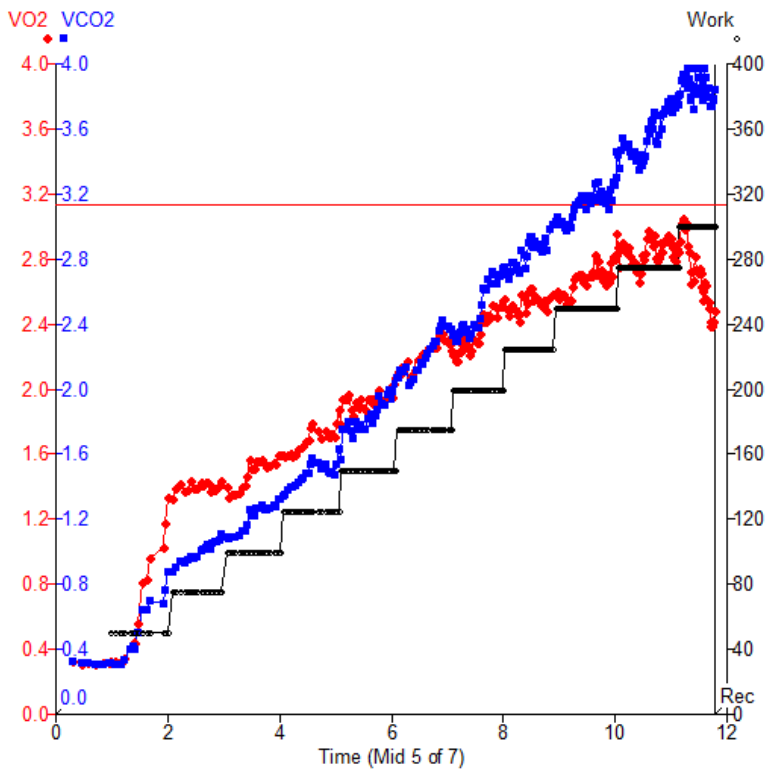

Figure 5: This graph illustrates data from a VO_2 peak test. The red line is volume of oxygen consumed per time. Around 10 minutes the subject's oxygen plateaus; this is when they hit their VO_2 peak.

The third day of testing consisted of an hour-long exercise protocol. Subjects came into the lab the day before testing to get their core temperature pill, which they were instructed to take 10 hours before testing. Subjects were provided 1 L of water and a sterile urine cup and were asked to drink the liter before going to bed to ensure they were adequately hydrated the next morning. The next morning, subjects were asked to collect a first void urine sample. When they came into the lab we performed a urine test to ensure they were adequately hydrated. Using a refractometer, we measured urine specific gravity (USG), which refers to the density of the urine sample compared to pure water. A USG < 1.025 indicated the participant was adequately

hydrated, with pure water giving a value of 1.000. We then obtained a nude body weight. We also tested to ensure that the core temperature pill was activated and working. Skin sensors were adhered to the subject's skin on the chest, deltoid, thigh, and calf. Tsk varies depending on the part of the body, so it was important to place sensors on different parts of the body. Four locations are adequate for measuring Tsk in a thermoneutral environment (Cramer and Jay 2019). The wired electrodes were connected to a thermometer, which allowed for continuous temperature readings during exercise (McFarlin 2015). Finally, we equipped the subject with a heart rate monitor and set them up on the cycle ergometer. Subjects then cycled for one hour at the workload calculated to elicit a Hprod of 7 W/kg of body weight. They alternated between breathing ambient air through a mouthpiece measuring inspiratory and expiratory humidity and temperature and breathing the ambient air without a mouthpiece.

Figure 6: A participant on the cycle ergometer during the 1-hour exercise protocol.

Data were collected from all 21 participants. Each anthropometric data point, including height, weight, change in weight (pre to post exercise), body surface area, and first void USG, was compared between the two groups using an unpaired, two-tailed t-test. Additional measures including Hprod and workload were also compared using an unpaired, two-tailed t-test. Significance was indicated by $p<0.05$. Tc and Tsk results of this study were collected from all participants during the hour-long exercise protocol. Tc and Tsk were compared both between the PFO- and PFO+ groups and within each group from rest (t=0) to the end of exercise (t=60). Measurements of both Tc and Tsk were recorded and compared at every 5-minute increment.

Comparisons were made using a two-way repeated measures ANOVA test and a $p<0.05$ indicated a significant difference.

Results

Ambient temperature and humidity were recorded during each subject's testing days. No significant difference was found in the conditions between the two groups (Table 2).

The following results are presented in Table 1. Hprod remained constant for all participants throughout exercise (PFO-: 7.1 ± 0.3 W/kg, PFO+: 7.1 ± 0.2 W/kg). No significant difference was found in the workloads during day 3 between the two groups (PFO-: 115 ± 17.0 W, PFO+: 112.7 ± 20.0 W). No significant difference was found between the groups for height (PFO-: 180.0 ± 5.3 cm, PFO+: 179.6 ± 4.9 cm), pre body weight (PFO-: 77.9 ± 6.1 kg, PFO+: 77.7 ± 9.2 kg), post body weight (PFO-: 77.3 ± 6.1 kg, PFO+: 77.2 ± 9.1 kg), USG (PFO-: 1.02 ± 0.006, PFO+: 1.02± 0.005), or body surface area (BSA) (PFO-: 2.0 ± 0.1 m^2, PFO+: 2.0 ± 0.1 m^2). No significant difference was found between the groups for % VO_2 peak (PFO-: 64.7 ± 9.8, PFO+: 63.1 ± 9.4), however in each group subjects were working at a range of % VO_2 peak values greater than 30% (PFO- range: 54.3-86.1%; PFO+ range: 50.0-82.6%).

	PFO- (n=10)	PFO+ (n=11)	P value
Ambient Temperature (°C)	22.2 ± 0.6	22.3 ± 0.5	0.75
Humidity (%)	40.5 ± 12.8	37.7 ± 9.9	0.58
Height (cm)	180.0 ± 5.3	179.6 ± 4.9	0.88
Pre Body Weight (kg)	77.9 ± 6.1	77.7 ± 9.2	0.96
Post Body Weight (kg)	77.3 ± 6.1	77.2 ± 9.1	0.96

Change in Body Weight (kg)	-0.6 ± 0.2	-0.6 ± 0.2	0.83
% Change in Body Weight	-0.6 ± 0.6	-0.7 ± 0.2	0.37
Heat Production (W/kg)	7.1 ± 0.3	7.1 ± 0.2	0.44
Workload (W)	115 ± 17.0	112.7 ± 20.0	0.78
USG	1.016 ± 0.006	1.017 ± 0.005	0.65
Pre Tc (°C)	37.1 ± 0.2	36.9 ± 0.2	0.009
Post Tc (°C)	37.9 ± 0.2	37.7 ± 0.2	0.03
ΔTc (°C)	0.8 ± 0.1	0.8 ± 0.2	0.71
Pre Tsk (°C)	30.6 ± 0.8	30.9 ± 1.0	0.41
Post Tsk (°C)	30.9 ± 1.4	31.3 ± 1.0	0.30
ΔTsk (°C)	0.3 ± 1.4	0.5 ± 0.8	0.64
BSA (m^2)	2.0 ± 0.1	2.0 ± 0.1	0.33
% VO_2 peak (mean)	64.7 ± 9.8	63.1 ± 9.4	0.70
%VO_2 peak (range)	54.3 – 86.1	50.0 – 82.6	N/A

Table 2: Descriptive and anthropometric data. Means were compared using an unpaired, two tailed t-tests with $p<0.05$ indicating a significant difference.

Core Temperature. PFO- participants had a significantly higher Tc at rest and throughout exercise compared to PFO+ subjects, as measured by the core temperature pill. The average Tc

at rest for the PFO- group was 37.1 ± 0.2°C and the average Tc at rest for the PFO+ group was 36.9 ± 0.2°C. At the end of the exercise protocol, the PFO- group had an average Tc of 37.9 ± 0.2°C and the PFO+ group had an average Tc of 37.7 ± 0.2°C. Comparing Tc at all time points, the PFO- group had an average Tc of 37.59°C and the PFO+ group had an average Tc of 37.40°C, indicating that there was a main effect of PFO on Tc. However, further Sidak post hoc tests indicated no significant pairwise differences. ΔTc for the PFO- group was 0.8 ± 0.1°C, and ΔTc for the PFO+ group was 0.80 ± 0.2°C. No significant difference was found for ΔTc between the two groups, p=0.7.

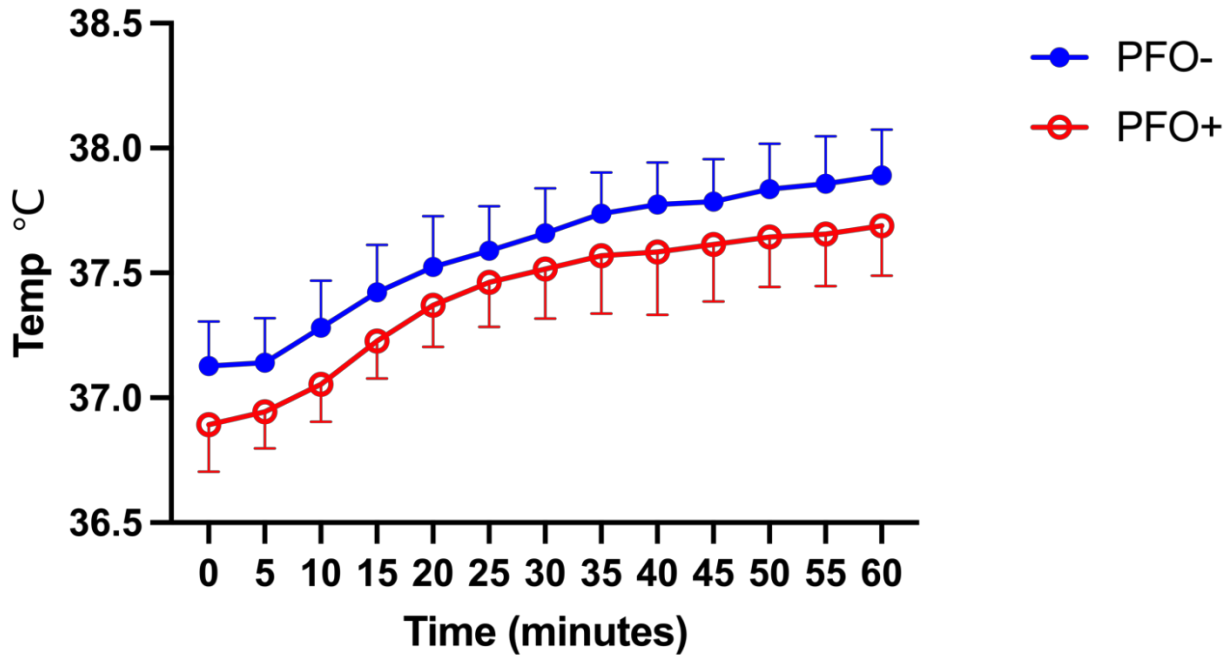

Figure 7: Core temperature, measured with a telemetric pill, at rest and during the hour-long exercise protocol. Two-way repeated measured ANOVA with $p<0.05$. There was a main effect of PFO status and time on Tc, with no pairwise differences.

	PFO-		PFO+	
Time	Mean	SD	Mean	SD
0	37.1	0.2	36.9	0.2
5	37.1	0.2	36.9	0.1
10	37.3	0.2	37.1	0.2
15	37.4	0.2	37.2	0.2
20	37.5	0.2	37.4	0.2
25	37.6	0.2	37.5	0.2
30	37.7	0.2	37.5	0.2
35	37.7	0.2	37.6	0.2
40	37.8	0.2	37.6	0.3
45	37.8	0.2	37.6	0.2
50	37.8	0.2	37.6	0.2
55	37.9	0.2	37.7	0.2
60	37.9	0.2	37.7	0.2

Table 3: Core Temperature in ℃ for the PFO- and PFO+ groups during the hour-long exercise bout.

Skin Temperature. No significant difference in Tsk was found between PFO- and PFO+ participants at any time ($p = 0.25$). At time 0 (rest), PFO- participants had an average Tsk of 30.6 ± 0.8°C, and PFO+ participants had an average Tsk of 30.9 ± 1.0°C, the difference between the means being 0.3. At the end of the 60 minutes of exercise, PFO- participants had an average Tsk of 30.9 ± 1.4°C, and PFO+ participants had an average Tsk of 31.3 ± 1.0°C. There was also no main effect of exercise (time) on Tsk for either group. PFO- subjects had $\Delta Tsk = 0.3 \pm 1.4$°C, and PFO+ subjects had $\Delta Tsk = 0.5 \pm 0.8$°C. This gives p values of 0.6 and 0.2 respectively, indicating no significant differences.

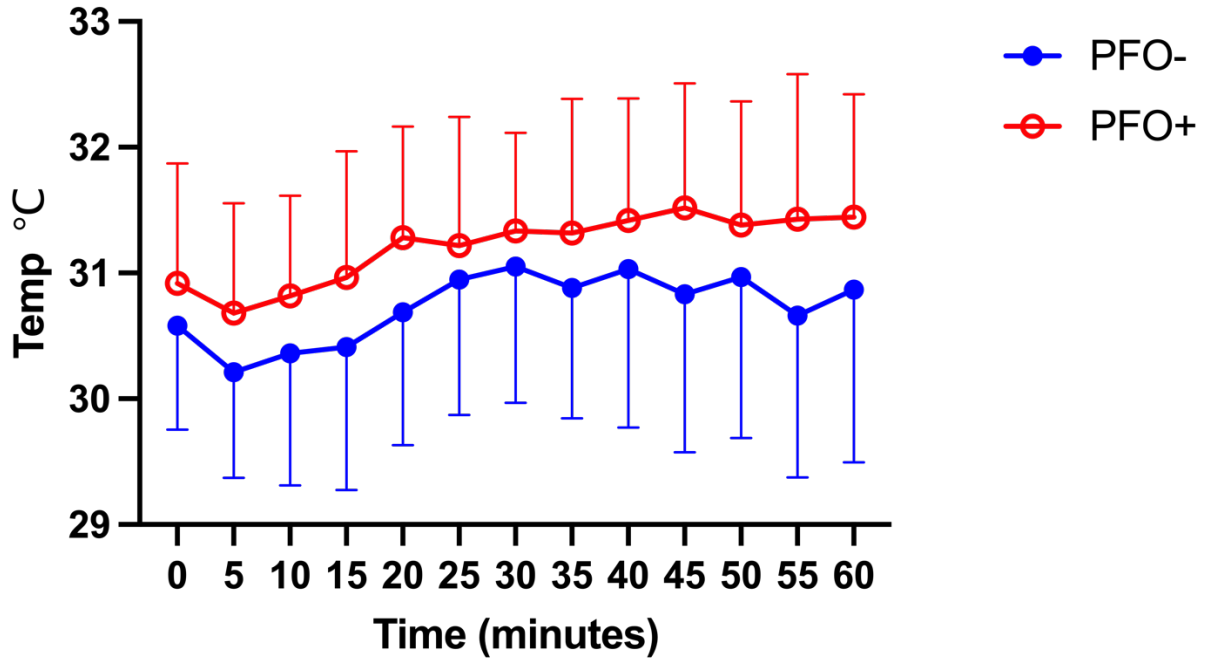

Figure 8: Skin temperature (skin thermistors) at rest and during the hour-long exercise protocol. Two-way repeated measures ANOVA with $p>0.05$. No effect of PFO status or time on Tsk was found.

	PFO-		PFO+	
	Mean	SD	Mean	SD
0	30.6	0.8	30.9	1.0
5	30.2	0.8	30.7	0.9
10	30.4	1.0	30.8	0.8
15	30.4	1.1	31.0	1.0
20	30.7	1.1	31.3	0.9
25	31.0	1.1	31.2	1.0
30	31.1	1.1	31.3	0.8
35	30.9	1.0	31.4	1.1

40	31.0	1.3	31.4	1.0
45	30.8	1.3	31.5	1.0
50	31.0	1.3	31.4	1.0
55	30.7	1.3	31.4	1.2
60	30.9	1.4	31.4	1.0

Table 4: Skin Temperature in ℃ for the PFO- and PFO+ groups during the hour-long exercise bout.

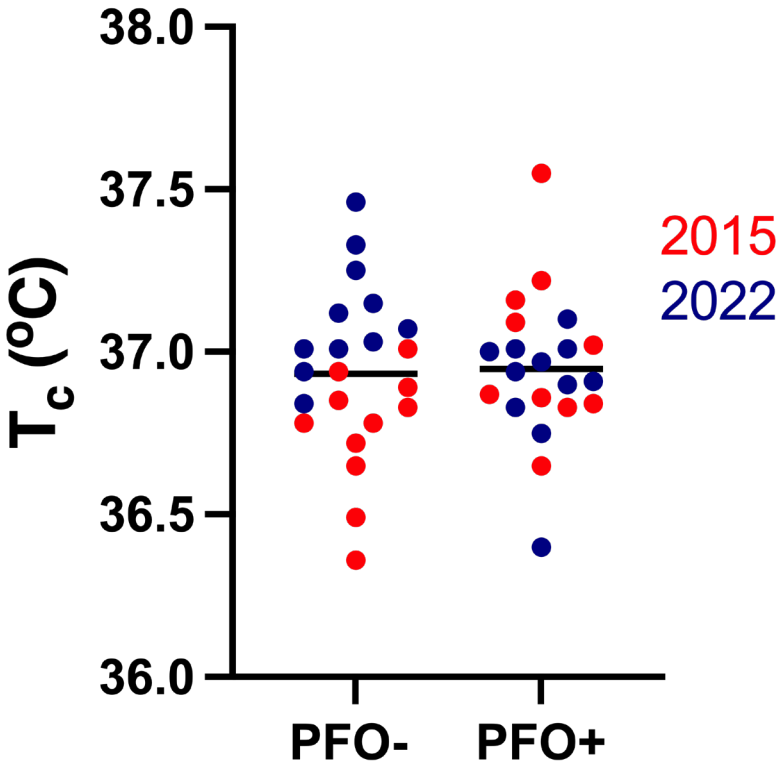

Figure 9: Combined Tc data at rest from the current study and unpublished data from Davis et al. 2015. Subjects from 2015 are shown in red and subjects from 2022 are shown in blue.

Discussion

This study found significantly higher Tc in the PFO- group pre-exercise and during exercise compared to the PFO+ group. Both the PFO- and PFO+ groups saw significantly higher Tc during exercise compared to rest, with ΔTc the same between the two groups. Tsk did not significantly change for the PFO- or PFO+ group from rest to the end of exercise, and PFO status did not have an effect on Tsk.

Both PFO- and PFO+ groups saw an initial decrease in Tsk between 0 and 5 minutes (Table 2). This is likely due to the initial vasoconstriction to the skin that occurs at the onset of exercise (Ramanlal and Gupta 2022). When we begin exercising, the muscles we are using must work harder, meaning that they require more oxygen due to their increased metabolic rate. To get more oxygen to the working muscles, we vasodilate blood vessels going to those muscles and vasoconstrict the blood vessels going to any non-working tissues, including the skin. With less blood going to the skin, Tsk decreases. However, this vasoconstriction to the skin is quickly overturned due to increases in blood temperature, as increased skin blood flow and sweating are the two most important heat loss mechanisms in humans. The quick reversal to vasodilation of the vessels going to the skin causes more blood to travel to the skin, which is why we see an increase in Tsk back to the initial temperature. This vasodilation is essential for maintaining our Tc within a safe range and keeping our bodies cool during exercise. Exercise did not cause an increase in Tsk for either group which is expected when exercising in a thermoneutral environment such as the lab.

Our initial hypothesis that PFO+ subjects would have a higher Tc at rest and throughout exercise was not supported by our current results. It is possible that despite previous thinking, the

fraction of blood that bypasses the lungs and passes through the PFO is small enough that it doesn't decrease respiratory heat loss enough to influence overall Tc. Respiratory heat loss only accounts for 10-15% of heat dissipation during exercise so it may not be significant enough to affect Tc (Lovering et al. 2022). This study found no significant difference in respiratory heat loss between PFO- and PFO+ groups, contradicting the hypothesis proposed in the study conducted in 2015 that PFO+ individuals would have significantly decreased respiratory heat loss during exercise (Davis et al. 2015).

It is also possible that PFO+ individuals are more effective in dissipating heat in other manners that can balance out the lack of respiratory system heat loss. This could include a lower onset threshold of sweating or skin blood flow, or higher whole body sweat rate. However further research would need to be done to investigate this hypothesis.

This study also found that PFO- men have a higher baseline Tc and a higher Tc during exercise compared to PFO+ men. There was also a main effect of exercise (time) on Tc in both PFO- and PFO+ men. There was no significant difference in ΔTc between PFO- and PFO+ groups. The mechanism responsible for increased Tc in the PFO- group was present both at baseline and during exercise. This indicates that the cause for higher Tc in the PFO- group is not due to thermoregulatory mechanisms. In addition, results from this study and the Davis et al. (2015) study illustrate relatively similar Tc between the PFO- and PFO+ groups, with a few people trending either higher or lower (Figure 7). The difference in Tc is therefore likely due to inter-individual variability, and not a result of the presence or absence of a PFO. Individual variability may be due to several factors including circadian rhythm differences, inflammatory markers, and body composition.

Circadian rhythm may have played a role in the Tc changes observed. The circadian rhythm regulates the sleep-wake cycle and is on a 24-hour clock. There is a general Tc trend that occurs with a 24-hour cycle. Tc follows a cosine shaped curve and has a minimum during the middle of the sleep period and a maximum during the middle of the wake period (Figure 10). The lower temperatures during the sleep period are due to active heat loss mechanism (e.g., release of melatonin, changes in the sensitivity of cold and warm sensing neurons and increased distal blood flow to the skin). The increased heat dissipation causes an overall decrease in Tc. While this is the same trend for each subject, we were not able to monitor what time each subject went to bed and woke up. We minimized variation by having all subject's come in for testing at 7:00am, however a subject that woke up 2 hours before testing would likely have a higher baseline Tc than a subject that woke up 30 minutes before testing. This is an important consideration due to the fact that we found no significance in ΔTc but found significant difference between baseline values of Tc between the two groups before exercise.

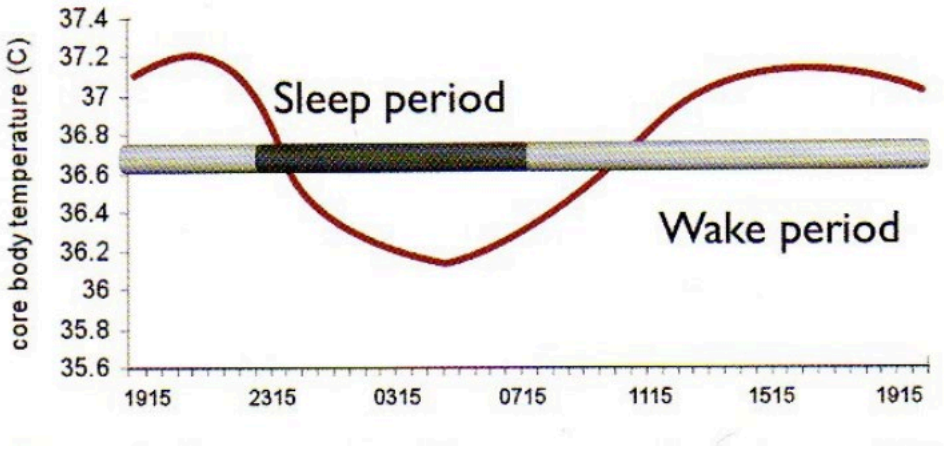

Figure 10: Core temperature changes that occur with the sleep wake cycle. Lowest temperatures occur in the middle of the sleep period, and temperatures peak during the middle of the wake period, (Amlaner and Fuller, 2009).

Inflammation is another potential factor that may have influenced Tc on an individual level. Cytokines are small protein mediators that can be either pro- or anti- inflammatory (Netea et al. 2000). TNF-α is a pro-inflammatory cytokine that is known to be linked to the febrile response. TNF-α, along with IL-1β and IL-6 are all endogenous pyrogens that can induce the synthesis of cyclooxygenase-2, which in turn produces prostaglandins (Zampronio et al. 2015). Prostaglandins increase Hprod and reduce heat dissipation, causing an overall increase in Tc which leads to fever (Zampronio et al. 2015). Therefore, any participant that came into lab with a cold or illness that they weren't necessarily feeling symptoms for yet, had the potential to have a higher baseline Tc due to certain cytokines causing a fever. Higher inflammatory markers do not conclusively mean a higher Tc, however depending on the specific cytokine, there may be a link between inflammation and Tc, and this may have been a source of variation within the current study.

Another factor that may have impacted what we saw is body composition. There are several body composition variables that may influence Tc. Body surface area (BSA) is a measure of total surface area of the body and is calculated using the following equation:

$$BSA = 0.007184 \times h^{0.725} \times w^{0.425}$$ (Flint & Hall 2022) (4)

In equation 4, h refers to height in meters and w refers to weight in kilograms.

A significant percentage of heat loss occurs at the surface of the skin through sweating and radiation. A larger skin surface area will allow for more heat dissipation and a lower Tc.

Individuals with a smaller BSA will have to increase sweating and skin blood flow more to achieve the same amount of heat loss as someone with a larger BSA (Havenith 2001). Our results showed several participants in both the PFO- and PFO+ groups that had Tc trending high or low. While the averages between the two groups do not show significant difference in BSA, BSA may have played a role in the few subjects that trended strongly in one direction. In other words, BSA may have played a role in Tc on an individual level. Figure 11 shows that subjects with a larger BSA tended to have a lower Tc at the end of exercise, possibly due to more heat loss through the surface of the skin.

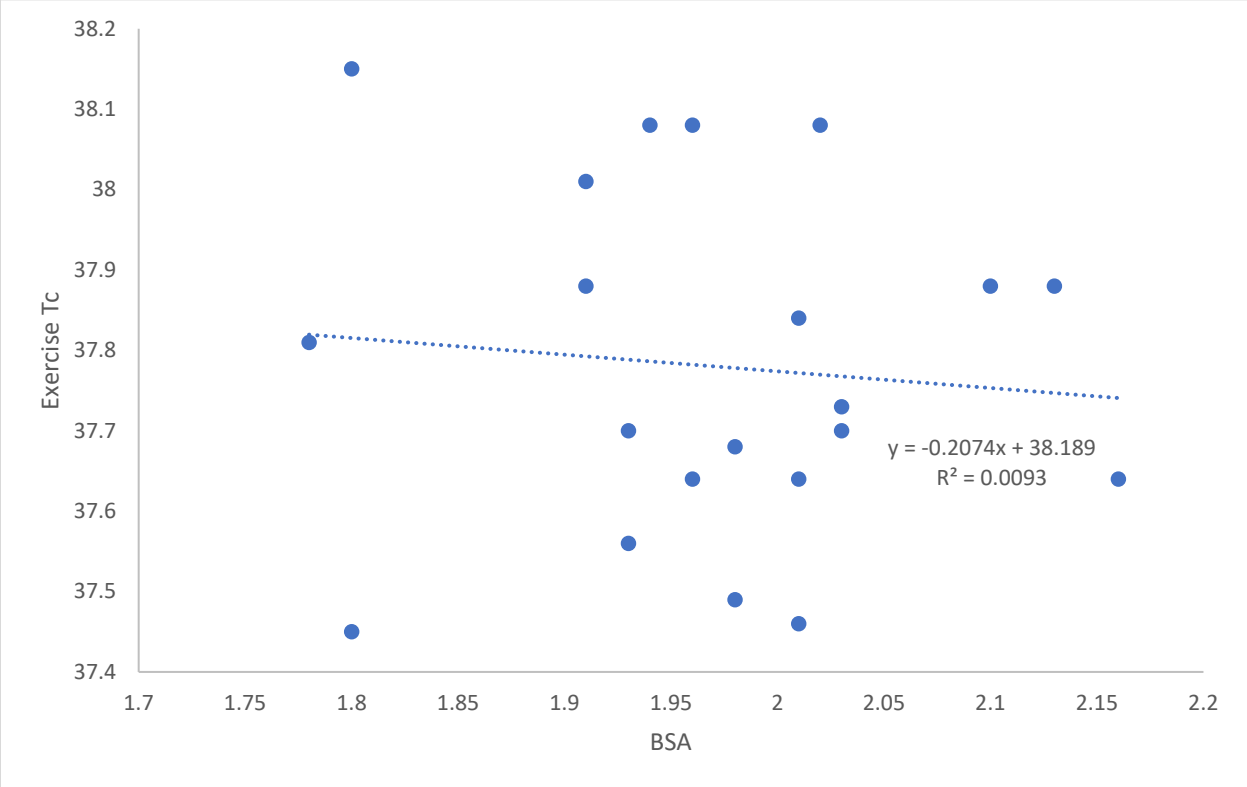

Figure 11: BSA and Tc (end of exercise) for all subjects (PFO- and PFO+). A slight negative relationship is shown, with larger BSA correlating with lower Tc at the end of exercise.

Additionally, body fat percentage can impact Tc. Body fat percentage is calculated by the following equation:

$$Body\ fat\ percentage = \frac{total\ mass\ of\ fat}{total\ body\ mass} \quad (5)$$

Higher body fat percentages have a lower average specific heat capacity of adipose tissue, meaning that it takes a smaller amount of heat to raise body temperature in individuals with higher fat content (Dervis et al. 2016). Further, higher fat content provides a layer of insulation that makes heat dissipation more difficult (Savastano et al. 2009). Therefore, individuals with a higher body fat percentage will likely have a higher Tc. We did not measure body fat percentage in this study, so we are unable to determine if participants with higher body fat percentages showed higher Tc, or if there was a difference in body fat percentage between groups.

Conclusions, Limitations & Next Steps

Based on previous research from our lab that showed significantly higher Tc in men with a PFO compared to men without a PFO, I hypothesized that when controlling for Hprod, (1) PFO+ men would have higher Tc than PFO- men, and (2) that PFO status would not influence Tsk. I further hypothesized that in both PFO- and PFO+ subjects (3) there would be a main effect of exercise (time) on Tc but (4) not on Tsk. While our results supported the second, third and fourth hypotheses, our results contradicted the first hypothesis and indicated a higher Tc in PFO- participants compared to PFO+ participants.

There were a few limitations within this research protocol that may have affected the results. The first is that this study only looked at men. It is known that women tend to have higher baseline Tc due to higher levels of progesterone in the luteal phase of the menstrual cycle. Women also have larger fluctuations in Tc depending on the phase of their menstrual cycle and their hormone levels. Future studies need to be done to see what, if any, thermoregulatory differences are present between PFO- and PFO+ women. There may also be interesting differences in baseline and change in Tc between men and women.

Another limitation is that the sample size was relatively small (n=21). While this was a large enough sample size to indicate significance, it was still small enough that we may need more subjects to represent the variability in Tc in the general population across PFO groups. Even when combining the results from this study with those from Davis et al. 2015, (Figure 9) it is seen that the trend of the results changes significantly. It is necessary to repeat this study with a larger sample size to determine if the data was skewed by just a few individuals, or to determine what the variability is within a PFO group.

All the participants within the study were within a narrow age range of 18-35. It is known that the ability to thermoregulate decreases with age. Changes in cardiovascular function due to heart and lung diseases that occur with age can alter thermoregulatory abilities (Balmain et al., 2018). In addition, it has been shown that older individuals have smaller increases in skin blood flow for a given increase in Tc (Balmain et al., 2018). These thermoregulatory differences that occur with age may be important to consider when looking at Tc and Tsk between PFO- and PFO+ groups. Subjects were also all moderately active and at a similar fitness level. This is not representative of the whole population, so future studies may look at either elite athletes or more sedentary individuals.

In continuing with this research, I would start by incorporating women into the study and looking at differences in baseline Tc and Tsk between PFO+ and PFO- women, as well as between men and women. Women are known to have increased Tc during the luteal phase of the menstrual cycle due to increased levels of progesterone. Future studies could look at the rate of ΔTc in different menstrual cycle phases and how these compare between women with and without a PFO and between men and women. I would continue to have all participants working at a standardized relative Hprod workload, as this appears to be the current gold standard for temperature studies (Cramer & Jay 2014). I would also want to further investigate what individual factors could have led to the differences in Tc that we observed in this study. Specifically, I would like to continue looking at body composition as a factor in Tc, and specifically how different BSA and adiposity combinations affect Tc.

This study found Tc to be significantly higher in PFO- individuals at rest and during exercise. However, when combining data from this current study and the results from Davis et al (2015), the Tc results between PFO- and PFO+ groups are not significantly different, and

therefore the Tc differences observed in this study are likely a result of interindividual variability and not PFO status. This study indicates that having a PFO is not a disadvantage in terms of thermoregulatory ability as previously thought. Further, this study confirmed humans' ability to thermoregulate and maintain Tsk in a thermoneutral environment during exercise. The next step in this research is to determine why certain subjects had a higher initial Tc at rest and if this difference is significant enough to cause advantage or disadvantage in particular individuals.

Glossary

Cardiac ultrasound: procedure used to determine the presence or absence of a PFO

Cellular respiration: process by which the cells in our body use oxygen and break down food molecules to obtain energy, generally in the form of ATP

Circadian rhythm: internal process that regulates the 24 hour sleep wake cycle

Conduction: heat loss from the body to a colder object or the air through contact

Convection: air currents move the warmer air away from the skin's surface

Core temperature: temperature of body's internal organs

Cycle ergometer: a type of stationary bike used for exercise research

Cytokine: protein mediators that have an effect on the immune system and can be either pro- or anti-inflammatory

Evaporation: phase change from a liquid to a gas

Forced expiratory volume in 1 second (FEV1): amount of air that can be forcibly exhaled in the first second of FVC

Forced vital capacity (FVC): maximum amount of air that you can forcibly exhale after a full inhale

Heat dissipation: mechanisms by which heat is released from the body

Heat production: heat as a byproduct of metabolism in the body

Metabolism: sum of reactions within the body that provide the body with energy

Mid expiratory flow (FEF 25-75%): average expiratory flow between 25-75% of forced vital capacity

Patent foramen ovale: tunnel between the right and left atria of the heart that allows a fraction of blood to bypass the respiratory system

Radiation: heat from the body is transferred to colder objects without contact

Respiratory exchange ratio (RER): volume of CO_2 produced by the body / volume of O_2 consumed by the body

Skin temperature: temperature of the surface of the skin

Slow vital capacity (SVC): maximum amount of air that you can exhale at a normal breathing pace, after a full inhale

Steady state: balance within the body between the physiological demand and response

Thermoregulation: maintaining core temperature within a narrow range despite outside factors

Vasoconstriction: narrowing of blood vessels

Vasodilation: dilation of blood vessels

VCO_2: volume of carbon dioxide production during exercise

VO_2: volume of oxygen consumption during exercise

VO_2 peak test: a test to exhaustion or a plateau in oxygen uptake. For this study it is measured on a cycle ergometer beginning at 50 watts and increasing by 25 watts every minute until the subject can no longer maintain 60 revolutions per minute

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