Physiological impact of patent foramen ovale on pulmonary gas exchange, ventilatory acclimatization, and thermoregulation

Andrew T. Lovering,1 Jonathan E. Elliott,2 and James T. Davis3

1University of Oregon, Department of Human Physiology, Eugene, Oregon; 2Oregon Health & Science University, Department of Neurology and VA Portland Health Care System, Portland, Oregon; and 3Indiana State University, Department of Kinesiology, Recreation, and Sport, Terre Haute, Indiana

Lovering AT, Elliott JE, Davis JT. Physiological impact of patent foramen ovale on pulmonary gas exchange, ventilatory acclimatization, and thermoregulation. J Appl Physiol 121: 512–517, 2016. First published July 15, 2016; doi:10.1152/japplphysiol.00192.2015.—The foramen ovale, which is part of the normal fetal cardiopulmonary circulation, fails to close after birth in ~35% of the population and represents a potential source of right-to-left shunt. Despite the prevalence of patent foramen ovale (PFO) in the general population, cardiopulmonary, exercise, thermoregulatory, and altitude physiologists may have underestimated the potential effect of this shunted blood flow on normal physiological processes in otherwise healthy humans. Because this shunted blood bypasses the respiratory system, it would not participate in either gas exchange or respiratory system cooling and may have impacts on other physiological processes that remain undetermined. The consequences of this shunted blood flow in PFO-positive (PFO+) subjects can potentially have a significant, and negative, impact on the alveolar-to-arterial oxygen difference (AaDO2), ventilatory acclimatization to high altitude and respiratory system cooling with PFO+ subjects having a wider AaDO2 at rest, during exercise after acclimatization, blunted ventilatory acclimatization, and a higher core body temperature (~0.4°C) at rest and during exercise. There is also an association of PFO with high-altitude pulmonary edema and acute mountain sickness. These effects on physiological processes are likely dependent on both the presence and size of the PFO, with small PFOs not likely to have significant/measureable effects. The PFO can be an important determinant of normal physiological processes and should be considered a potential confounder to the interpretation of former and future data, particularly in small data sets where a significant number of PFO+ subjects could be present and significantly impact the measured outcomes.

In the case of the other two (vena cava and pulmonary vein), which lie in contact with each other, there is a kind of orifice or fenestra (foramen ovale), common to both. At this orifice there is attached a membrane, like a lid or cover, opening toward the pulmonary vessel [left atrium], so that it will yield to the influx of blood from the vena cava, but will prevent its regurgitation into that vessel. So far, no doubt, we have much to admire in these contrivances of nature; but what surpasses them all is the way in which the foramen not long afterward becomes occluded. For soon after birth, either within a day or two, or, in some animals, after four or five days or a little longer, you will find the membrane at the foramen coalescing but not yet fully adherent. Looking at the same place in the adult animal, you would say there had never been a time when it was open; and, on the other hand, in a fetus, before or immediately after birth, when this membrane is attached, so to speak, only by its root, the rest of it hanging free in the vascular cavity, you would hardly believe in its ever becoming agglutinated. —Claudius Galen, c.200 AD, from the Opera Omnia, vol. IV, p. 243; translation by Dalton, 1884, p. 69 (7).

Background and Historical Aspects of PFO

Embryonic development of the fetal heart begins as a single common cavity and eventually separates into four distinct chambers (i.e., the atria and ventricles) (32). In doing so, one-way valves develop between the right atria and right ventricles and the left atria and left ventricles with the purpose being to permit unidirectional blood flow through them. In contrast, separation between the right and left atria and the right and left ventricles takes the form of septal walls with the purpose being to prevent blood flow across them. However, as described by Galen above, before birth the atrial septal division remains incompletely formed and therefore allows blood to flow directly from the right atrium to the left atrium. Indeed it is advantageous for pulmonary blood flow to be minimal in utero, because gas exchange occurs at the level of the placenta via the mother rather than at the lungs. During development,
the foramen ovale progresses from an opening between the atria to the unfused septum primum and septum secundum (named based on their sequential appearance). By birth the septum secundum is continuous with the perimeter of the atrial septal division but lacks an interior continuity, which creates the foramen ovale. The septum primum extends the length of the atrial septal division but is not yet fully adherent to the septum secundum, such that it creates a flap of tissue (i.e., the valvula foramina ovalis) that permits only right-to-left blood flow between the atria. Accordingly, right-to-left atrial blood flow in utero is facilitated by an elevated right atrial pressure secondary to an elevated pulmonary vascular resistance. After birth, gas exchange in the infant occurs in the lung and no longer via the placenta, and thus pulmonary blood flow increases from ~20% in utero to 100% of the cardiac output (33). This increase in pulmonary blood flow occurs because of a fall in pulmonary vascular resistance, whereas systemic vascular resistance gradually increases (17). When systemic vascular resistance exceeds pulmonary vascular resistance, mean left atrial pressure then exceeds mean right atrial pressure, and the valvula foramina ovalis is pushed against the septum secundum, thereby preventing right-to-left blood flow across the foramen ovale (21, 22, 25, 32).

Over the next several months, the valvula foramina ovalis progressively adheres to the septum secundum, thus forming a permanent anatomical closure of the foramen ovale and preventing right-to-left atrial blood flow. However, permanent anatomical closure of the foramen ovale does not occur after birth in all humans, with the resulting opening called a “patent foramen ovale” (PFO) in those humans without complete closure (16, 30, 42). PFOs can occur because of the valvula foramina ovalis failing to completely adhere to the septum secundum or the valvula foramina ovalis being too small to cover the foramen ovale (32). However, the reason why a PFO does not close in everyone is unknown.

In a comprehensive review by Patten (32), the author summarized PFO data that was determined during autopsy from nine studies dating from 1837 to 1934. This summary identified the presence of a probe patent PFO in 864 out of the combined 4,083 subjects and prevalence ranged from 1 to 43% (average ~21%). More recent autopsy studies (22, 25) not included in the review by Patten have confirmed the observation that PFO occurs in 25-40% of the population. Additionally, other studies using saline contrast echocardiography show similar findings in living humans (16, 30, 42).

In addition to determining the overall prevalence of a PFO, Hagen et al. (22) found that the incidence of PFO decreases with age, declining from 34% in subjects between the ages of 0 and 29 yr to 25% in subjects between the ages of 30 and 79 yr. Although the incidence reportedly decreases, the average size of the PFO reportedly increases from 3.4 mm during the first decade of life to 5.8 mm during the 10th decade of life. These changes in incidence and size are likely due to the fact that complete adhesion of the valvula foramina ovalis and septum secundum can happen at any point and that smaller PFOs are more likely to experience complete adhesion compared with larger PFOs.

Despite the fact that a significant proportion of the population has a PFO, little research has examined its impact on normal physiological processes, presumably because it has been assumed to be of little significance. This is surprising because the normal model of cardiovascular physiology states that blood travels from the right side of the heart through the pulmonary circulation to the left side of the heart and then into the systemic circulation before it returns to the right side of the heart. This “normal model” of blood flow allows the lung to effectively perform several physiologically important roles, including pulmonary gas exchange, filter particles out of the venous circulation, and respiratory system cooling. However, PFO + subjects have an opening between the right and left atria that can allow for a varying, but potentially physiologically significant, amount of the cardiac output to bypass the pulmonary circulation in otherwise healthy humans. For a PFO to have a physiologically significant impact, right atrial pressure must exceed left atrial pressure for a time sufficient to allow for right-to-left blood flow across the foramen ovale. Importantly, these conditions exist in the adult human at the end of a normal inspiration occurring concomitant with diastole (18) and would likely occur to a greater degree under conditions of elevated right heart pressures such as exercise, high altitude, and in patients with pulmonary hypertension. Accordingly, blood that circumvents the pulmonary circulation will not undergo pulmonary gas exchange, be filtered, or participate in respiratory system cooling and there are certainly consequences that can occur as a result.

PFO and Pulmonary Gas Exchange

Contributors to pulmonary gas exchange efficiency, as measured by the alveolar-to-arterial oxygen difference (AaDO₂) include shunt, diffusion limitation, and ventilation-to-perfusion (V/Q) heterogeneity; for reviews on this topic, see Refs. 11 and 37. There are several reports in the literature suggesting that the presence of a PFO does have a negative impact on pulmonary gas exchange efficiency and/or atrial hypoxemia in patient populations (13, 24, 27, 35, 36, 38). Additionally, surgical closure of a PFO has been shown to improve arterial oxygenation at rest and during exercise, demonstrating that blood flow through a PFO can have a measurable impact on pulmonary gas exchange efficiency (12, 19).

Work by Lovering et al. (28), reported that the presence of a PFO in healthy subjects resulted in an ~5 Torr greater AaDO₂ at rest in both normoxic and hypoxic conditions (28). However, the presence of a PFO did not result in a wider AaDO₂ during exercise. The size of the PFO and/or the potential for blood to flow through the PFO can be estimated by the degree of left heart saline contrast (i.e., bubble scores), as was recently suggested (18). Thus it is possible that the size of the PFO and/or the potential for blood to flow through the PFO is more important than simply the presence of a PFO. Future research in this area of pulmonary gas exchange efficiency in healthy humans should take both the presence and size of a PFO into consideration when assessing the mechanisms of abnormal pulmonary gas exchange efficiency.

PFO and Pulmonary Gas Exchange at Altitude

It is well known that pulmonary gas exchange efficiency gets worse with acute ascent to high altitude but improves with acclimatization (3, 10, 29). The improvement in gas exchange with acclimatization has been classically attributed to improvement in lung diffusing capacity (1, 40). Recent work by our group investigated the effect of PFO on pulmonary gas ex-
change after acclimatization to high altitude. We found no significant effect of the presence of a PFO on AaDO2 with acute ascent to high altitude (5,260 m), as may be expected because the impact of a shunt on the AaDO2 is reduced under acute hypoxic conditions. However, after 16 days of acclimatization, there would be an expected increase in arterial PO2 (PaO2) caused by increased alveolar ventilation (VA). This augmented VA could increase PaO2 sufficiently so that it would be on the flat portion of the oxyhemoglobin dissociation curve. Consequently, the impact of a shunt would be greater after acclimatization than it would be under acute hypoxic conditions. Accordingly, in PFO+ subjects, the AaDO2 at rest and during exercise after acute ascent to high altitude was 7.7 ± 2.5 and 20.7 ± 2.5 Torr, respectively, which did not improve after 16 days of acclimatization (5.0 ± 3.1 and 18.0 ± 1.7 Torr, rest and exercise, respectively). However, in PFO− subjects, the AaDO2 at rest and during exercise after acute ascent to high altitude was 8.0 ± 1.2 and 20.1 ± 1.2 Torr, respectively, which improved after 16 days of acclimatization to 3.2 ± 1.9 and 13.5 ± 4.7 Torr. We calculated the total venous admixture after acute ascent to high altitude at rest to be 27.6 ± 9.3 and 27.4 ± 3.7% in PFO+ and PFO− subjects, respectively. After 16 days of acclimatization, total calculated venous admixture at rest remained significantly higher in PFO+ subjects (14.3 ± 6.8%) compared with PFO− subjects (6.1 ± 4.7%). Similarly, we calculated the total venous admixture after acute ascent to high altitude during exercise to be 32.9 ± 2.8 and 33.5 ± 3.2% in PFO+ and PFO− subjects, respectively. After 16 days of acclimatization, total calculated venous admixture during exercise remained significantly higher in PFO+ subjects (22.4 ± 5.1%) compared with PFO− subjects (15.3 ± 6.0%). Importantly, after 16 days of acclimatization, diffusion limitation would not be expected to contribute to either the wider AaDO2 (39, 40) or to the increased calculated venous admixture at rest in PFO+ and PFO− subjects. Thus, at rest, it is possible that PFO+ subjects had a greater degree of V/Q heterogeneity. However, during exercise (VO2 ~2 l/min) the potential contribution from diffusion limitation should not be excluded, and therefore it is possible that PFO+ subjects had a greater degree of diffusion limitation and/or V/Q heterogeneity. Additionally, with acclimatization our PFO+ subjects had lower VA at rest (VA = 12.4 ± 5.1 vs. 19.4 ± 7.8 l/min in PFO− subjects) and, as a result, a lower PaO2 (45.9 ± 3.1 vs. 52.7 ± 3.7 Torr in PFO− subjects) and a higher PaCO2 (21.1 ± 2.7 vs. 18.7 ± 2.9 Torr in PFO− subjects).

Of note, there were an unequal number of men and women in our groups, with a larger number of women in the PFO+ group. It was previously shown in some, but not all, studies that women have a greater degree of gas exchange impairment during exercise than men (14, 23, 31), which may also explain our pulmonary gas exchange efficiency results. Additionally, female-specific hormones (estrogen and/or progesterone) have been shown to stimulate ventilation at sea level (SL) and at altitude (41), so if anything we would have expected even greater VA in the PFO+ group (in either phase of the menstrual cycle) when in fact we found the opposite (15). Future studies should investigate the possibility of differences in VA after acclimatization in women with and without a PFO to help clarify our findings.

The reasons why the multiple inert gas elimination technique (MIGET) has not detected PFO+ subjects with significant atrial level shunting are unknown. One possibility is that only PFO− subjects and those with small PFOs have participated in previous studies using the MIGET and these subjects may not have a sufficient volume of right-to-left shunt to result in a measureable impact on pulmonary gas exchange efficiency. Additionally, these MIGET studies may have included PFO+ subjects, either small or large, that may have been functionally closed under the conditions studied.

**PFO and Ventilatory Acclimatization to High Altitude**

Hypoxic ventilatory acclimatization is one of the cardinal adaptations to hypoxia (41). This increase in ventilation occurs over 2–8 wk of acclimatization and is important for increasing PaO2, and as a result, increasing SaO2. In the only study investigating the differences in ventilatory acclimatization between PFO+ and PFO− subjects, we found that ventilatory acclimatization was impaired in PFO+ subjects after 16 days at 5,260 m (15). Specifically, the change in \( \Delta VA/\Delta SaO2 \) from altitude day 1 to altitude day 16 in PFO+ subjects was only 0.17, resulting in a PaCO2 of −21 Torr, whereas the \( \Delta VA/\Delta SaO2 \) from altitude day 1 to altitude day 16 in PFO− subjects was 1.12, resulting in a PaCO2 of −19 Torr. Of note, the 2–3 Torr difference in PaCO2 is significant, because the ventilatory response to CO2 would be expected to be much greater after acclimatization (9). The reasons for this difference in ventilatory acclimatization within this 16-day time frame is not currently well understood. It is possible that increased ventilation in the presence of an intracardiac shunt would be less effective at increasing PaO2 than it would be in someone without an intracardiac shunt. Accordingly, it may be adaptive for PFO+ individuals to have blunted ventilatory acclimatization to high altitude inasmuch as it would prevent a nonfunctional increase in the work of breathing. However, this remains only speculative. The hypoxic ventilatory response and ventilatory acclimatization are dependent on changes to both peripheral and central chemosensitivity so it is also possible that differences in chemosensitivity and/or cerebral blood flow exist between subjects with and without PFO. As previously mentioned, there were an unequal number of men and women in our groups, with a larger number of women in the PFO+ group and there may be an undetermined effect of sex on ventilatory acclimatization to high altitude.

**Pathophysiological Consequences of PFO at High Altitude?**

These data suggesting impaired gas exchange with acclimatization combined with impaired ventilatory acclimatization in PFO+ subjects are particularly provocative as a reduced ability to acclimatize to high altitude may predispose these subjects to developing high-altitude sequelae (2, 26). Retrospective analysis of 16 subjects who have developed high-altitude pulmonary edema (HAPE) found a prevalence of PFO of 56% vs. 11% in 19 subjects who were not HAPE-susceptible (2). There are also data from our group and others to support the idea that the presence of a PFO increases susceptibility to Acute Mountain Sickness (15). Although speculative, the most obvious reason for the increased susceptibility to high-altitude illnesses in subjects with a PFO are worsened pulmonary gas exchange and blunted ventilatory acclimatization. However, other factors may be at play, including, but not limited to, a reduction in the

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metabolic role of the lung when blood flows through a PFO and bypasses the lung.

If the presence of a PFO at high altitude is maladaptive, then it could be hypothesized that a PFO would be less prevalent and/or smaller in high-altitude populations that are believed to be well adapted to live at altitude. However, this has not been the finding between several recent studies. Foster et al. (20) were the first to report that the prevalence of PFO in Sherpas (50%) was similar to the prevalence of PFO in lowlanders (41%). Work later that year investigating the prevalence of PFO in high-altitude natives with and without Chronic Mountain Sickness found an equal prevalence of PFO between groups (32%) that was not different from that reported in low-altitude natives (4). Finally, work examining the prevalence in 19 Han Chinese and 19 Tibetans found a similar prevalence (47%) of PFO between the two groups (unpublished observations). The critical function of the PFO in fetal life may simply prevent this trait from being selected out of the high-altitude population. Alternatively, increased pulmonary artery pressure is known to lead to persistent patent ductus arteriosus due to the high right heart pressures favoring right-to-left blood flow through the ductus. Likewise, high pulmonary pressures associated with altitude may also enhance right-to-left blood flow across the PFO and therefore keep the PFO from closing in all high-altitude dwellers, despite the obvious benefit of not having a PFO. More research in this area is needed.

**PFO and Body Temperature Regulation**

While investigating the effect of a PFO on pulmonary gas exchange during exercise, Lovering et al. (28) reported the surprising finding that PFO+ subjects ($n = 8$) had a higher core temperature ($T_{core}$) of $-0.4^\circ$C as measured by esophageal temperature during maximal exercise compared with PFO− subjects ($n = 8$). This reported difference in $T_{core}$ between PFO+ and PFO− subjects in that study should be interpreted with caution because there was no control for ambient temperature, exercise trials were conducted at different times of day, subjects included men and women (with no control for menstrual cycle), and no control for food intake or hydration status. Because this study was neither well designed nor appropriately powered to examine differences in $T_{core}$ between PFO+ and PFO− subjects, a recent study done by Davis et al. (8) set out to determine if in fact there is a difference in $T_{core}$ between PFO+ and PFO− subjects (8). Unlike the study done by Lovering et al. (28), the work done by Davis et al. used a larger sample size ($n = 30$ men, $15$ PFO+) with appropriate controls and power to accurately determine the effect of a PFO on $T_{core}$. Findings from this study reported that in a thermoneutral environment, PFO+ subjects have a $-0.4^\circ$C greater $T_{core}$ compared with PFO− subjects during pre-exercise and throughout exercise (Fig. 1). One possible explanation for this finding is that blood flowing through the PFO acts as a “right-to-left temperature shunt,” whereby warm mixed venous blood bypasses the pulmonary circulation and therefore mixes with the cooled pulmonary venous effluent and increases the resulting temperature of blood in the left atrium. Indeed, previous work suggests that $-10\%$ of total body heat loss occurs through respiratory system cooling (5, 6) via convective and evaporative heat loss. Blood flowing through the PFO would not go through the respiratory system, which would prevent it from dissipating heat into the airways. Unlike PFO+ subjects, where pulmonary blood flow is equal to cardiac output less blood flow through the PFO, pulmonary blood flow is equal to cardiac output in PFO− subjects. Because of this difference in pulmonary blood flow, it follows that PFO− subjects are able to dissipate more heat into the airways than PFO+ subjects. Findings from Davis et al. (8) showed that compared with breathing ambient temperature air ($-20^\circ$C), PFO− subjects did not increase $T_{core}$ by the same amount as they did while breathing cold air ($-0^\circ$C). However, PFO+ subjects increased $T_{core}$ by about the same amount (Fig. 2) (8). Of note, calculations of the effect that a $5\%$ shunt through the PFO would have on respiratory system cooling suggest that $-25\%$ of the difference in temperature could be accounted for by the PFO blood flow (8). Thus there are additional factors
contributing to this difference in temperature, such as sweating, skin blood flow, etc. (34).

We also found that the effect of a PFO on $T_{core}$ appears to be dependent upon the amount of blood flow that could flow through the PFO. Specifically, subjects with a “large PFO” (those with ≥13 bubbles upon the release of a Valsalva, bubble score of 3 or greater) had a significantly higher $T_{core}$ than PFO− subjects. However, subjects with a “small PFO” (those with <13 bubbles upon the release of a Valsalva, bubble score 2 or less) were not significantly different from PFO− subjects. This finding can be partially explained by the fact that more blood flow traveling through a PFO would result in more blood bypassing the respiratory system, which would decrease the amount of heat lost through the airways. Additionally, the other unidentified factors that are likely playing a role in creating this temperature difference between PFO+ and PFO− subjects appear also to be dependent upon the amount of blood flow traveling through the PFO. Accordingly, our subjects identified as “small PFO” appear to have a physiologically insignificant amount of blood flow through their PFO, because their temperature responses are more similar to PFO− subjects than subjects identified as “large PFO.”

Pathophysiological Consequences of Higher Body Temperature in PFO+ Subjects?

Because it appears that PFO+ subjects have a greater $T_{core}$ than PFO− subjects, this means that PFO+ subjects have a right-shifted oxyhemoglobin dissociation curve that in combination with worse pulmonary gas exchange efficiency could result in a lower $SaO_2$. Findings from Lovering et al. (28) support this idea, because that study found that in addition to having a higher $T_{esoph}$, PFO+ subjects had a reduced $SaO_2$ of ~1.5% compared with PFO− subjects during maximal exercise, and a right-shifted curve. We found a similar right-shifted curve, as evidenced by a significantly higher calculated p50 in PFO+ subjects in the high-altitude studies (15). In otherwise healthy individuals at SL, this difference is likely to be of little consequence, because the PaO2 is on the flat part of the oxygen hemoglobin dissociation curve. However, under hypoxic conditions, the differences in $SaO_2$ between these two groups might be magnified because the PaO2 approaches the shoulder of the oxygen hemoglobin dissociation curve.

Additionally, because blood flowing through a PFO is unable to dissipate heat into the airways, PFO+ subjects might be susceptible to heat-related illness such as heat stroke, but conversely would possibly remain warmer while in a cold environment. As a result, PFO+ subjects could reach a critical $T_{core}$ sooner than PFO− subjects. However, while having a PFO could be detrimental in hot environments, it might be beneficial in cold environments. Because PFO+ subjects do not have 100% of their cardiac output flowing through the pulmonary circulation, it follows that they do not lose as much heat through the airways as PFO− subjects. Consequently, in a cold environment, blood flowing through a PFO might be protective and allow PFO+ subjects to maintain $T_{core}$ better than PFO− subjects. However, this has yet to be determined.

Summary

This mini-review highlights the potential for a PFO to contribute to measureable and physiologically impactful effects on pulmonary gas exchange efficiency, high-altitude acclimatization, high-altitude illnesses, and thermoregulation at rest and during exercise. It is likely that the impact of this common anatomic trait has measureable and significant impact on numerous other physiological processes; an impact that is likely dependent upon the size of the PFO and the amount of blood flowing through the PFO at any given time. In addition to explaining some sources of “biological variability” between humans, future studies should consider the impact of PFO on their respective question of interest.

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REFERENCES


