Journal of Thermal Biology 121 (2024) 103826

Contents lists available at ScienceDirect

Journal of Thermal Biology

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

Confounding factors in peripheral thermal recovery time after active cooling

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ARTICLE INFO

Keywords:
Thermal imaging
Thermoregulation
Dynamic imaging
Thermal recovery
Age
Sex

ABSTRACT

Objectives: The effectiveness of normal physiological thermoregulation complicates differentiation between pathologic changes in medical thermography associated with peripheral artery disease and a number of other clinical conditions. In this study we investigate a number of potential confounding factors to the thermal recovery rate after active limb cooling, with the main focus on age and sex.

Approach: The source data consists of 53 healthy individuals with no diagnosed cardiovascular disease or reported symptoms and with a mean age of 38.4 ($\pm$ 12.1) years. The sample population was further divided into male (N = 14) and female groups (N = 39). The thermal recovery time was measured using two thermal cameras from both lower limbs on plantar and dorsal sides. The active cooling was achieved using moldable cold pads placed on the plantar and dorsal side of the lower limb. The recovery was measured until the temperature had reached a stable level. The recovery time was determined from an exponential fit to the measured data.

Results: The correlation between the thermal recovery time constant and age varied from low to moderate linear correlation ($0.31 \leq \rho \leq 70$), depending on the inspected region of interest, with a higher statistically significant correlation in the medial regions. The contralateral limb temperature differences or the thermal time constants did not have statistically significant differences between the male and female sexes. Further, the secondary metrics such as participant's body mass, body-mass index, or systolic blood pressure had low or no correlation with the thermal recovery time in the study group.

Conclusion: The thermal recovery time constant after active cooling appears as a relatively independent metric from the majority of the measured potential confounding factors. Age should be accounted for when performing thermal recovery measurements. However, dynamic thermal imaging and its methodologies require further research and exploration.

1. Introduction

Thermal imaging (TI) has become increasingly popular in medical research and in clinical practice adaptations due to high sensitivity to small temperature differences with high spatial and temporal resolution. While measurement of absolute temperatures from traditional TI has been a popular and convenient method in clinical research, its predictive power may have reached its limit due to high inter-individual variation and lack of classification constraints (Ilo et al., 2020; Kontos et al., 2011; Zaproudina et al., 2011; Zaproudina et al., 2008). Therefore, there is a need for more research on dynamic TI (DTI) approaches and investigation of the underlying physiological principles and their relation to thermal behavior. The late advances in thermal imaging technology, especially for affordable microbolometer-based thermal imaging have introduced DTI as a new perspective in the field of medical imaging, where the target temperature is recorded and analyzed in a spatiotemporal manner, instead of solely individual images (Kaczmarek and Nowakowski, 2016; Soliz et al., 2017; Sagaidachnyi et al., 2016; Geyer et al., 2004). DTI also allows the analysis of thermal changes due to physiological or interventional processes in real-time, whereas traditional TI is fundamentally tied to steady-state measurements or dynamic measurements with low temporal resolution. Overall, thermal imaging is a relatively new method in clinical practice in comparison to the long history behind the technology (Lahiri et al., 2012). Additionally, the thermal variance is especially large in peripheral body parts due to the

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https://doi.org/10.1016/j.jtherbio.2024.103826
Received 27 October 2023; Received in revised form 22 January 2024; Accepted 19 February 2024
Available online 7 March 2024
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Abbreviations

PAD	Peripheral Artery Disease
CLTI	Chronic Limb Ischemia
TBI	Toe-Brachial Index
ABI	Ankle-Brachial Index

Nomenclature

t	Time (s)
T_0	Initial temperature ($^\circ C$)
$T(t)$	Temperature with respect to time ($^\circ C$)
τ	Time constant (s)
A	Thermal recovery scaling constant ($^\circ C/s$)
ρ	Pearson rho correlation coefficient
$RMSE$	Root-mean squared difference (goodness-of-fit)
ΔT	Temperature difference due to active cooling

effective heat regulation of the body, and as a consequence of a large number of confounding factors (Sagaidachnyi et al., 2016; Yanovich et al., 2020; Pakarinen et al., 2023). In order to investigate the clinical importance of thermal behavior in a certain frame of reference, such factors must be identified, and minimized or compensated.

Despite the complexity of the peripheral thermal metabolism, an increasing number of publications considering both, traditional TI and DTI are focusing on peripheral artery disease (PAD) (Bagavathiappan, et al., 2009; Zenunaj et al., 2021; Huang et al., 2015) and its complications, such as lower limb ulceration (Khosa et al., 2023; Aliahmad et al., 2019) and chronic limb threatening ischemia (Pakarinen et al., 2023). However, a number of recent studies have reported concerns about the quality of current medical TI research. For instance, a systematic review by Piva et al., in 2022 (Piva, et al., 2022) reported concerns, such as low sample sizes and disparity between measurement locations, measurement equipment and analysis protocols. Although the differences within the field are largely understandable since TI utilization in PAD diagnostics and its complications are still under novel research, the environmental standardization and minimization of the confounding factors tends to be insufficient. In this paper, we focus on two such factors, i.e. the effect of age and sex in temperature modulated dynamic TI, aiming to gradually unravel the problem.

Previous research has identified that active cooling and alterations in the subsequent thermal recovery could potentially serve as an indicator of an underlying medical condition (Merla et al., 2000; Strzelecki et al., 2017). In 2008, Bharara et al. (Bharara et al., 2008) studied the possible difference between diabetic patients with and without accompanying neuropathy, finding a significant difference between the recovery temperature difference at a 10-minute point in time after active cooling. In our previous pilot study, we found moderate to high negative correlation with the exponential recovery time constant and clinically used metrics, i.e. Toe-Brachial Index (TBI) and Ankle-Brachial Index (ABI) (Pakarinen et al., 2023). Even Though the recovery time constant is not a direct measure of any regulatory function, it provides secondary information about peripheral blood flow during the recovery period. We also concluded that the alternative DTI method, the hydrostatic modulation test did not seem to have significant effect on peripheral thermal behavior. However, the sample size in this pilot research was small, thus further research in this methodology is also required. As pointed out in (Strzelecki et al., 2017) and in our previous research, there are a number of unclear factors affecting the validity of the measurement, which must be considered. The correlation between thermal recovery time and age has not been extensively studied, though recent research by (Lahiri et al., 2012; Lahiri et al., 2020) found a strong correlation between age and inversion time, similar to the methodology in our research. Another potential confounding factor in thermal regulation is the biological sex, which affects thermoregulation through a number of mechanisms such as hormonal regulation (Yanovich et al., 2020; Marriott and Carlson, 1996), though the for peripheral recovery is unclear. Our goal in this study is to explore the effect of age, sex, and a number of secondary confounding factors on peripheral thermal recovery after active cooling in healthy study participants with no history of cardiovascular disease or symptoms. Establishing the connection, or the lack thereof, may help in the future to compensate for these factors in thermal DTI research.

2. Methods

2.1. Study participants

The study has been approved by Tampere University Hospital (TAUH) ethical committee (R19075L) and by the National Competent Authority, FIMEA (2020/001201). The data collection was conducted at the Centre of Vascular Surgery and Interventional Radiology at Tampere University Hospital. Measurements were collected from 53 healthy

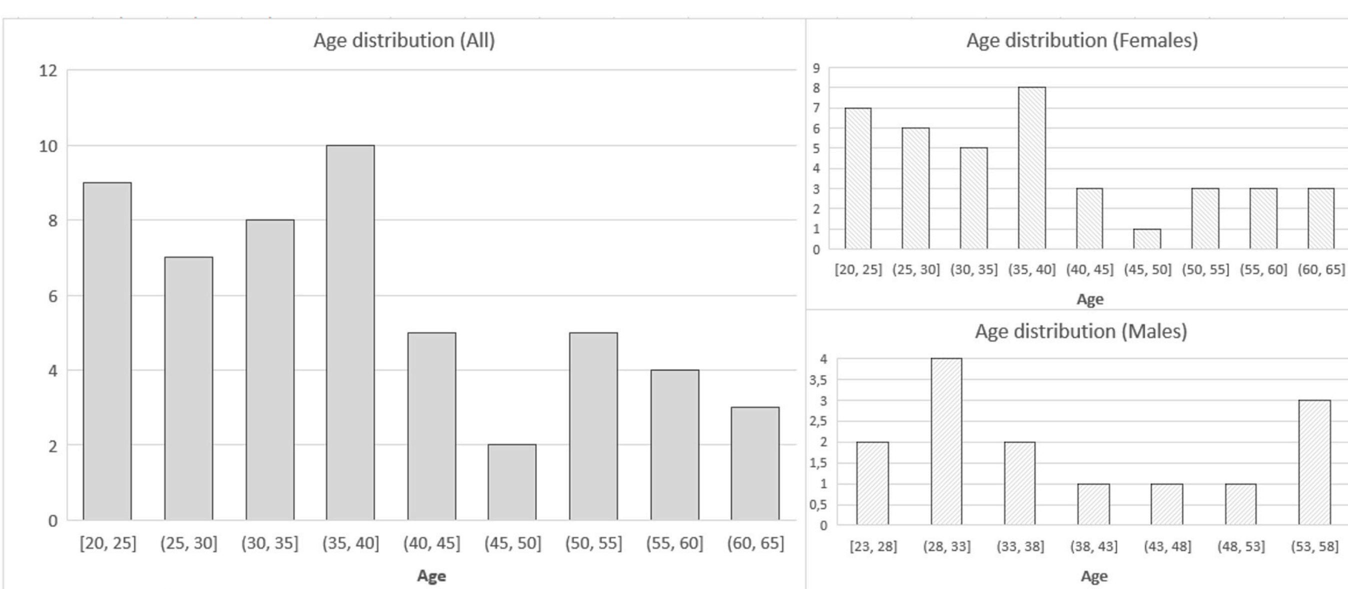

Fig. 1. Study participant age distribution.

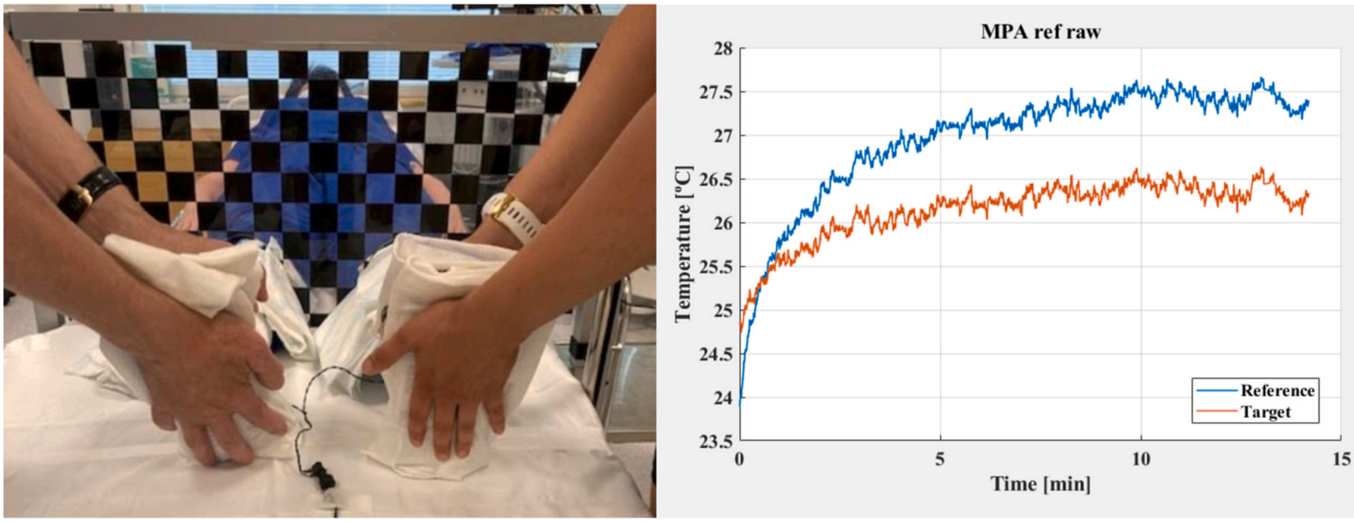

Fig. 2. Left: Cooling of the lower limbs with moldable and cooled gel pads of approximately 4 °C temperature. Right: An example measurement from a desired recovery curve obtained from bilateral measurement, where "reference" refers to the right limb and "target" to the left.

subjects with mean age (std) of 38.4 (12.12) years. The age distributions of the subjects are presented in Fig. 1.

The distribution of sex was 39 females with mean age of 38.1 (12.5) years and 14 males with mean age of 39.4 (10.9) years.

2.2. Measurement and analysis

2.2.1. Measurement setup

The thermal measurements were conducted with two FLIR E8 cameras with noise-equivalent temperature difference (NETD) $<$ 60 mK, absolute accuracy $\pm 2°C$ or 2% from the reading (Teledyne FLIR, Oregon US). The emissivity value was set as 0.98. No further calibrations were performed apart from the manufacturer calibration and the non-uniformity sensor calibration (NUC). Cameras were turned on 15 min prior to each measurement to ensure sensor stability. The cameras were mounted on the plantar and dorsal sides, approximately at 0.5m distance from the lower limbs. However, the camera positions were adjusted for each participant so that the field of view covered both limbs with sufficient margin for movement. The measurements were conducted in a clinical environment with controlled room temperature (24

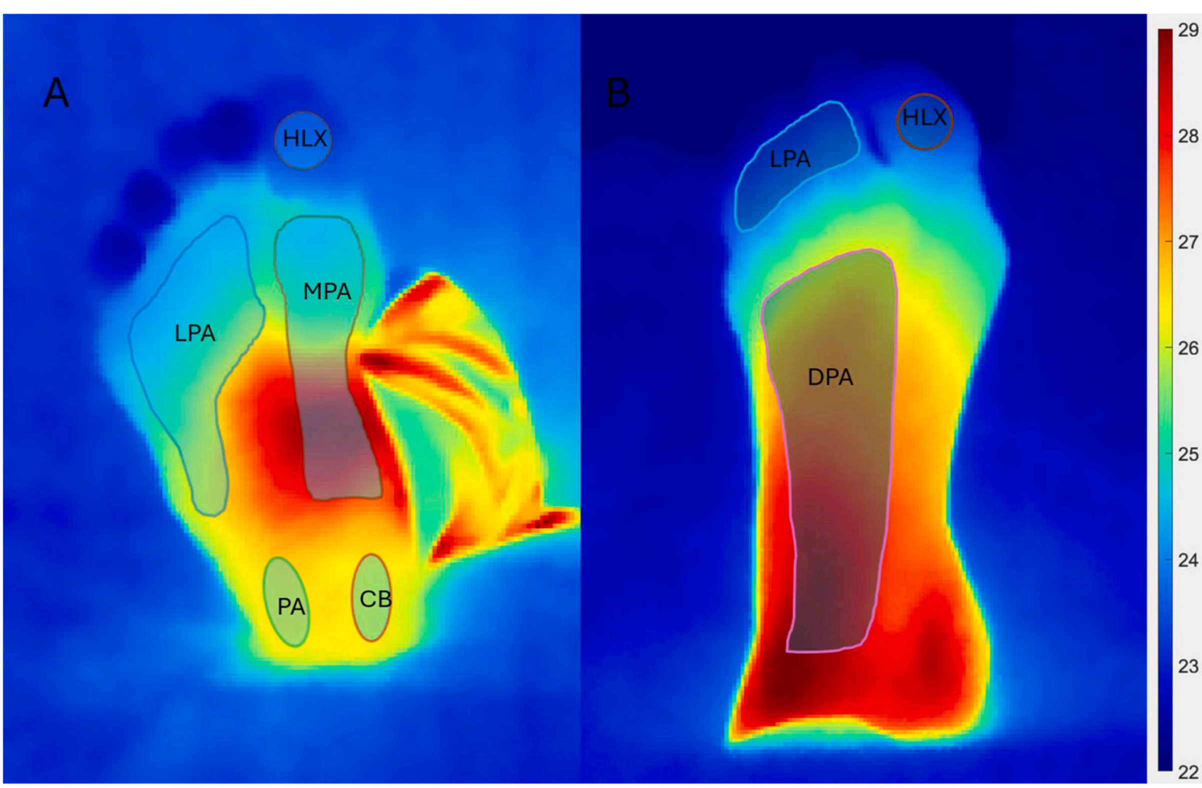

Fig. 3. Lower limb measurement locations, where A) is the plantar side of the limb including medial plantar (MPA), lateral plantar (LPA), calcaneal branch (CB) and posterior tibial (PA) angiosomes. B) is the dorsal side of the lower limb consisting mainly of the dorsalis pedis angiosome (DPA), though the digits (excluding hallux) are supplied via LPA. In addition, hallux was measured as a conjugate angiosome, consisting of MPA and DPA.

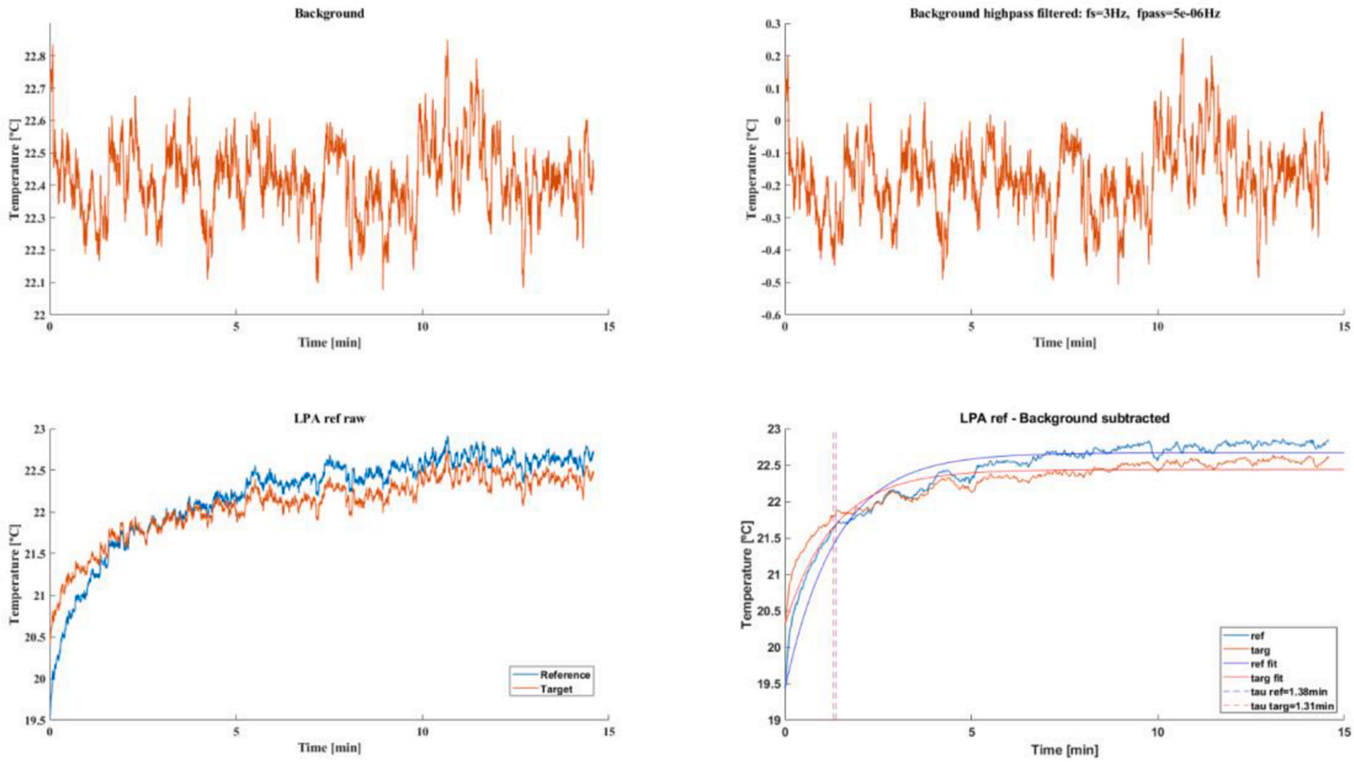

Fig. 4. Background subtraction process to reduce spatially uniform detector noise from the data for the exponential function fitting. In the top row are presented the raw and high-pass filtered background measurements. The bottom row presents a contralateral measurement from the LPA angiosome with and without the background subtraction. The contralateral time constants are determined from the background-subtracted data.

± 1.5 °C). Mean temperatures from each region of interest (ROI) were measured after an 8-min accommodation period, where the study participant stays inactive in a supine position to minimize the thermal contribution from physical activation. The duration of the accommodation period was considered as sufficient, since ABI and TBI were measured prior to the accommodation in the same position, thus the effective accommodation to the study environment with no physical activity was considerably longer. After the accommodation period, both lower limbs were cooled simultaneously from plantar and dorsal sides until a 15% temperature decrease (°C) was achieved in the warmest region of interest. The immediate thermal recovery of the feet was followed with a 9 Hz sampling rate, until the recovery curve had stabilized, i.e. 1 min window average limb temperature does not increase more than 0.5 °C. Fig. 2 presents the cooling phase and the resulting example recovery curve.

2.2.2. Data processing

The recovery curves are a spatial median over the ROI area, which were further averaged in 3 frame intervals to reduce temporal noise. The processed frames were corrected for large motion artifacts and to ensure constant ROI positioning via image registration. Finally, function fitting and thermal time constant determination was conducted using Matlab based software (Pakarinen et al., 2022), utilizing the following the Newtonian heating equation as the fit function.

$$T(t) = T_0 exp(-t/\tau) + A\tau(1 - exp(-t/\tau)) \quad (1)$$

where T(t) is the time dependent temperature, T_0 is the initial temperature after cooling, A is a scaling constant and τ is the time constant and the product $A\tau$ is the recovery temperature. The anatomical ROI areas were delineated within the lower limb angiosomes, based on the angiosome concept (Alexandrescu et al., 2012; Morales-Caporal, 2014; Khor and Price, 2017; Pakarinen et al., 2023), as shown in Fig. 3.

The delineation was performed manually with sufficient area coverage, yet with a clear margin between the evaluated angiosome locations. The acquired angiosome-specific curves were further processed by subtracting the high-pass filtered background from the signal in order to reduce uniform detector noise. The operation is illustrated in Fig. 4.

Finally, least-squares optimization function fitting was performed with the time constant and constant A set as optimization parameters (Pakarinen et al., 2022). Additionally, Goodness-of-fit (GOF) parameters were collected, including the root-mean-squared error (RMSE), which was used contiguously with the temperature difference thresholds to find the dependence between the thermal recovery constant, age, and sex.

2.2.3. Statistical analysis

The statistical analysis was performed using Excel (Microsoft, USA) with a two-sided homoscedastic T-test with a statistical significance threshold of ($p \leq 0.05$), and basic correlation methods, including Pearson-Rho (ρ) correlation coefficient for linear correlation. The linear correlation was determined either as high ($|\rho| \geq 0.70$), high to moderate ($0.70 > |\rho| \geq 0.60$), moderate ($0.60 > |\rho| \geq 0.40$) or low to no correlation ($|\rho| < 0.40$). Additionally, the Pearson Rho correlation and study N were mapped over ΔT, and RMSE with 0.1 °C and 0.02 increments, respectively. The mapping serves multiple purposes; mapping with respect to ΔT indicates the required initial temperature drop in the inspected angiosomes exhibiting statistically significant differences, i.e. finding a threshold value. Mapping of the RMSE serves the purpose of finding a set of data with sufficient fit, i.e. satisfying our hypothesis for the recovery following an exponential form, yet retaining statistically significant N.

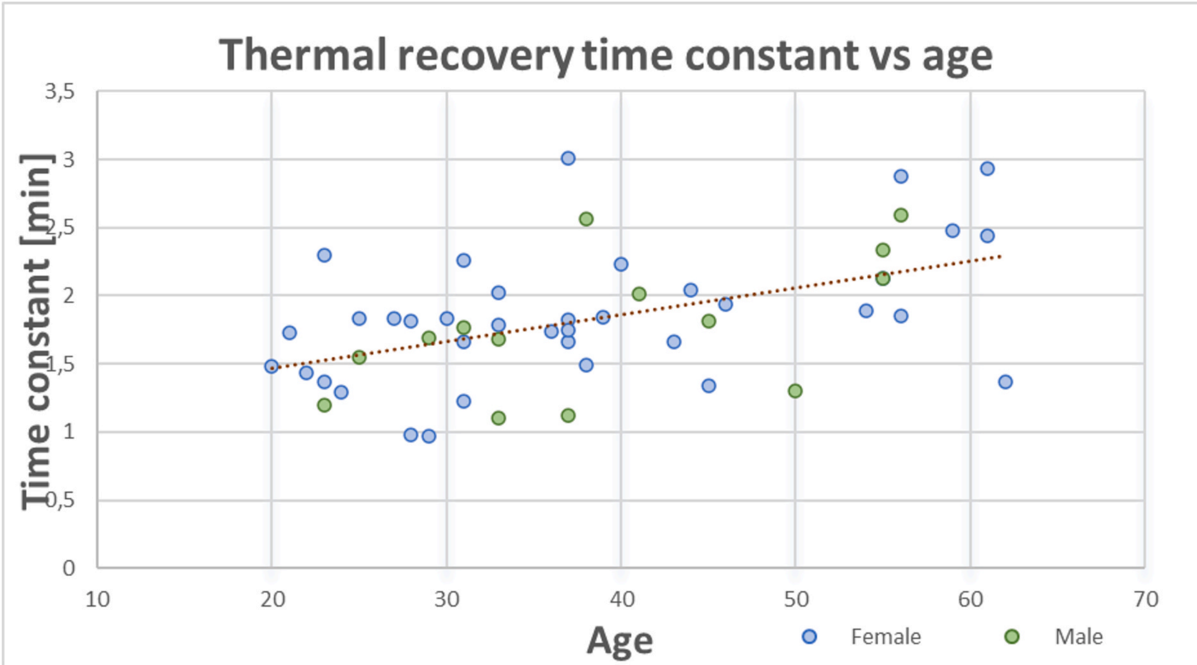

Fig. 5. Correlation between age and all plantar and dorsal angiosomes for each sex with $\rho = 0.49$ ($p < .0001$), indicating a statistically significant moderate linear correlation with N = 51.

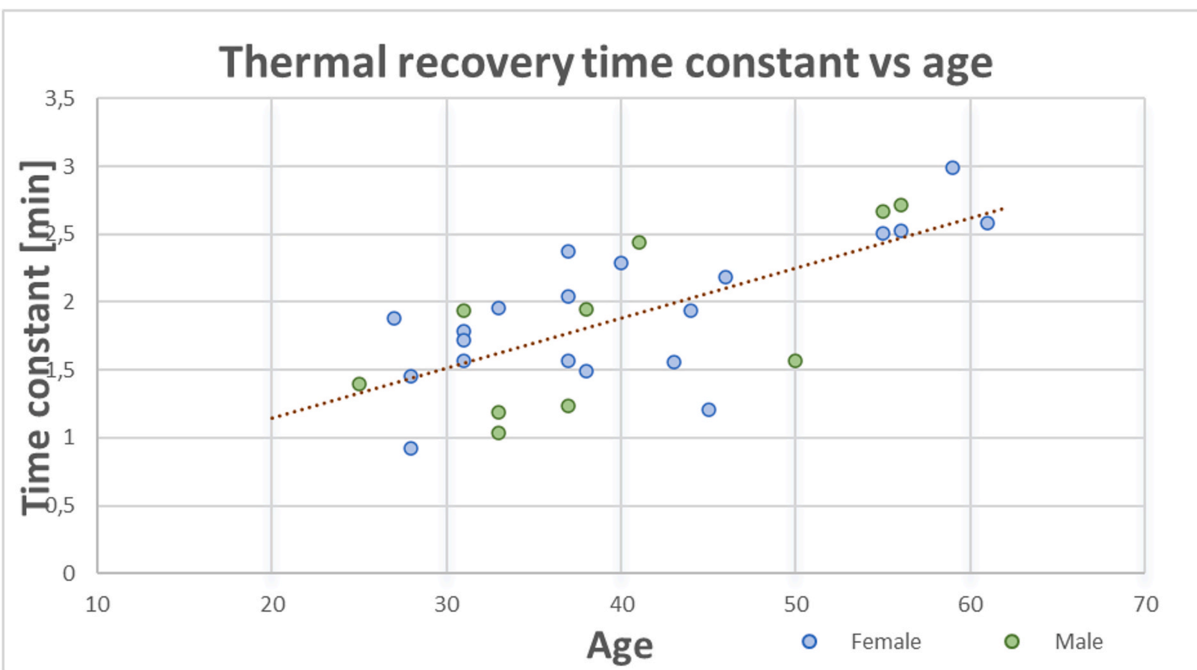

Fig. 6. Age correlation with respect to participant's age in the central MPA angiosome (including hallux). MPA angiosome had the highest correlation with the participant's age with $\rho = 0.70$ ($p < .0001$). The number of samples reduces to 30 with RMSE >0.1 and $\Delta T \geq 1.5$ °C constraints.

3. Results

3.1. Age correlation

The age correlation with lower limb thermal time constant average over all angiosomes is presented in Fig. 5 with bounds RMSE >0.1 and $\Delta T \geq 1.5$ °C, where RMSE ensures the analyzed fit functions having a desired level of agreement with the measurement data. The ΔT constraint is the minimum cooling required for each analyzed angiosome.

It is clear based on Fig. 5 that the variance for the thermal time constant is high. Further inspection of individual angiosomes shows that the inter-individual variance depends on the angiosome combinations in such a way that lateral angiosomes tend to exhibit higher variation in comparison to the central angiosomes. As an example, in Fig. 6 the MPA and the Pearson Rho correlation are presented with the same parameters as above.

As illustrated in Fig. 6, the medial plantar angiosome including

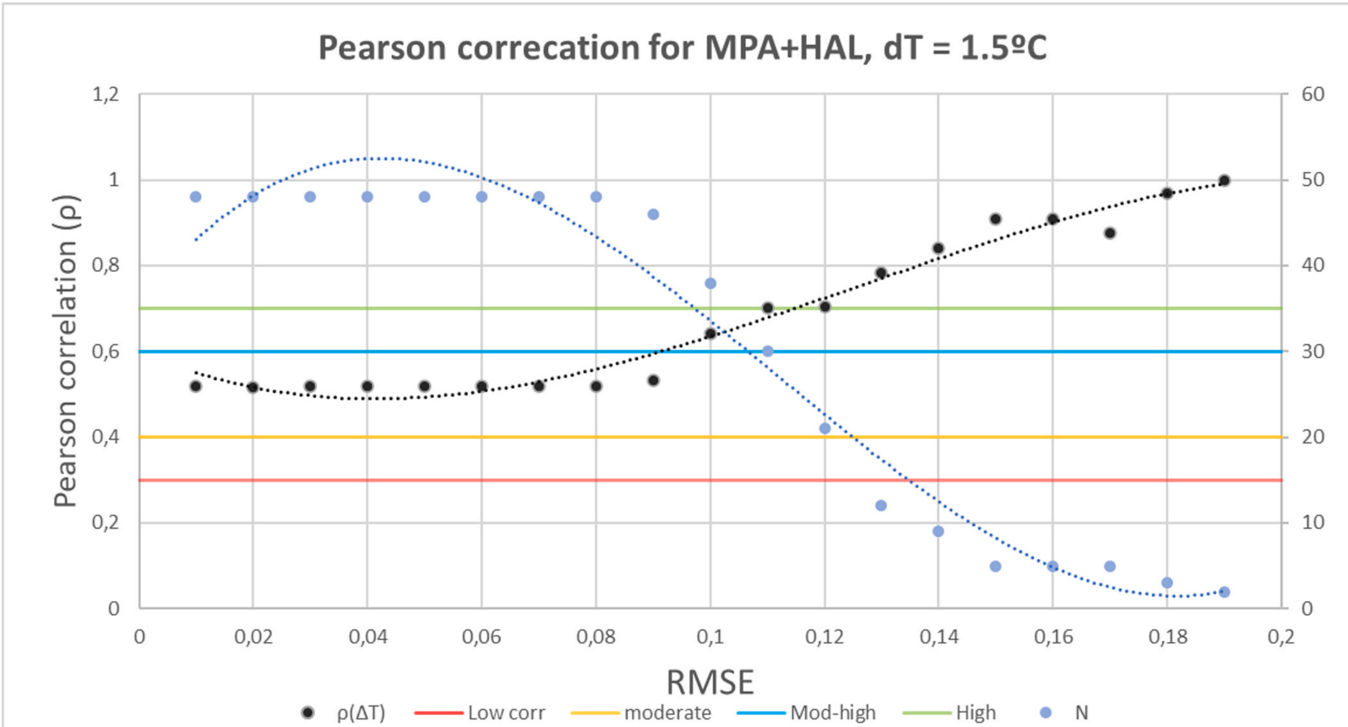

Fig. 7. Correlation of MPA and hallux thermal recovery time constant with age as a function of GOF RMSE. The plot was used to determine the limits for the minimum threshold for function fit with a sufficient number of samples.

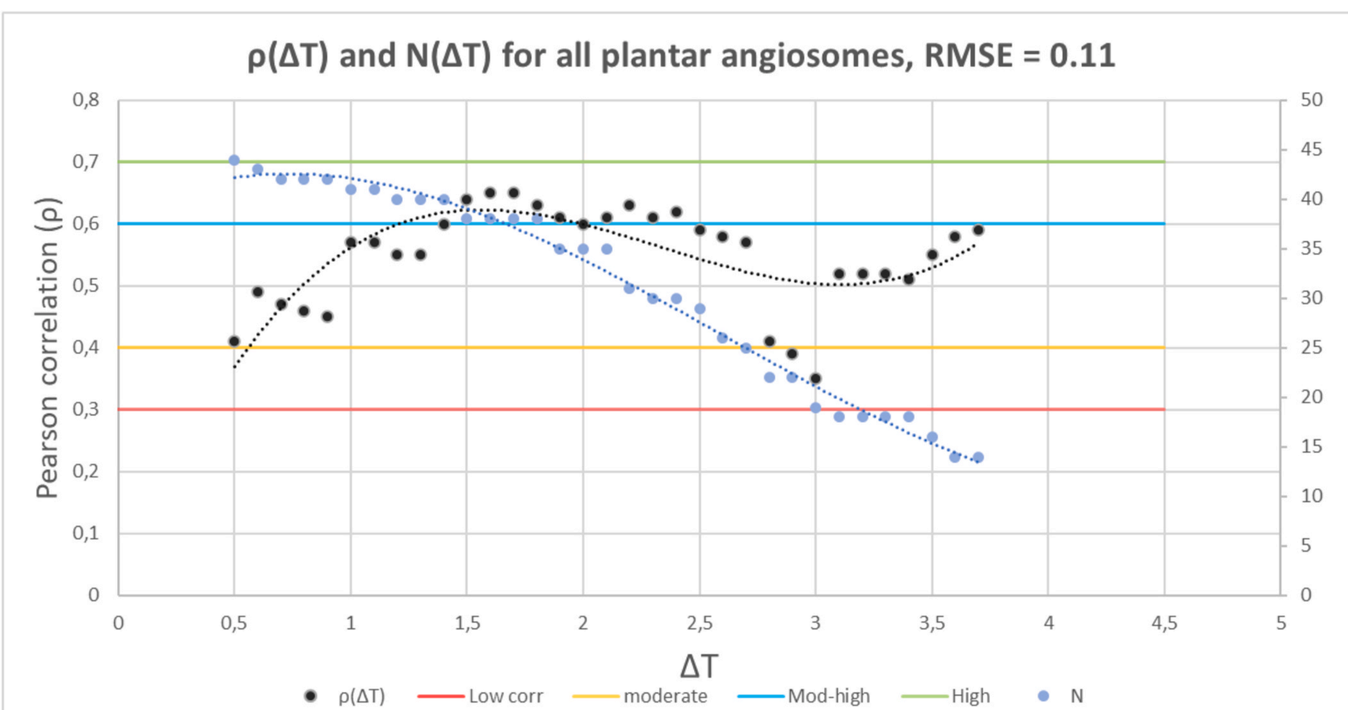

Fig. 8. MPA and hallux recovery correlation with age with respect to induced temperature difference within the angiosomes. The plot indicates that the age correlation disappears with too small temperature differences during cooling, as expected.

hallux presents high correlation with age. However, it is also clear that the test constraints (RMSE and *ΔT)* applied to fewer angiosome combinations (only MPA) reduce the applicable sample size, thus reducing the statistical significance. However, it is important to have sufficient cooling within the angiosome and thus, reliability in time constant determination. Figs. 7 and 8 illustrate how the correlation of the recovery time constant of MPA and hallux angiosome and participant age behaves when RMSE and ΔT constraints are altered, respectively.

Table 1 combines time constants for different angiosome combinations with RMSE 0.10 and ΔT 1.5 °C. The difference in the number of

Table 1
individual angiosome combinations for age correlation.

	ρ	N	p
Plantar angiosomes (averaged)	0.47	47	<.0001
MPA with hallux	0.70	30	<.0001
MPA without hallux	0.53	33	.0015
LPA	0.52	23	.011
CB	0.34	38	.037
PA	0.31	34	.074
Hallux	0.49	22	.021
Dorsal angiosomes (DPA)	0.39	43	.009

samples (*N*) depends on the number of measurements that pass the analysis constraints for the given set of angiosomes.

3.2. Sex correlation

Sex and test parameters were compared using a two-sided *t*-test. The bar plots with standard deviations are presented in Fig. 9.

The deviations in test parameters were high for both groups and no statistically significant differences were found. The results were similar for all angiosome combinations.

A number of secondary metrics were also included in the analysis, including ankle-brachial and toe-brachial indices (ABI, TBI), systolic

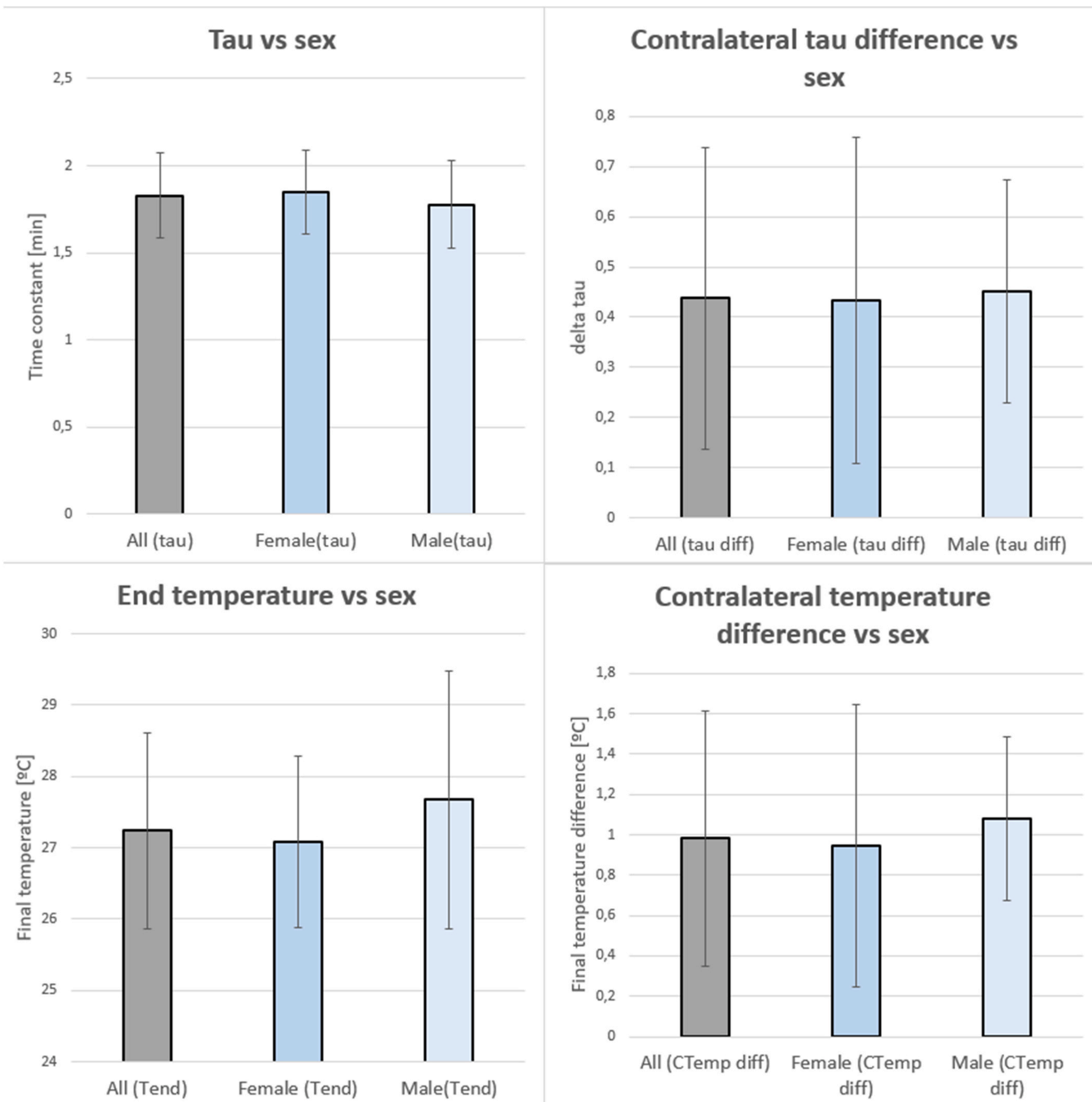

Fig. 9. Distributions of thermal time constant, time constant difference between contralateral angiosomes (top panel), final temperatures after thermal recovery, and contralateral temperature difference between measured angiosomes (bottom panel) for male and female participants. There were no statistically significant differences between the two sexes in any of the parameters with p = .651, p = .921, p = .050, p = .735, respectively.

Table 2
Thermal recovery time (tau) constant correlations between all test parameters over all angiosomes.

	ρ	N	p
τ vs. age	0.49	51	.00026
τ vs. TBI (individual limbs)	−0.15	113	.134
τ vs. TBI (limb average)	−0.08	51	.563
τ vs. Systolic blood pressure	−0.12	51	.039
τ vs. Height	−0.02	51	.874
τ vs. ABI (Individual limbs)	−0.15	113	.134
τ vs. ABI (limb average)	−0.17	51	.233
τ vs. Body mass	−0.35	51	.012
τ vs. Body-mass index	−0.32	51	.024

blood pressure, height, body mass, and BMI. The results of the secondary metrics are presented in Table 2.

As shown in Table 2, the thermal time constant is independent of most test parameters, having a statistically significant, yet only slight negative correlation with respect to body mass and BMI, in addition to the statistically significant moderate correlation with participant age as presented earlier. The exact reason for the opposite direction of the correlation for the secondary metrics and age for this dataset is unclear.

4. Discussion

In this study, we presented our findings considering age and sex as potential confounding factors in medical dynamic thermal imaging. Our research focuses especially on the lower limb thermal recovery time and time constant after active cooling. Previous research has shown substantial evidence supporting differences between sexes and thermoregulation (Yanovich et al., 2020; Marriott and Carlson, 1996; Charkoudian and Stachenfeld, 2016). However, the notion of less effective thermoregulation in females resulting in higher core or lower peripheral temperatures is not straightforward and rather depends on the environmental exposure (Yanovich et al., 2020), such as exercise, where sudomotor activity plays an important role (Gagnon, 2012). Additionally, a number of relevant thermoregulatory effectors and related body properties have been identified to be inseparable by sex in some previous research; such as tissue insulation and metabolic rate during cold stress (Kaciuba-Uscilko, 2001) evaporative heat loss or local sweat rate or onset threshold, shivering activity and patterns during cold stress, though the shivering onset temperature was observed higher for women (Greenfield et al., 2023). In the context of DTI, it is also an interesting research question whether biological sex is an independent factor in thermoregulation considering dynamic thermal imaging in the absence of physical activity.

Patients suffering from peripheral vascular disease and chronic limb-threatening ischemia are often at the higher end of age distribution, yet the disease does affect the younger population so that about 20% of the patients are under 65 years old. Our results showed that thermal recovery time had a moderate to high correlation with age, depending on the inspected angiosome. The lateral angiosomes, such as PA, CB, and LPA (including 2–5 digits) had high variance and poor to no correlation with age. The central MPA angiosome denotes a high correlation when the hallux is included and a moderate correlation when the hallux is excluded. The results indicate that age should be considered and possibly compensated when considering thermal recovery analysis, especially for the central angiosomes. It is clear that the variance in temperatures and in thermal recovery times is higher for outermost angiosomes (PA, CB, phalanges). This suggests that the reliability of simple metrics such as thermal time constant for vascular assessment may be limited in such sites.

Our results for the biological sex dependency did not show statistically significant differences for thermal recovery parameters, thus indicating the independence of thermal recovery time from sex. However, this may not be true for longer cold exposure times or for higher temperature gradients during the exposure.

In our earlier pilot study, we found a moderate to high negative correlation between clinical parameters such as ABI and TBI, and the thermal recovery time. The results in the present study show that part of the correlation could be explained by age dependency, which should be considered in future research. On the other hand, the secondary metrics such as body mass, height, BMI, or systolic blood pressure had low or no correlation with the recovery time constant, advocating its use in future research as a relatively independent metric from many confounding factors. The results considering the thermal recovery with respect to the confounding factors are in line with previous studies (Lahiri et al., 2012; Lahiri et al., 2020), though the exact methodology, measurement areas and the recovery time metric (recovery time constant vs inversion time) differ between the studies.

5. Conclusions

In this work, we examined the relation of age, sex, and other possible confounding factors with respect to thermal recovery time for healthy participants. The thermal recovery time of central plantar angiosomes were found to be moderately correlated solely with age, thus indicating independence from other factors, i.e. biological sex, systolic blood pressure, height, body mass, and the body-mass index. Additionally, the lateral angiosomes showed large variation between participants, and medium to low correlation. Age should be considered and possibly compensated in future research when considering thermal recovery times in clinical settings. Dynamic thermal imaging (DTI) is a promising technology, expanding the use of traditional thermal imaging techniques. However, the clinical usefulness of traditional thermal imaging and DTI is still debatable, and the methodology with a clear understanding of the confounding factors requires more research and standardization.

This study has several limitations. The used thermal camera equipment was not optimal in terms of thermal accuracy and sensitivity. Additionally, the relative humidity was not tracked adequately, and environmental temperature control should be stricter in future research. The participant background information, including comprehensive medical history, exercise habits, and number of other factors could have been collected. For future research, we suggest rigorous environmental control and upgraded imaging equipment.

Funding sources

This research was funded by the Academy of Finland (351471, 351472), State Research Fund (VTR, 9AP052), and by Instrumentarium Science Foundation, Finland, as a personal grant for Tomppa Pakarinen's doctoral research.

CRediT authorship contribution statement

Tomppa Pakarinen: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Niku Oksala:** Conceptualization, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing. **Antti Vehkaoja:** Conceptualization, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Research nurses Annamaija Purosola, Milka Ahola, and Julia Koskela are acknowledged for collecting the measurement data.

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