Journal of Thermal Biology 79 (2019) 199–208

Contents lists available at ScienceDirect

Journal of Thermal Biology

journal homepage: www.elsevier.com/locate/jtherbio

Exploring the human thermoneutral zone – A dynamic approach

H. Pallubinsky[a,*], L. Schellen[b], W.D. van Marken Lichtenbelt[a]

[a] Department of Human Biology and Movement Sciences, NUTRIM, Maastricht University, the Netherlands
[b] School for the Built Environment and Infrastructure, Gilde Opleidingen, Roermond, the Netherlands

ABSTRACT

To date, the position and shape of the human thermoneutral zone (TNZ) remain uncertain. Indications exist that the individual TNZ might be influenced by age, body composition and level of acclimatisation. The objective of the present study was to explore the individual metabolic TNZ, using dynamic thermal conditions to assess both metabolic lower and upper critical temperatures (LCT and UCT) and, secondly, to test the effect of passive mild heat acclimation on the human metabolic TNZ.

A dynamic protocol consisting of two experimental conditions was designed: starting from a thermoneutral condition (28.8 ± 0.3 °C), temperature gradually increased to 37.5 ± 0.6 °C during warming (UP) or decreased to 17.8 ± 0.6 °C during cooling (DOWN). For six participants, temperature increased further to 41.6 ± 1.0 °C during UP. Eleven healthy men (19–31 y) underwent UP and DOWN twice, i.e. before and after passive mild heat acclimation (PMHA, 7 days at ~33 °C for 6 h/day). Energy expenditure, body temperatures and heart rate were measured during UP and DOWN.

We show that the generally assumed LCT of approximately 28 °C for an average male person does not match the dynamically assessed LCTs in this study, as those were considerably lower in most cases (23.3 ± 3.2 °C pre-acclimation; 23.4 ± 2.0 °C post-acclimation). Distinct inter-individual variation of the dynamic LCT was evident (range pre-PMHA:9.7 °C; post-PMHA:5.4 °C). Regarding the metabolic response to increasing temperatures, only minor or no increases in energy metabolism occurred. PMHA did not significantly change the positioning of the LCTs, but lowered Tcore (pre-PMHA: −0.13 ± 0.13 °C, P = 0.011; post-PMHA: −0.14 ± 0.15 °C, P = 0.026) and affected skin temperature distribution.

The applied method allowed for the determination of individual dynamic LCTs, however, distinct metabolic UCTs were not evident in humans. For a better understanding of the human UCT, future studies should incorporate individualised temperature ranges and also a measurement of evaporative heat loss, to allow for a two-factor analysis of both metabolic and evaporative human UCT.

1. Introduction

The thermoneutral zone (TNZ) reflects the range of ambient temperatures at which internal temperature regulation is solely achieved by control of dry heat loss, which means that the metabolic rate is relatively constant without regulatory changes in heat production or evaporative heat loss (IUPS, 2001; Jessen, 2001).

To date, the TNZ has mainly been studied in (small) animals (Gordon, 2012; Scholander et al., 1950a, 1950b; Speakman, 2013). According to the Glossary of Terms for Thermal Physiology (IUPS, 2001), the lower critical temperature (LCT) is defined as “the ambient temperature below which the rate of metabolic heat production of a resting thermoregulating tachymetabolic animal must be increased by shivering and/or non-shivering thermogenesis in order to maintain thermal balance”. Hence, the relation between ambient temperature and metabolic rate below the LCT can be described according to the classical Newtonian cooling model for an endotherm (Scholander et al., 1950a).

For the upper critical temperature (UCT), a distinction between an evaporative UCT and a metabolic UCT is recommended, defined by either an increase of evaporative heat loss or an increase of metabolic rate (IUPS, 2001). Gordon (1990, 1993, 2012) extensively investigated the thermoregulatory properties and TNZ of laboratory rodents (Fig. 1). In the author's publications, a distinction has been made between two different UCTs for mice and rats: on the one hand, the UCT can be defined by an increase of evaporative water loss, and on the other hand, by metabolic rate (Gordon, 2012). According to the author, evaporative water loss again can be divided in two components: a passive component characterised by passive evaporation and water loss via the skin, and an active component characterised by active water loss through sweating, panting or grooming moisture on the skin (Gordon, 1990, 1993, 2012). Whereas the evaporative UCT has been defined as the ambient temperature where passive evaporative water loss increases considerably and additional active evaporative water loss commences, the metabolic UCT has been specified as the ambient temperature at which the metabolic rate increases significantly from the basic metabolic rate (Gordon, 2012).

With respect to the human TNZ, limited studies are available (Craig and Dvorak, 1966; Hardy and DuBois, 1937, 1938, 1940; Hey and Katz, 1970; Hill et al., 2013). Few publications present data for the human LCT (Ouellet et al., 2012; van der Lans et al., 2013; Yoneshiro et al., 2011), but regarding the human UCT, hardly any information is available. Data derived from the few human studies indicate that the

* Correspondence to: Universiteitssingel 50, 6229 ER Maastricht, the Netherlands.
E-mail address: h.pallubinsky@maastrichtuniversity.nl (H. Pallubinsky).

https://doi.org/10.1016/j.jtherbio.2018.12.014
Received 15 August 2018; Received in revised form 11 December 2018; Accepted 11 December 2018
Available online 18 December 2018

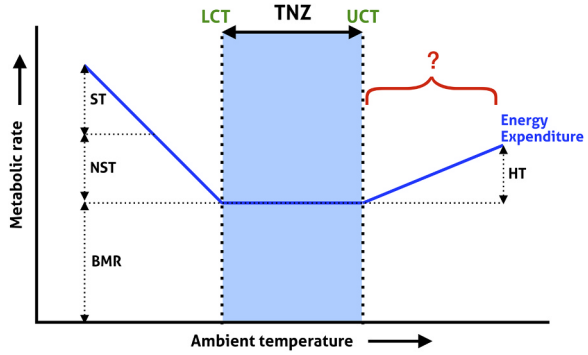

Fig. 1. The thermoneutral zone. The thermoneutral zone (TNZ) reflects the ambient temperature range wherein the energy expenditure is at basal level (basal metabolic rate, BMR) and there are no thermoregulatory changes in metabolic rate (non-shivering thermogenesis, NST; shivering thermogenesis, ST; heat-related thermogenesis, HT). In the present paper, metabolic rate is used to describe the TNZ. As shown in the graph, below the lower critical temperature (LCT) and above the upper critical temperature (UCT), metabolic rate (heat production) is expected to increase due to a respectively decrease or increase of the ambient temperature. The graph is derived from animal studies (adapted from (Gordon, 2012)).

generally assumed human thermoneutral range lies between approximately 28 °C and 32 °C (Hardy and DuBois, 1937, 1938). In the respective aforementioned studies, the upper critical value was based on evaporation, not on the metabolic rate. It is, however, unsure, whether the concept of a metabolic UCT is applicable in humans (Fig. 1). An increase of metabolic rate might not be expected to occur when behavioural thermoregulation is ruled out, as the contribution of sweating to the metabolic rate is considered negligible. Additional energy consuming processes that might occur in the heat are increased cardiovascular workload and elevated breath rate. Moreover, Arrhenius law, also called the Q10-effect, which postulates a temperature-dependence of biochemical reaction rates in the body, might play a role for the upper critical limit.

Importantly, earlier research and theoretical considerations suggest that the TNZ differs remarkably *between individuals*, since its width and positioning is likely to be influenced by a number of parameters, whereof body composition, age, and gender (Kingma et al., 2012). Furthermore, temperature acclimatisation might play a significant role, as it has, for example, earlier been shown in hamsters that acclimation shifts the thermoneutral zone significantly, resulting in changes of the LCT (up to 7.5 °C difference in LCT between cold and heat acclimation) (Zhao et al., 2014). The latter might be of great relevance for future practical implications, in the light of climate change and the increasing risk for overheating in the built environment (EEA, 2015).

Despite the earlier efforts to define the human TNZ, its determination remains problematic to this day. In many animal studies, the TNZ has been measured at fixed ambient temperatures in order to establish steady-state energy expenditure values for each temperature, which is relatively easy to accomplish in small mammals (Aujard and Vasseur, 2001; Romanovsky et al., 2002; Speakman, 2013). However, due to the great thermal mass and depending on the thermal history, it might take hours to reach a steady state for the human body. Hence, one would have to expose each individual participant to a specific temperature for several hours until thermal balance is achieved and repeat this until both metabolic LCT and metabolic and/or evaporative UCT are manifested. Therefore, a stepwise temperature protocol for the study of the human TNZ in ambient air is practically very challenging, complex, and costly. Other techniques, for example incorporating a water-perfused suit for superior conductivity and thus better temperature transfer, do not necessarily reflect human physiological responses in ambient air and the results of such experiments would thus be difficult to translate to daily living circumstances. Therefore, an alternative method is needed to allow for evaluation of the critical physiological temperatures in ambient air.

Being able to determine the individual TNZ and understanding the impact of thermal acclimation on its limits, is of relevance to various (scientific) fields. For example, it has recently been suggested that a causal relation might exist between the time spent in thermoneutral environments and increased adiposity (Johnson et al., 2011). Excursions to ambient conditions outside the TNZ can increase energy expenditure and improve glucose metabolism, and subsequently may reduce susceptibility to obesity and Diabetes type 2 (Hanssen et al., 2015; Kingma, 2012). Our daily living environment, however, is often controlled very tightly. These tightly controlled indoor ambient conditions have their background in thermal comfort research. According to Hensel (Hensel, 1981), the TNZ in resting humans is equal to the zone of thermal comfort. However, in an earlier study, we showed that thermoneutrality and thermal comfort are not necessarily the same (Kingma et al., 2014). Moreover, indications exist that the TNZ might be shifted by acclimation to warm or cold ambient conditions (Pallubinsky et al., 2017; van der Lans et al., 2013). Although the nature of this shift remains elusive and has, to the best of the authors' knowledge, not yet specifically been studied in humans, it can be deducted from both physiological and thermal perception studies that the thermoneutral range is likely to be accustomed to the specific thermal habitat of an individual (Brown et al., 2004; Kingma et al., 2012).

From both health and building energy-use perspectives, it could be highly beneficial to extend the control range at which the indoor environmental temperature is regulated (Hill et al., 2013; van Marken Lichtenbelt et al., 2017; van Marken Lichtenbelt and Kingma, 2013). With regard to the constant and undeniable progress of global warming and increasing indoor and outdoor temperatures, it is important to assess the influence thereof on human physiology and health. In order to design a more healthy, sustainable and comfortable indoor environment, it is relevant to obtain more insight into the individual human TNZ and the effect of acclimation to mildly elevated temperatures on the latter.

Also, with respect to the design of studies on metabolism, thermoregulation and cardiovascular aspects, it is relevant to control for the ambient temperature as a factor of influence and to account for individual differences in the TNZ. Ideally, the ambient temperature that participants are exposed to during an experiment should be individually attuned to each person, depending on the goal of the respective study (Kingma et al., 2012). However, to be able to account for thermal neutrality and to potentially adjust the ambient conditions to an individual, it should be identifiable whether a person is actually situated within their TNZ.

In summary, the TNZ, based on metabolic rate, has been studied thoroughly in animals. For humans, however, the understanding of the TNZ, as well as possible individual differences remains limited (Schlader, 2014). It is not clear if a metabolic UCT, as incorporated in the TNZ model derived from rodent data, is at all existent in humans. Therefore, the objective of the present study was to explore the human metabolic LCT and to investigate the existence and positioning of the human metabolic UCT. As described in the above, steady-state situations are not easily met and practically challenging, which is why we chose to apply a pragmatic solution by measuring LCT and UCT during dynamic temperature conditions. This novel, practical, approach has been employed as, to the best of the authors' knowledge, there is yet no other method described in the literature explicitly to measure the human thermoneutral zone. Moreover, considering the possible influence of temperature acclimation on the width and positioning of the individual TNZ, we aimed to measure both individual LCTs and UCTs before and after passive mild heat acclimation (PMHA).

2. Methods

Eleven healthy, white Western European male volunteers participated in this study (Table 1). Participants were given detailed

Table 1
Participant characteristics.

	Mean ± SD
Age (year)	24.6 ± 2.7
Height (m)	1.79 ± 0.07
Area (m^2)	1.90 ± 0.13
Body mass (kg)	72.2 ± 8.9
BMI (kg/m^2)	22.6 ± 2.9
Body fat% (%)	19.7 ± 3.0
Fat mass (kg)	14.5 ± 3.3

Data is presented as mean ± SD, N = 11.

information regarding the purpose and the methods of the study before written informed consent was obtained. The protocol was approved by the ethics committee of Maastricht University Medical Center+ and designed and performed according to the Declaration of Helsinki (Fortaleza, Brazil, 2013). The measurements were conducted in the period of December 2014 till August 2015, as part of a larger experiment. In the following, only those methods and results with importance for the aim of this particular study are presented.

2.1. Experimental conditions

2.1.1. Passive mild heat acclimation and dynamic temperature protocols

Participants underwent a passive mild heat acclimation (PMHA) protocol, i.e. without exercise, which reflects thermal challenges likely to occur in everyday situations, for example, due to prolonged occupancy of an overheated building (AECOM, 2012), during a holiday in a warm country or during a warm summer or heat wave. Considering the progress of global warming, the occurrence of those events is likely to be more frequent, even in European oceanic and humid continental climates (Köppen climate classification) (Frich et al., 2002; Meehl and Tebaldi, 2004; Schär et al., 2004). PMHA consisted of 7 consecutive days of PMHA at 33.3 ± 1.6 °C for 4 h at acclimation day 2 and 6 h per day for the remaining 6 days (Fig. 2). As the formal acclimation terminated after day 8 of the study protocol, the UP protocol at day 9 was regarded as an additional heat stimulus, which supposedly prevented a possible decay of potentially acquired physiological adaptation before the last DOWN measurement.

Before and after PHMA, subjects were exposed to two thermal conditions: an increasing and a decreasing temperature ramp, respectively UP and DOWN (Fig. 3). For both conditions, the protocol started at a constant temperature of 28.8 ± 0.3 °C for the first 60 min, which served as a baseline measurement. Given the boundary conditions, this baseline temperature has been assessed as neutral based on a literature review of Kingma et al. (2012) for humans in a resting, semi-nude state. It has been adjusted for the insulation of the stretcher on which participants lay in supine position. The first 30 min of both conditions were regarded as familiarisation period.

To cover a temperature range that expectedly includes the human TNZ (which has previously been estimated to be positioned between approximately 28 and 32 °C (Hardy and DuBois, 1938)), the ambient temperature increased to 37.5 ± 0.6 °C during UP over the course of 90 min and decreased to 17.8 ± 0.6 °C during DOWN over the course of 120 min (Fig. 3). For the last 6 study participants, an additional 30 min of ramp was added subsequently to the UP protocol to cover an

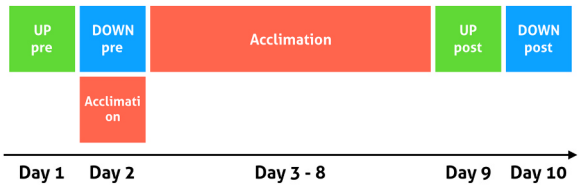

Fig. 2. Study timeline.

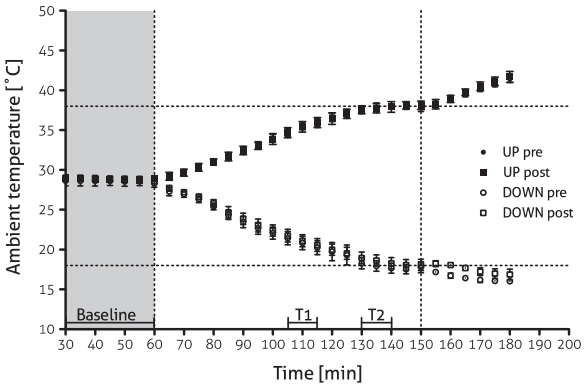

Fig. 3. Dynamic temperature ramp protocols. Data is presented as mean ± SD over the course of 5 min per time point. UP: N = 11 until t = 150 and N = 6 until t = 180, DOWN: N = 8 until t = 120, where after participants started to drop out due to severe shivering. For DOWN pre, 2 out of 8 participants completed the full 180 min and for DOWN post, 3 out of 8 participants reached t = 180. Baseline, T1 and T2 represent the respective intervals used for data analysis.

even wider temperature range. This was due to the fact that during the experiments, it appeared that the initially applied UP temperature range did not induce increases of metabolic rate. Therefore, to test an even broader temperature range, the UP ramp was extended for the last six participants. On average, the final temperature that was reached for these six participants during UP was 41.6 ± 1.0 °C (averaged over the last 10 min).

If severe shivering, paired with a noticeable increase of metabolic rate, occurred during DOWN, the measurement was terminated prematurely. Moreover, the measurement was terminated when participants reported strong discomfort, which only occurred during DOWN (paired with shivering) but never during UP. Six DOWN measurements were stopped early before PMHA and five after PMHA. Due to technical problems with the climate chambers during DOWN in three cases, data of these participants was excluded from analysis.

Air temperature and relative humidity (Hygrochron iButton, DS1923, Maxim Integrated Products, USA,) were measured according to EN-ISO 7726 (ISO, 2001) at 1-min intervals at 0.1 m, 0.6 m, 1.1 m and 1.7 m height. Relative humidity (RH) was allowed to drift with changes in temperature, resulting in an average RH of 25.82 ± 7.18% during UP and 35.31 ± 8.71% during DOWN.

During the measurements, participants were situated in a semi-supine position on a stretcher with air-permeable fabric, wearing underpants only (0.05 clo (McCullough et al., 1989)). They were allowed to watch television, but they were instructed to refrain from any movement. During one of the measurement days, body composition was determined by means of a DEXA-scan (Discovery A, Hologic Inc.). Participants were advised to drink sufficient amounts of water the day and morning before the measurement days (UP and DOWN) and also during acclimation, to ensure euhydration.

2.1.2. Data analysis

The first 30 min of both conditions were excluded from the data analyses since this was regarded as a familiarisation period. For the analyses of energy expenditure, data was averaged over one minute. For the comparisons of core temperature, skin temperatures, heart rate and energy expenditure within each of the protocols and before and after PMHA, three periods were selected during UP and two during DOWN: baseline (t = 30–60 min, 28.81 ± 0.40 °C ambient temperature), T1 (t = 105–115 min, UP: 34.81 ± 0.50 °C, DOWN: 21.40 ± 0.8 °C ambient temperature) and T2 (t = 130–140 min, UP: 37.53 ± 0.58 °C ambient temperature). Due to a technical problem with the applied heart rate monitor, data of two participants was excluded from analysis for both UP and DOWN.

The commercially available software package PASW Statistics 21.0 for Mac (SPSS Inc.) was used for the statistical data analyses. Differences in physiological parameters before and after passive mild heat acclimation, i.e. core temperature, mean skin temperature and proximal and distal skin temperatures, were tested using paired-sample *t*-tests. Heart rate increments during the ramp protocols before and after PMHA were tested using a repeated measures design and corrected for multiple testing using the Bonferroni method. Correlations between energy expenditure, physiological parameters, and body characteristics were assessed using Pearson correlations. Significant effects are reported for $P < 0.05$. Determination of the lower and upper critical temperatures of the TNZ was performed using MATLAB 2012a for Mac (The Mathworks Inc.).

2.1.3. Determination of the individual LCTs and UCTs

The main objective of this study was to explore the positioning and width of the individual human TNZ, based on the individual metabolic rate.

According to the Newtonian cooling model (Scholander et al., 1950a) (assuming a constant body core temperature and 'perfect' thermoregulation), the steady state relationship between the ambient temperature (Ta) and the metabolic rate (MR) that are needed to sustain a stable body core temperature can be described by the application of two linear functions:

(1) For ambient temperatures lower than the LCT: $MR = -a_1 T_a + b_1$
(2) For ambient temperatures between LCT and UCT (TNZ): MR = constant

Function (1) describes a situation where the body increases its metabolic rate to maintain stable core temperature (below LCT) and function (2) is applicable when the body is capable of maintaining a stable core temperature only by the modification of tissue insulation (TNZ). Beyond the UCT, increased metabolic rate is in contradiction with the Newtonian cooling model. Nevertheless, as the metabolic rate is expected to increase above the UCT, we applied a similar approach:

(3) For ambient temperatures higher than the UCT: $MR = a_2 T_a + b_2$

Here, the LCT was assumed to be equal to the point of intersection of function (1) and (2) and the UCT as the intersection of function (2) and (3) respectively.

For each individual participant, the three functions were fitted through the measured data points simultaneously. The 'best fit' for each function was determined by the least squares method. For the determination of metabolic LCT and UCT, energy expenditure relative to the resting metabolic rate (RMR, as measured during baseline period) was applied, and presented as a moving average over a triangular window of 10 min. The resulting LCT and UCT were counter-checked by subjective observation of the measured data for each individual dataset.

2.1.4. Physiological measurements

For both protocols UP and DOWN, participants arrived at the laboratory in the morning after an overnight fast (as of 22:00 h at the evening before). At all four days before the measurements took place (day 0, day 1, day 6 and day 7), participants consumed the same standardised evening meal, as chosen by them on the evening before the first measurement day.

Upon arrival at the laboratory, participants ingested a telemetric pill (Vital Sense, Philips Healthcare, NL) to measure core temperature. To detect the signal of the telemetric pill, an Equivital apparatus was attached to the participant's body using a chest strap (Equivital Hidalgo, UK). The same device was used to record heart rate. Wireless skin temperature sensors (iButton, Maxim Integrated Products, California, USA) were attached to 14 ISO-defined body sites with semi-adhesive tape (Fixomull stretch, BSN medical GmbH, GER) to measure mean, proximal and distal skin temperatures. Proximal skin temperature was calculated as an average of the ISO-defined sites of scapula, lower back paravertebral, upper chest and abdomen. For the distal skin temperature, skin temperatures of hand and instep were averaged. After preparations, participants took place on a stretcher (approximately 0.15clo) in the climate chamber. A face mask was attached to measure energy expenditure continuously by means of indirect calorimetry using a facemask (Omnical, Maastricht Instruments, NL). Energy expenditure, i.e. metabolic rate, was calculated according to Weir (1949), using the measured consumed oxygen and produced carbon dioxide which were multiplied by a factor 4.186 to convert data into kJ/min. Core temperature, heart rate and skin temperatures and energy expenditure were recorded at 1-min intervals. Physiological data for core and skin temperature as well as cardiovascular parameters for the UP protocol have been reported in an earlier publication (Pallubinsky et al., 2017).

3. Results

First, the results for the individual critical temperatures observed during the dynamic temperature protocols will be presented, followed by results for the effect of PMHA on critical temperatures and thermophysiological parameters.

3.1. Individual critical temperatures

Table 2 provides an overview of all observable LCTs and UCTs. The individual critical temperatures were assessed before and after PMHA. Fig. 4 shows examples of the energy expenditure curve of five representative participants, as measured during UP and DOWN, before and after PMHA.

Overall, in most participants, the LCT was observable as a strong inflection point in the relation between energy metabolism and air temperature, and, except for one occasion, LCTs could be calculated by the application of the functions as described in the above (Fig. 4, Table 2). As for the UCT, most participants did not exhibit a clear inflection point of energy expenditure with increasing ambient temperature. Few participants show a gradual small increase, mostly starting from the baseline temperature. However, several participants did not show an increase of metabolic rate during UP at all (Fig. 4). One participant showed no detectable increase of energy expenditure at all - neither during UP, nor during DOWN (Table 2, Fig. 4D).

Due to the very few identifiable UCTs, only LCTs could be statistically analysed to evaluate the effect of PMHA. There was no significant influence of PMHA on the positioning of the LCT ($P = 0.962$). RMR as measured during baseline was 4.82 ± 0.52kj/min before PMHA and 4.79 ± 0.61kj/min after PMHA. RMR was not significantly altered by PMHA (Schellen et al., 2012).

Table 2
Critical temperatures before and after PMHA.

Participant ID	LCT pre [°C]	LCT post [°C]	UCT pre [°C]	UCT post [°C]
1			/	/
2 (A)	20.4	24.0	/	/
3			/	/
4 (B)	19.2	21.2	29.0	29.8
5 (C)	24.6	25.0	/	/
6	22.8	22.1	/	/
7 (D)	/	/	/	/
8			/	/
9 (E)	22.9	21.2	/	31.2
10	28.9	23.4	/	/
11	24.3	26.6	/	/
Total	23.3 ± 3.2	23.4 ± 2.0	n/a	n/a

Slash = no detectable inflection point, grey field = no data obtained, *LCT* lower critical temperature, *UCT* upper critical temperature. The letters next to the participant numbers refer to the graphs shown in Fig. 4.

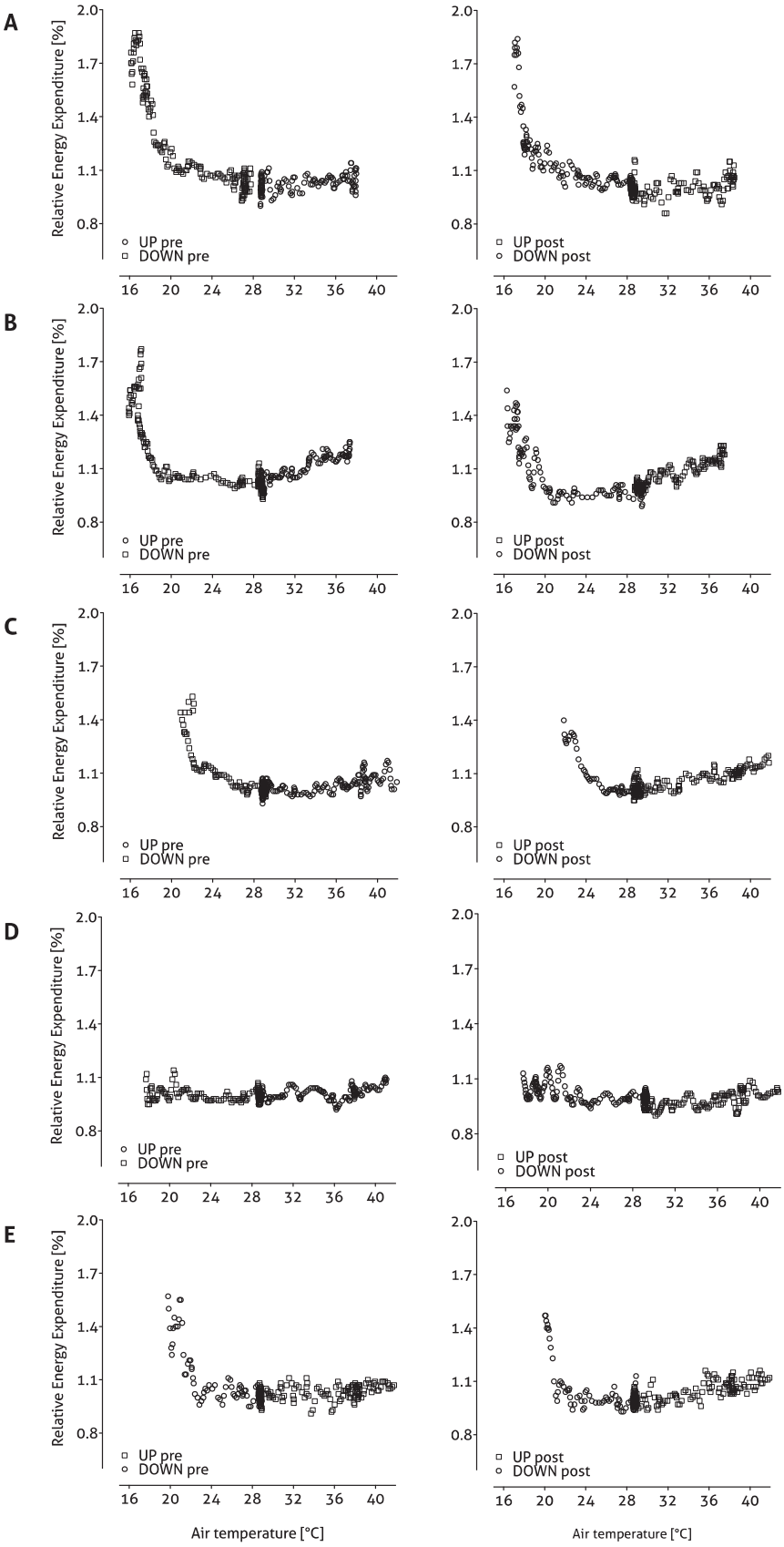

Fig. 4. Relative energy expenditure during UP and DOWN in relation to ambient temperature. Five representative participants (A, B, C, D and E) pre (left hand side) and post (right hand side) PMHA.

Table 3
Body temperatures during UP and DOWN before and after PMHA.

Protocol UP	Baseline pre	T1 pre	T2 pre	Baseline post	T1 post	T2 post
Core temperature [°C]	36.80 ± 0.27	36.74 ± 0.25	36.87 ± 0.22	36.72 ± 0.18	36.62 ± 0.23*	36.73 ± 0.26*
Mean skin temperature [°C]	33.89 ± 0.50	35.08 ± 0.42	35.72 ± 0.37	33.97 ± 0.30	35.08 ± 0.30	35.79 ± 0.25
Proximal skin temperature [°C]	34.41 ± 0.49	35.60 ± 0.35	36.18 ± 0.28	34.30 ± 0.43	35.38 ± 0.38*	36.03 ± 0.32
Distal skin temperature [°C]	32.44 ± 0.75	32.11 ± 0.52	34.97 ± 0.52	33.18 ± 0.55**	34.60 ± 0.49	35.48 ± 0.46*

Protocol DOWN	Baseline pre	T1 pre	Baseline post	T1 post
Core temperature [°C]	36.71 ± 0.19	36.78 ± 0.26	36.72 ± 0.14	36.80 ± 0.28
Mean skin temperature [°C]	33.86 ± 0.54	30.89 ± 0.71	33.97 ± 0.23	31.03 ± 0.50
Proximal skin temperature [°C]	34.26 ± 0.61	31.58 ± 0.85	34.25 ± 0.25	31.41 ± 1.03
Distal skin temperature [°C]	32.36 ± 0.64	27.81 ± 0.45	32.99 ± 0.82	28.31 ± 0.83

Data is presented as mean ± SD.
* $P < 0.05$ for changes post PMHA.
** $P < 0.01$ for changes post PMHA. N = 11 for UP, N = 8 for DOWN.

To assess the influence of individual characteristics and body composition on the results of the LCT position, the correlation with age, fat percentage, fat mass, lean mass, height, weight, and BMI were analysed for LCT and UCT, both before and after PMHA. No significant correlations ($P > 0.05$) were found between demographic characteristics and the positioning of the LCT before or after PMHA.

3.2. Body temperatures

After PMHA, core temperature was significantly decreased during protocol UP, at T1 (−0.13 ± 0.13 °C, P = 0.011) and T2 (−0.14 ± 0.15 °C, P = 0.026) but not at baseline (−0.12 ± 0.23 °C, P = 0.115, Table 3 and Fig. 5). No significant change of core temperature was observed during DOWN at baseline or T1 (Table 3, Fig. 5). Average mean skin temperature after acclimation was not significantly different from the pre-measurement at any time point. However, average proximal skin temperature significantly decreased at T1 (−0.22 ± 0.29 °C, P = 0.029) and average distal skin temperature increased at baseline (+0.74 ± 0.77 °C, P = 0.009), and T2 (+0.51 ± 0.63 °C, P = 0.022) and tended to be higher at T1 (+0.49 ± 0.76 °C, P = 0.057) upon warmth exposure during UP post PMHA (Table 3, Fig. 5).

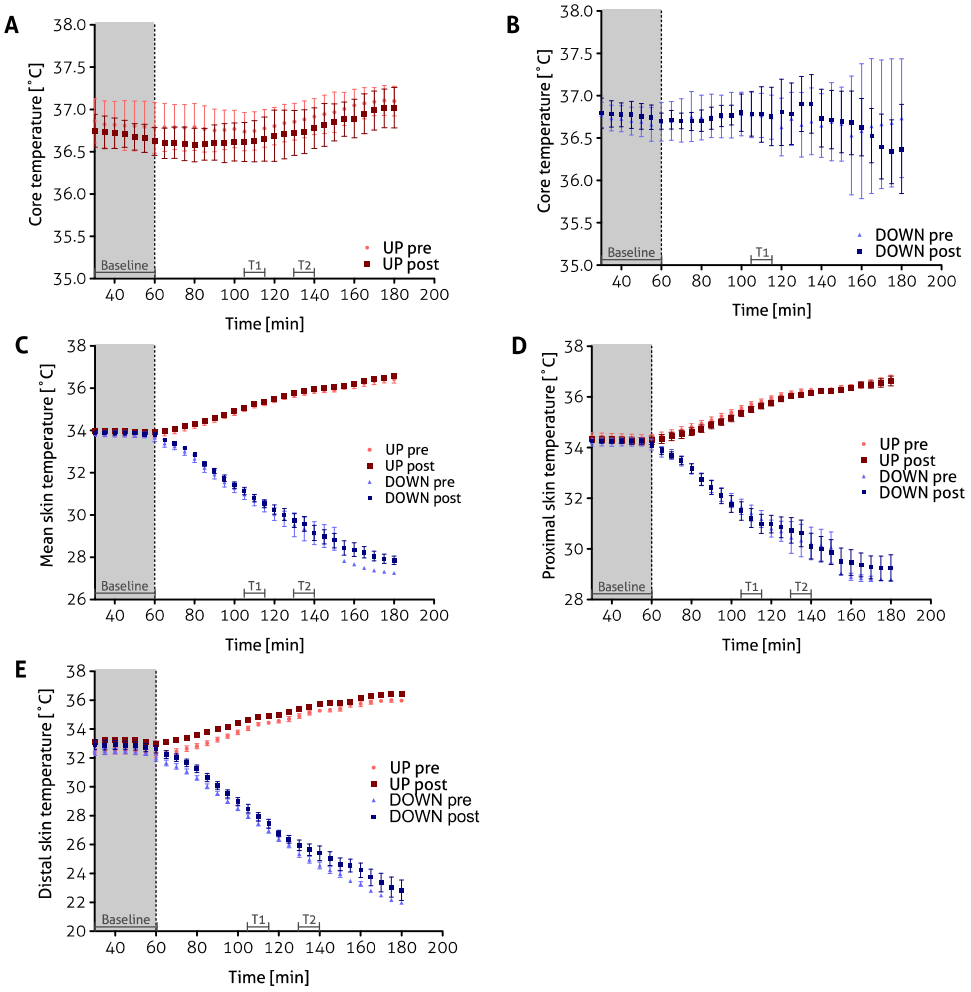

Fig. 5. Body temperatures during UP and DOWN before and after PMHA. Data is presented as mean ± SD over the course of 5 min per time point. A: Core temperature during UP, B: Core temperature during DOWN, C: Mean skin temperature, D: Proximal skin temperature, E: Distal skin temperature. UP: N = 11 until t = 150 and N = 6 until t = 180, DOWN: N = 8 until t = 120, where after participants started to drop out due to severe shivering. Note that for DOWN pre, 2 out of 8 participants completed the full 180 min and for DOWN post, 3 out of 8 participants reached t = 180 (hence the increasing standard deviation, due to less participants, towards the end of the protocol). Baseline, T1 and T2 represent the respective intervals used for data analysis.

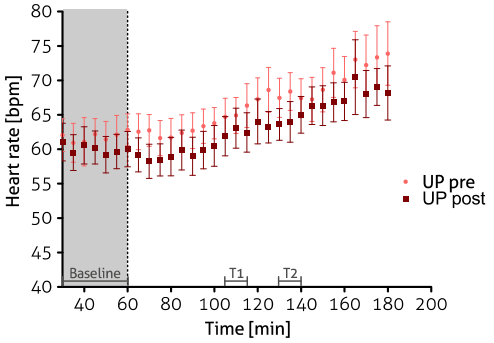

Fig. 6. Heart rate during UP before and after PMHA. Data is presented as mean ± SD over the course of 5 min per time point. N = 9 until t = 150 and N = 6 until t = 180.

3.3. Heart rate

Before PMHA, heart rate (HR) significantly increased from baseline to T1 (Δ3.6 ± 0.94, P = 0.019), from baseline to T2 (Δ6.9 ± 1.1, P = 0.001) and from T1 to T2 (Δ3.3 ± 0.6, P = 0.03) (Fig. 6). After PMHA, HR increased significantly from baseline to T1 (Δ2.4 ± 0.8, P = 0.039) and from baseline to T2 (Δ3.6 ± 0.9, P = 0.007), but not from T1 to T2 (Fig. 6). No significant change of HR during DOWN was observed, neither before or after PMHA.

Regarding the effect of PMHA, heart rate was not significantly affected by PMHA during UP, neither in thermoneutral conditions, nor during warming (Fig. 6A). During cooling, heart rate was significantly lower post-PMHA at T1 of DOWN (Δ−4.1 ± 2.0, P = 0.004, N = 6).

4. Discussion

The objective of the present study was to explore the human metabolic LCT and to investigate the existence and positioning of the human metabolic UCT, using a novel, dynamic approach with increasing and decreasing thermal conditions. Moreover, this study aimed to assess the effect of passive mild heat acclimation on the (dynamic) human TNZ, to evaluate the impact of acclimation to elevated temperatures on the critical temperatures.

The results of this study show that for the great majority of participants, a clearly observable and distinct increase of metabolic rate was evident when temperatures decreased, allowing for the calculation of the individual dynamic LCTs. However, during warming, several participants showed only a very slight and gradual increase of energy metabolism, whereas others did not exhibit observable changes of the metabolic rate at all. Hence, a clear inflection point for the metabolic UCT was not identifiable and therefore not quantifiable in most cases. The latter supports the hypothesis that there might not be a distinct metabolic UCT in humans, other than reported in other species (Gordon, 2012; Scholander et al., 1950b), at least not in the measured range of temperatures reaching up to 42 °C.

Interestingly, there appeared to be considerable differences in metabolic response to decreasing ambient temperatures *between* the individuals, denoted by the wide range of LCTs observed both before and after PMHA (temperature range: pre: 9.7 °C, post: 5.4°; Table 2). However, the results show that repeated measurements lead to a characteristic metabolic response over time *within* the same individual for both UP and DOWN protocols (Fig. 4).

With respect to the effect of PMHA on the TNZ, or at least on the LCT, no changes of the metabolic rate, neither basal nor during warming or cooling were evident after acclimation. Although the LCT remained unaffected by PMHA, core temperature decreased upon PMHA and skin temperature distribution changed towards warmer distal parts and cooler proximal parts, indicating enhanced heat loss mechanisms.

4.1. Assessing the individual thermoneutral zone in humans

The TNZ for small mammals has been described in detail by Scholander et al. (1950a) and later modified by Gordon (2012). However, hitherto, the width and positioning of the human TNZ has been difficult to measure. An earlier study by Mekjavic et al. (1991) established that core temperature thresholds for shivering and evaporative heat loss are significantly different from each other. This indicates that a so-called 'null-zone' exists, a core temperature range with a magnitude of ~0.6 °C, at which no sweating or shivering occurs. Importantly, the present study aimed to identify the *metabolic* TNZ, which is not assessed by measuring the critical ambient temperatures at which core temperature changes, but those at which changes of the metabolic rate are observed. With respect to the *metabolic* TNZ, several attempts have been made to determine the critical limits (Craig and Dvorak, 1966; Hardy and DuBois, 1937, 1938, 1940; Hey and Katz, 1970; Hill et al., 2013), whereof one in water (Craig and Dvorak, 1966) and one in naked babies (Hey and Katz, 1970), but structural and sufficient data is lacking.

One of the major issues concerning determination of the human TNZ is the great thermal mass of the human body. Hypothetically, in order to determine the metabolic rate characteristic for a specific ambient temperature, an individual would have to remain in that particular ambient condition until thermal equilibrium is achieved. However, in order to test a wide range of ambient temperatures (e.g. 18–42 °C), a person would have to remain in a resting and fasted state for many hours, which is extremely time consuming and practically very difficult. Using the example of a range from 18 °C to 42 °C, assuming one measurement day per tested temperature would be needed, a total of 24 measurement days per subject would be required to assess the entire temperature range. Additionally, circadian physiological changes, such as increasing and decreasing core temperature during the course of the day, might affect energy expenditure, which would further complicate the procedure. Consequently, in order to bypass these practical issues, we explored a dynamic approach to test the human TNZ, consisting of two temperature ramp protocols as described in the methods section above (2.1.1).

In the literature, the metabolic TNZ for males in air has been suggested to range between 28 and 32 °C, as mentioned earlier (Hardy and DuBois, 1937, 1938). Hill et al. (2013) has reported a lower LCT of 26–27 °C for naked humans. Furthermore, a study using a biophysical model has suggested that the steady state human TNZ might even span from 26 °C to 33 °C (Kingma et al., 2014). However, the ranges listed above are from experiments that were conducted with a very limited number of subjects and were not all specifically designed to uncover the human TNZ. Importantly, sex has been suggested to have a significant influence on both LCT and UCT, considering the fact that females are more susceptible to heat loss due to a larger surface to mass ratio and also have a lower metabolic rate (up to −35%) (Byrne et al., 2005). Hence, the female TNZ, or at least the LCT, might be shifted to higher ambient temperatures. Apart from sex, also body composition and age are strong determinants for the width and positioning of the individual TNZ (Kingma et al., 2012).

4.1.1. LCT

As for the LCT, the applied protocol indeed allowed for the evaluation and calculation of the critical inflection points of metabolic rate during decreasing temperatures (Table 2). For 1 out of 8 participants, metabolic rate did not increase and it was therefore not possible to determine an LCT, neither before nor after PMHA for this particular participant (Table 2, Fig. 4D).

The great majority of LCTs measured in the present study were situated at considerably lower temperatures than those reported in the literature (Table 2). All but 2 calculated LCTs, for both pre- and post-PMHA, were lower than 26 °C (group average: 23.3 ± 3.2 °C before and 23.4 ± 2.0 °C after acclimation). Possible explanations might, on

the one hand, lie in the insulation of underwear (0.05clo) and the stretcher (0.15clo) used during the ramp protocols. The estimated insulation value for underwear and stretcher together approximates 0.2clo, which might lower the anticipated LCT by as much as 3 °C.

On the other hand, the dynamic nature of our protocols might have, to some extent, caused the low LCT values in this study. During the ramps, temperature drifted with approximately 10 K/h. During static exposure to a certain low temperature, heat loss may be higher than heat production, which, over time, might results in extra heat production by NST or ST. The relatively short time span spent in one specific temperature due to the temperature ramp, therefore, assumedly shifts this metabolic increase to lower temperatures. In other words, the body might not face the same amount of heat loss when a specific ambient temperature is reached during the dynamic protocol as under static conditions at the same ambient temperature. In conclusion, the LCTs obtained in the present study must be considered as 'dynamic metabolic LCTs', as they might differ from hypothetical static values. The benefit of a dynamic protocol for the assessment of the human TNZ is, however, that it is relatively easy to implement (compared to tedious static protocols) and it may, moreover, be a more realistic approach for the comparison with every-day life situation, which often are *not* static. For scientific purposes, characterisation of subjects and environments, and for comparisons between studies, standardisation of such dynamic protocols are desirable.

4.1.2. UCT

Interestingly, as opposed to the clearly observable LCTs, the increase of metabolic rate was much less pronounced or even completely absent during warming. Several participants exhibited a slight gradual increase of metabolic rate (for example Fig. 4B (pre and post), but for other participants, the metabolic rate was not affected by the increasing ambient temperatures (for example Fig. 4A and D). Hence, using the calculation methods applied in this study, it was only possible to quantify one complete set of UCTs before and after PMHA (Table 2, Fig. 4B) and for one more participant after PMHA only (Table 2, Fig. 4E).

When considering the difference between humans and non-primate mammals, the latter only have eccrine sweat glands (the type of sweat glands primarily involved in thermoregulation) on their hand palms and foot soles (with only very few exceptions, for example horses). Therefore, their capacity for active evaporative water loss through sweating is much smaller than those for humans, considering the fact that humans have eccrine sweat glands spread over the greatest part of their skin surface (Gordon, 1993, 2012). Non-primate mammals, however, can still employ other mechanisms to actively wet the surface of their skin for cooling purposes, such as grooming moisture on the skin or panting. However, these behavioural activities inevitably affect the metabolic rate, which is why they also play a role for the metabolic UCT. On the contrary, as already mentioned in the introduction, the human evaporative UCT is predominately determined by active sweating and not by other behavioural (metabolically costly) strategies for active evaporative water loss as engaged by, for example, mice and rats.

Which mechanisms actually cause the metabolic increase in those humans that show a slight increase of metabolic rate during warming (which is much less pronounced when compared with the distinct inflection of metabolic rate at the LCT) is not completely understood. As sweating is a largely energy-neutral process, it can be concluded that sweating is not likely to influence the metabolic response to increasing ambient temperatures. Possibly, a combination of increased heart- and ventilation rate due to increasing ambient temperatures partly accounts for the increase of energy expenditure in humans. Heart rate indeed increased significantly during warming in this experiment (Fig. 6), but breath rate was not measured. Another possible factor of influence for the gradual and slow increase of energy expenditure during warming might be found in the Q10 effect. According to the Arrhenius law, a 1 °C change in mean body temperature might account for an increase of the energy expenditure of as much as 8% (assuming Q10-factor = 2.3) (Fiala et al., 1999). Hence, if observed, the increase of energy expenditure during warming might have been due to a combination of several factors, but the exact magnitude and mechanism of the energy expenditure increase remains uncertain.

It might therefore be concluded that the human (dynamic) LCT can be defined based on metabolic rate, whereas the human UCT should not be assessed based on energy metabolism, but by the evaluation of both the evaporative and metabolic UCT.

4.1.3. Individual variation of the LCT

Our data suggests that despite the relatively narrow inclusion criteria and comparable participant characteristics in the present study, metabolic responses to both decreasing and increasing temperatures varied greatly between the individuals. The latter suggests that parameters other than body size, age, gender and acclimation are very likely to influence the individual TNZ, for example thermoregulatory capacity of the individual. One could speculate that there might be, on the one hand, the more 'insulative type', reacting predominantly with vasoconstriction and blood redistribution when exposed to cold, and there might also be the 'metabolic type', reacting with more pronounced/earlier increase of (non-)shivering thermogenesis (van Marken Lichtenbelt et al., 2002). Other than that, also psychological factors (e.g. positive or negative emotions (McFarland, 1985; Ziegler and Cash, 1938) might play a modifying role. The fact that no significant correlations could be obtained between the calculated LCTs and demographic characteristics such as height, weight, BMI, %body fat and fat mass supports the assumptions mentioned above. Future studies should try to elucidate which other parameters can affect the human TNZ, and to what extent.

4.1.4. Passive mild heat acclimation and the human TNZ

Other than previously shown in hamsters and suggested in the literature (Kingma et al., 2012; Zhao et al., 2014), passive acclimation to mild heat did not affect the critical temperatures (LCTs) observed in the present study. Although LCTs remained unaffected, typical physiological adjustments to regular heat exposure were evident: core temperature and proximal skin temperatures decreased whereas distal skin temperature increased. Together, these adjustments are beneficial for increased heat loss to the environment. Despite the fact that metabolic changes did not occur, heat acclimation has been shown to affect evaporative heat loss (i.e. water loss, (Pallubinsky et al., 2017)), and thus might potentially shift the evaporative UCT. The latter has, as previously mentioned, not been assessed in the present research, but should be incorporated in future human TNZ studies. Moreover, more prolonged acclimation to heat or cold might still lead to significant shifts of the human (metabolic) critical temperatures and should also be addressed in future research.

4.2. Limitations

It was not possible to detect critical temperatures for all participants, which was due to one or more of the following reasons: Firstly, we encountered a technical problem with the air conditioning in our respiration chamber in three cases, which is why the data of the DOWN protocol of these three participants had to be excluded from analysis. Secondly, the ambient temperatures applied during the temperature ramps were, at least in some cases not extreme enough to induce a metabolic response. It remains unclear whether there is a measurable increase of the metabolic rate at even higher ambient temperatures. With respect to future studies of the human TNZ, it is essential to ensure that the applied temperature protocols are sufficiently broad to allow for an assessment of the full metabolic response for all individuals. Moreover, the present study only assessed the metabolic responses to dynamic thermal conditions in young healthy men, which might not

reflect thermal responses of other individuals, for example, women and elderly people.

4.3. Future perspectives

In order to adequately measure the TNZ, future studies should also incorporate a measure of evaporative water loss, additionally to the assessment of energy expenditure, for the identification of the evaporative UCT. Moreover, in order to adequately measure the full metabolic as well as evaporative response, future studies should attune the protocol to each individual, as such that for every measured participant, the critical temperatures (LCT and UCT, metabolic and evaporative) are reached and thus made identifiable. Moreover, next to heart rate, also breath rate should be assessed to investigate their involvement in the metabolic response to increasing ambient temperatures. Additionally, a slower increase of the ambient temperature should be tested to evaluate the influence of the temperature slope (i.e. the effect of time in the respective ambient condition) on the metabolic response as well as the width and positioning of the human TNZ.

Future research is needed to gather important yet unavailable information on the TNZ of women, and, for example, older age groups and obese persons or patients with type 2 diabetes mellitus (T2DM). The latter is of great significance as an increasing proportion of the World population suffers from obesity and metabolic diseases such as T2DM. Presumably, these conditions influence the range and position of the TNZ, due to, for example, altered thermophysiology and changes of body composition.

4.4. Conclusion

The results of the present study show that the generally assumed LCT of approximately 28 °C, which has earlier been indicated in the literature, does not match with the dynamically assessed LCTs in this study, as those were considerably lower in most cases. PMHA did not significantly change the positioning of the LCT, indicating that the relatively mild and passive acclimation to heat does not affect energy metabolism. Substantial individual variation of the positioning of the dynamic LCT was evident between the participants, both before and after PMHA. The latter could not solely be explained by age or body composition, as these parameters did not correlate with the obtained LCTs.

As for the measured metabolic UCT, a distinct inflection point was not evident for the great majority of participants.

In conclusion, the applied dynamic method allowed for the determination of individual dynamic LCTs, however, distinct inflection points of the metabolic rate in increasing temperature were absent in most cases. Suggestions for protocol adjustments for the determination of the dynamic metabolic and evaporative UCT are discussed.

Acknowledgements

The authors would like to express their gratitude to P. Schoffelen and L. Wouters for their technical assistance. Furthermore, they would like to thank Dr. J. van Schijndel of Eindhoven University of Technology as well as Prof. Dr. G. Havenith for their help and fruitful discussions with respect to the analysis methods of the critical temperatures. Moreover, Dr. B. Kingma is acknowledged for the valuable discussions on the analyses and obtained data. Appreciation is also expressed to the subjects who participated in the experiments. This study was supported by the Netherlands Enterprise Agency (Rijksdienst voor Ondernemend Nederland, RVO), formerly known as Agentschap NL (EOS-LT 10033 INTEWON and TKI EnerGO UCER).

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

References

AECOM, 2012. Investigation into Overheating of Homes: Literature Review. Department for Communities and Local Government, London.
Aujard, F., Vasseur, F., 2001. Effect of ambient temperature on the body temperature rhythm of male gray mouse lemurs (Microcebus murinus). Int. J. Primatol. 22, 43–56.
Brown, J.H., Gillooly, J.F., Allen, A.P., Savage, V.M., West, G.B., 2004. Toward a metabolic theory of ecology. Ecology 85, 1771–1789.
Byrne, N.M., Hills, A.P., Hunter, G.R., Weinsier, R.L., Schutz, Y., 2005. Metabolic equivalent: one size does not fit all. J. Appl. Physiol. 99, 1112–1119.
Craig Jr., A.B., Dvorak, M., 1966. Thermal regulation during water immersion. J. Appl. Physiol. 21, 1577–1585.
EEA, E.E.A., 2015. European Briefings: Climate Change Impacts and Adaptation, SOER 2015. European Environment Agency.
Fiala, D., Lomas, K.J., Stohrer, M., 1999. A computer model of human thermoregulation for a wide range of environmental conditions: the passive system. J. Appl. Physiol. 87, 1957–1972.
Frich, P., Alexander, L.V., Della-Marta, P., Gleason, B., Haylock, M., Tank, A.M.G.K., Peterson, T., 2002. Observed coherent changes in climatic extremes during the second half of the twentieth century. Clim. Res. 19, 193–212.
Gordon, C.J., 1990. Thermal biology of the laboratory rat. Physiol. Behav. 47, 963–991.
Gordon, C.J., 1993. Temperature Regulation in Laboratory Rodents. Cambridge University Press.
Gordon, C.J., 2012. Thermal physiology of laboratory mice: defining thermoneutrality. J. Therm. Biol. 37, 654–685.
Hanssen, M.J.W., Hoeks, J., Brans, B., van der Lans, A.A.J.J., Schaart, G., van den Driessche, J.J., Jorgensen, J.A., Boekschoten, M.V., Hesselink, M.K.C., Havekes, B., Kersten, S., Mottaghy, F.M., Lichtenbelt, W.D.V., Schrauwen, P., 2015. Short-term cold acclimation improves insulin sensitivity in patients with type 2 diabetes mellitus. Nat. Med. 21, 863–865.
Hardy, J.D., DuBois, E.F., 1937. Regulation of heat loss from the human body. Proc. Natl. Acad. Sci. USA 23, 624–631.
Hardy, J.D., DuBois, E.F., 1938. Basal metabolism, radiation, convection and vaporization at temperatures of 22 to 35°C. J. Nutr. 15, 477–497.
Hardy, J.D., DuBois, E.F., 1940. Differences between men and women in their response to heat and cold. Physiology 26, 389–398.
Hensel, H., 1981. Thermoreception and Temperature Regulation. Academic Press Inc Ltd, London.
Hey, E.N., Katz, G., 1970. The optimum thermal environment for naked babies. Arch. Dis. Childhood 45, 328–334.
Hill, R.W., Muhich, T.E., Humphries, M.M., 2013. City-scale expansion of human thermoregulatory costs. PLoS One 8, e76238.
ISO, 2001. Ergonomics of the Thermal Environment - Instruments for Measuring Physical Quantities. International Standards Organization, Geneva (ISO 7726:2001).
IUPS, 2001. Glossary of terms for thermal physiology. Jpn J. Physiol. 51.
Jessen, C., 2001. Temperature Regulation in Humans and Other Mammals. Springer, Berlin; New York.
Johnson, F., Mavrogianni, A., Ucci, M., Vidal-Puig, A., Wardle, J., 2011. Could increased time spent in a thermal comfort zone contribute to population increases in obesity? Obes. Rev. 12, 543–551.
Kingma, B., 2012. Human Thermoregulation - A Synergy Between Physiology and Mathematical Modelling. NUTRIM School for Nutrition, Toxicology and Metabolism. Maastricht University, Maastricht.
Kingma, B.R.M., Frijns, A.J.H., Schellen, L., van Marken Lichtenbelt, W.D., 2014. Beyond the classic thermoneutral zone: including thermal comfort. Temperature 1, 10–17.
Kingma, B.R.M., Frijns, A.J.H., van Marken Lichtenbelt, W.D., 2012. The thermoneutral zone: implications for metabolic studies. Front. Biosci. 4, 1975–1985.
McCullough, E.A., Jones, B.W., Tamura, T.A., 1989. A database for determining the evaporative resistance of clothing. ASHRAE Trans. 95.
McFarland, R.A., 1985. Relationship of skin temperature changes to the emotions accompanying music. Biofeedback Self Regul. 10, 255–267.
Meehl, G.A., Tebaldi, C., 2004. More intense, more frequent, and longer lasting heat waves in the 21st century. Science 305, 994–997.
Mekjavic, I.B., Sundberg, C.J., Linnarsson, D., 1991. Core temperature "null zone". J. Appl. Physiol. 71, 1289–1295.
Ouellet, V., Labbe, S.M., Blondin, D.P., Phoenix, S., Guerin, B., Haman, F., Turcotte, E.E., Richard, D., Carpentier, A.C., 2012. Brown adipose tissue oxidative metabolism contributes to energy expenditure during acute cold exposure in humans. J. Clin. Investig. 122, 545–552.
Pallubinsky, H., Schellen, L., Kingma, B.R.M., Dautzenberg, B., van Baak, M.A., van Marken Lichtenbelt, W.D., 2017. Thermophysiological adaptations to passive mild heat acclimation. Temperature 4, 176–186.
Romanovsky, A.A., Ivanov, A.I., Shimansky, Y.P., 2002. Selected contribution: ambient temperature for experiments in rats: a new method for determining the zone of thermal neutrality. J. Appl. Physiol. 92, 2667–2679.
Schär, C., Vidale, P.L., Lüthi, D., Frei, C., Häberli, C., Liniger, M.A., Appenzeller, C., 2004. The role of increasing temperature variability in European summer heatwaves. Nature 427, 332–336.
Schellen, L., Loomans, M.G., de Wit, M.H., Olesen, B.W., van Marken Lichtenbelt, W.D., 2012. The influence of local effects on thermal sensation under non-uniform environmental conditions–gender differences in thermophysiology, thermal comfort and productivity during convective and radiant cooling. Physiol. Behav. 107, 252–261.
Schlader, Z.J., 2014. The human thermoneutral and thermal comfort zones: thermal comfort in your own skin blood flow. Temperature.

Scholander, P.F., Hock, R., Walters, V., Irving, L., 1950a. Adaptation to cold in arctic and tropical mammals and birds in relation to body temperature, insulation, and basal metabolic rate. Biol. Bull. 99, 259–271.
Scholander, P.F., Hock, R., Walters, V., Johnson, F., Irving, L., 1950b. Heat regulation in some arctic and tropical mammals and birds. Biol. Bull. 99, 237–258.
Speakman, J.R., 2013. Measuring energy metabolism in the mouse - theoretical, practical, and analytical considerations. Front. Physiol. 4, 34.
van der Lans, A.A., Hoeks, J., Brans, B., Vijgen, G.H., Visser, M.G., Vosselman, M.J., Hansen, J., Jorgensen, J.A., Wu, J., Mottaghy, F.M., Schrauwen, P., van Marken Lichtenbelt, W.D., 2013. Cold acclimation recruits human brown fat and increases nonshivering thermogenesis. J. Clin. Investig. 123, 3395–3403.
van Marken Lichtenbelt, W., Hanssen, M., Pallubinsky, H., Kingma, B., Schellen, L., 2017. Healthy excursions outside the thermal comfort zone. Build. Res. Inf. 1–9.
van Marken Lichtenbelt, W.D., Kingma, B.R.M., 2013. Building and occupant energetics: a physiological hypothesis. Archit. Sci. Rev.
van Marken Lichtenbelt, W.D., Schrauwen, P., Van De Kerckhove, S.V., Westerterp-Plantenga, M.S., 2002. Individual variation in body temperature and energy expenditure in response to mild cold. Am. J. Physiol.-Endoc M 282, E1077–E1083.
Weir, Jd.V., 1949. New methods for calculating metabolic rate with special reference to protein metabolism. J. Physiol. 109, 1.
Yoneshiro, T., Aita, S., Matsushita, M., Kameya, T., Nakada, K., Kawai, Y., Saito, M., 2011. Brown adipose tissue, whole-body energy expenditure, and thermogenesis in healthy adult men. Obesity 19, 13–16.
Zhao, Z.-J., Chi, Q.-S., Liu, Q.-S., Zheng, W.-H., Liu, J.-S., Wang, D.-H., 2014. The shift of thermoneutral zone in striped hamster acclimated to different temperatures. PLoS One 9, 1932–6203.
Ziegler, L.H., Cash, P.T., 1938. A study of the influence of emotions and affects on the surface temperature of the human body. Am. J. Psychiatry 95, 677–696.

Hannah Pallubinsky is a Postdoctoral researcher at the Department of Nutrition and Movement Sciences, Maastricht University, the Netherlands. She holds a Ph.D. in Health Sciences. Her research focuses on human thermoregulation and thermophysiology, with special interest in heat adaptation and the interaction between environmental parameters, thermal comfort, and health.

Lisje Schellen is head of the Department of Built Environment and Infrastructure of Gilde Opleidingen, Roermond, NL. She holds a Ph.D. in Building Physics. Her research focuses on human thermophysiology, thermal comfort and human performance in relation to the indoor environment.

Wouter D. van Marken Lichtenbelt is professor of Ecological Energetics and Health at the Department of Nutrition and Movement Sciences, Maastricht University, the Netherlands. Here, he leads the research group of Thermoregulation and Metabolism. His research focuses on the effects of environmental conditions, such as (indoor) temperature, light and nutrition on physiological processes and health.