Temperature in the hot spot: oesophageal temperature and whole body thermal status in patent foramen ovale

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Journal Club Target Article:

Davis J, Ng C, Hill S, Padgett R & Lovering A (2015). Higher oesophageal temperature at rest and during exercise in humans with patent foramen ovale. J Physiol; DOI: 10.1113/JP270219.

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Seemingly effortless interactions between our physiological systems allow for our remarkable ability to constantly adapt to the changing forces and environments to which we are exposed. Hence, it is no surprise that the study of human physiology requires integrative approaches to understand interactions in physiological function in health and disease. An example of integrative approach to physiological function is provided by the study of Davis et al. (Davis *et al.*, 2015), as recently reported in the *Journal of Physiology*. The human cardiovascular, respiratory and thermoregulatory systems are brought together by these authors in their investigation of oesophageal temperature and respiratory heat loss in individuals with a patent foramen ovale.

A foramen ovale is a flap-like opening in the heart between the right and left atria that is present during fetal development. As a result of birth, initiation of lung breathing, and increases in atrial pressures, the foramen ovale naturally closes. However, a significant number of individuals face a lack of foramen ovale closure (incidence: 25-40% of the population). The so-called patent foramen ovale (PFO+) represents a condition where individuals present a permanent hole in the atrial wall, which translates in various degrees of cardiac output (up to 5%) from the right atrium to bypass the pulmonary circulation, to move directly into the left atrium and to mix with arterialized blood coming from the pulmonary artery. While a PFO+ often goes undetected and causes no complications, its association with the occurrence of ischemic strokes in younger adults with otherwise no identifiable causes for stroke has been previously proposed (Lechat *et al.*, 1998). It has been also shown that PFO+ results in lower pulmonary gas exchange efficiency at rest (Lovering *et al.*, 2011). In this context, the study of Davis and colleagues add the thermoregulatory system to the “equation”, highlighting the link between cardiovascular, respiratory and thermoregulatory function in PFO+ individuals.

Previously, this group reported that PFO+ individuals presented a higher (+0.6°C) oesophageal temperature than control counterparts (PFO-) following maximal cycling exercise (Lovering *et al.*, 2011). This greater change in oesophageal temperature was hypothesized to result from the foramen-induced reduction in the total volume of blood flowing through the pulmonary circulation, which could have in turn translated in a lower respiratory heat loss. Indeed, as well as serving a respiratory function, the lungs

contribute to heat loss by cooling the blood flowing through the pulmonary circulation. As respiratory heat loss in humans accounts for 10% of total body heat loss (i.e. ~10-15 W) under resting conditions, Davis et al. hypothesized that, given the same rate of heat production, a reduction in respiratory heat loss, with no concurrent differences in other avenues for heat loss (e.g. evaporative and conductive heat loss from the skin), could result in a greater rate of body heat storage, and consequently in a greater change in core (i.e. oesophageal) temperatures in PFO+ individuals during exercise. To explore the relationship between PFO+ and core temperature, Davis et al. investigated whether PFO+ and its size modulates esophageal temperature at rest and during maximal exercise; and whether breathing cold air during incremental exercise modifies the effect of PFO+ on exercise-induced rises in esophageal temperature. Following ultrasound screening, 15 PFO+ individuals (i.e. 8 with large and 7 with small PFO+) and 15 PFO- young controls were enrolled. Participants underwent 3 experimental trials consisting of: 1) a maximal cycling exercise; 2) & 3) an incremental cycling test during which participants breathed either cold-dry air (~2°C) or ambient temperature air (~21°C). Trial 2 & 3 were aimed at investigating the effect of respiratory air cooling on respiratory heat loss.

The first finding arising from Davis et al.'s study is that both resting and end-exercise esophageal temperature were significantly higher (+0.4°C) in PFO+ than PFO-. Interestingly, both PFO+ and PFO- experienced the same relative change in oesophageal temperature (+0.8°C) during the maximal exercise test (Trial 1). Also, individuals with the larger PFO+ presented higher oesophageal temperatures than small PFO+ and PFO-. Finally, while cold air breathing blunted the exercise-induced raise in oesophageal temperature in PFO-, the same was less effective and ineffective in the Small and Large PFO+ group respectively. Altogether, these findings indicated that the presence and size of a PFO+ determined a higher resting and end-exercise oesophageal temperature, possibly as a result of reduced respiratory heat loss.

At first, the findings of Davis et al.'s study would make it tempting to suggest that PFO+ individuals were actually "hotter" than PFO-. However, caution should be taken when considering oesophageal temperature as the primary and only indicator of core

temperature and whole-body thermal status. Due to its anatomical location (i.e. adjacent to the ascending area of the aorta), oesphageal temperature is considered a sensitive indicator of changes in temperature of the blood leaving the heart. However, while its proximity to the heart makes this a good indicator of *dynamic changes* in arterial blood temperature, the same measurement is known to be influenced by both ventilatory- and non ventilatory-induced changes in local tissue temperature (e.g. local convective heat exchange due to blood perfusing the oesophagus) and by thermal gradients within the esophagus (Caputa, 1980). In light of this, it could be suggested that observing a higher oesophageal temperature could be indicative of only higher local tissue temperatures and therefore of a perturbation in local thermal balance, and not necessarily of an alteration of whole-body thermal balance. Indeed, given the same inspired air temperature, for net respiratory heat loss to be lower in PFO+, expired air temperature should be lower in this group. However, while air temperature could be lower around the alveoli in PFO+, it is likely that the same air would increase and equilibrate its temperature to that of the surrounding tissues as it travels through the respiratory tract back to the mouth. In turn, this could result in similar expired air temperature (and therefore similar net respiratory heat loss, and whole-body thermal balance) between PFO+ and PFO-. Furthermore, the presence of a greater oesophageal temperature does not necessarily imply that temperature in other core regions of the body (e.g. the hypothalamus, where the human thermoregulatory controller is located) would be in turn concurrently elevated. In this respect, in order to confirm that whole-body heat balance is equally perturbed in PFO+ and that this is not a local phenomenon limited to an elevated oesophageal temperature *per se*, similarly elevated core temperature measured elsewhere (e.g. rectal and tympanic) would need to be observed.

Recently, Cramer and Jay (Cramer & Jay, 2014) have demonstrated that for the unbiased comparison of thermoregulatory response between independent groups, relative changes in rectal temperature should be compared by standardizing the rate of heat production (watts; W) per unit of body mass (Kg), as expressed in watts per kilogram of total body mass (W/Kg). In this respect, Davis et al.' study is of great interest because it allows for an unbiased comparison of thermoregulatory responses in PFO+. In this study: 1) PFO+ and PFO- groups presented no significant differences in

body mass and maximal oxygen consumption; 2) during the maximal exercise test, the external workload was fixed and equal between PFO+ and PFO-; 3) no differences in oxygen consumption (hence rate of energy expenditure) were recorded at any stage of the exercise protocol between PFO+ and PFO-. It follows that PFO+ and PFO- individuals were likely performing their incremental exercise test at the same incremental intensities expressed in W/Kg. As no differences in the relative changes in oesophageal temperature were recorded between PFO+ (0.8°C) and PFO- (0.9°C) individuals during maximal exercise, it could be therefore concluded that no specific differences in the ability to regulate body temperature and thermal status were present between these two independent groups. This observation could support the hypothesis that the greater resting and end-exercise oesophageal temperature observed in PFO+ individuals could represent a *hot temperature spot*, rather than being indicative of an elevation in whole-body thermal status due to the PFO+. Nevertheless, until thermoregulatory effector responses (i.e. oesophageal temperature onset thresholds and sensitivity for sweating and vasomotor tone, whole body sweat losses) are investigated under conditions where the assessment of changes in deep body temperature at multiple sites (e.g. oesophageal, rectal and tympanic) is performed at the same rates of heat production per unit of body mass in both PFO+ and PFO-, whether PFO+ individuals present an impaired ability to thermoregulate or just a different heat distribution across the body, cannot be determined conclusively.

The findings of Davis et al. open to the interest for the investigation of thermoregulatory function in PFO+ individuals and of its clinical implications. As evidence has pointed towards a potential association between PFO+ and the risk for ischemic strokes in younger adults (Lechat *et al.*, 1998), it appears clear that, due to the known impact of heat stress on cardiovascular function, increasing the knowledge on thermoregulatory function in PFO+ could help identifying additional predisposing factors to the risk of heat stroke in younger adults.

Acknowledgements

The authors would like to acknowledge Dr Ollie Jay for insightful discussion and mentoring. D. Filingeri is supported by an Endeavour Research Fellowship from the

Australian Government, Department of Education. N. B. Morris is supported by an International Postgraduate Research Scholarship from the University of Sydney.

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