THE EFFECT OF A PATENT FORAMEN OVALE ON THERMOREGULATORY AND VENTILATORY RESPONSES DURING PASSIVE HEATING AND COOLING

by

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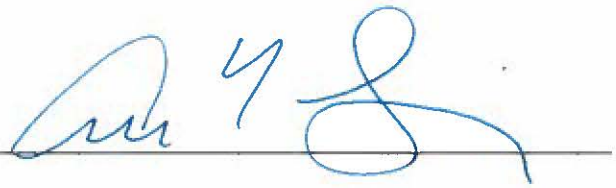
Approved: 

Andrew T. Lovering

A patent foramen ovale (PFO) is an intracardiac shunt present in ~1/3 of the general population that allows varying degrees of blood flow to bypass pulmonary circulation and respiratory cooling. The aim of this research was to determine how the presence of a PFO affected thermoregulatory and ventilatory responses to passive heating and cooling. During passive heating, ventilation increases in order to augment heat dissipation from the respiratory system. Because individuals with a PFO (PFO+) have a higher resting core temperature (T_{core}), it was hypothesized that PFO+ subjects would increase their ventilation at a higher T_{core} than subjects without a PFO (PFO-) during passive heating. Additionally, shivering is implemented in order to generate heat during passive cooling. Because PFO+ individuals have a higher resting T_{core}, it was hypothesized that the PFO+ group would shiver at a higher T_{core}. To test these hypotheses, 22 well-matched males (11 PFO+ and 11 PFO-) completed a passive heating and a passive cooling trial. In the passive heating environment, individuals were immersed in a 40.5±0.3°C water bath until1) 30 minutes had elapsed, 2) their

esophageal temperature (T_{esoph}) reached 39.5°C, 3) they became lightheaded, or 4) they requested to get out. In the passive cooling environment, individuals were immersed in a 19.7±0.6°C water bath until 1) 60 minutes elapsed, 2) their T_{esoph} dropped to 35.5°C, 3) sustained shivering occurred, or 4) they requested to get out. In both trials, PFO+ had a higher T_{esoph} ($p < 0.05$). At the end of hot water immersion, PFO+ subjects had significantly lower minute ventilation than PFO- subjects ($p < 0.05$). Additionally, PFO+ subjects shivered at a significantly higher T_{esoph} than the PFO- subjects during the cold water immersion ($p < 0.05$). The results suggest that individuals with a PFO have a significantly higher T_{core}, and that this greater temperature is defended in both hot and cold environments. These results may help us further understand how the presence of a PFO affects an individual's response to environmental conditions, as well as why some people may be more prone to certain thermal illnesses.

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Abbreviations

$AaDO_2$: Alveolar-to-arterial partial pressure of oxygen difference

CO_2: Carbon dioxide

DL_{CO}: Lung diffusion capacity for carbon monoxide

FEF25-75: Forced mid-expiratory flow

FEV1: Forced expiratory volume in 1 s

FVC: Forced vital capacity

HR: Heart rate

O_2: Oxygen

PFO: Patent foramen ovale

PFO+: Subjects with a PFO

PFO−: Subjects without a PFO

PFT: Pulmonary functions tests

PO_2: Partial pressure of oxygen

RHL: Respiratory heat loss

RR: Respiratory rate

SpO_2: Predicted arterial oxygen saturation

T_{core}: Core temperature

$T_{esoph.}$ Esophageal temperature

V_A: Alveolar ventilation

VCO_2: Carbon dioxide elimination

V_E: Minute ventilation

VO_2: Oxygen uptake

V_t: Tidal volume

Introduction:

What has been called for a very long time a “hole in the heart” has now been divided among three distinct conditions - patent foramen ovale (PFO), atrial septal defect, and ventricular septal defect - with the PFO affecting a much greater percentage of the population and being easily distinguished from other congenital heart defects (Ferencz *et al.,* 1985; Elliott *et al.,* 2013). Individuals with a PFO (PFO+) have an opening between the left and right atria of their heart that allows varying degrees of blood to pass through without travelling to the lungs. While the prevalence of a PFO in the general population is significant and well-documented (Elliott *et al.,* 2013; Marriott *et al.,* 2013; Woods *et al.,* 2010), the impact of this intracardiac shunt on physiological responses to thermal challenges in otherwise healthy individuals has not been determined.

Blood travelling through a PFO bypasses the pulmonary circulation, and thus does not undergo gas or heat exchange in the lungs. Research has shown that PFO+ individuals have greater gas exchange inefficiency at rest because blood travelling through this shunt pathway fails to travel to the lungs and participate in gas exchange (Lovering *et al*., 2011; Fenster *et al.*,2013).

Respiratory cooling allows for the dissipation of heat from the blood and occurs via convective and evaporative heat loss. Thus, in addition to an increase in gas exchange inefficiency (Lovering *et al,* 2011; Fenster *et al.*,2013), the presence of a PFO also impacts an individual’s ability to dissipate heat and regulate body temperature. Previous work has measured esophageal temperature (T_{esoph}) in PFO+ individuals to be ~0.4°C higher at rest than individuals without a PFO (PFO-) (Davis, *et al.,* 2015). This

research shows that the presence of a PFO not only impacts gas exchange inefficiency, but also affects an individual's thermoregulatory responses and thus, core body temperature (T_{core}). While these studies reveal that the presence of a PFO significantly affects multiple important functions of the cardiopulmonary system, the impact of this intracardiac shunt on thermoregulatory and ventilatory responses has not been well-studied.

The purpose of this study was to understand how the presence of a PFO affects an individual's thermoregulatory and ventilatory responses during passive heating and cooling. It was hypothesized that, compared to PFO- subjects:

1. PFO+ subjects would have blunted ventilatory responses to passive heating.

   This hypothesis was based on research suggesting that PFO+ individuals have a 0.4°C higher T_{core}, and thus may increase ventilation at a higher T_{core} threshold than PFO- individuals (*Figure 1*).

2. PFO+ subjects would shiver at a higher T_{core}.

   This hypothesis was based on research suggesting that PFO+ individuals have a higher resting T_{core}, and thus may begin shivering at a higher T_{core} than PFO- individuals (*Figure 1*).

Background:

Cardiopulmonary Physiology:

Systemic venous blood is delivered to the right side of the heart before being pumped to the lungs for gas exchange (*Figure 2*). After undergoing gas exchange, the blood travels back to the left side of the heart through the pulmonary veins before being delivered back out to the body. This blood circulates to deliver oxygen (O_2) and retrieve carbon dioxide (CO_2), which is a necessary process because O_2 is required for the production of energy in aerobic tissues. Thus, while blood in the left side of the heart is oxygenated, the blood in the right side of the heart has not yet travelled to the lungs for gas exchange.

Functions of the Lungs:

The primary function of the pulmonary system is to allow blood vessels to meet with the alveoli in order to undergo gas exchange. The alveoli are the saccular micro-units of the lung that fill with air during respiration to allow for diffusion between the blood and air. During this exchange, O_2 diffuses from the air into the blood, where it is bound to hemoglobin for delivery to the tissues. Carbon dioxide, a byproduct of metabolism, diffuses out of the blood and into the air to be exhaled. Metabolic processes generate CO_2 and heat, which must be dissipated as they accumulate.

Besides gas exchange, another key function of the lungs is heat dissipation. Similar to CO_2 and O_2 diffusing between the blood and inspired air, heat exchange also occurs at the lungs. Although the majority of heat loss occurs at the level of the skin, it

is estimated that approximately 10% of total heat loss occurs through respiratory cooling (Burch, 1945).

Under normal conditions, the main drive to breathe comes from central chemoreceptors located in the ventrolateral medulla. These receptors primarily sense fluctuations in hydrogen ion concentration in the cerebral spinal fluid. Carbon dioxide diffuses across the blood brain barrier and into the cerebral spinal fluid, where carbonic anhydrase catalyzes the dissociation of hydrogen ions, which are then sensed by the central chemoreceptors (Hall, 2006). Thus, the central chemoreceptors indirectly measure the CO_2 content in the arterial blood through changes in cerebrospinal fluid pH. These receptors send signals to the respiratory pattern generator in the medulla, which then relays this information to respiratory muscles via motor neurons to cause contraction of the diaphragm and accessory muscles. Contraction of these respiratory muscles causes an increase in ventilation in order to decrease arterial CO_2 levels. The presence of a PFO can disrupt this mechanism because blood flowing through a PFO bypasses the pulmonary circulation and does not undergo gas exchange, allowing for a greater arterial CO_2.

Patent Foramen Ovale:

In the human embryo, blood travelling to the fetus has already travelled through the mother's lungs for gas exchange, and thus the fetal lungs are not needed to oxygenate the blood. A few structures exist to allow blood to travel through fetal circulation without going through the developing lungs, one of which is the foramen ovale. The foramen ovale is a fetal structure that allows blood to bypass the pulmonary

circulation through an opening in the interatrial septum, which divides the left and right atria of the heart. When ventilation commences after birth, inspired O_2 decreases pulmonary vascular resistance, allowing blood to fill the pulmonary vessels. This causes a subsequent increase in left atrial pressure as this blood enters the left side of the heart. This new pressure gradient across the left and right atria forces the septum primum, a flap of tissue in the left atria, to cover the foramen ovale. In most individuals, the tissue eventually fuses with the interatrial wall and functionally closes off this shunt pathway. However, in ~25-40% of the general population, the foramen ovale fails to close completely (Woods *et al.*, 2010; Marriott *et al.*, 2013; Elliott *et al.*, 2013) and is termed a patent foramen ovale, or PFO (*Figure 3*). This shunt pathway allows varying degrees of cardiac output to bypass the lungs and travel through systemic circulation without passing through pulmonary microcirculation.

Thermoregulation and Ventilation:

A T_{core} threshold exists to determine when it is appropriate to respond to both passive heating (Cabanac and White, 1995) and passive cooling environments (Tikuisis *et al.*, 2000). While sweating is thought to be the main avenue of heat loss in hyperthermic humans, ventilation increases two-to-three fold when T_{core} reaches approximately 38.5°C (Cabanac and White, 1995). Although this response has been observed, the cause of this increase in ventilation is not fully understood. One explanation is that the rise in ventilation is a physiological mechanism implemented to increase heat dissipation through respiratory cooling. An alternative explanation is that the augmented ventilation is an indirect result of an increased metabolic rate in hyperthermia. Because metabolic reactions require O_2, as metabolic rate increases, the

amount of O_2 required to sustain this activity rises, and thus ventilation must increase in order to supply the tissues with enough O_2 to sustain the increased metabolic flux. This increase in metabolic rate due to temperature can be estimated using the temperature coefficient (Q_{10}), which states that for every increase in temperature by 1°C, there is an increase of 12-14% in metabolism. However, the increase in oxygen consumption (VO_2) does not fully account for the increase in ventilation observed during hyperthermia, and thus, thermoregulation, the homeostatic regulation of T_{core}, is likely modulating this ventilatory response in order to increase respiratory heat loss (RHL) (Cabanac and White, 1995).

Ventilation also increases when an individual is placed in a hypothermic environment. When first exposed to the cold, peripheral vasoconstriction causes blood to be redirected towards the core, temporarily increasing T_{core}. However, shortly after exposure, T_{core} decreases as heat is lost to the environment. It is estimated that when T_{core} drops to ~36°C, shivering ensues to maintain T_{core} (Tikuisis, *et al.*, 2000). Shivering occurs through involuntary muscular contractions that do not produce any movement, but that do generate heat. It has been estimated that shivering, due to passive cooling, can increase the metabolic rate of the working muscles three-fold from resting values (Tikuisis, *et al.*, 2000). VO_2 and CO_2 production (VCO_2) increase as a result of these contractions, and thus ventilation must increase in order to sustain the increased metabolic activity. Because shivering requires an increase in ventilation and metabolic rate, VO_2 can be used to quantify shivering.

The Effect of a Patent Foramen Ovale on Thermoregulatory and Ventilatory Responses:

While the ventilatory responses to thermal challenges have been well-studied, they are highly variable between individuals. One possible contributing factor to this variability between individuals could be the presence of a PFO. The resting T_{esoph} (a gold-standard measure of T_{core}) has been measured to be ~0.4°C higher in PFO+ subjects compared to PFO- individuals (Davis *et al.,* 2015). PFO+ individuals have a higher resting T_{core} and varying amounts of blood bypassing the lungs, which suggests that they may thermostatically operate at a higher T_{core} and thus may respond differently to passive heating and cooling than PFO- subjects.

Blood bypassing pulmonary circulation through a PFO also fails to undergo respiratory gas exchange. Gas exchange inefficiency is measured by comparing the partial pressure of oxygen (PO_2) in the arteries to the PO_2 in the alveoli. This alveolar-to-arterial PO_2 difference ($AaDO_2$) is used to describe gas exchange inefficiency. Because PFO+ individuals have some amount of blood bypassing the lungs, research has shown that PFO+ individuals not only have a higher resting T_{core}, but they also have worse gas exchange efficiency compared to PFO- individuals (Lovering *et al.* 2011; Fenster *et al*, 2013).

Summary:

Gas exchange inefficiency (Lovering *et al.,* 2011; Fenster *et al.,*2013) and T_{esoph} (Davis *et al.,* 2015) are significantly augmented in PFO+ individuals at rest. Because PFO+ individuals have a higher resting T_{core} and varying degrees of cardiac output bypassing respiratory cooling in the lungs, this raises questions as to how the

homeostatic regulation of T_{core} is affected in these individuals. While extensive research on thermoregulation and ventilation has been done, the effect of a PFO on these responses remains to be determined.

Methods:

This study was approved by the University of Oregon's Office for Protection of Human Subjects. Each subject was given documentation outlining the study and provided written consent prior to participation. All experimental procedures were conducted in accordance of the *Declaration of Helsinki.*

Subjects:

A total of 22 individuals volunteered to participate in this study. The nature of the study was described to all subjects orally and in writing, and the subjects provided their written consent. The subjects were non-smoking male subjects, age 27 ± 8, with no history of cardiopulmonary disease. 11 of these subjects were found to have a PFO as determined by ultrasound screening (described below). There were no significant anthropometric differences between PFO- and PFO+ groups (*Table 2).*

Ultrasound Screening:

The presence of a PFO was determined using saline-contrast echocardiography as previously described (Lovering and Goodman, 2012). The screening was performed with the subject breathing room air and seated, reclined at a 45° angle on the subject's left side. Three ml of sterile saline with 1 ml of room air was manually agitated between two 10 ml syringes connected in parallel to two 3-way stopcocks. The microbubbles created were immediately injected into a peripheral vein using an IV catheter (20-22G) while ultrasound imaging (Philips ie33) was used to clearly view all four chambers of the heart. The injections were performed during normal breathing and

immediately following the release of a Valsalva maneuver, which was confirmed effective by the leftward shift of the interatrial septum. After injection of the bubbles, the following 20 cardiac cycles were recorded. The appearance of any microbubbles in the left atrium or ventricle during the next 20 cardiac cycles was considered a positive result for either a PFO or transpulmonary passage of contrast. If contrast appeared ≤ 3 cardiac cycles in the left heart after being seen in the right heart, the subject was classified as PFO+. The absence of bubbles in the left heart ≤ 3 cardiac cycles after injection indicated that no PFO was present in that individual.

Pulmonary Function and Diffusion Capacity:

Subjects performed pulmonary functions tests (PFT) to ensure that their lung function and diffusion capacity was within the normal range. Baseline PFT included measures of forced vital capacity (FVC), forced expiratory volume in 1 sec (FEV_1), and forced mid-expiratory flows (FEF_{25-75}). Measurements were made with a computerized spirometry system (Ultima PFX, MedGraphics, St Paul, MN, USA) according to American Thoracic Society/European Respiratory Society (ATS/ERS) standards (Macintyre *et al.*, 2005). Lung volumes and capacities were determined using whole-body plethysmography (Wanger *et al.*, 2005). Lung diffusion capacity for carbon monoxide (DL_{CO}) was determined using the single-breath, breath-hold method (Knudson *et al.*, 1987; Macintyre *et al.*, 2005) using the Jones and Meade method for timing and alveolar sample collection (MedGraphics Ultima PFX, Breeze v.6.3.006). Predicted values for DL_{CO} were calculated as previously described (Gutierrez *et al.*, 2004).

Study Days:

Each subject came in on two separate days, no less than 48 hours apart, to complete one of two trials. The subject underwent these trials in a randomized and balanced order on separate days and started in the early morning (6:30 – 8:00am). Both trials were performed at the same time of day (+/- 1 hour). After subject arrival, experimenters verified that controls were in place (i.e. last time they ate; what time they went to sleep and woke up; and any recent alcohol or caffeine consumption). An esophageal probe was placed through the nostril to a specific depth beyond the nasal flare based on the subject's sitting height to measure T_{esoph}, as before (Mekjavic & Rempel, 1990). Nude weight was then obtained, and the subject was instrumented with a forehead pulse oximeter (Tyco, Nellcor Oximax N-600, Mansfield, MA, USA) to measure oxygen saturation (SpO_2) and heart rate (HR).

The subject was seated, wearing only swimming trunks, for 15 minutes while resting data was recorded. During this time, the subject breathed on a low-resistance two-way non-rebreathing mouthpiece (model 2400, Hans Rudolph, Kansas City, MO, USA), and pneumotachograph (MedGraphics Pre-Vent). After this 15-minute resting period, the subjects entered the hot or cold tub.

Hot tub trial: Subjects entered a water bath heated to 40.5±0.3°C and were immersed to the level of their shoulders. Once seated, subjects were fitted with a thick, fur lined, felt hat to prevent heat loss from the head. Subjects remained in the tub until 1) 30 minutes had elapsed, 2) their T_{esoph} reached 39.5°C, 3) they became lightheaded, or 4) they requested to get out. During immersion,

measurements of T_{esoph}, inspired and expired air humidity and temperature, VO_2, VCO_2, minute ventilation (V_E), alveolar ventilation (V_A), tidal volume (V_t), respiratory rate (RR), and HR were taken continuously. Every 5 minutes, measurements of aural temperature (Braun, IRT 4520, Southborough, MA, USA) and thermal sensation were recorded.

Cold tub trial: Subjects entered a water bath cooled to 19.7±0.6°C and were immersed to the level of their nipples, where they remained until 1) 60 minutes had elapsed, 2) their T_{esoph} dropped to 35.5°C, 3) sustained shivering occurred, or 4) they requested to get out. Sustained shivering was determined to be when VO_2 increased 25% above initial immersion steady-state values for 5 minutes (Doufas *et al.,* 2003; Wadhwa *et al.,* 2005). During immersion, measurements of T_{esoph}, inspired and expired air humidity and temperature, VO_2, VCO_2, V_E, V_A, V_t, RR, and HR were taken continuously. Every 5 minutes, measurements of aural temperature (Braun, IRT 4520, Southborough, MA, USA) and thermal sensation were recorded.

After the water immersion, the subject exited the water and dried off. The pulse oximeter was removed and nude weight was again obtained. The esophageal probe was then removed and the subject was free to leave.

Statistical Analyses:

GraphPad Prism software (v 5.0b) was used for data analysis. Differences in anthropometric data between groups were analyzed using unpaired t-tests. Overall and group descriptive statistics (mean, standard deviation, and standard error of the mean) were calculated for all test variables. To determine significance between PFO+ and PFO- subjects, 15-second averages were used to analyze data using a 2-way mixed ANOVA (group x time) with an α-level of 0.05. For the hot tub trial, data were analyzed at two time points: 1) at the end of the resting period, and 2) at the end of the water immersion period. Additionally, T_{esoph} and V_E were also measured at the peak ventilatory threshold. This threshold was determined to be the time at which the end-tidal CO_2 was 5 Torr less than the final resting value (Lucas *et al.*, 2015). For ventilatory measures during the hot tub trial, an *a-priori test* was used to determine significance because no difference was expected to be observed between groups at rest. For the cold tub trial, data was analyzed at three time points: 1) at the end of the resting period, 2) at the peak T_{esoph} during immersion, and 3) at the end of the water immersion period. Additionally, a Fisher's exact test was used to determine significance in the reason for exiting the tub between PFO+ and PFO- during both trials.

Results:

Environmental Conditions:

There were no significant differences between PFO- and PFO+ groups in room temperature, humidity, barometric pressure, or water temperature (*Table 1*). Additionally, there were no significant differences in room temperature, humidity, or barometric pressure between the passive heating and passive cooling trials.

Lung Function and Anthropometric Data:

There were no significant differences between PFO+ and PFO- groups in anthropometric, pulmonary function, or DL_{CO} data (*Table 2).*

Thermal Sensation:

There were no significant differences between PFO+ and PFO- groups during either the passive heating or passive cooling trials in thermal sensation (data not shown).

Heart Rate:

Heart Rate During Hot Water Immersion:

During the hot tub trial, there was no significant difference in HR between PFO+ and PFO- groups ($p > 0.05$) (*Figure 4*).

Heart Rate During Cold Water Immersion:

During the cold tub trial, there were no significant differences in HR between PFO+ and PFO- groups however, HR trended ~9 bpm higher in the PFO+ group than the PFO- group ($p = 0.07$) (*Figure 5*).

Metabolic Measures:

Metabolic Measures During Hot Water Immersion:

During the hot tub trial, there were no significant differences between PFO+ and PFO- groups in VO_2 or VCO_2 (data not shown).

Metabolic Measures During Cold Water Immersion:

During the cold tub trial, there were no significant differences between PFO+ and PFO- groups in VO_2 or VCO_2 (data not shown).

Respiratory Measures:

Respiratory Measures During Hot Water Immersion:

During the hot tub trial, there was a main effect of PFO on V_E ($p < 0.05$), with PFO+ individuals ventilating significantly less than PFO- individuals (*Figure 6*). Amongst subjects who did not reach ventilatory threshold, there was not a significant difference between the two groups in V_E ($p > 0.05$). However, amongst those who did reach ventilatory threshold ($n = 12$), PFO+ individuals had a significantly lower V_E compared to PFO- individuals during hot water immersion ($p < 0.05$) (*Figure 6*). Additionally,

the PFO- group had a significantly lower T_{esoph} at the ventilatory threshold than the PFO+ group ($p < 0.05$) (*Figure 7*).

Respiratory Measures During Cold Water Immersion:

During the cold tub trial, there were no significant differences between PFO+ and PFO- groups in V_t, RR, V_E, or SpO_2 at any of the three time points measured (data not shown).

Esophageal Temperature:

Esophageal Temperature During Hot Water Immersion:

During the hot tub trial, there was a main effect of PFO on T_{esoph} amongst all subjects ($p < 0.05$), and amongst just those who reached the ventilatory threshold ($p < 0.05$), with a specific pairwise difference occurring at the ventilatory threshold ($p < 0.05$) (*Figure 8*).

Esophageal Temperature During Cold Water Immersion:

During the cold tub trial, there was a main effect of PFO on $T_{esoph,}$ with significant pairwise differences occurring at all three time points measured ($p < 0.05$) (*Figure 9*).

Reason for Exiting:

Reason for Exiting During Hot Water Immersion:

There was a main effect of PFO on the reason for exiting the tub, with 6 PFO+ subjects reaching the 39.5°C threshold compared to 0 PFO- subjects, and 5 PFO- subjects (compared to 0 PFO+ subjects) staying in the tub for the full 30 minute time limit without reaching the T_{esoph} threshold ($p < 0.05$) (*Table 3).*

Reason for Exiting During Cold Water Immersion:

There was no main effect of PFO on the reason for exiting the tub, however, 4 PFO- subjects and 0 PFO+ subjects reached the 35.5°C threshold before 60 minutes had elapsed ($p > 0.05$) (*Table 4).*

Shivering Threshold During Cold Water Immersion:

During cold water immersion, there was a main effect of PFO on the temperature of shivering onset, where PFO+ individuals had a significantly higher T_{esoph} at which shivering commenced compared to PFO- individuals ($p < 0.05$) (*Table 4).*

Discussion:

The purpose of this study was to determine how the presence of a PFO affected thermoregulatory and ventilatory responses. It was hypothesized that, compared to PFO- subjects, 1) PFO+ subjects would have a blunted ventilatory response during passive heating and 2) PFO+ subjects would shiver at a higher T_{esoph} during passive cooling.

Effect of a PFO on Esophageal Temperature:

PFO+ individuals have some amount of blood bypassing the lungs, and thus may be less able to dissipate heat through respiratory cooling. During the experimental conditions, PFO+ individuals had a ~0.3˚C higher T_{esoph} than PFO- individuals overall (*Figure 8, 9*). This supports previous research suggesting that PFO+ individuals have a higher resting T_{esoph} than PFO- individuals (Davis *et al,* 2015), but this experiment showed that this higher T_{esoph} is maintained during both passive heating and passive cooling. The results indicate that the presence of a PFO is correlated with a higher T_{esoph} and suggests that PFO+ individuals may be at a greater risk of heat-induced injuries.

Effect of a PFO on Heart Rate:

While HR was not significantly different between the PFO+ and PFO- groups in either trial (*Figures 4-5*), HR trended ~9 bpm higher in the PFO+ group during the cold tub trial ($p = 0.07$. Previous research has determined that PFO+ subjects have a significantly higher resting HR than PFO- subjects, and that this may be explained by

the increased T_{esoph} observed in PFO+ subjects (Davis *et al.*, 2015). Because HR can be augmented by an increase in T_{core} (Cabanac and White, 1995), PFO+ individuals may have higher resting HR because their resting T_{esoph} is higher. A higher T_{core} augments metabolic rate, which then requires an increase in ventilation and HR in order in deliver the necessary O_2 to metabolically active tissues. Thus, resting HR in PFO+ subjects could have trended higher, in part, due to their higher resting T_{core}.

Effect of a PFO on Ventilatory Responses During Hot Water Immersion:

Research has shown that humans not only sweat in hyperthermic environments to dissipate heat, but also increase ventilation possibly in an effort to augment respiratory cooling (Cabanac and White, 1995). When looking at all subjects, PFO+ individuals had a significantly lower V_E during passive heating ($p < 0.05$) (*Figure 6*). However, there was not a significant difference in V_E between the groups amongst subjects who did not reach ventilatory threshold ($p > 0.05$). Even though PFO+ subjects have a higher T_{esoph} at rest possibly due to less respiratory cooling, we would not expect to see a significant difference in V_E at rest between the two groups because this augmented T_{esoph} in the PFO+ group is not thought to be due to them ventilating less, but rather due to some blood bypassing respiratory cooling through the PFO. Thus, because there was not a significant difference in V_E at rest, and these subjects did not increase their ventilation enough to reach ventilatory threshold, there was not a significant difference overall between the two groups. There was a main effect of PFO on V_E for those subjects who reached the ventilatory threshold, where PFO- individuals had a significantly higher V_E ($p < 0.05$) (*Figure 6*). Additionally, PFO+ individuals had

a significantly higher T_{esoph} at the ventilatory threshold than PFO- individuals, suggesting that they require a higher T_{esoph} in order to have a ventilatory response to passive heating and to ventilate to the same degree as a PFO- individual (*Figure 7*). These data support the hypothesis that PFO+ individuals have a blunted ventilatory response to passive heating and may defend a higher T_{core} than PFO- individuals.

Effect of a PFO on Shivering During Cold Water Immersion:

Shivering is used as a thermoregulatory mechanism in humans in order to generate heat through the quick contraction of muscles. Because muscle contractions produce heat as a byproduct, this mechanism is an effective way to generate heat without producing any net movement. During cold water immersion, the PFO+ group shivered at a significantly higher T_{esoph} than the PFO- group (*Table 4*). This suggests that PFO+ subjects not only maintained a higher T_{core} at rest, but also defended this augmented T_{core} by implementing shivering as a heat-generation mechanism at a significantly higher T_{core} than PFO- subjects.

Effect of a PFO on Reason for Exiting During Hot Water Immersion

There was a statistically significant difference in the reason for people exiting the hot tub between the PFO+ and PFO- groups. 6 PFO+ subjects exited early due to T_{esoph} reaching 39.5°C, compared to 0 PFO- subjects. Additionally, 5 PFO- subjects remained in the tub for the entire 30 minutes without reaching 39.5°C, compared to 0 PFO+ subjects. This indicates that PFO+ individuals reached the hot tub temperature threshold more frequently than the PFO- individuals, and thus may be at a physiological

disadvantage in the heat, which could be due to an elevated resting T_{core} as well as a blunted ventilatory response to passive heating.

Effect of a PFO on Reason for Exiting During Cold Water Immersion:

While there were no significant differences between the PFO+ and PFO- groups in the reason for exiting the cold tub, only PFO- individuals reached the 35.5°C cold tub temperature threshold. PFO- subjects shivered at a significantly lower T_{esoph}, suggesting that they defended a lower T_{core}. PFO+ individuals may have some amount of blood bypassing respiratory cooling, and thus, may be better suited at retaining heat in cold environments. This could help explain why none of the PFO+ individuals reached the 35.5°C threshold during the 60 minute immersion. Conversely, PFO- individuals have 100% of their cardiac output travel to their lungs to potentially participate in respiratory cooling and contribute to the heat loss. This suggests that PFO+ individuals may have a physiological advantage in cold environments because some of their blood bypasses respiratory cooling through the PFO. Additionally, PFO+ individuals have a higher resting T_{core} and appear to shiver at a significantly higher T_{core}, indicating that they may be more apt to defend their elevated T_{core} in a cold environment.

Summary:

In both the passive heating and passive cooling trials, PFO+ subjects had a significantly higher T_{esoph}. In the hot tub trial, PFO+ subjects not only had a higher T_{core}, but also had significantly lower V_E, suggesting that their ventilatory response to

the heat was blunted with respect to PFO- individuals. Additionally, PFO+ subjects shivered at a higher T_{esoph} in the cold tub trial and no PFO+ individual reached the 35.5°C cold tub threshold. These data support the hypotheses that PFO+ individuals have 1) a blunted ventilatory response to passive heating and 2) a higher temperature threshold for shivering onset. The results indicate that individuals with a PFO have a significantly higher T_{core} at rest, and this augmented T_{core} is defended during both passive heating and passive cooling. Thus, what has previously been suggested to be an absolute temperature threshold at which both the ventilatory response during passive heating and the shivering response during passive cooling occur may actually be better described as the change in T_{core} from resting values that causes these responses.

Limitations:

While it is assumed that the effect of PFO on the female population would be the same as the changes observed in men, females were not studied in this experiment due to the difficulty associated with accounting and controlling for thermal changes throughout the menstrual cycle. Because body temperature in women fluctuates based on the phase of their menstrual cycle, the study of women in thermoregulatory experiments requires frequent blood draws and strict schedules in order to obtain all measurements within the same menstrual cycle phase for every woman, making the experiment more complicated and more expensive. Thus, these results cannot be conclusively applied to the female population because women were not directly tested in this experiment.

Conclusion:

While there has been extensive research on the effects of passive heating and cooling in humans, it had not been determined how the presence of a PFO affects physiological responses to environmental challenges. Because PFOs are so prevalent in healthy humans (25-40%), elucidating the effect that a PFO has on individuals is incredibly important in furthering our understanding of physiological variability between humans. These results indicate that PFO+ individuals may be better adapted for cold environments because they have some amount of blood bypassing respiratory cooling; they have a higher T_{core}; and they are able to retain heat more effectively by shivering at a higher temperature threshold. PFO- individuals may be better adapted for hot environments because 100% of their blood travels to the lungs and can participate in respiratory cooling; they have a lower T_{core},; and they have an increased ventilatory response to passive heating. Conversely, PFO+ individuals may be more susceptible to hyperthermic challenges, such as heat stroke, because their ability to maintain a lower T_{core} is decreased by the presence of a PFO and the blunted ventilatory responses that they experience as a result. PFO- individuals may be more prone to cold environmental challenges, such as hypothermia, because they are able to dissipate more heat through respiratory cooling and have a blunted shivering response. This experiment has helped us to understand how an individual's response to environmental challenges is affected by the presence of PFO, as well as why some people may be more susceptible to certain thermal illnesses.

Figures:

Figure 1: The effect of a PFO on resting core temperature and temperature differences from the passive heating and cooling thresholds.

Figure 2: Cardiopulmonary Circulation.

Figure 3: Blood flow through a PFO.

Figure 4: HR during the hot tub trial during rest and at the end of water immersion. There was no main effect of PFO on HR ($p > 0.05$).

Figure 5: HR during the cold tub trial at rest, peak T_{esoph}, and at the end of water immersion. There was no main effect of PFO on HR however, the PFO+ group trended 9 beats per minute (bpm) higher than the PFO- group ($p = 0.07$).

Figure 6: A. V_E during the hot tub trial at rest and the end of water immersion for all subjects. There was a main effect of PFO on V_E. B. V_E during the hot tub trial at rest and the end of water immersion for subjects that did not reach the ventilatory threshold ($n = 10$). There was not a main effect of PFO on V_E. C. V_E during the hot tub trial at rest, at the ventilatory threshold, and at the end of water immersion for subjects that reached ventilatory threshold ($n = 12$). There was a main effect of PFO on V_E. An * indicates $p < 0.05$.

Figure 7: V_E vs. T_{esoph} during the hot tub trial at rest, ventilatory threshold, and the end of water immersion for subjects that reached ventilatory threshold. PFO+ individuals had a significantly higher T_{esoph} at the ventilatory threshold than PFO- individuals. An * indicates $p < 0.05$.

Figure 8: A. T_{esoph} during the hot tub trial at rest and at the end of water immersion for all subjects. Overall, PFO+ had a significantly higher T_{esoph} than PFO-. B. Amongst those subjects that reached ventilatory threshold, PFO+ also had significantly higher T_{esoph}, with a specific pairwise difference occurring at the ventilatory threshold. An * indicates $p < 0.05$.

Figure 9: T_{esoph} during the cold tub trial at rest, peak T_{esoph}, and at the end of water immersion. Overall, the PFO+ group had a significantly higher T_{esoph}. At all three time points measured, a significant pairwise difference existed between PFO+ and PFO- groups. An * indicates $p < 0.05$.

Table 1: Environmental Conditions

	Hot Tub Trial				Cold Tub Trial			
	Room Temperature (°C)	Relative Humidity (%)	Barometric Pressure (mm Hg)	Water Temperature (°C)	Room Temperature (°C)	Relative Humidity (%)	Barometric Pressure (mm Hg)	Water Temperature (°C)
PFO-	24±1	34±6	754±5	40.5±0.2	24±1	33±6	753±4	19.7±0.7
PFO+	23±1	32±5	750±6	40.5±0.2	23±1	29±8	752±4	19.6±0.6

Values are means ± standard deviation. No significant differences between groups.

Table 2: Anthropometric and Pulmonary Function Data

	PFO– (*n*=11)	**PFO+(*n*=11)**	**Overall (*n*=22)**
Age (years)	27±8	27±8	27±8
Height (cm)	182.0±6.9	178.5±7.9	180.3±7.5
Weight (kg)	84.1±10.4	80.8±8.5	82.4±9.4
BSA (m^2)	2.06±0.15	2.00±0.14	2.03±0.1
FVC (L)	5.69±0.69	5.37±0.91	5.54±0.80
FEV_1(L)	4.56±0.67	4.34±0.76	4.45±0.71
***DL_{CO}*(ml $min^{-1}Torr^{-1}$)**	40.9±6.9	40.7±10.3	40.8±8.5

Values are means ± standard deviation. No significant differences between groups.

Table 3: Reason for Exiting Hot Tub

Reason	PFO–	PFO+*
T_{esoph} Reached 39.5 °C	0	6**
Lightheaded or nauseous	6	4
30 minutes elapsed	5	0
Chose to exit	0	1

An * signifies a significant difference between groups.
**Two subjects exited the tub because 30 minutes had elapsed and their T_{esoph} reached 39.5°C. There was a main effect of PFO on the reason for exiting the hot tub ($p < 0.05$)

Table 4: Reason for Exiting Cold Tub

Reason	PFO–	PFO+
T_{esoph} Reached 35.5 °C	4**	0
Shivering	2 (35.8±0.2 °C)	5 *(36.2 ± 0.2 °C)
60 minutes elapsed	5	4
Chose to exit	0	2

An * signifies a significant difference between groups.
**One subject exited the tub because 60 minutes had elapsed and their T_{esoph} reached 35.5°C. There was not a significant difference between groups in the reason for exiting the tub ($p > 0.05$). There was a main effect of PFO on the T_{esoph} of shivering onset ($p < 0.05$).

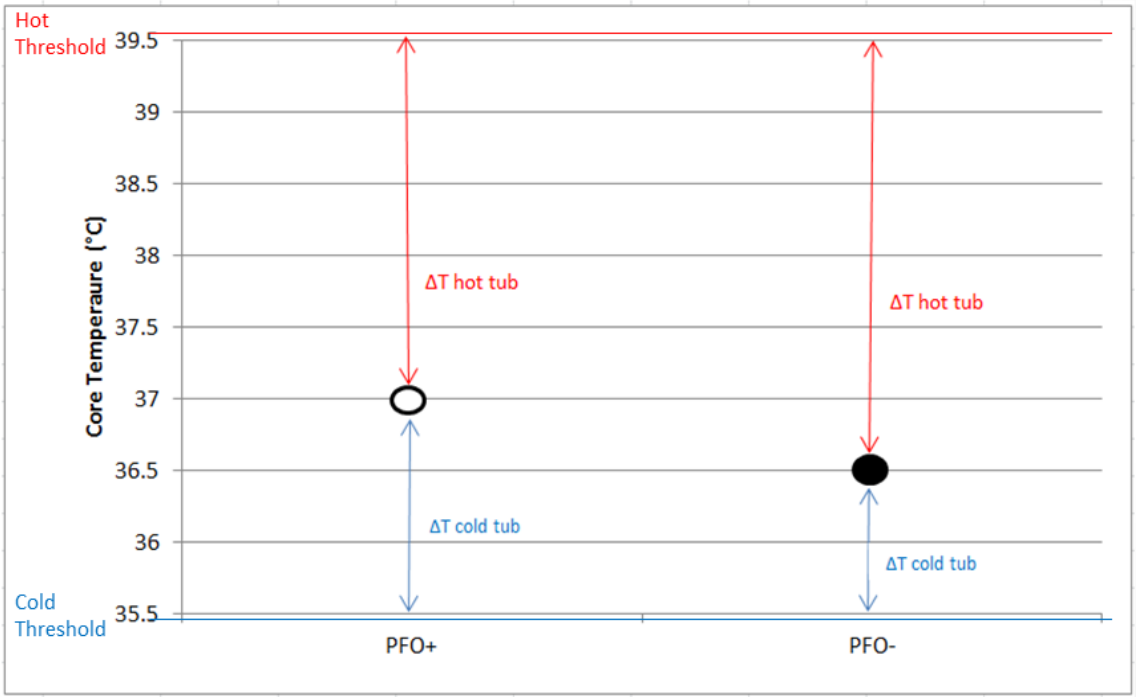

Figure 1.

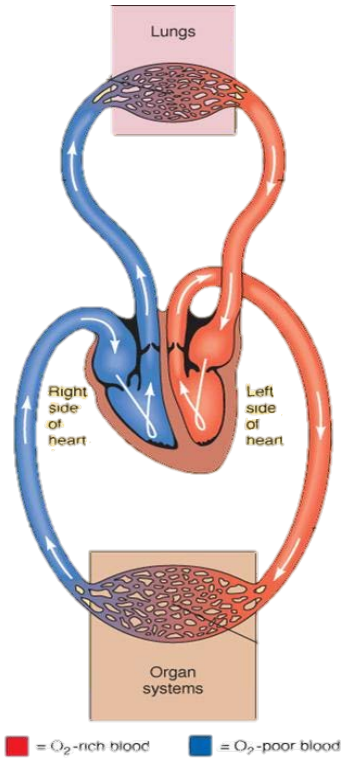

Figure 2.

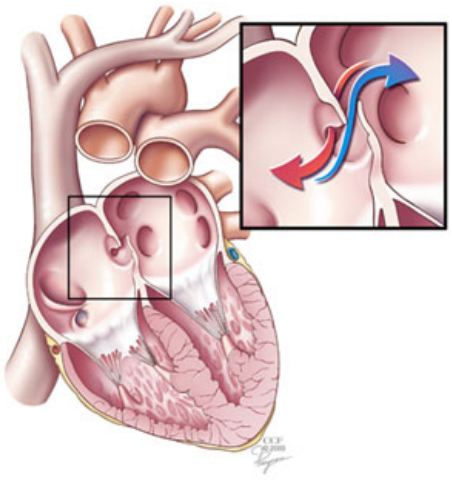

Figure 3.

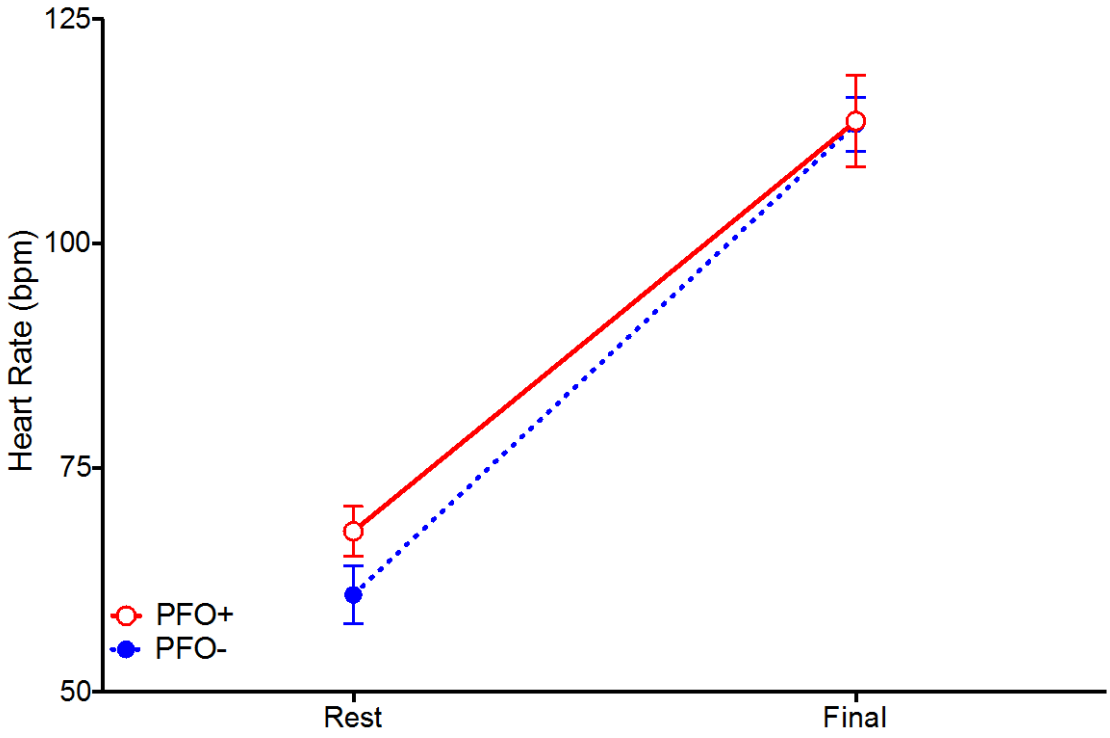

Figure 4.

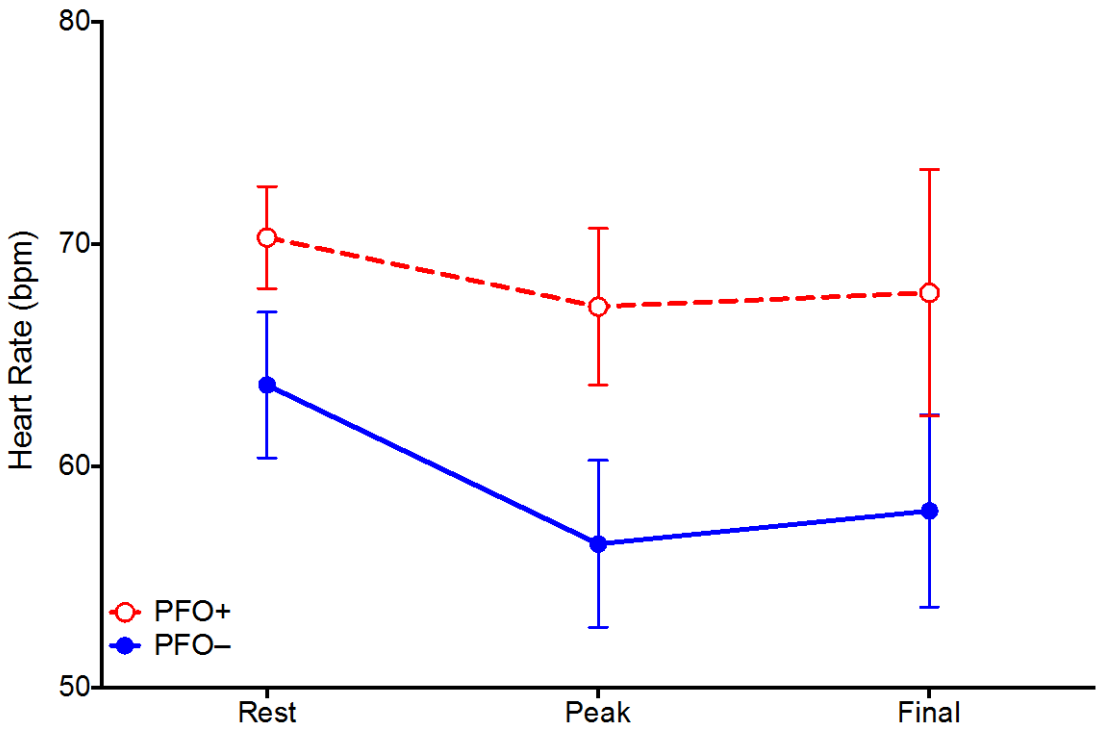

Figure 5.

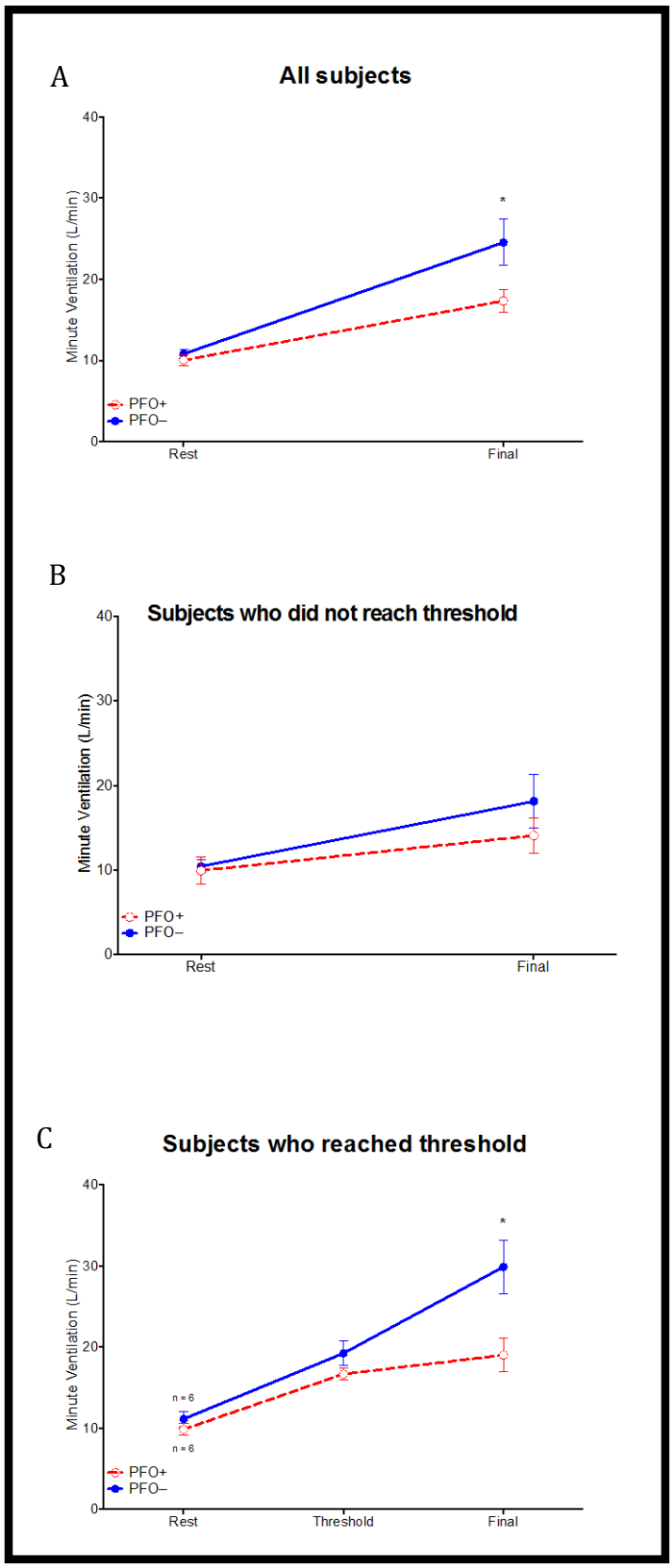
A
All subjects
Minute Ventilation (L/min)
40
30
20
10
0
*
PFO+
PFO–
Rest
Final
B
Subjects who did not reach threshold
Minute Ventilation (L/min)
40
30
20
10
0
PFO+
PFO–
Rest
Final
C
Subjects who reached threshold
Minute Ventilation (L/min)
40
30
20
10
0
*
n = 6
n = 6
PFO+
PFO–
Rest
Threshold
Final

Figure 6.

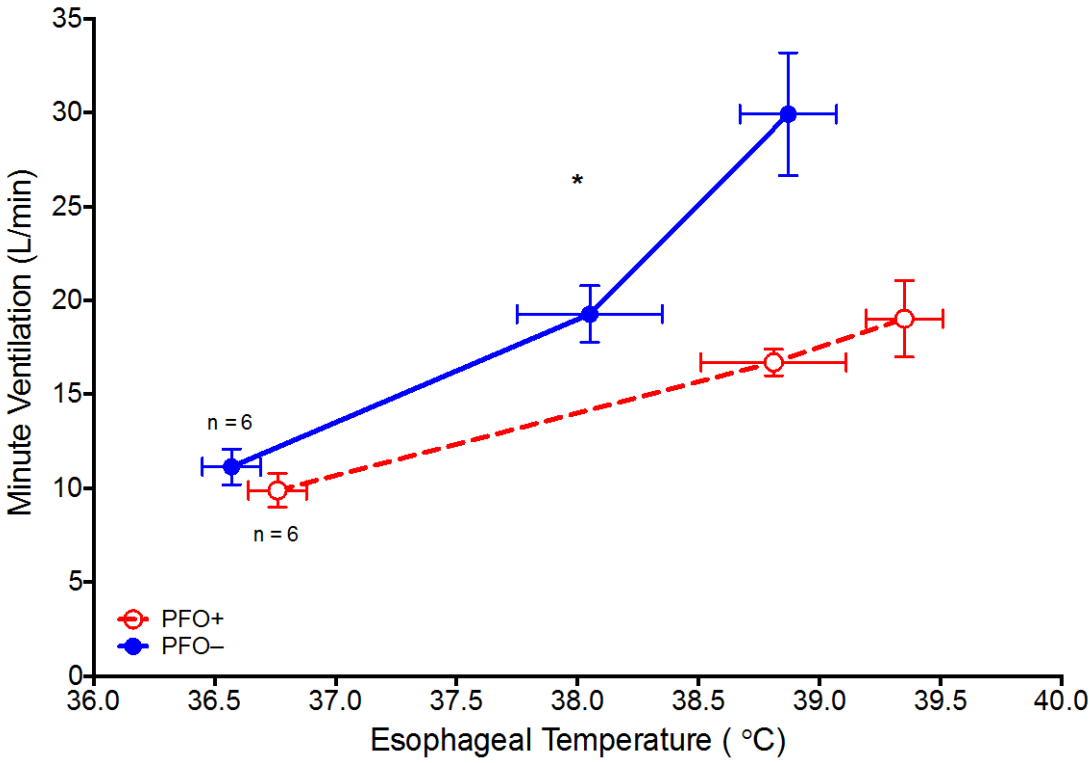

Figure 7.

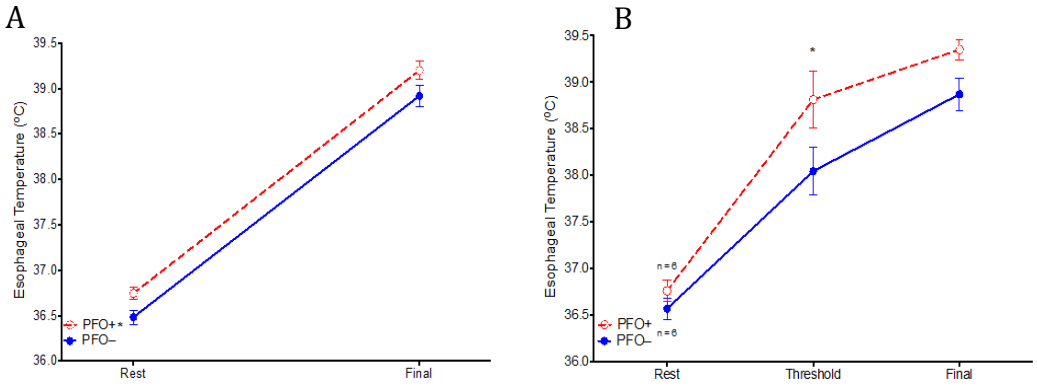

Figure 8.

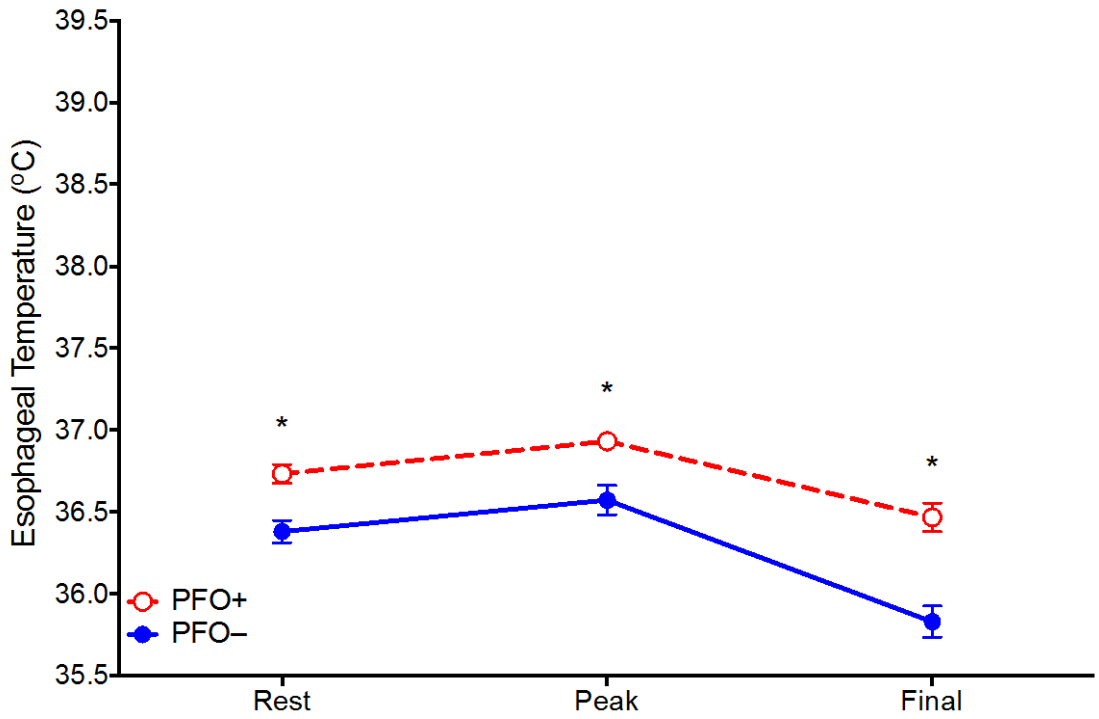
39.5
39.0
38.5
38.0
37.5
37.0
36.5
36.0
35.5
Esophageal Temperature (°C)
PFO+
PFO–
*
*
*
Rest
Peak
Final

Figure 9.

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