ASSOCIATION OF PATENT FORAMEN OVALE WITH RESPIRATORY HEAT LOSS AT REST AND DURING EXERCISE IN MEN

by

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During exercise, approximately 10-14% of heat loss occurs via respiration, termed respiratory heat loss (RHL). RHL involves components of both evaporative (Eres) and convective (Cres) heat loss from the upper respiratory tract. Previous research has shown that men with a patent foramen ovale (PFO) have higher core temperatures (Tc) at rest and during exercise. It is unknown whether differences in RHL contribute to the differences seen in Tc between PFO+ and PFO- men. PURPOSE: The purpose of the study was to test whether there are differences in RHL (Eres, Cres, and total RHL (Tres)) between PFO+ and PFO- men at rest and during 60 min of exercise at a workload eliciting a heat production (Hprod) of 7 W/kg. METHODS: Twenty-one healthy males (11 PFO+, 10 PFO-, 18-36 y/o) participated in the study. Visit 1 included an ultrasound screening to test for the presence or absence of a PFO and lung function testing. Visit 2 involved a graded exercise protocol to determine the workload that would elicit a heat production of 7 W/kg, followed by a VO_{2peak} test. During the graded exercise protocol, subjects cycled at 4 different workloads for 5 min each. For visit 3, subjects completed 60 min of cycling exercise at a previously determined workload eliciting a Hprod of 7 W/kg in a thermoneutral laboratory environment (22°C, 39% rh). Minute ventilation (VE) and inspired and expired temperature and humidity were measured. RHL was calculated at baseline (BL) and

during min 0-10, 25-30, and 55-60 of exercise. Tc was measured using a telemetric pill ingested ~10 hrs prior to testing. RESULTS: There were no differences in RHL (Cres, Eres, or Tres) between PFO+ and PFO- men at rest or during exercise ($p>0.05$). Using a two-way ANOVA (Tres RHL X Exercise), there was a main effect of exercise on RHL ($p<0.01$), with RHL being greater at all 3 time points compared to rest and at min 55-60 vs min 0-10 ($p<0.01$). Tc was significantly higher in PFO- vs PFO+ men at rest and during exercise (PFO- 37.13 ± 0.18 °C, PFO+ 36.89 ± 0.19 °C at rest vs. PFO- 37.62 ± 0.16°C, PFO+ 37.44 ± 0.16°C during exercise; $p<0.05$). CONCLUSION: As expected, RHL increased from rest to exercise due to increases in VE and metabolic heat production. However, since there was no difference in RHL between PFO+ and PFO- men in this study, RHL is not likely the mechanism to explain the differences in Tc seen between PFO+ and PFO- men. Why the PFO- subjects had a higher core temperature in this study remains unknown.

Acknowledgements

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Table of Contents

Introduction: 7

Background : 10

Purpose & Hypothesis: 12

Methods: 12

Hydration assessment via urine specific gravity 15

Core temperature measurement (telemetric pill) 15

Respiratory heat loss (Expiratory & inspiratory humidity and temperature) 16

Metabolic Heat Production (Hprod): 16

Statistical Analyses: 17

Results: 17

Discussion: 20

Limitations: 24

Conclusion: 25

Bibliography 26

Abbreviations

PFO: Patent Foramen Ovale

PFO+: With a Patent Foramen Ovale

PFO-: Without a Patent Foramen Ovale

RHL: Respiratory Heat Loss

H_{prod}: Heat Production

T_c: Core Temperature

Cres: Convective Respiratory Heat Loss

Eres: Evaporative Respiratory Heat Loss

Tres: Total Respiratory Heat Loss

VE: Minute Ventilation

List of Figures

Figure 1. PFO location and blood flow circulation

Figure 2. Labeled Hans Rudolph exercise mouthpiece

Figure 3. Relationship between time and convective heat loss at rest and during exercise

Figure 4. Relationship between time and evaporative heat loss at rest and during exercise

Figure 5. Relationship between time and total respiratory heat loss at rest and during exercise

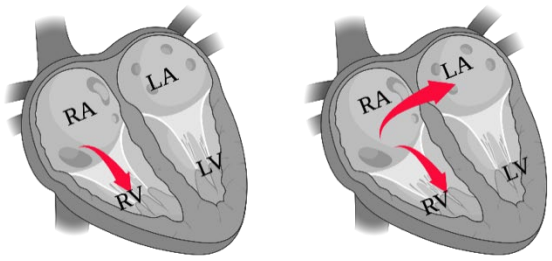
List of Tables

Table 1. Anthropometric data for subject population

Introduction:

A patent foramen ovale (PFO) is a congenital heart abnormality defined as an interatrial shunt that is present in approximately 25% of the population (Homma et al., 2016). The foramen ovale is present in all fetal hearts and serves the purpose of directing blood flow of the fetus directly through the atria of the heart and into systemic circulation. During development, the fetus receives oxygen from the placenta, thus blood does not need to flow to through the pulmonary circulation to be oxygenated. After birth, blood begins to flow through the pulmonary circulation and increased pressure in the left atrium, and decreased pressure in the right atrium of the heart favor closure of the foramen ovale. If this interatrial shunt fails to close then the remnant structure is termed a patent foramen ovale (Cole-Jeffrey et al., 2012).

The PFO has an impact on the circulation of blood flow through the heart. In normal circulation, blood enters the right atrium of the heart, flows into the right ventricle where it is pumped into the pulmonary arteries and microvasculature of the lungs and before returning to the heart through pulmonary vein into the left atrium, left ventricle, and finally into systemic circulation. In individuals with a PFO, some blood is transferred directly through the interatrial shunt, bypassing the pulmonary circulation. Blood flowing through the pulmonary circulation participates in both the exchange of heat and gas with the air in the lungs. It may be that subjects with a PFO may have slight differences in respiratory heat loss (RHL) due to shunted blood not going through the pulmonary circulation.



PFO- PFO+

Figure 1. Circulation of blood through the heart in subjects with and without a PFO (PFO+/PFO-). The red arrow depicts blood flow through the heart beginning in the right atrium (RA) then flowing into the right ventricle (RV) in subjects without a PFO. Red arrows entering the left atrium (LA) and RV in the PFO+ subject shows altered blood flow traveling between the interatrial tunnel known as a PFO.

Thermoregulation can be defined as the body's mechanism of maintaining a set internal temperature range. Control of internal temperature is a self-regulatory process that aims to maintain homeostatic conditions independent of external temperatures. As endotherms humans maintain a core temperature (Tc) around 37 ° C through a series of heat conservation and heat dissipation mechanisms (Yousef et al., 2023). The human body utilizes 4 avenues of heat loss/gain to maintain Tc. These mechanisms include evaporation, radiation, convection, and conduction. In terms of decreasing heat storage or heat loss, radiation is the most significant contributor and accounts for 60% of total heat loss at rest. Radiation occurs when heat is transferred from the deeper tissues to subcutaneous blood vessels and this heat is dissipated into the external environment through the temperature gradient. Evaporation is the second largest contributor accounting for 22% of heat loss and is occurs as liquid is converted to a gas.

Evaporation contributes to heat loss primarily through sweating, but also contributes to a portion of respiratory heat loss. When humans sweat, water is evaporated from the skin and heat is lost to the environment. When we breathe, humidification of air we exhale requires energy that utilizes the excess heat within the body (Robertshaw, 2006). Convection and conduction both contribute to the remaining heat loss. Conduction is heat loss through contact with a substance that absorbs heat from the skin while convection can be described as the movement of heated respiratory gasses through the lungs and respiratory passage into the environment.

RHL contributes to ~10-14% of heat loss during exercise (Hanson, 1974). RHL is comprised of both convective (Cres) and evaporative (Eres) heat loss and is determined by factors such as expired air temperature and humidity, inspired air temperature and humidity, and minute ventilation. As humans breathe, heat is lost through heating of gas molecules and humidification of respired air. Additionally, RHL is also dependent on ventilation. Ventilation is the rate of airflow through the lungs and increases during exercise (Powers & Dhamoon, 2022). The increase in ventilation as well as the increase in pulmonary blood flow and pulmonary blood volume (due to recruitment and distension) will increase the amount of surface area in the lungs that can participate in the exchange of heat, and therefore respiratory heat loss (Langleben et al., 2019).

As previously mentioned, subjects with a PFO (PFO+) have some degree of blood that is shunted from the right side of the heart to the left side of the heart, bypassing pulmonary circulation. This shunted blood does not participate in RHL, which may have implications for thermoregulation and core temperature responses in those with a PFO.

Background:

Two main studies from our laboratory on PFO and core temperature have contributed to the investigation of thermoregulatory differences and RHL between these two groups (PFO+/PFO-). In one previous study it was reported that subjects with a PFO had a higher core temperature (~0.4 °C) measured via esophageal temperature probe at rest and during exercise. In this study, subjects completed an exercise protocol twice, once while breathing ambient air (21 ± 1°C) and once while breathing cold dry air (2.0 ± 3.5°C). The exercise protocol for this study was a graded exercise protocol involving 4 stages on a cycle ergometer (25, 50, 75, and 90% of the subjects maximum oxygen consumption). This study examined the question of whether blood flow through the PFO had a significant impact on preventing respiratory system cooling of the human body. It was hypothesized that since the PFO+ subjects had blood bypassing pulmonary circulation that respiratory heat loss would be decreased. However, it was determined that differences in RHL only explained about 25% of Tc differences between those with and without a PFO (Davis et al., 2015). It is important to note that during this study heat production at each workload was not controlled for, which may have impacted Tc results.

Another study examined Tc differences in PFO+ and PFO- men during both passive heating and cooling. In this study, the subjects were submerged in tubs both hot (40.5 ± 0.2 °C) and cold water (19.5 ± 0.9 °C) and Tc was measured via an esophageal probe. In both the hot and cold tub, the PFO+ subjects had higher core temperatures than PFO- subjects. The authors concluded that regardless of environmental conditions, men with a PFO maintained a higher Tc compared to men without a PFO (Davis et al., 2017).

In terms of RHL, in the hot tub trial participants with a PFO experienced hyperpnea or increased breathing at a higher Tc than participants without a PFO in the hot tub, exhibiting a delayed ventilatory threshold for increasing ventilation in response to the heat. This delayed ventilatory response seen in PFO+ men may contribute to Tc differences observed between groups. For this trial PFO+ subjects displayed a lower minute ventilation at the end of immersion by ~10 L/min when compared to the PFO- group. Thus, delayed thermal hyperpnea and blunted ventilatory responses may partially explain the differences in Tc Between the two groups.

Based on these Tc differences seen between PFO- and PFO+ men at rest and during exercise as well as in various thermal conditions, it was hypothesized that there may be differences in either factors regulating baseline Tc or in thermoregulatory responses during thermal stressors. The contribution of RHL to these differences in Tc between PFO+ and PFO- men is still unknown and therefore warrants further investigation.

The limitations of the previous studies were taken into account while designing the current study. In the previous exercise study (Davis et al., 2015), the exercise intensity was selected based on relative exercise intensity (i.e., percent of maximal oxygen consumption). It is possible that at the same relative exercise intensity, two subjects were producing different amounts of heat, therefore contributing to differences in Tc. In the current study, we are selecting exercise intensity based on a workload that will elicit a heat production of 7 W/kg of body weight in all subjects, while measuring both respiratory heat loss and core temperature responses. In this project, we measured RHL in men at rest and during exercise. The overall aim of the study was to determine if there were differences in RHL for men with and without a PFO at rest and during submaximal exercise.

Purpose:

To test whether there are differences in RHL (Eres, Cres, and Tres) between PFO+ and PFO- men at rest and during 60 min of exercise at a workload eliciting a heat production (Hprod) of 7 W/kg of body weight.

Hypothesis:

We hypothesized that respiratory heat loss would be lower in PFO+ men compared to PFO- men at rest and during exercise and this difference in RHL would contribute to a higher core temperature in men with a PFO at rest and during exercise.

Methods:

Research for this study was approved by the University of Oregon Research Compliance Services. Researchers collected informed consent and relevant participant medical history. Twenty-one healthy male subjects age 18-36 years old participated in the study. Participants completed a total of 3 visits. Visit 1 consisted of a cardiac ultrasound screening for a patent foramen ovale (PFO) and pulmonary function tests. Visit 2 involved a graded exercise protocol for the determination of a workload eliciting 7 W/kg of heat production followed by a VO_2 max test. In the 3rd and final visit, participants completed a 60-minute exercise protocol on a cycle ergometer at a workload previously determined to elicit 7W/kg of heat production (from visit 2).

During the first visit, participants were screened for a PFO using an agitated saline contrast technique and ultrasound. Saline agitated with air was injected into the subject's arm vein while ultrasound screens showing an apical 4 chamber view of the heart were used to detect the presence (PFO+) or absence (PFO-) of a PFO. Presence of a PFO (PFO+) was detected if the agitated saline bubble mixture traveled from the right atrium to the left atrium of the heart within

3 beats. Failure to see bubbles transfer into the left atria of the heart within 3 heart beats determined that there was an absence of a PFO (Attaran et al., 2006; Lovering et al., 2012). Eleven PFO+ and 10 PFO- males were identified from the 21 total participants. Additionally, pulmonary function tests (PFTs) were conducted to evaluate the subject's lung health and rule out any potential lung pathologies. The three pulmonary function tests that were performed were forced vital capacity test (FVC), slow vital capacity (SVC), and the diffusing capacity of the lungs for carbon monoxide (D_LCO). All test were performed to society standards (Stanojevic et al., 2021). The FVC is a test designed to measure how much air the subject can forcibly exhale after a full breath and the purpose is to ensure that no subject has obstructive or restrictive lung diseases. The SVC is also conducted to determine vital capacity of the subject or maximum volume of air exhalated after a maximal inhalation. The D_LCO measures the lungs diffusing capacity for carbon monoxide which is a surrogate measure of the ability of oxygen to diffuse across the lungs into the red blood cells in the pulmonary capillaries. The purpose of conducting DLCO is to further ensure that no significant lung disease is present in the subject.

During the second visit the subjects were asked complete 2 exercise protocols. During both exercise protocols the subject's heart rate and oxygen saturation was monitored using an oxygen saturation (SpO_2) monitor and metabolic data was collected while the subject breathed into an exercise mouthpiece. The metabolic data collected included VO_2 and RER.

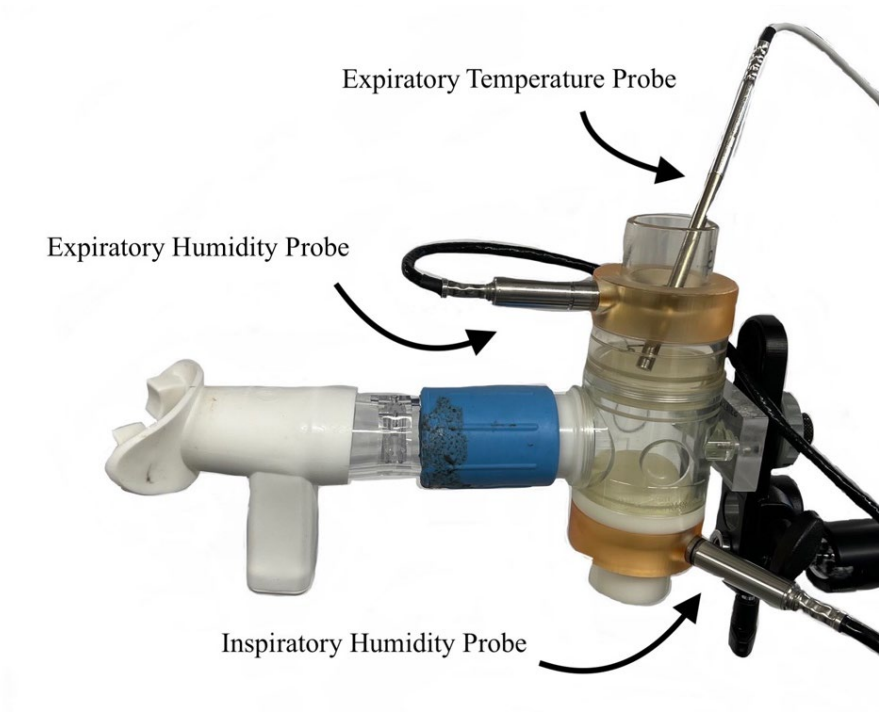


Figure 1. Labeled Hans Rudolph Exercise Mouthpiece. Arrows shown in figure point to probes inserted in the exercise mouthpiece to calculate inspiratory humidity and expiratory humidity and temperature.

The two exercise protocols conducted were a graded exercise protocol to determine a workload that would elicit a Hprod of 7 W/kg of body weight, followed by a VO_{2max} test. Participants were asked to complete a 4-stage cycling exercise protocol that would cover a range heat productions (Hprod) and allow for the calculation of a workload that would find the heat production for the hour-long exercise test. The range of workloads assigned for the 4 workloads protocol were predetermined based on body weight to estimate a work rate that would elicit a heat production of 7 W/kg of body weight. The VO_{2max} test was administered to determine the maximum amount of oxygen consumption at a peak exercise workload in order to quantify the fitness level of the subject. In this protocol the participant first cycled at a low workload (50 W).

From 50 W the workload was gradually increased in increments of 25 W every minute, until volitional exhaustion or the participant could no longer maintain a peddling pace of 60 rpm.

In the final visit, the subject performed a 60-minute submaximal exercise bout (on a cycle ergometer) breathing ambient air through the exercise mouthpiece to determine respiratory heat loss during a steady state, constant heat production exercise test. Workload for the submaximal bout is previously determined during visit 2 to provide a workload eliciting 7 W/kg of heat production. This predetermined workload eliciting 7 W/kg of heat production for each subject is used as a control measure to ensure that all participants are producing the same amount of heat during the exercise to rule out potential core temperature differences caused by variations in heat production between subjects. The individual components of this test are described below:

Hydration assessment via urine specific gravity

The night prior to testing, subjects consumed 1 L of water to ensure they were adequately hydrated the morning of test. The morning of testing, subjects were instructed to collect a small volume of first morning void into a sterile urine cup for measurement of urine specific gravity (USG). USG is used to determine the hydration status of the subject. Using a refractometer, solutes in the urine are examined to indicate if the subject is hydrated enough to participate in the study or not. The purpose of determining hydration status is to prevent the confounding influence of dehydration on thermoregulation. If a subject had a USG > 1.025, they were asked to consume an additional 250 mL of water prior to the start of exercise.

Core temperature measurement (telemetric pill)

Subjects were asked to ingest a core temperature pill at ~10 pm the night prior to the final exercise trial morning. This ensures that the subject's intestinal temperature can be measured

wirelessly/telemetrically through the duration of the protocol.

Respiratory heat loss (Expiratory & inspiratory humidity and temperature)

The five variables used to calculate respiratory heat loss are expiratory & inspiratory temperature and humidity and minute ventilation. To measure respiratory heat loss, Vaisala temperature and humidity probes are inserted into the expiratory and inspiratory sides of the Hans Rudolph exercise mouthpiece. Minute ventilation of the subject is measured using the metabolic cart. Using these variables, respiratory heat loss data were calculated at rest, during min 0-10, min 25-30 and min 55-60 of the 60 min exercise protocol.

Metabolic Heat Production (Hprod):

Metabolic heat production was calculated using two equations: Metabolic energy expenditure equation and heat production (Hprod) equation. The metabolic Hprod equation takes into account external workload (workrate), metabolic work (M), and weight for the given subject (kg). Metabolic energy expenditure equation (M) involves measures of oxygen uptake rate (VO_2) and respiratory exchange ratio (RER). RER is calculated using rate of carbon dioxide output in liters (VCO_2) per liter of oxygen consumed (VO_2) ($\frac{VCO2}{VO2}$) (Ravanelli et al., 2020). Units for metabolic heat production equation are calculated in (W/kg).

$$M = VO_2 \frac{((\frac{RER-.07}{0.3})e_c) + ((\frac{1-RER}{0.3})e_f)}{60} * 1000$$

$$H_{prod} = \frac{M - Workrate\ (W)}{kg}$$

Statistical Analyses:

All data calculations were performed using GraphPad Prism software 9.1.2 (GraphPad Software, La Jolla, CA). Data was obtained using the exercise mouthpiece and allotted temperature and humidity probes. Statistical significance was denoted at $p < 0.05$. Differences in convective, evaporative, and total respiratory heat loss between PFO+/- groups were analyzed using a 2-way repeated measures ANOVA. Additionally, a 2-way repeated measures ANOVA was also used to determine the relationship between time and convective, evaporative and total respiratory heat loss at all time points. Posthoc tests were utilized as necessary when significant relationship results were reached.

Results:

	PFO- (n = 10)	PFO+ (n = 11)
Ambient Temperature (°C)	22.2 ± 0.6	22.2 ± 0.5
Humidity (%)	41 ± 13	38 ± 10
Height (cm)	180 ± 5	180 ± 5
Weight (kg)	77.9 ± 6.1	77.7 ± 9.2
Heat Production (W/kg)	7.1 ± 0.3	7.1 ± 0.2
USG	1.016 ± 0.006	1.017 ± 0.005
Change in weight (kg)	-0.6 ± 0.2	-0.6 ± 0.2
% Change in weight	-0.6 ± 0.6	-0.7 ± 0.6
Baseline Tc	37.13 ± 0.18 °C*	36.89 ± 0.19 °C
End Exercise Tc	37.62 ± 0.16°C*	37.44 ± 0.16°C

Table 1. Environmental, anthropometric, heat production, hydration status and temperature data for all subjects . Data (means +/- SD) presented for 11 PFO+ and 10 PFO– men during 60 minute exercise protocol. * P < 0.05 vs PFO+.

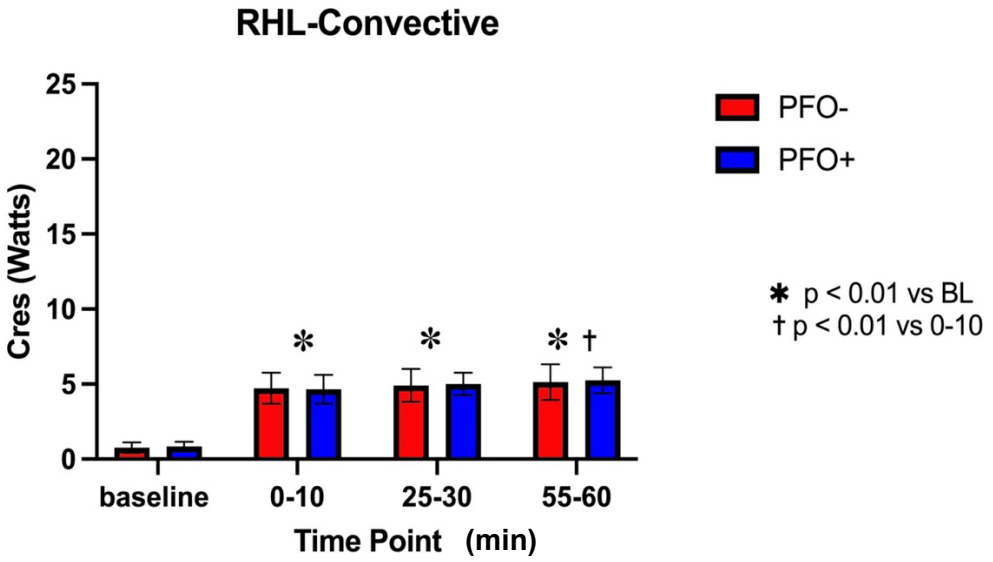


Figure 2. Relationship between time and convective heat loss at rest and during exercise. Significant main effect of time on convective heat loss with pairwise differences from BL at all time points and at 0-10 vs 55-60 minutes.

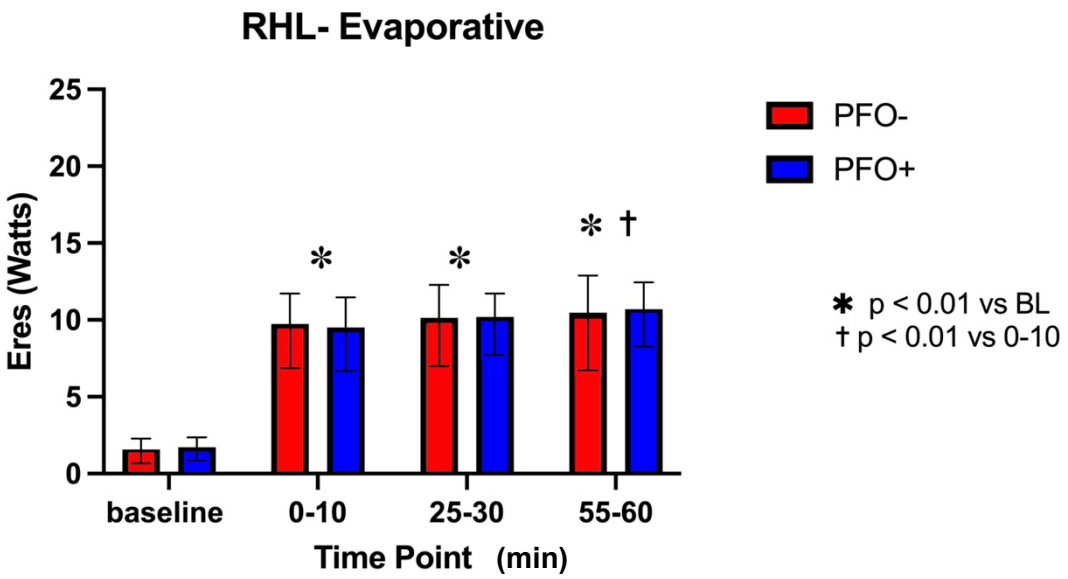


Figure 3. Relationship between time and evaporative heat loss at rest and during exercise Significant main effect of time on evaporative heat loss with pairwise differences from BL at all time points and at 0-10 vs 55-60 minutes.

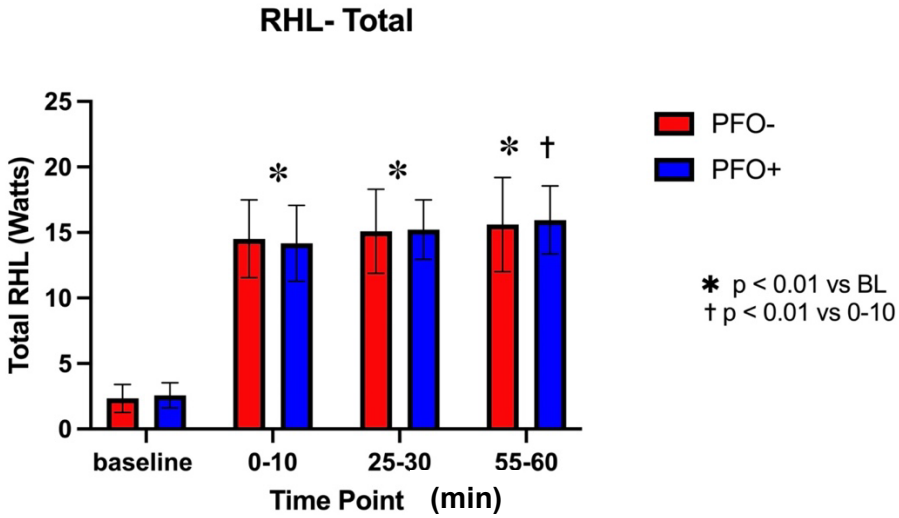


Figure 4. Relationship between time and total respiratory heat loss (Tres) at rest and during exercise for 60-minute bout. Main effect of time on respiratory heat loss from BL to all time points and 0-10 vs 55-60 minutes (* p< 0.01 vs. BL, † p<0.01 vs. 0-10).

Relationship between PFO and RHL at rest and during exercise (Cres, Eres & total RHL)

There were no differences in RHL (Cres, Eres, or total RHL) between PFO+ and PFO- men at rest or at any time point during exercise ($p>0.05$). There was a significant main effect of exercise time on convective, evaporative, and total respiratory heat loss where RHL was greater and pairwise differences in RHL at min 0-10, 25-30, and 55-60 vs baseline ($p < 0.05$). Additionally, post hoc tests revealed that all 3 components of RHL were significantly higher at min 55-60 vs min 0-10 ($p < 0.01$).

Core temperature: PFO+ vs. PFO-

Tc was significantly higher in PFO- vs PFO+ men at rest (PFO- 37.13 ± 0.18 °C, PFO+ 36.89 ± 0.19 °C, $p <0.05$) and during exercise (PFO- 37.62 ± 0.16°C, PFO+ 37.44 ± 0.16°C, $p < 0.05$).

Discussion

The purpose of this study was to determine whether there are differences in RHL between PFO+ and PFO- men at rest and during 60 min of exercise at a controlled heat production of 7 W/kg. Our findings for this study did not in support of our original hypothesis. Originally, we hypothesized that we would see lower rates of RHL in PFO+ men compared to PFO- men at rest and during exercise and this would be associated with higher core temperatures in subjects with a

PFO. Therefore, in our study we sought to determine whether there were differences in RHL between men with and without a PFO and whether or not these differences in RHL were associated with differences in Tc. We used a long duration exercise protocol at a controlled heat production values that were calculated at baseline and during exercise to analyze the relationships between 1) PFO status and exercise time on RHL (cres, eres, & total RHL), 2) PFO status and RHL, and 3) Exercise time and RHL.

PFO status, Exercise time & RHL

As previously mentioned, there was no influence of the presence of a PFO on RHL during 60 min of steady state exercise at an Hprod at 7 W/kg of body weight. Despite potential alterations in blood flow due to the interatrial shunt in participants with a PFO, our findings between groups showed that there were no differences in RHL between PFO+ and PFO- subjects. Initially we hypothesized that PFO+ subjects would have a higher core temperature at rest and during exercise, potentially due to differences in respiratory system cooling that resulted from differences in blood circulation through the heart. In PFO+ subjects, shunted blood travels through the right atrium of the heart directly into the left atrium of the heart bypassing respiratory system cooling. Additionally, by bypassing the pulmonary semilunar valve leading to circulation in the lungs, this blood is unable to participate in crucial gas exchange and respiratory cooling through contact with inhaled ambient air. Anatomically as we breathe, as blood in the pulmonary capillaries in contact with the alveolar sacs can exchange heat and moisture through the temperature and vapor pressure gradients present between the two structures. Inspired air from the thermoneutral lab environment travels through the respiratory passage of the subject where it is conditioned through the exchange of heat from blood circulating through the pulmonary and bronchial circulation (McFadden, 1992). In PFO+ subjects, inspired air from the

lab would only encounter blood circulating through the pulmonary and bronchial circulations and not shunted blood traveling through the PFO. Thus, if a percentage of shunted blood does not reach its destination in the lungs, respiratory system cooling may be diminished due to incomplete cooling of all the venous blood entering the heart. Based off shunted blood's inability to enter pulmonary circulation, individuals with a PFO in our study were suspected to have lower rates of RHL because that blood did not release its heat into the airways. However, the amount of blood shunted in men PFO may not be great enough to influence RHL. While the size of a PFO (large vs small PFO) may affect volume of blood shunted between men with a PFO in our study, we found no effect of PFO size on RHL ($p > 0.05$).

Therefore, our original hypothesis stating that men with a PFO would have higher core temperature due to diminished RHL was not supported by our data. Data collected through the study contradicts our original hypothesis as there was no significant difference in RHL between the two groups at rest or during exercise. Any core temperature differences seen in our study between PFO+/PFO- groups are not likely due to differences in RHL.

Exercise time & RHL

As expected, RHL increased from rest/baseline to all exercise time points. As the participant started cycling after the baseline measurement, there was an increase in ventilation, which contributes to increased O_2 delivery to match metabolic demand of the exercising muscles. The duration of exercise may have also played a role in increased RHL seen in both groups. During exercise, steady state is reached when heat loss balances metabolic heat production during exercise (Ferretti et al., 2017; Research & Marriott, 1993). This process may take time to balance, thus increases in RHL between the first ten minutes of exercise and the last five minutes

(min 55-60) may be indicative of metabolic adjustments in response to work done on the cycle ergometer.

PFO Status & Core Temperature

Previous studies have shown that men with a PFO have a higher core temperature at rest and during a graded exercise protocol compared to men without a PFO by about ~0.3-0.4 °C (Davis et al., 2015) when measured via esophageal probe. Core temperature in the current study was measured via the telemetric pill that all subjects were instructed to ingest ~10 hrs prior to exercise. Originally our hypothesis stated that participants with a PFO would have a higher core temperature and a decrease in RHL would contribute to this higher core temperature. Contrary to our hypothesis, in this study we found that participants without a PFO had a core temperature that was significantly higher than PFO+ subjects ($p < .05$) both at rest and during exercise. At rest we found that PFO- men had a core temperature of 37.13 ± 0.18 °C while PFO+ men had a core temperature around 36.89 ± 0.19 °C. Additionally, PFO- men had an exercising core temperature of 37.62 ± 0.1°C while PFO+ men had an exercising core temperature of 37.44 ± 0.16°C. However, since RHL was not different between PFO+ and PFO- men at rest or any time point during exercise, we can conclude that RHL did not significantly contribute to differences in Tc reported in this study. The cause of elevated core temperature seen in subjects without a PFO remains unknown, however this result may provide insight into the variability of core temperature between humans (Osilla et al., 2022). Intrasubject core temperature variability may be a possible explanation for core temperature differences seen between groups and between studies, but further research still needs to be provided to quantify this hypothesis.

Limitations:

In our current investigation of the association of a PFO on RHL at rest and during exercise we excluded women from our study. This limitation potentially excluded all significant results in core temperature differences and RHL potentially seen in women. By not including women in our investigation, known temperature differences between the different phases of the menstrual cycle such as the luteal and follicular phase were not studied. While it is well established that there are higher core temperatures during the luteal phase of the menstrual cycle due to elevations in progesterone, it is unknown if there are differences in RHL across phases of the menstrual cycle. Progesterone is a ventilatory stimulant, and whether increases in progesterone contribute to elevations in ventilation enough to increase RHL at rest or during exercise is unknown (Baker et al., n.d.). The influence of a PFO on RHL or whether women with a PFO have elevated core temperatures in either phase of the menstrual cycle compared to PFO- women is unknown and warrants investigation. By excluding women from this study the results cannot be applied to the general population and is limited to men.

The second limitation for this study could be attributed to circadian rhythm disruptions. Core temperature regulation may have been affected by natural circadian rhythm for each subject. All subjects arrived to the lab at 7 am and began the 1 hour exercise protocol promptly at 8 am, however differences in nature sleep/ wake cycles may have affected regulated core temperature in subjects who do not routinely wake up at the time of testing (Refinetti, n.d.). Ultimately, while the impact of circadian rhythm and metabolic heat production might contribute minimally to overall core temperature regulation and RHL, this variable may be significant enough to control in future investigations.

Conclusion:

Previous studies investigating core temperature and thermoregulation in men with and without a PFO determined that men with a PFO have higher core temperatures compared to men without a PFO. In order to continue investigating the potential mechanisms contributing to these differences in core temperature between these groups, we were able to develop our working hypothesis that participants with a PFO would have an elevated core temperature vs PFO- men and RHL may be a mechanism to potentially explain core temperature. Additionally, the previously determined elevated core temperature for PFO+ subjects were unable to be replicated in our study. In the current investigation, we found that PFO- subjects had a higher core temperature both at rest and during exercise. Having all subjects cycle at a workload producing 7 W/kg of steady heat production unlike earlier research using graded exercise protocols allowed us to rule out the influence of varying levels of heat production influences on core temperature changes during exercise. In both groups, there was an increase in RHL from baseline to exercise due to increases in VE and metabolic heat production. This result was to be expected based off previously known physiological adjustments at the onset and during exercise. Thus, the reason for higher Tc in PFO- men in our study but not on previous studies remains unknown but could be related to other variables such as differences in other thermoregulatory mechanisms outside the scope of RHL (i.e. skin blood flow, sweating, etc.) or due to factors contributing the intraindividual variability among a group of individuals in resting core temperature (i.e. inflammatory markers, differences in circadian rhythms, etc.).

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