ASSOCIATION OF PATENT FORAMEN OVALE WITH THE METABOLIC HEAT PRODUCTION AND CORE TEMPERATURE RELATIONSHIP IN MEN

A THESIS

by

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A patent foramen ovale (PFO) is an intracardiac shunt between the right and left atria that allows deoxygenated blood to flow from the right atrium through the shunt to the left atrium. Previous studies from our laboratory have shown that men with a PFO (PFO^+) had a higher body core temperature (T_{core}) of ~0.3-0.4 °C during active heating (exercise), passive heating (hot tub immersion) and passive cooling (cold tub immersion). This project was a retrospective analysis that examined unpublished metabolic and core temperature data from several previous studies from our laboratory. Specifically, we analyzed individual subject's metabolic heat production (H_{prod}) as a possible mechanism for the increase in T_{core} observed in PFO^+ men. During active heating, there was a strong correlation between H_{prod} and T_{core} during stages 25% Max to 90% Max, indicating that an increase in the H_{prod} due to increased exercise intensity is contributing to an increase in the T_{core} in both groups. Both passive heating and passive cooling demonstrated a curvilinear relationship between H_{prod} and T_{core}. There were similar relationships between H_{prod} and T_{core} during active heating, passive heating, and passive cooling for PFO^+ and PFO^- subjects, indicating that both groups had similar changes in T_{core} in response to the various stressors. Despite having a significantly higher T_{core}, PFO^+ subjects had the same H_{prod} as PFO^- subjects at each exercise/time stage during all three conditions. This result implies that H_{prod} is not a mechanism that causes PFO^+ subjects to have a higher T_{core} than PFO^- subjects.

Acknowledgements

I would like to express my gratitude to my mentors Dr. Andrew Lovering and Karleigh Bradbury for their guidance and assistance in completing my thesis. Providing me with a valuable learning environment and patiently explaining complex physiology, they inspired me to think deep. I would like to recognize Dr. James T. Davis, Dr. Christopher T. Minson, and Dr. Nisha Charkoudian for their inspiration and support. I am greatly indebted to these amazing researchers for providing their time and energy for my research, an act that I sincerely wish to pay forward. I'd like to express my special thanks to Dr. Lindsay Hinkle for serving as the Clark Honors College representative for my thesis committee and encouraging me throughout this process. Lastly, I could not have undertaken this journey without the support of my family and Lord Ranganatha, whose blessings and support were essential to complete my thesis and eventually complete my degree as well.

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List of Abbreviations

PFO: Patent foramen ovale

PFO^+: Subjects with a PFO

PFO^-: Subjects without a PFO

T_{core}: Core (Esophageal) temperature

H_{prod}: Metabolic heat production

$\dot{V}O_2$: Rate of Oxygen uptake per minute

$\dot{V}CO_2$: Rate of Carbon dioxide elimination per minute

RER: Respiratory exchange ratio $\left(\frac{\dot{V}CO_2}{\dot{V}O_2}\right)$

Introduction

A patent foramen ovale (PFO) is an intracardiac shunt between the right and left atria that allows deoxygenated blood to flow from the right atrium through the shunt to the left atrium. Previous studies from our laboratory have shown that men with a PFO (PFO^+) had a higher body core temperature (T_{core}) of ~0.3-0.4 °C at rest and during active heating (exercise), passive heating (hot tub immersion) and passive cooling (cold tub immersion). This project was a retrospective analysis utilizing unpublished metabolic and core temperature data from two previous studies (Davis et al. 2015 and 2017). In the current study we analyzed individual subject's metabolic heat production (H_{prod}) and their T_{core} responses during active heating, passive heating, and passive cooling. The purpose of this study was to determine whether a relationship exists between H_{prod} and T_{core} in all 3 conditions and whether this relationship is affected by the presence of a PFO.

Questions

1. Is there a relationship between H_{prod} and T_{core} during active heating, passive heating, and passive cooling?
2. Does the presence of a PFO influence the relationship between H_{prod} and T_{core}?

Hypotheses

1. There will be a significant relationship between H_{prod} and T_{core} during active heating, passive heating, and passive cooling.

2. PFO^+ subjects will have a higher H_{prod} during active heating, passive heating, and passive cooling compared to PFO^- subjects, which may help explain why PFO^+ subjects have a higher T_{core}.

Background

A PFO is an intracardiac shunt between the right and left atria **(Figure 1)** that allows deoxygenated blood to flow from the right atrium through the shunt to the left atrium (Lovering et al., 2016). The deoxygenated blood that enters the left atrium through the shunt does not pass through the respiratory system, resulting in the blood not experiencing gas-exchange, leading to worse pulmonary gas exchange efficiency and less respiratory system cooling (Davis et al., 2015). A foramen ovale is present during embryonic and fetal stages of development and allows oxygenated blood from the placenta to bypass the fetal lungs and directly oxygenate the fetus. This is achieved by permitting the oxygenated blood from the placenta, traveling to the inferior vena cava via the umbilical vein and ultimately the right atrium, to directly pass to the left atrium, through the foramen ovale, and then deliver oxygen to the fetal body. After birth, the pressure difference between the right and the left atrium, facilitated by the decrease in pulmonary vascular resistance and an increase in systemic vascular resistance, causes the foramen ovale to close in majority of the people. An unclosed foramen ovale after birth is termed as a patent foramen ovale, or PFO. The prevalence of PFO in the general population is at least 25% (Das, 2020; Lovering et al., 2022).

One method for detection of a PFO is using transthoracic saline contract echocardiography. This process requires injecting bubbles suspended in saline through the subject's antecubital vein, where the bubbles will reach the right atrium through the inferior vena cava. A PFO is diagnosed when the bubbles that appear in the right atrium also appear in the left atrium within 3-4 cardiac cycles. The size of the PFO is estimated

by the amount of bubbles that enter the left atrium (Attaran et al., 2006; Lovering & Goodman, 2012).

Previous work from our lab has demonstrated that PFO^+ men have a ~0.4 °C higher T_{core} than men without a PFO (PFO^-), both at rest, during active heating, passive heating, and passive cooling (Davis et al., 2015, 2017). In all 3 studies, T_{core} was measured using an esophageal temperature probe. Passive heating and cooling involved subjects being immersed in a hot-water or cold-water tub, respectively. During passive heating, both PFO^+ and PFO^- had the same rate of increase in T_{core} from pre-immersion to end of immersion. During passive cooling, both PFO^+ and PFO^- subjects that shivered had the same rate of decrease in T_{core}, however PFO^- subjects who didn't shiver had a greater rate of decrease in T_{core} compared to the PFO^+ subjects who didn't shiver (Davis et al., 2017).

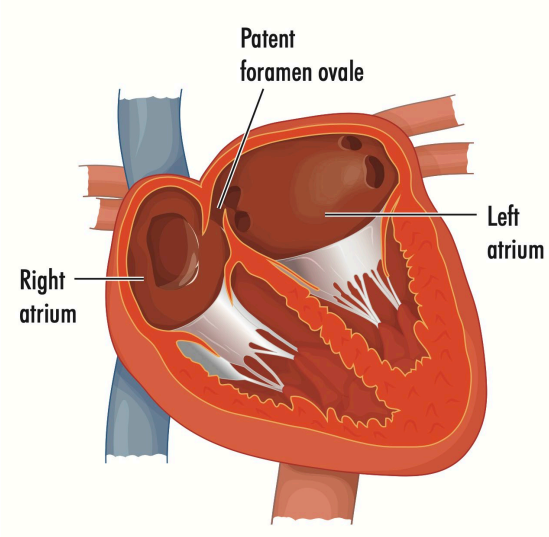

Figure 1: Location of the Patent Foramen Ovale (PFO)

(Ghosh & Jain, 2015)

Respiratory system cooling occurs as the blood passes through the lungs, through processes of evaporative and convective heat loss (Burch, 1945). The blood that

passes through the PFO into the systemic circulation is not cooled by the respiratory system, possibly contributing to the higher T_{core} in PFO^{+} men. It may also be that there are differences in other thermoregulatory mechanisms such as skin blood flow, sweating, etc., that contribute to the differences in T_{core} between PFO^{+} and PFO^{-} men. Nevertheless, the precise reason(s) for the differences in T_{core} between those humans with and without PFO remain unknown.

Metabolic heat production (H_{prod}) is one possible reason for the difference in T_{core} between PFO^{+} and PFO^{-} subjects. Metabolic heat production is a byproduct of oxygen consumption and is influenced by exercise workload and metabolic energy expenditure. The equation for the metabolic heat production (2) includes exercise workload and the subject's metabolic energy expenditure for that workload (1). Metabolic energy expenditure is defined as internal energy an individual uses to perform essential body functions in addition to external physical work (Ravanelli et al., 2020).

$$M = \dot{V}O_2 \frac{\left(\left(\frac{RER-0.7}{0.3}\right)e_c\right)+\left(\left(\frac{1-RER}{0.3}\right)e_f\right)}{60} * 1000 \qquad (1)$$

$$H_{prod} = \frac{M-\text{work rate}}{\text{weight}} \qquad (2)$$

In the current retrospective analyses, we examined the association of PFO with the relationship between H_{prod} and T_{core} in men. The main purpose of the research was to determine if there was a relationship between H_{prod} and T_{core} during active heating (exercise), passive heating, and passive cooling. In addition, we also wanted to understand whether metabolic heat production was a mechanism contributing to the increased T_{core} observed in PFO^{+} subjects.

Methods

Exercise Protocol (Active Heating)

This study received approval from the University of Oregon Research Compliance Services. Informed consent was also received from all the participants and a medical history was obtained. Out of the 55 male subjects who were screened, 30 subjects were enrolled in the study. There were 15 PFO^+ and 15 PFO^- subjects in the active heating study. All the subjects were screened for a PFO through the agitated saline contrast studies, where the PFO was detected using ultrasound. If a subject had a PFO (PFO^+), any of the bubbles injected in the subject's vein appear in the left atrium within 3 beats of appearing at the right atrium (Attaran et al., 2006; Lovering & Goodman, 2012). The size of the PFO was also categorized based on the number of bubbles that cross to the left atrium (Fenster et al., 2014; Lovering & Goodman, 2012). Pulmonary function tests were also performed to assess the subject's lung health and function. For all exercise protocols, the subjects were instrumented with a heart rate and oxygen saturation (SpO_2) monitor. Subjects breathed through an exercise mouthpiece for measures of metabolic data such as $\dot{V}O_2$ and $\dot{V}CO_2$ during both the VO_2max protocol and the graded exercise protocol.

All enrolled subjects completed a VO_2max test on an exercise bike to determine the maximum amount of oxygen they could consume during peak exercise. Subjects started cycling at 50 W and researchers increased the workload every minute until volitional exhaustion or their rate of pedaling was consistently below 60 revolutions per minute. On the next testing day, subjects completed a graded exercise protocol at four different workloads for 2.5 min each. The workloads were 25%, 50%, 75%, and 90% of

their VO_2max workload. During the graded exercise protocol, the subjects were instrumented with an esophageal temperature probe to measure their T_{core}.

Passive Heating and Cooling

This study received approval from the University of Oregon Research Compliance Services. Informed consent was also received from all the participants and a medical history was obtained. Out of the 41 male subjects who were screened, 27 subjects were enrolled in the study. There were 13 PFO^+ and 14 PFO^- subjects in the passive heating and cooling study. All the subjects were screened for a PFO through the methods explained above.

For the hot tub trial (passive heating), the subjects were immersed at the level of their clavicle in hot water (40.5 ± 0.2°C). During their time of immersion, the subject's metabolic data ($\dot{V}O_2$ and $\dot{V}CO_2$) were collected. Additionally, the subjects were instrumented with an esophageal temperature probe to measure their T_{core}. The subjects remained in the hot tub for 30 minutes, until their T_{core} reached 39.5°C, or the subjects requested to exit the tub.

For the cold tub trial (passive cooling), the subjects were immersed at the level of their nipples in cold water (19.5 ± 0.9°C). During their time of immersion, the subject's metabolic data ($\dot{V}O_2$ and $\dot{V}CO_2$) were collected. Additionally, the subjects were instrumented with an esophageal temperature probe to measure their T_{core}. The subjects remained in the cold tub for 60 minutes, until their T_{core} dropped to 35.5°C, the subjects exhibited constant shivering (a 25% increase in $\dot{V}O_2$ for more than 5 minutes), or the subjects requested to exit the tub.

Metabolic Heat Production Calculation

The metabolic heat production (H_{prod}) was calculated from using metabolic energy expenditure, the external work rate, and the subject's weight (Ravanelli et al., 2020). The metabolic energy expenditure equation (1) involves the subject's rate of oxygen uptake ($\dot{V}O_2$) and rate of carbon dioxide elimination ($\dot{V}CO_2$), which are used to calculate their respiratory exchange ratio (RER) which is $\frac{\dot{V}CO_2}{\dot{V}O_2}$. The caloric equivalent per liter of oxygen for the oxidation of carbohydrates (e_c, 21.13 kJ per liter of O_2 consumed) and the caloric equivalent per liter of oxygen for the oxidation of lipids (e_f, 19.62 kJ per liter of O_2 consumed) were constants used to convert the oxygen consumption of a subject into their energy expenditure. The metabolic heat production (W/kg) is then calculated by subtracting the external workload from the metabolic energy expenditure at each exercise intensity and standardizing the value for the subject's weight using equation 2. For the passive heating and cooling studies there were no external workload.

$$M = \dot{V}O_2 \frac{\left(\left(\frac{RER-0.7}{0.3}\right)e_c\right)+\left(\left(\frac{1-RER}{0.3}\right)e_f\right)}{60} * 1000 \qquad (1)$$

$$H_{prod} = \frac{M-\text{work rate}}{\text{weight}} \qquad (2)$$

Analyses

Relationship Between H_{prod} and T_{core}

To calculate whether there was a relationship between H_{prod} and T_{core} during active heating, the average H_{prod} and T_{core} values for the different stages of exercise (Rest, 25% Max, 50% Max, 75% Max, and 90% Max) were plotted and a linear

regression test was conducted. To calculate whether there was a relationship between H_{prod} and T_{core} during passive heating, the average H_{prod} and T_{core} values for different time stages (Pre-immersion, Threshold, and End of Immersion) were plotted and a linear regression test was conducted. To calculate whether there was a relationship between H_{prod} and T_{core} during passive cooling, the average H_{prod} and T_{core} values for different tame stages (Pre-immersion, Maximum temperature, and End of Immersion) were plotted and a linear regression test was conducted. The strength of the relationships was determined by their R-squared value.

Effect of the presence of a PFO

A 2-way repeated measures ANOVA was conducted between PFO^+ and PFO^- subjects' H_{prod} for the active heating, passive heating, and passive cooling conditions to determine whether there was a significant difference between the H_{prod} at the different stages of the various conditions. Additionally, a 2-way repeated measures ANOVA was conducted to determine if there were differences in T_{core} at different stages between PFO^+ and PFO^- for active heating, passive heating, and passive cooling conditions. For both H_{prod} and T_{core}, if a significant difference was found in the 2-way repeated measures ANOVA, post-hoc tests (Šídák's multiple comparisons test) were conducted to identify significant pairwise differences at the different time stages between PFO^+ and PFO^- subjects. If there was a main effect of PFO for both H_{prod} and T_{core}, then it would support the idea that the H_{prod} was a mechanism for the increased T_{core} in PFO^+ subjects for that condition.

Results

Anthropomorphic data for the subjects are presented in **Table 1**

Relationship between H_{prod} and T_{core}

There were strong relationships for both the PFO^+ and PFO^- subjects ($R^2 = 0.99$, $R^2 = 0.98$ respectively) between H_{prod} and T_{core} during active heating above an H_{prod} of 5 W/kg **(Figure 2**). The increase in T_{core} for a given increase in H_{prod} was similar between the PFO^+ and PFO^- subjects for the exercise stages of 25% Max, 50% Max, 75% Max, and 90% Max **(Figure 2)**, despite differences in absolute resting and exercise T_{core} between PFO^+ and PFO^- subjects. The relationships between H_{prod} and T_{core} were not a linear relationship but were rather a curvilinear relationship with passive heating and passive cooling **(Figures 3 and 4)**. During the hot tub immersion, the subjects gain heat from producing metabolic heat and the external environment at a greater rate than heat is dissipated, leading to increases in T_{core} **(Figure 3)**. During the cold tub immersion, the initial increase in T_{core} is due to peripheral vasoconstriction (Lovering et al., 2022) that increases blood flow to the core, conserving heat and increasing the T_{core}. Also, after reaching a maximum temperature, T_{core} decreases with increasing H_{prod} (generated by shivering), because the subjects cannot produce or conserve heat at the same rate that they are losing heat to the cold environment **(Figure 4)**.

Influence of PFO on H_{prod} and T_{core} relationship

There was no significant main effect of PFO presence on H_{prod} during all three conditions of active heating, passive heating, and passive cooling (**Figures 5 to 7**). At all stages of active heating, passive heating, and passive cooling, the H_{prod} of the PFO^+

and PFO^- subjects were similar, suggesting that differences in T_{core} between PFO^+ and PFO^- subjects are not caused by differences in H_{prod}. A significant main effect of PFO presence on T_{core} was observed at all three conditions **(Table 2)**. During active heating, there were no pairwise differences between PFO^+ and PFO^- subjects' T_{core} **(Table 2)**. During passive heating, PFO^+ had a significantly higher T_{core} than PFO^- subjects at the pre-immersion time stage **(Table 2)**. During passive cooling, PFO^+ subjects had a significantly higher T_{core} than PFO^- subjects at all three time stages (pre-immersion, maximum temperature, and end of immersion/ onset of shivering) **(Table 2)**. Since there was a significant main effect of PFO presence on T_{core} during active heating, passive heating, and passive cooling but no significant difference in H_{prod}, H_{prod} is not a likely mechanism contributing to the differences in T_{core} between PFO^+ and PFO^-.

		Age (years)	Weight (kg)	Height (cm)	BSA (m^2)
Active Heating	PFO^-	24 ± 5	78.2 ± 9.6	178.4 ± 5.6	1.94 ± 0.13
	PFO^+	23 ± 5	76.0 ± 9.1	176.3 ± 5.1	1.95 ± 0.14
Passive Heating & Passive Cooling	PFO^-	26 ± 8	83.1 ± 10.1	181.6 ± 6.3	2.04 ± 0.14
	PFO^+	26 ± 8	80.9 ± 7.8	179.0 ± 7.5	2.00 ± 0.13

Table 1. Anthropomorphic data for the active heating, passive heating, and passive cooling conditions

Table 1. Active heating condition had 15 PFO^+ and 15 PFO^- subjects. Both passive heating and passive cooling conditions contained the same subjects, 13 PFO^+ and 14 PFO^- subjects. Data are mean +/- standard deviation.

Active Heating *		Rest	25% Max	50% Max	75% Max	90% Max
	PFO^-	36.4 ± 0.3	36.5 ± 0.3	36.6 ± 0.4	37.0 ± 0.5	37.4 ± 0.6
	PFO^+	36.7 ± 0.4	36.7 ± 0.3	36.9 ± 0.3	37.2 ± 0.4	37.5 ± 0.4
Passive Heating *		Pre-immersion *		Threshold		End of Immersion
	PFO^-	36.5 ± 0.3		37.9 ± 0.6		39.0 ± 0.4
	PFO^+	36.8 ± 0.3		38.6 ± 0.5		39.2 ± 0.4
Passive Cooling *		Pre-immersion *		Max Temp *		End of Immersion *
	PFO^-	36.4 ± 0.3		36.6 ± 0.3		36.0 ± 0.4
	PFO^+	36.8 ± 0.2		37.0 ± 0.2		36.6 ± 0.3

Table 2. Core Temperature (T_{core}) during active heating, passive heating, and passive cooling

Table 2. All T_{core} data are presented in °C. There was a significant main effect of PFO presence on T_{core} between the PFO^- and PFO^+ subject during active heating ($P < 0.05$). However, there were no significant pairwise differences observed during any active heating time stages ($P > 0.05$). During passive heating, there was a significant main effect of PFO presence ($P < 0.05$) and at the pre-immersion stage there was a significant pairwise difference in T_{core} between the PFO^- and PFO^+ subject ($P < 0.05$). Additionally, there was a significant main effect difference in T_{core} between the PFO^- and PFO^+ subject during passive cooling ($P < 0.001$). At all time stages of passive cooling (pre-immersion, maximum core temperature reached (Max Temp), and end of immersion or the onset of shivering), there were significant pairwise difference in T_{core} between the PFO^- and PFO^+ subject ($P < 0.05$). T_{core} analysis done in passive heating and cooling conditions are from Davis et al. 2015. Asterisks indicate a significant difference. Data are mean +/- standard deviation.

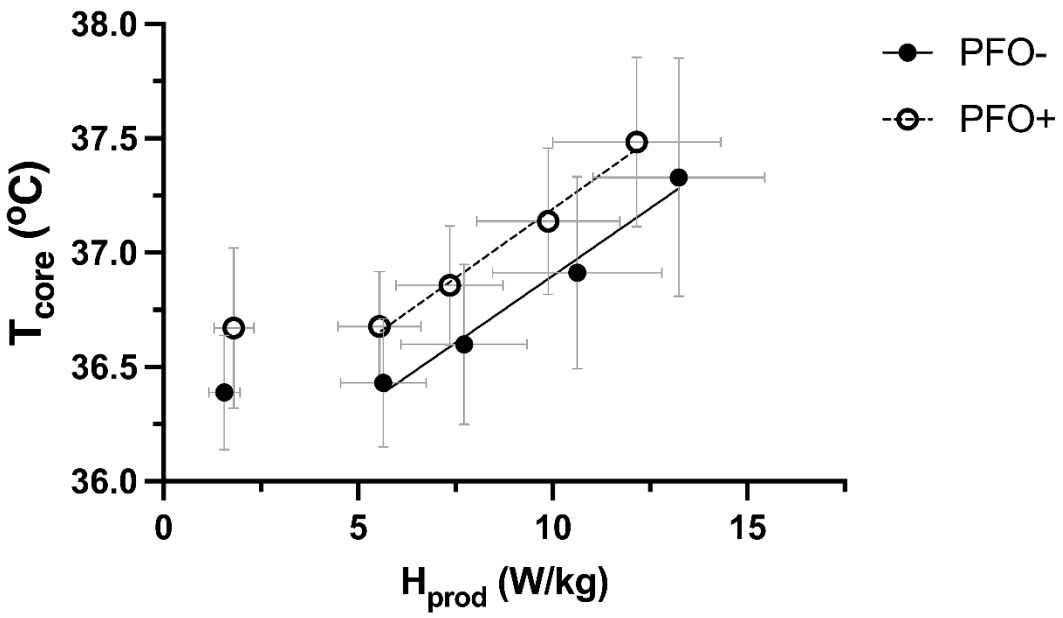

Figure 2. Relationship between heat production (H_{prod}) and body core temperature (T_{core}) in PFO^+ and PFO^- subjects during active heating

Figure 2. The individual data points show the average H_{prod} and T_{core} data at rest (data points below 5 W/ kg) and different stages of exercise (data points >5 W/kg; 25% Max, 50% Max, 75% Max, and 90% Max). For a given increase in H_{prod}, PFO^+ and PFO^- subjects had the same increase in T_{core} ($P = 0.81$) for data points greater than 5 W/kg. Also, for both PFO^+ and PFO^- subjects there was a strong relationship between the average H_{prod} above 5 W/kg and T_{core} ($R^2 = 0.99$, $R^2 = 0.98$ respectively). Data are mean +/- standard deviation.

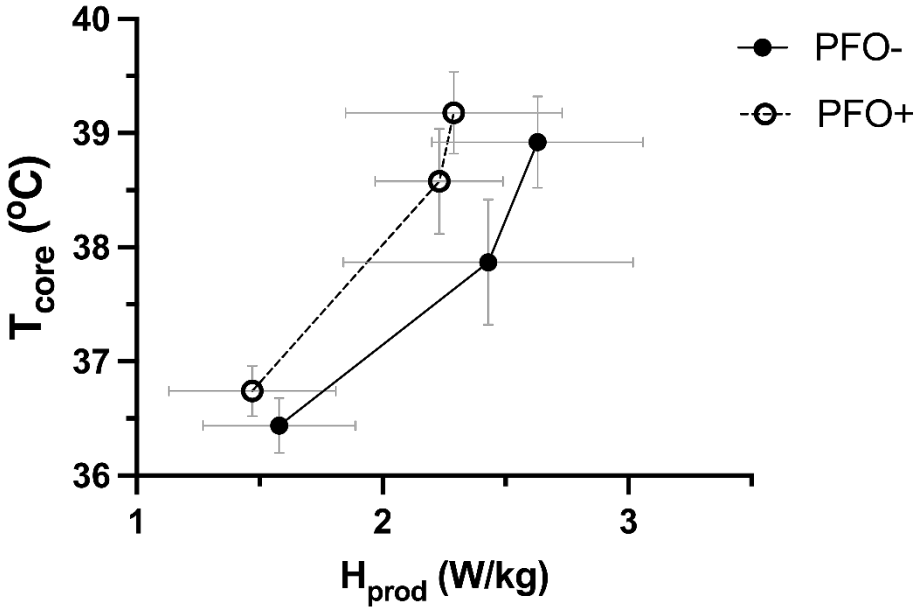

Figure 3. Relationship between heat production (H_{prod}) and body core temperature (T_{core}) in PFO^+ and PFO^- subjects during passive heating

Figure 3. The individual data points show the average H_{prod} and T_{core} data through the duration of the hot tub immersion (pre-immersion, ventilatory threshold, and end of immersion, data points left to right respectively) The relationship has a curvilinear model. For a given increase in H_{prod}, PFO^+ and PFO^- subjects had the same increase in T_{core} from pre-immersion to ventilatory threshold ($P = 0.58$) and ventilatory threshold to end of immersion ($P = 0.25$). Data are mean +/- standard deviation.

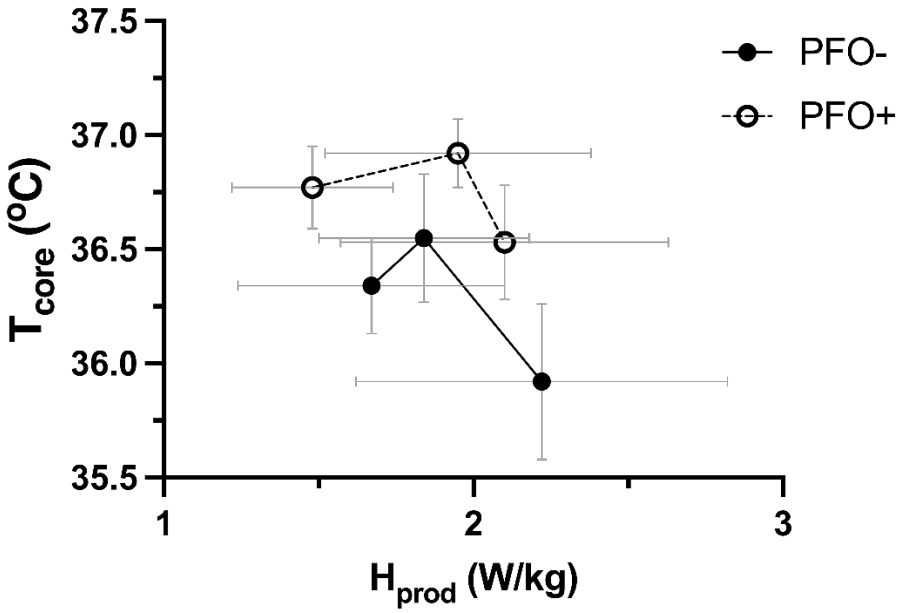

Figure 4. Relationship between heat production (H_{prod}) and body core temperature (T_{core}) in PFO^+ and PFO^- subjects during passive cooling

Figure 4. The individual data points show the average H_{prod} and T_{core} data through the duration of the cold tub immersion (pre-immersion, maximum temperature, and end of immersion/onset of shivering, data point left to right respectively.) The relationship has a curvilinear model. For a given increase in H_{prod}, PFO^+ and PFO^- subjects had the same increase in T_{core} from pre-immersion to maximum body temperature reached (P = 0.17) and maximum body temperature reached to end of immersion or the onset of shivering (P = 0.85). Data are mean +/- standard deviation.

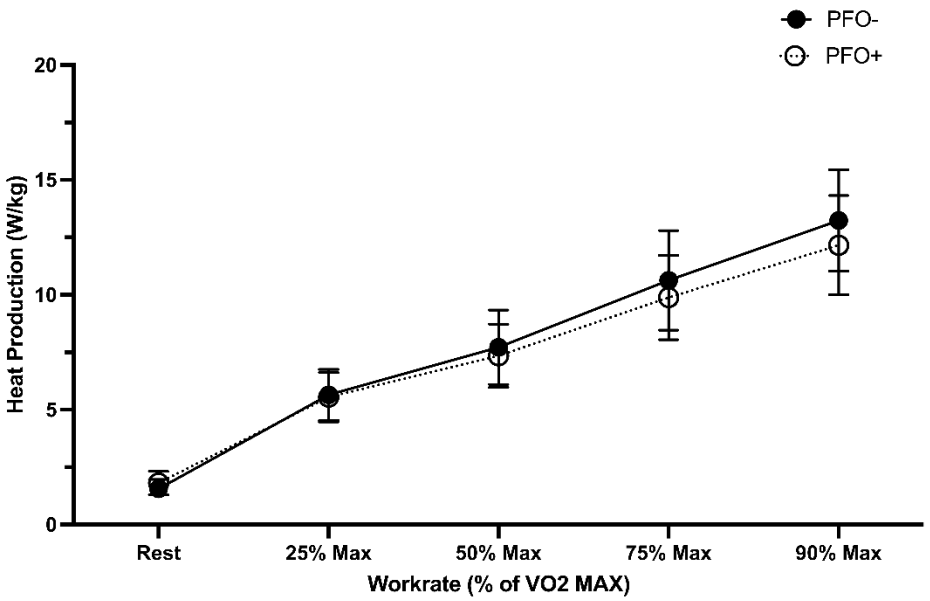

Figure 5. Heat production (H_{prod}) during active heating

Figure 5. H_{prod} for PFO^- (n = 15) and PFO^+ (n = 15) subjects at the different stages of exercise (Rest, 25% Max, 50% Max, 75% Max, and 90% Max). There was no significant main effect difference in H_{prod} between the PFO^- and PFO^+ subject at any exercise stage ($P < 0.05$). Data are mean +/- standard deviation.

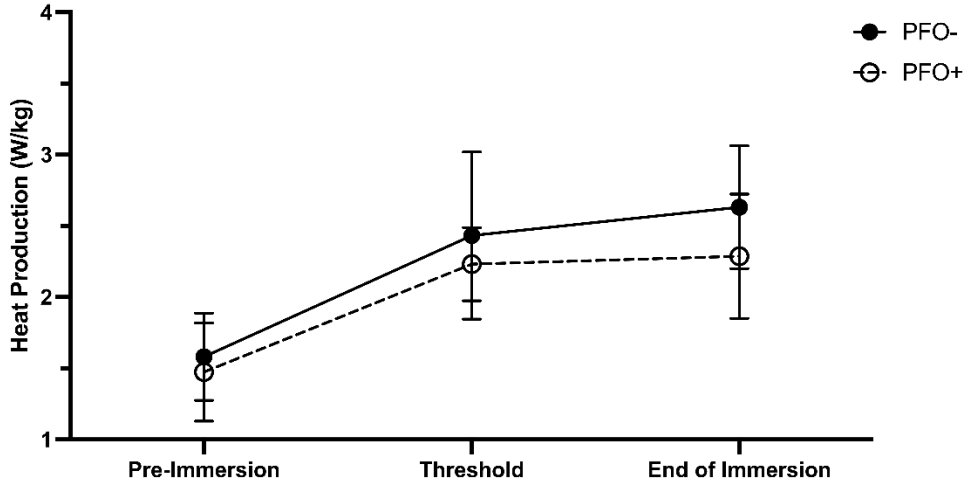

Figure 6. Heat production (H_{prod}) during passive heating

Figure 6. H_{prod} during hot tub immersion (pre-immersion, ventilatory threshold (Threshold), and end of immersion) for PFO^- (n = 13) and PFO^+ (n = 14) subjects. There was no significant main effect difference seen in H_{prod} between the PFO^- and PFO^+ subject at any time stage during hot tub immersion ($P < 0.05$). Data are mean +/- standard deviation

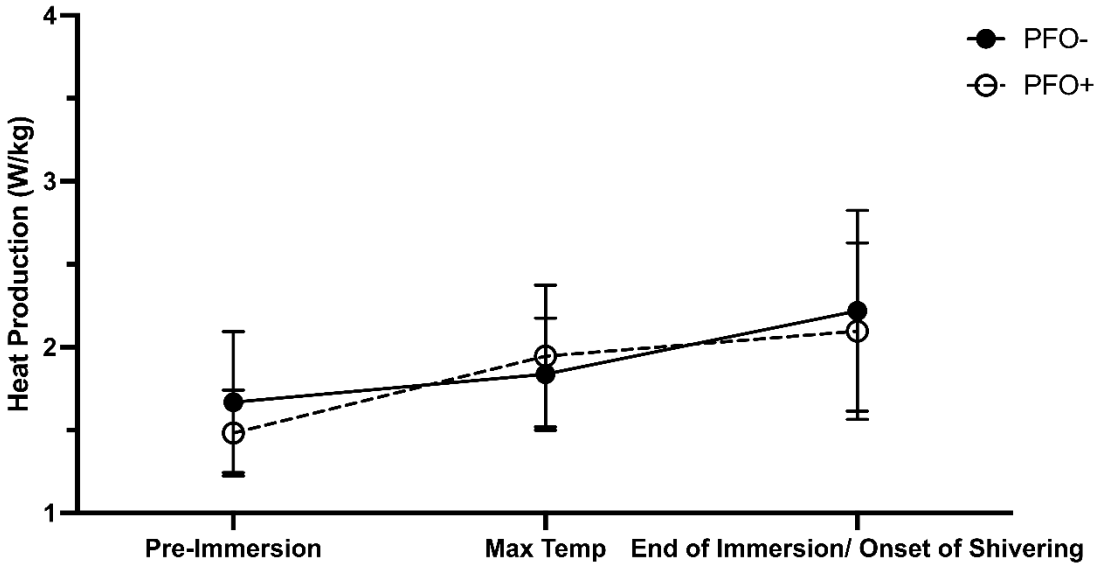

Figure 7. Heat production (H_{prod}) during passive cooling

Figure 7. H_{prod} during cold immersion (pre-immersion, maximum core temperature reached (Max Temp), and end of immersion or the onset of shivering) for the PFO^- (n = 13) and PFO^+ (n = 14) subjects. There was no significant main effect difference in H_{prod} between the PFO^- and PFO^+ subject at time stage during cold tub immersion ($P < 0.05$). Data are mean +/- standard deviation.

Discussion

The purpose of this retrospective study was to determine whether a relationship between H_{prod} and T_{core} existed during active heating, passive heating, and passive cooling and whether the presence of a PFO influenced this relationship. Through this study, we sought to understand the physiological mechanism(s) that may explain why men with a PFO have a higher T_{core} than men without a PFO. One potential mechanism is that there are differences in H_{prod} which would influence T_{core}. For the three conditions (active heating, passive heating, and passive cooling) there were two main analyses performed: 1) determining the relationships between H_{prod} and T_{core} and 2) determining the influence of a PFO on this relationship. We found that despite similarities in the relationship between T_{core} and H_{prod} in both groups, the absolute T_{core} for a given level of H_{prod} was higher in PFO^{+} subjects vs PFO^{-} subjects. This indicates that H_{prod} is not a mechanism to explain the differences in T_{core} between PFO^{+} and PFO^{-} men.

Metabolic heat production for this study was calculated using ventilatory measures of $\dot{V}O_2$ and RER. $\dot{V}O_2$ can increase or decrease based on cardiac output and tissue oxygen extraction. Exercise or shivering will increase $\dot{V}O_2$ due to increased tissue oxygen extraction and/or increasing cardiac output (Beck et al., 2006). Similarly, the calculation of $\dot{V}O_2$ using a metabolic cart takes into consideration ventilation and the oxygen inspired and exhaled during each breath. Thus, $\dot{V}O_2$ can also be influenced by changes in breathing such as thermal tachypnea and hyperthermia-induced hyperventilation whereby ventilation increases. Per the metabolic heat production equation (1), an increase in $\dot{V}O_2$ will cause an increase in the calculated $H_{prod,}$ therefore,

it is possible that increases in ventilation from heat stress can increase metabolic heat production.

Increases in T_{core} also increase cardiac output due the effect of temperature on heart rate. There are two main mechanism that increase heart rate with increasing T_{core}: increased firing of the sinoatrial node (SA node) and increased sympathetic nervous system activity. Increases in T_{core} lead to increased calcium release in the SA node, increasing the rate of depolarization, which directly contributes to an increase in heart rate (Wilson & Crandall, 2011). Also, increases in T_{core} increases sympathetic nervous system activity, leading to an increase in norepinephrine release, which increases heart rate (Wilson & Crandall, 2011). Stroke volume also increases during exercise and maintained or slightly increases with heat stress due to increases in contractility of the heart (Crandall & Wilson, 2015). Per the cardiac output equation (3), increases in heart rate and stroke volume will cause an increase in cardiac output. Per the Fick equation (4), an increase in cardiac output will cause an increase in $\dot{V}O_2$ as mentioned above. Per the metabolic heat production equation (1), an increase in $\dot{V}O_2$ will cause an increase in the calculated H_{prod}. Thus, anything that results in an increased cardiac output or ventilation will results in a greater calculated metabolic heat production.

$$\text{Cardiac output} = \text{Stroke volume} * \text{Heart rate} \qquad (3)$$

$$\dot{V}O_2 = \text{Cardiac output} * C_{(a-\overline{v})}O_2 \qquad (4)$$

Active Heating

During all stages of active heating there were no significant differences in H_{prod} between PFO^+ and PFO^- subjects. This indicates that although PFO^+ and PFO^- subjects

had differences in T_{core}, all the subjects produced similar amounts of metabolic heat per kg of body weight at each relative workload. Analysis of the relationship between H_{prod} and T_{core} revealed a curvilinear relationship between exercise stages of Rest through 90% Max. There was no change in T_{core} from Rest to 25% Max exercise stage, indicating that an increase in the H_{prod} didn't contribute to a change in T_{core}. At such low workloads (eliciting a low H_{prod}), heat dissipation mechanisms (increased skin blood flow, sweating), can match the increase in H_{prod}, preventing an increase in T_{core} (Vargas et al., 2020). From the 25% Max to the 90% Max exercise stages, there was a strong and positive linear correlation between the H_{prod} and T_{core} for both the PFO^+ and PFO^- subjects, indicating that an increase in the H_{prod} with each workload is contributing to an increase in the T_{core} which is an expected finding. This increase in T_{core} from the increase in $H_{prod,}$ starting at 25% Max, indicates that the body is producing more heat than it can dissipate through heat dissipation mechanisms such as skin blood flow and sweating. Comparing the PFO^+ and PFO^- subjects, there were no significant differences between the linear regression analyses for the 25% Max to the 90% Max exercise stages, indicating that both the PFO^+ and PFO^- subjects have similar rates of H_{prod} and heat dissipation during exercise. Since PFO^+ subjects have a similar H_{prod} with significantly higher T_{core} during workloads of active heating, H_{prod} is not likely the primary mechanism for the higher T_{core} in the PFO^+ subjects vs PFO^- subjects.

Passive Heating

Increases in environmental temperature can lead to an increase in T_{core}. Depending on the environmental conditions, increases in ambient temperature and/or humidity may prevent or decrease the effectiveness of heat dissipation mechanisms,

causing T_{core} to rise. When the hypothalamus senses an increase in T_{core}, there is an increase in skin blood flow and sweating is initiated, leading to increased heat dissipation from the skin to the environment (Osilla et al., 2022). During the hot tub immersion, although sweating occurs, it cannot be evaporated, thus no heat is lost through sweating. The body is therefore more reliant on respiratory cooling mechanisms. Elevations in T_{core} increases ventilation due to increased activation of the carotid body, which increases respiratory heat loss (Gibbons et al., 2022). The increase in ventilation is termed as thermal tachypnea until the ventilatory threshold and after the threshold it is termed as hyperthermia-induced hyperventilation because ventilation exceeds carbon dioxide production. Hyperthermia-induced hyperventilation occurs when T_{core} increase beyond 38.5°C in humans (Tsuji et al., 2016; White, 2006). As described above, increases in T_{core} increases $\dot{V}O_2$ through increases in both cardiac output (the major component) and ventilation. Per the metabolic heat production equation (1), an increase in $\dot{V}O_2$ will cause an increase in the calculated H_{prod}. Accordingly, this physiological response of thermal tachypnea until the ventilatory threshold and hyperthermia-induced hyperventilation after the ventilatory threshold will lead to an increase $\dot{V}O_2$ output which in turn could lead to an increase H_{prod}.

At all time stages during passive heating condition, there was no significant difference in H_{prod} between the PFO^+ and PFO^- subjects. This indicates that all the subjects produced similar amounts of metabolic heat, which was standardized for their weight, in response to an increase in their external temperature. The hot tub immersion has a curvilinear relationship. The curvilinear relationship is due to the differences in homeostatic mechanisms of thermal tachypnea and hyperthermia induced

hyperventilation. Comparing the PFO^+ and PFO^- subjects, there were no significant differences between the relationships between H_{prod} and T_{core} of the subjects from pre-immersion to ventilatory threshold and from ventilatory threshold to end of immersion, indicating that both the PFO^+ and PFO^- subjects have similar rates of H_{prod} and heat dissipation during immersion. Since PFO^+ subjects have a similar H_{prod} with significantly different T_{core} during most stages of immersion, H_{prod} is not likely the primary mechanism for the higher T_{core} in the PFO^+ subjects vs PFO^- subjects.

Passive Cooling

There are several thermoregulatory mechanisms at play during passive cooling. To maintain core temperature in a cold environment, peripheral vasoconstriction occurs. Peripheral vasoconstriction decreases blood flow to the skin, directing the blood flow towards the core, protecting vital organs from cold exposure and decreasing the rate of heat loss to the environment (Potter et al., 2018). Shivering also occurs during exposure to a cold environment to increase metabolic heat production by consuming skeletal muscle glycogen and blood glucose (Sellers et al., 2021). Both peripheral vasoconstriction and shivering work to maintain body core temperature in a cold environment.

During all time stages of cold tub immersion, there was no significant difference in H_{prod} between the PFO^+ and PFO^- subjects, despite differences in T_{core} at all time stages. This indicates that all the subjects produced similar amounts of metabolic heat, which was standardized for their weight, in response to a decrease in their external temperature. The data indicated that there was a curvilinear relationship between H_{prod} and T_{core} during the cold tub immersion. From the pre-immersion to the maximum

temperature reached by the subject, T_{core} increased with increasing H_{prod}, however after the maximum temperature was reached the subject's T_{core} started to decrease even with increasing H_{prod}. This trend indicates that during a cold tub immersion, the subjects could increase their T_{core} during the initial period of immersion by increasing their H_{prod}. However, towards the end of immersion, after reaching their maximum temperature, despite their increasing H_{prod}, subjects couldn't increase or maintain their T_{core} during cold tub immersion. Comparing the PFO^+ and PFO^- subjects, there were no significant differences between the H_{prod} and T_{core} relationship of the subjects from pre-immersion to maximum temperature reached and from maximum temperature reached to end of immersion or onset of shivering. These data indicate that both the PFO^+ and PFO^- subjects have similar rates of H_{prod} and heat dissipation during immersion. Since PFO^+ subjects have a similar H_{prod} with significantly different T_{core} during all stages of immersion, H_{prod} is not the primary mechanism for the higher T_{core} in the PFO^+ subjects vs PFO^- subjects.

Limitations

There are two main limitations of this study: 1) the participant pool and 2) the absence of steady state during active heating. Data used in this current retrospective analysis were all from male participants, yet women represent 50% of the population (Davis et al., 2015, 2017). Since, women experience T_{core} changes during the menstrual cycle, it was determined that the menstrual changes would confound the PFO influence so they were excluded from the current data set. During the luteal phase, women experience 0.3-0.7° C increase in their T_{core} due to the increased progesterone levels (Baker et al., 2020). Due to the T_{core} changes in women, thermoregulatory studies require menstrual cycle questionaries and blood draws to determine a subject's exact stage in the menstrual cycle. Also, all the conditions (active heating, passive heating, and passive cooling) must be repeated in the luteal and follicular phase to account for the menstrual cycle effect on T_{core} or all subjects must be tested in the same menstrual cycle phase. At the time these studies were performed, there was inadequate funding for the inclusion of women. Thus, we cannot generalize the relationship between H_{prod} and T_{core} and the influence of PFO from this study for the female population. Ongoing studies in the lab with sufficient funding are now enrolling women to examine this PFO relationship with T_{core}.

During the active heating condition, subjects exercised for 2.5 minutes in each stage of exercise (25% Max, 50% Max, 75% Max, and 90% Max), during which $\dot{V}O_2$ measurements was taken. However, to reach steady state metabolic conditions, where the rate of oxygen intake and carbon dioxide emission meet the demands of exercise, the subjects must exercise for a minimum of 3 minutes depending on the exercise

intensity (Koike et al., 1995). Achieving steady state ensures that the $\dot{V}O_2$ and RER measurements are stable to accurately report the H_{prod} for that workload. Additionally, the non-standardized metabolic heat production could have confounded the influence of PFO on the relationship between H_{prod} and T_{core}, however there were no significant differences in H_{prod} between PFO^+ and PFO^- subjects. Controlling for the heat produced during exercise would have allowed for us to be able to rule out differences in metabolic heat production as a mechanism to explain the differences in T_{core}.

Conclusion

Previous research has shown that men with a PFO have a higher T_{core} of ~0.3-0.4 °C during active heating, passive heating and passive cooling compared to men without a PFO. However, the physiology or reasoning behind this increase in T_{core} that PFO^+ men experience has not been determined. Two major hypotheses include decreased respiratory cooling and increased metabolic heat production. The purpose of this retrospective study using data from two previously published studies examining the influence of a PFO on T_{core} responses (Davis et al., 2015, 2017) was to determine whether H_{prod} is responsible for the increase in T_{core} observed in PFO^+ men during 3 different conditions (active heating, passive heating, and passive cooling). We found this was not the case. Specifically, we found that both PFO^+ and PFO^- subjects had different core temperatures at nearly identical levels of heat production. These data suggest that either PFO^+ subjects are losing less heat or PFO^- subjects are losing more heat at a given level of heat production. Additionally, there were similar relationships between H_{prod} and T_{core} during active heating, passive heating, and passive cooling for PFO^+ and PFO^- subjects, indicating that there were no differences in the effectiveness of heat dissipation/ conservation mechanisms between PFO^+ and PFO^- in these conditions. Future studies should investigate heat loss mechanisms in both PFO^+ and PFO^- subjects to determine the causes for the different core body temperatures.

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