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Sex difference in cold perception and shivering onset upon gradual cold exposure

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ABSTRACT

To maintain a thermal balance when experiencing cold, humans reduce heat loss and enhance heat production. A potent and rapid mechanism for heat generation is shivering. Research has shown that women prefer a warmer environment and feel less comfortable than men in the same thermal condition. Using the Blanketrol® III, a temperature management device commonly used to study brown adipose tissue activity, we tested whether the experimental temperature (T_E) at which men and women start to shiver differs. Twenty male and 23 female volunteers underwent a cooling protocol, starting at 24 °C and gradually decreasing by 1–2 °C every 5 min until an electromyogram detected the shivering or the temperature reached 9 °C. Women started shivering at a higher T_E than men (11.3 ± 1.8 °C for women *vs* 9.6 ± 1.8 °C for men, $P = 0.003$). In addition, women felt cool, scored by a visual analogue scale, at a higher T_E than men (18.3 ± 3.0 °C for women *vs* 14.6 ± 2.6 °C for men, $P < 0.001$). This study demonstrates a sex difference in response to cold exposure: women require shivering as a source of heat production earlier than men. This difference could be important and sex should be considered when using cooling protocols in physiological studies.

1. Introduction

Humans tightly control their core body temperature (T_c) by balancing heat loss and heat production (Costanzo, 2017). When exposed to mild cold, humans first reduce heat loss by energy-inexpensive mechanisms such as the constriction of blood vessels supplying the peripheral tissues. This peripheral vasoconstriction not only reduces the heat transfer from the isothermal core to the non-isothermal shell, but also increases the insulating capacity of the skin and subcutaneous tissues. The shift of blood from superficial layers to deeper vessels results in an increased total body insulation since the bloodless layer, where the convective heat loss substantially diminishes, becomes thicker (Anderson, 1999). However, if the thermal balance cannot be accomplished by a reduction in heat loss, heat production is required (Tansey and Johnson, 2015).

Heat production can be achieved by many mechanisms (Castellani and Young, 2016; Hall, 2015). Exposure to cold activates the sympathetic nervous system (SNS), immediately increasing the metabolic rates of all cells in the body that consequently generate heat as a by-product of metabolism. The direct stimulation of β-adrenergic receptors by the SNS also activates brown adipose tissue (BAT), a specialized metabolic tissue that can convert energy into heat (Lee et al., 2013). When the metabolic heat production (non-shivering thermogenesis) together with the cutaneous vasoconstriction is not sufficient to maintain the optimal T_c, shivering begins.

Shivering, which is the involuntary rhythmic contraction of skeletal muscles, is the most potent and rapid mechanism to generate heat in response to cold stress. When the skin senses cold via the transient receptor potential cation channel subfamily M member 8 (TRPM8) on the sensory nerves (Voets et al., 2004), it signals to the temperature center in the hypothalamus. The primary motor center for shivering in the posterior hypothalamus is then activated and transmits signals to the skeletal muscles to initiate shivering throughout the body (Hall, 2015). At the maximum intensity of shivering, metabolic heat production can rise to five times of the resting levels (Eyolfson et al., 2001).

Various cooling techniques have been used to study the physiological responses to cold environment, especially after the rediscovery of BAT in adult humans in the last decade (Nedergaard et al., 2007) because cold is a well-known stimulant for the thermogenic function of BAT. The cooling methods include cold-water immersion, cold-air

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exposure, cold-air exposure combined with localized cooling e.g. feet cooling in ice water, and water-filled cooling blankets or suits (Castellani and Young, 2016; van der Lans et al., 2014). The cooling blanket with temperature of the filling water set at 1–2 °C above the shivering point (also known as a personalized cooling protocol) is likely the method that maximally activates BAT (Bahler et al., 2017). Using this cooling method, conduction will be the mode of heat transfer at those body areas that are covered and in direct contact with the cooling blankets whereas convection will occur at areas without direct contact with the blankets. One of the frequently used cooling blankets is the Blanketrol® III, a temperature management device that can control the temperature of the circulating water in a range from 4 °C to 42 °C.

Research has shown that sex is one of the important factors that influence thermal perception and physiological responses to cold. Karjalainen (2007) demonstrated that women prefer a higher ambient temperature and feel less comfortable than men in the same thermal environment, especially during the winter season. Furthermore, Kingma and van Marken Lichtenbelt (2015) showed that women require more heat production than men in the standard indoor climate setting that was mainly based on male metabolic rates. Castellani and Young (2016) revealed that the primary source of the variable capability to maintain a normal T_c between men and women during whole-body cold exposure is body anthropometric and body composition characteristics. At the same body mass and surface area, women generally have a higher subcutaneous fat content than men that enhances insulation (Anderson, 1999; Castellani and Young, 2016; Kuk et al., 2005). On the other hand, when the subcutaneous fat thickness is equal between a man and a woman, the latter in general will have a larger body surface area (BSA) and a smaller body mass contributing to a greater total heat loss and a lower heat-production capacity during resting cold exposure (Castellani and Young, 2016; Graham, 1988).

Understanding sex differences in thermal regulation and cold-induced physiological responses is beneficial in many aspects. For instance, Iyoho et al. (2017) proposed a sex-specific modification of the thermoregulation model for predicting thermal response in a wide range of the operational conditions for military relevant tasks, especially in the cold-stress responses. Chaudhuri et al. (2018) showed that different physiological parameters from male and female occupants were needed to accurately predict the thermal comfort status in a range of the general indoor climate setting. Graham (1988) demonstrated that men and women respond differently in many physiological parameters when exercising or resting in either a cold room or cold water, which frequently could not be explained solely by sex-specific morphological differences. A review of chamber experiments and field studies to identify the factors influencing individual differences on thermal comfort by Wang et al. (2018) revealed that women are more critical about indoor thermal settings and more sensitive to deviations of thermal environment than men, but a consistent conclusion on sex differences in thermal comfort could not be drawn. Moreover, it has not been addressed whether men and women differ in the shivering onset after a gradually cold exposure using the Blanketrol® III, a common method for studying BAT activation. To test this, we exposed healthy volunteers to cold progressively and determined the experimental temperature (T_E) at which the volunteers started to shiver. This study demonstrates sex differences in the physiological responses to a gradual cold exposure.

2. Methods

2.1. Participants

We recruited 43 participants (20 men and 23 women) who met the inclusion criteria: age 16–35 years; being physically healthy; Caucasian ethnicity; body mass index (BMI) 18.5–29.9 kg/m^2 for participants aged more than 20 years old, or BMI standard deviation score (BMI-SDS) between −2 and + 2 for participants aged 16–19 years old. The following exclusion criteria were used: diabetes mellitus, thyroid disorders, substance use disorders, pregnancy, breastfeeding, and using β-adrenergic blocking medication. Participants were requested to eat, drink, and sleep as their usual routines, and requested not to smoke, eat, or drink any caffeinated or alcohol beverage within one hour before an appointment.

Since female sex hormones fluctuate during the reproductive cycle and could potentially influence the thermal balance (Charkoudian and Stachenfeld, 2014), female participants were included as follows. When a female participant was using contraceptive pills, she could only participate on a day she was taking a hormone-containing pill. When the female participant was not using contraceptive pills, she could not participate in the early follicular phase of her menstrual cycle, i.e. her menstruation period. In addition, we asked the female participants about their menstrual history to identify the phase of reproductive cycle at the day of experiment.

The experiment was performed after the participants had signed the written informed consent. The study was conducted according to the principles of the Declaration of Helsinki (version 19 October 2013). The procedures had been approved by the IRB of Erasmus MC, University Medical Center Rotterdam, the Netherlands.

2.2. Study design

To limit the influence of the environmental temperature on thermal perception (Makinen et al., 2004), the experiment was performed during the summer (July–September 2017). Daily mean temperatures of Rotterdam, the city where the experiment was performed, were obtained from the Royal Dutch Meteorological Institute (KNMI) via a publicly accessible database (KNMI, 2017). For further analysis, the outside temperature for each individual was calculated from three-day daily-mean-temperatures (2 days before and the day of the experiment).

The experiment was performed in the same laboratory with a standard heating, ventilation and air-conditioning system at a spot without direct air flow. The overall experimental design is illustrated in Fig. 1. Room temperature was recorded to verify the thermal condition. After arriving at the laboratory, participants acclimatized to the thermal setting of the room for at least 30 min. During the acclimatization period, participants changed their clothing to shorts and a T-shirt, filled in a questionnaire (Fig. 2A), rated their thermal perception,

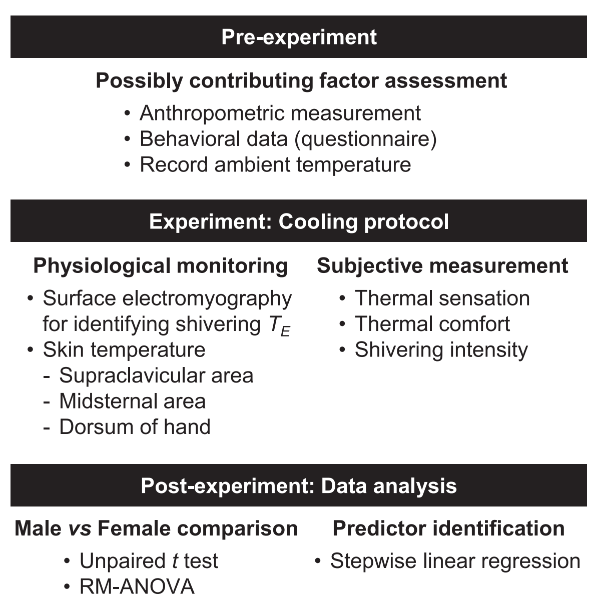

Fig. 1. Overall experimental procedure, The primary outcome is to identify a shivering T_E: the experimental temperature at which shivering started.