physiologia

MDPI

Article

Heat Stress but Not Capsaicin Application Alleviates the Hypertensive Response to Isometric Exercise

Alexandros Sotiridis [1,2,*], Anastasios Makris [1], Maria D. Koskolou [1] and Nickos D. Geladas [1]

[1] Section of Sports Medicine and Biology of Exercise, School of Physical Education and Sport Science, National and Kapodistrian University of Athens, 106 79 Athens, Greece; tasosmakris@phed.uoa.gr (A.M.); mkoskolu@phed.uoa.gr (M.D.K.); ngeladas@phed.uoa.gr (N.D.G.)
[2] Department of Automation, Biocybernetics and Robotics, Jozef Stefan Institute, SI-1000 Ljubljana, Slovenia
* Correspondence: asotiridis@phed.uoa.gr

Abstract: Heat stress and cutaneous capsaicin application act independently to reduce mean arterial blood pressure (MAP) at rest. The present study investigated whether a mixed intervention might alleviate to a greater extent the hypertensive response to isometric exercise. An end-exercise systolic blood pressure (SBP) lower than 215 mmHg or higher than 220 mmHg was set for the inclusion in the group observed with typical (CON, $n = 9$) or hypertensive (HRE, $n = 8$) response to dynamic exercise, respectively. The participants performed four trials held in thermoneutral (TN:23 °C) or hot (HT:33 °C) conditions with capsaicin (CA:4.8 mg·patch^{-1}) or placebo (PL) patches (12 × 18 cm^2) applied to their two quadriceps, left pectoralis major and left scapula. The trials comprised: a 5 min baseline period preceding patch application, a 30 min rest period and a 5 min isometric handgrip exercise (20% maximal voluntary contraction, 10.1 ± 1.9 kg). Thermoregulatory and cardiovascular data were analyzed using mixed three-way ANOVA. End-resting MAP and pain sensation were higher in PL-TN ($p = 0.008$) and CA-HT ($p = 0.012$), respectively. End-exercise SBP tended to be higher in HRE individuals across environments ($p = 0.10$). Total peripheral resistance and MAP remained lower in HT across groups ($p < 0.05$). Despite the alleviating effect of the heat stressor, an augmented burning sensation-induced peripheral vasoconstriction might have blunted the pressure-lowering action of capsaicin.

Keywords: capsaicin; heat exposure; hypertensive response to exercise; isometric handgrip exercise; thermoregulation

Citation: Sotiridis, A.; Makris, A.; Koskolou, M.D.; Geladas, N.D. Heat Stress but Not Capsaicin Application Alleviates the Hypertensive Response to Isometric Exercise. *Physiologia* **2024**, *4*, 64–80. https://doi.org/10.3390/physiologia4010004

Academic Editor: Philip J. Atherton

Received: 8 November 2023
Revised: 17 January 2024
Accepted: 19 January 2024
Published: 23 January 2024

1. Introduction

Arterial hypertension is defined as systolic (SBP) and diastolic (DBP) blood pressure, >140 mmHg and >90 mmHg, respectively [1]. According to a recent national epidemiological study, the prevalence of hypertension in Greece seems to be rising and affects 40% of the adults [2]. If not treated early, arterial hypertension might cause the development of cardiovascular diseases such as strokes, heart and renal failure [3] or harm other systems of the body with severe complications further, including elevated blood sugar levels [4], hypertensive retinopathy [5] and erectile dysfunction [6]. Among others, capsaicin—the major ingredient of red hot chilli peppers—has been shown to counteract acute increases in blood pressure [7]. Although capsaicin is rapidly absorbed by a nonactive process from the stomach and whole intestine [8] due to the lipophilic nature of the substance [9], oral administration remains a clinical challenge in humans [10]. As capsaicin is absorbed by human skin following local application [11], commercially available capsaicin creams or patches have been deemed safe and effective enough to be sold without medical prescription. Skin application might provide individuals that feel pain at the oral cavity and/or gastrointestinal disorders following the consumption of spicy foods [12] with a safe alternative. By contrast, whether the previously reported capsaicin-elicited burning sensation [13]

might potentiate sympathetic vasoconstrictor outflow [14,15] and act against the expected dilatory effect of capsaicin is unknown.

The transient TRPV1 ion channels that are stimulated at temperatures higher than 43 °C act mainly as nociceptors in the human body. From a clinical perspective, capsaicin skin application reduces pain by a process best described as defunctionalization of nociceptor fibres [16]. TRPV1 channel stimulation mediates the secretion of NO-synthase and eventually nitric oxide [17]. As such, TRPV1 ion channels contribute to the cutaneous hyperemia observed following local extreme heat application [18]. Capsaicin application to the skin has been further shown to augment the expected cutaneous vasodilation in humans resting under hot conditions [13,19].

As a separate stressor, heat is long known to lower arterial blood pressure by up to 10 mmHg depending on the level of heating [20–23]. The heat-related significant fall in systemic vascular resistance is counteracted by cardiovascular adjustments, including increases in sympathetic activity [24] and cardiac output [25]. Dynamic exercise profoundly increases cardiac output if metabolic demands of the exercising muscles are to be sufficiently met. Since systemic vascular resistance is not decreased to the same degree, systolic arterial pressure is substantially increased. Despite the fact that there is no consensus on the cut-off values of systolic blood pressure [26], the hypertensive response to exercise is generally defined as an abnormally exaggerated rise in arterial blood pressure during the end stages of dynamic incremental exercise [27], usually reflected in values of SBP >210 mmHg and >190 mmHg for men and women, respectively [28]. Since the previous definition applies only to maximal exercise, a threshold SBP of 160 mmHg has been recommended that involves a submaximal cycling power output of 100 W [28]. While ACSM has suggested that an exercise test be terminated when SBP exceeds 250 mmHg [29], recent evidence suggests that an end-exercise SBP pushed over a predetermined "critical" limit could be targeted as a means to enhance aerobic performance [30]. The hypertensive response to exercise has been correlated with relatively high 24 h SBP levels [31], increased risk for future hypertension [32] and cardiovascular events [33]. Similarly, the cardiovascular responses to isometric exercise result from the intramuscular tension that mechanically compresses the surrounding vasculature and hinders blood flow therein. Muscular contraction of an intensity exceeding 20% of maximal voluntary contraction would amplify the chemoreflex activity and thus increase muscle sympathetic nerve activity [34] and both SBP and DBP [34,35]. Past studies have applied capsaicin cream/patches and reported lower isometric exercise-induced increases in arterial blood pressure [7] being present even during the application of post-exercise ischemia [36]. These studies had selected this specific exercise type and site of application to isolate the activation of mechano- and metabo-receptors in the muscular group of finger flexors (activated during handgrip exercise). The exercise pressor reflex is a feedback neural mechanism originating in human skeletal muscle that elicits circulatory adjustments to exercise and raises blood pressure [37]. More specifically, group III and IV muscle afferent fibres are stimulated by metabolic and mechanical stimuli. Lower arterial blood pressure values have been reported after the local application of capsaicin in cats [38]. Somewhat paradoxically, local capsaicin administration might block nociceptive neurons and render them unable to be subsequently stimulated [39]. Whether capsaicin application would bear an effect on the activation of the exercise pressor reflex remains unresolved.

Arterial hypertension emerges as a major health problem, and has been recently correlated with the hypertensive response to isometric exercise [40]. Whereas heat exposure alleviates the rise in blood pressure both at rest [25] and during isometric exercise [41], the combined thermoregulatory and antianalgesic action of capsaicin patches remains underexplored on that regard. We have selected isometric exercise as a means to acutely increase arterial blood pressure. A capsaicin-induced inhibition of central command would be reflected in lower heart rate and higher RPE values during constant-load isometric exercise [7]. An augmented peripheral vasodilation would indirectly support the hypothesis that the metabolic component of the exercise pressor reflex is impaired following

capsaicin patch application on the exercising muscles [42]. The purpose of the present study was to investigate whether application of commercially available capsaicin patches on an extensive region of the human skin ($4 \times 12 \times 18$ cm^2) would decelerate the expected increase in arterial blood pressure with particular reference to individuals that demonstrate an exaggerated response. We tested the hypothesis that capsaicin skin application and acute heat stress would act synergistically to blunt the expected increase in arterial blood pressure during isometric exercise.

2. Results

2.1. Thermoregulatory Parameters

T_{sk} was higher in HT (main effect of environment, $p < 0.001$). No main effects for patch application, environment or group were observed on baseline T_{re} ($p > 0.05$). ΔT_{re} was lower across groups in HT, and capsaicin application did not affect that response (Figure 1) (main effects of group, environment and patch: $p = 0.43$, 0.003 and 0.28, respectively).

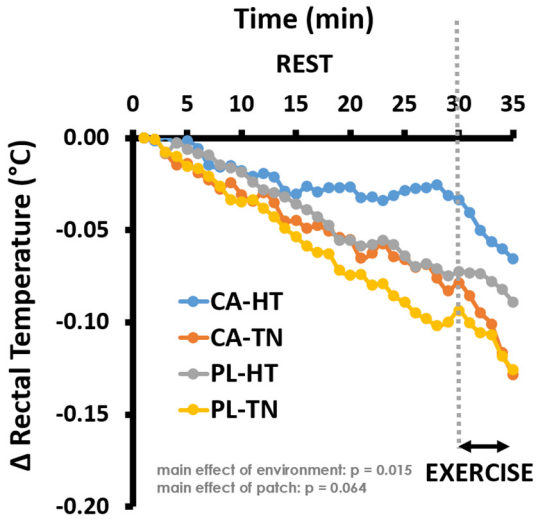


Figure 1. Relative changes in rectal temperature during rest and isometric exercise with individuals grouped together ($n = 17$).

Across groups, whole-body sweat rate was higher in HT (main effect of environment: $p = 0.005$) with the CON group sweating more than the HRE group in that specific environment (group X environment interaction: $p = 0.047$). Interestingly, $T_{f\text{-}f}$ was lower in HT (main effect of environment: $p = 0.005$) but tended to be higher in CA conditions (main effect of patch: $p = 0.064$) (Figure 2).

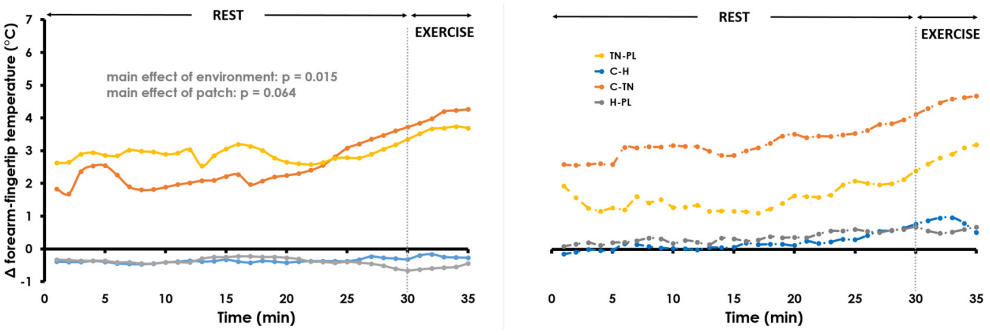


Figure 2. Forearm–fingertip temperature difference during 30 min rest and the following 5 min isometric exercise. Panels (**a**,**b**) indicate values for the individuals presented with typical ($n = 9$) and hypertensive ($n = 8$) response to exercise, respectively.

2.2. Cardiovascular Parameters

2.2.1. Resting Values

Table 1 presents end-resting values of several cardiorespiratory parameters. End-resting SBP was lower in PL-HT conditions (environment X patch interaction: $p = 0.024$), with the difference to PL-TN reaching significance only for the HRE group (114 ± 13 vs. 137 ± 18, $p = 0.013$). A tendency for correlation ($r = 0.50$, $p < 0.079$) was noted between peak dynamic and isometric exercise SBP when values across groups were grouped together.

Table 1. Cardiorespiratory parameters measured during the last 5 min of the resting period.

HRE Group	**CA**		**PL**		**Main Effects**		**Temperature X Patch Interaction**
	HT	**TN**	**HT**	**TN**	**Temperature**	**Patch**	
Systolic Pressure (mmHg)	131 ± 15	136 ± 18	114 ± 13	137 ± 18	0.001	0.21	0.024
Diastolic Pressure (mmHg)	80 ± 11	78 ± 10	69 ± 10	77 ± 11	0.059	0.58	0.025
Mean Arterial Pressure (mmHg)	96 ± 8	94 ± 10	86 ± 6	100 ± 10	0.05	0.69	0.008
Total Peripheral Resistance ($mmHg \cdot s \cdot mL^{-1}$)	0.72 ± 0.11	0.95 ± 0.26	0.70 ± 0.09	0.89 ± 0.19	0.088	0.545	0.591
Heart Rate (bpm)	63 ± 23	58 ± 20	66 ± 23	57 ± 22	0.006	0.516	0.435
Cardiac Output ($L \cdot min^{-1}$)	6.89 ± 1.24	6.87 ± 1.17	5.98 ± 1.07	6.01 ± 1.23	0.17	0.36	0.15
VO_2 ($mL\ O_2 \cdot kg^{-1} \cdot min^{-1}$)	4.45 ± 0.69	4.00 ± 0.47	3.92 ± 0.39	4.07 ± 0.39	0.36	0.72	0.048
CON group	**CA**		**PL**				**Main Effect of Group**
	HT	TN	HT	TN			
Systolic Pressure (mmHg)	122 ± 13	132 ± 16	119 ± 11	135 ± 13			0.42
Diastolic Pressure (mmHg)	70 ± 6	75 ± 7	70 ± 4	81 ± 6			0.386
Mean Arterial Pressure (mmHg)	88 ± 8	96 ± 10	85 ± 13	99 ± 7			0.828
Total Peripheral Resistance ($mmHg \cdot s \cdot mL^{-1}$)	0.91 ± 0.17	0.91 ± 0.36	0.90 ± 0.14	0.98 ± 0.18			0.172
Heart Rate (bpm)	75 ± 12	65 ± 11	72 ± 8	68 ± 6			0.077
Cardiac Output ($L \cdot min^{-1}$)	7.49 ± 0.87	6.35 ± 1.04	7.42 ± 1.03	6.85 ± 1.21			0.20
VO_2 ($mL\ O_2 \cdot kg^{-1} \cdot min^{-1}$)	4.05 ± 0.76	4.06 ± 0.68	4.05 ± 0.36	4.40 ± 0.41			0.93

Values are means ± SD. Abbreviations: HRE: hypertensive responders to exercise, CON: control group, CA: capsaicin trials, PL: placebo, HT: trials in the heat, TN: trials in thermoneutral environment, VO_2: oxygen uptake.

A main effect of environment ($p = 0.059$) and patch X environment interaction effect ($p = 0.025$) but no main effect of patch ($p = 0.58$) were (or tended to be) observed for DBP across groups. With values grouped together, end-resting MAP was higher in PL-TN (main effect of environment: $p = 0.05$, patch X environment interaction effect, $p = 0.008$). Cardiac output was not affected by environmental conditions, whereas time-average values were higher in the heat (main effects of environment: $p = 0.17$ and $p = 0.077$, respectively) across groups and patch conditions. Heart rate tended to be lower in the HRE group (main effect of group: $p = 0.077$) but higher in HT across groups and patch conditions (main effect of environment: $p = 0.001$). Expectedly, total peripheral resistance was higher in TN conditions across groups (main effect of environment: $p = 0.048$). Again, the HRE group tended to demonstrate higher total peripheral resistance values across the resting period (main effect of group: $p = 0.056$).

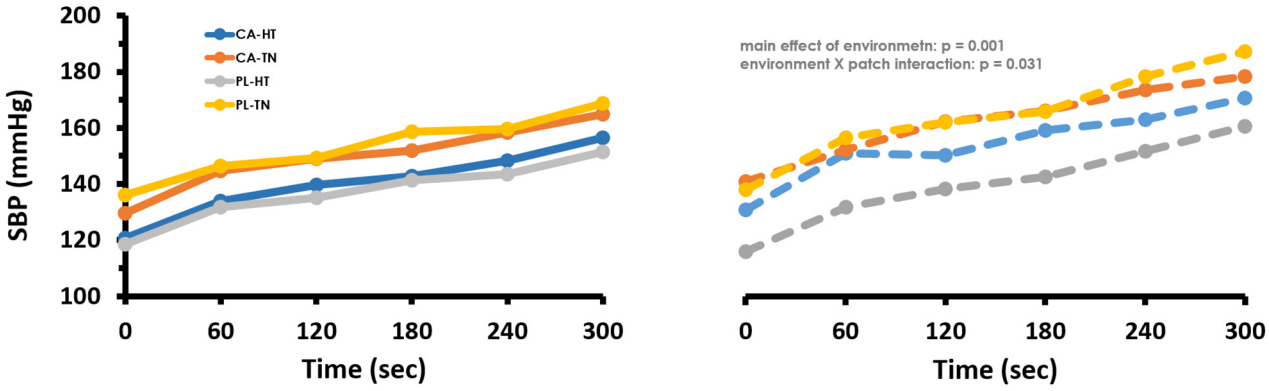
2.2.2. Exercise Values

Table 2 presents end-exercise values of cardiorespiratory parameters. SBP, DBP and MAP increased over exercise time (main effects of time: $p < 0.001$). The exercise-induced increase in SBP remained unaltered across groups ($p = 0.44$), patch ($p = 0.21$) or environmental conditions ($p = 0.71$). End-exercise SBP tended to be higher in the HRE group across environments (main effect of group, $p = 0.10$, Figure 3). A patch X environment interaction ($p = 0.031$) together with a main effect of environment ($p < 0.001$) indicates lower values of end-exercise SBP in HT with the exception of the HRE group in CA conditions ($p = 0.61$).

Table 2. Cardiorespiratory parameters and rating of perceived exertion measured during isometric handgrip exercise performed at 20% maximal voluntary contraction.

HRE Group	CA		PL		Main Effects		Temperature X Patch Interaction
	HT	TN	HT	TN	Temperature	Patch	
Systolic Pressure (mmHg)	171 ± 11	178 ± 5	161 ± 11	187 ± 6	<0.001	0.125	0.031
Diastolic Pressure (mmHg)	102 ± 13	103 ± 8	92 ± 13	102 ± 13	0.007	0.089	0.27
Mean Arterial Pressure (mmHg)	114 ± 15	121 ± 18	113 ± 12	125 ± 11	0.003	0.023	0.295
Total Peripheral Resistance ($mmHg \cdot s \cdot mL^{-1}$)	0.92 ± 0.15	1.10 ± 0.29	0.78 ± 0.20	1.03 ± 0.30	0.017	0.3	0.764
Heart Rate (bpm)	89 ± 21	81 ± 18	92 ± 17	84 ± 10	0.001	0.92	0.074
Cardiac Output ($L \cdot min^{-1}$)	2.36 ± 1.95	1.27 ± 1.46	3.30 ± 2.84	2.04 ± 1.79	<0.001	0.349	0.40
VO_2 ($mL\ O_2 \cdot kg^{-1} \cdot min^{-1}$)	5.10 ± 1.23	5.03 ± 0.94	4.57 ± 0.58	5.44 ± 0.40	0.909	0.445	0.046
End-exercise rating of perceived exertion (a.u.)	16 ± 3	16 ± 3	15 ± 2	16 ± 2	0.907	0.498	0.863
CON group	**CA**		**PL**		**Main effect of group**		
	HT	TN	HT	TN			
Systolic Pressure (mmHg)	156 ± 20	165 ± 24	151 ± 15	169 ± 19	0.100		
Diastolic Pressure (mmHg)	90 ± 13	96 ± 14	89 ± 11	101 ± 7	0.505		
Mean Arterial Pressure (mmHg)	126 ± 16	133 ± 9	115 ± 14	131 ± 19	0.657		
Total Peripheral Resistance ($mmHg \cdot s \cdot mL^{-1}$)	0.75 ± 0.18	1.11 ± 0.38	0.75 ± 0.13	1.07 ± 0.30	0.133		
Heart Rate (bpm)	85 ± 14	72 ± 11	80 ± 10	72 ± 4	0.039		
Cardiac Output ($L \cdot min^{-1}$)	1.83 ± 1.88	0.36 ± 0.92	1.72 ± 1.48	0.36 ± 0.48	0.103		
VO_2 ($mL\ O_2 \cdot kg^{-1} \cdot min^{-1}$)	5.11 ± 1.01	4.34 ± 0.54	4.51 ± 0.52	4.21 ± 0.90	0.127		
End-exercise rating of perceived exertion (a.u.)	16 ± 3	15 ± 3	16 ± 2	15 ± 3	0.473		

Statistic effects refer to time-pooled values except for systolic pressure and Δ cardiac output (end values). Main effects of time were significant ($p < 0.05$) across parameters. Values are means ± SD. Abbreviations: HRE: hypertensive responders to exercise, CON: control group, CA: capsaicin trials, PL: placebo, HT: trials in the heat, TN: trials in thermoneutral environment, VO_2: oxygen uptake.



(**a**) (**b**)

Figure 3. Systolic blood pressure (SBP) during 5 min of isometric exercise @ 20% of maximal voluntary contraction. Panels (**a**,**b**) indicate values for the individuals presented with the typical ($n = 9$) and hypertensive ($n = 8$) response to exercise, respectively.

DBP remained lower in HT across time, groups and patch conditions (main effect of environment: $p = 0.007$). Post hoc tests revealed lower (time-pooled) DBP values for the HRE group in PL-HT (81 ± 12) as compared to CA-HT (92 ± 10, $p = 0.04$) and PL-TN (91 ± 12, $p = 0.05$). End-exercise MAP values for the HRE group in PL-HT (115 ± 14) were lower as compared to CA-HT (126 ± 16, $p = 0.007$) and PL-TN (131 ± 19, $p < 0.001$). The exercise-induced rise in cardiac output tended to be higher in the HRE group across environments (main effect of group: $p = 0.10$). While cardiac output expressed in absolute values was higher in HT (main effect of environment: $p = 0.020$), the increase in cardiac output

was lower in HT conditions for the CON group (PL: 1.72 ± 1.48 vs. 0.36 ± 0.48 L·min^{-1}, $p = 0.017$; CA: 1.83 ± 1.88 vs. 0.36 ± 0.92 L·min^{-1}, $p = 0.042$). Total peripheral resistance increased over time only in TN conditions (environment X time interaction: $p = 0.002$) across groups (main effect of group: $p = 0.13$) and remained lower in HT conditions (main effect of environment: $p = 0.017$). Oxygen uptake during exercise was higher compared to resting conditions (main effect of time: $p < 0.001$) and remained lower in PL-HT (4.53 ± 0.53 mL O_2·kg^{-1}·min^{-1}) when compared to PL-TN (4.74 ± 0.95 mL O_2·kg^{-1}·min^{-1}, $p = 0.018$) and CA-HT (5.10 ± 1.09 mL O_2·kg^{-1}·min^{-1}, $p = 0.004$).

3. Discussion

We investigated the thermoregulatory and cardiovascular responses to combined heat exposure and capsaicin application on the skin during rest and a 5 min bout of isometric exercise. The main findings of the study were (a) heat stress but not capsaicin application alleviated the hypertensive response to exercise, as reflected in lower SBP; and (b) the blood pressure-related lowering action of capsaicin was confirmed during rest. Acute heat stress was found to alleviate the exaggerated increase in hypertensive responders to isometric exercise.

3.1. Cardiovascular Responses

3.1.1. Rest

The multifaceted impact of capsaicin (chili pepper extract) on human health and performance remains underexplored. Recent meta-analyses have attempted to explore the effects of capsaicin supplementation on obesity [43], energy balance [44], blood pressure [45] and even endurance performance [46]. The present study confirmed the hypotensive effect of capsaicin application during rest, as end-resting MAP remained higher in the PL-TN condition across groups. In a cross-over design, a notable reduction in arterial blood pressure was reported when four capsaicin patches were applied at the skin of young males in hot conditions [13]. Not only are commercial capsaicin patches/creams highly used without medical prescription, but also, their application on the skin emerges as an alternative to oral ingestion. We opted for our participants not to eat capsaicinoids to ensure a high degree of external validity as well as to protect them from reported symptoms of gastrointestinal discomfort such as pain and diarrhea [12]. As far as the classification of our participants into groups is concerned, individuals that were included in the HRE group demonstrated relatively high blood pressure values in the 30 min rest period. Since they were not actually resting (they were anticipating to perform isometric exercise), HRE participants should not necessarily be reported with arterial hypertension (SBP > 130 mmHg) [47]. A central command-initiated effect might have influenced the arterial blood pressure response especially towards the end of the resting period in the HRE group. Indeed, the groups were not characterized by different baseline values in mean arterial pressure, total peripheral resistance or cardiac output (unpublished data, $p > 0.10$).

In our past study, resting MAP was lower only when capsaicin application at the skin was superimposed to the heat stressor [13], whereas a higher MAP is currently reported in the absence of both stressors (condition: PL-TN, Table 1). The temperature-dependent nature of the capsaicin action on arterial blood pressure was reasoned to be explained by the involvement of differential TRPV channels on vascular regulation. Among other TRPV channels, characteristic activation temperatures for TRPV1 and TRPV4 range from mild to extreme heat (ambient temperatures, >43 and 25 °C, respectively) [48,49]. As such, exposure to a warm environment would preferentially stimulate TRPV4 but not TPRV1 ion channels. Independent stimulation of both channel types has been shown to inhibit α-adrenergic vasoconstriction in human skeletal muscle feed arteries [50,51]. Even though total peripheral resistance was not affected by capsaicin application, the possibility that the commercial patches were spread over a relatively small region of the body (~5% of body surface area) to exert a physiologically meaningful effect can be safely excluded as the sites of application remained similar compared to the previous study from

our laboratory [13]. From an integrative physiology standpoint, redundant mechanisms might have been recruited to prevent an excessive drop in arterial blood pressure [52] in the simultaneous presence of heat and capsaicin stressors. As a separate stressor, heat is known to elicit reductions in arterial blood pressure [53] mediated by reductions in arterial stiffness [54], even in young individuals, which were reflected in lower total peripheral resistance in HT conditions [55]. As such, capsaicin application could serve as an adjunct to heat exposure if the goal is to regulate resting blood pressure within physiological limits. Whether this finding is of clinical relevance and capsaicin-based treatments could be included in antihypertensive therapy warrants further investigation.

3.1.2. Exercise

The hypertensive response to dynamic exercise is defined as an abnormally exaggerated rise in systolic arterial blood pressure [27]. In the present study, wherein blood pressure values were measured during isometric exercise, end-exercise SBP tended to be again higher in the HRE group across environments. The exercise-mediated rise in SBP was not different between groups. Thus, higher values observed in the HRE group might be attributed to higher SBP values observed at the onset of isometric exercise. At that specific timepoint, the feedforward neural mechanism of central command could be activated at the absence of sensory input from the isometrically exercising muscles [56]. Beyond the suspected influence of the central command, the hypertensive response to exercise—as observed in young individuals—has been further attributed to overactivity of the exercise pressor reflex [57]. The exercise pressor reflex is a feedback neural mechanism originating in human skeletal muscle that elicits circulatory adjustments to exercise and raises cardiac output and total peripheral resistance; both adjustments function to increase blood pressure and enhance tissue oxygenation [37]. In disease states like heart failure [58] or arterial hypertension [59], the heart demonstrates a failing ability to increase cardiac output during exercise; whether the exercise-induced increase in SBP reported in our HRE individuals is predominantly driven by cardiac output or total peripheral resistance remains unclear, as marginal changes were observed for either factor (main effects of group: $p = 0.10$ and 0.13, respectively). To further investigate the origin of the response, the cardiac output to total peripheral resistance ratio is proposed as an index of sympathetic stimulation to be assessed in future studies. Lower and higher values of the proposed ratio would be indicative of reduced aortic compliance (peripheral) and augmented myocardial contractility (central), respectively [60]. Even though a recent study highlighted "large" correlation values between end-handgrip exercise and 24 h SBP and DBP [40], no study to date has investigated the connection between peak dynamic and isometric exercise values. Given the between-exercise type differential hemodynamic (cardiac output and central peripheral resistance) response, the tendency for correlation, observed herein, could postulate that the reported increase in SBP might be predominantly of central origin.

Even in hot conditions and across individuals, SBP was increased during intense isometric handgrip exercise. The exercise pressor reflex is initiated during isometric exercise through the activation of the central command and the stimulation of muscle metabo/mechanoreceptors; these mechanisms act in synergy to lower vascular conductance, with the values remaining higher in the heat compared to thermoneutral conditions [41]. The findings of the present study confirm that the end-exercise increase in SBP is alleviated in the presence of the heat stressor (Figure 2) and a concomitantly lower total peripheral resistance.

In sharp contrast to the effect of the heat, the extent to which capsaicin application on the skin ameliorates the exercise-induced increase in arterial blood pressure seems rather limited. Previous studies have investigated whether capsaicin cream application would suppress the expected increase in arterial blood pressure as elicited during bouts of isometric exercise. The capsaicin-induced TRPV1 channel activation has been suggested to attenuate the release of prostaglandins and the concomitant activation of group III and IV afferent fibers and partly deactivate the exercise pressor reflex [7]. Regarding the

impact of capsaicin application on central command, unaltered values of heart rate and RPE speak against the activation of the proposed mechanism. The inability of capsaicin application to attenuate the exercise-induced rise in arterial blood pressure might be further explained by additional mechanisms. The intramuscular tension developed during isometric exercise and the concomitant partial restriction of blood flow might not have been of the intensity required to activate the exercise pressor reflex. A dose–response relationship between handgrip exercise intensity and the stimulation of metabo-sensitive skeletal muscle afferents has been implied but not directly verified to date. Dawson, Walser, Jafarzadeh and Stebbins [7] had their participants perform a 90 sec bout of isometric handgrip exercise (@40% maximal voluntary contraction) before and 50 min after the application of 100 mg of commercially available capsaicin cream at the respective forearm. Whereas the exercise-induced increase in arterial blood pressure was lower in the capsaicin condition, the brachial artery blood flow was higher in the experimental condition at rest but not following isometric exercise. To further isolate the influence of capsaicin on metaboreceptors, Vianna, Fernandes, Barbosa, Teixeira and Nobrega [36] investigated the effect of capsaicin cream application on the (180 sec period of) post-exercise ischemia-induced metaboreflex stimulation. Local application of capsaicin cream did not affect the exercise-induced increases in arterial blood pressure and heart rate. During the post-exercise ischemia intervals, the increases in muscle sympathetic nerve activity and arterial blood pressure were of a lower magnitude 30 and 60 min following capsaicin application. Taken together, an attenuated increase in blood pressure has been reported when the muscles rendered ischemic via occlusion but not during submaximal isometric exercise following capsaicin cream application. In contrast to past studies, we aimed to apply commercially available capsaicin patches on an extensive region of the human skin ($4 \times 12 \times 18$ cm^2) investigating a systemic (or not localized) cardiovascular effect. Presumably, capsaicin application did not exert an additive effect to the heat-related reduction in total peripheral resistance and end-exercise blood pressure potentially owing to the augmented pain sensation experienced during the specific (CA-HT) trial. Ever-increasing values of thermal and pain sensation on the sites of patch application might further indicate a capsaicin-induced increase in muscle sympathetic nerve activity that can lead to peripheral vasoconstriction [14]. Future studies are warranted to examine the interaction between exercise intensity, capsaicin application and pain/burning sensation on arterial blood pressure regulation.

3.2. Thermoregulatory Responses

Core temperature increases when humans perform dynamic exercise. The capsaicin-related mitigation of the increase has been attributed to enhanced convective (vasodilation) and evaporative (sweating response) heat loss [61]. Such thermoregulatory responses to exercise in the heat are probably mediated by the action of the NO-synthase enzyme [62,63]. Changes in core temperature reflect the balance between heat production and heat loss responses. Whereas core temperature remained lower in thermoneutral as compared to hot conditions (Figure 2), capsaicin application on the skin did not act additively to further reduce core temperature. This finding comes in contrast to previous findings from our laboratory: a profound decrease in rectal temperature had been observed in our capsaicin-treated resting individuals across environmental conditions [13]. Such an effect was attributed to both enhanced heat loss and reduced metabolic heat production. With regards to the metabolic heat production, oxygen uptake remained unaltered across conditions during rest, and the respective increase during exercise should not have been of physiological relevance (CA-HT vs. PL-HT: ~ +0.5 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$). Paradoxically, the forearm–fingertip temperature difference—serving as an index of local vasomotor tone—tended to be higher when capsaicin patches were applied to our participants (Figure 3). Again, a pain/burning sensation-induced vasoconstriction effect could be mediating such a response [14]. The discrepancy might be explained by the time interval between the application of capsaicin and the start of the resting period; a time interval that was longer in

the present (31 ± 11 min) and other studies (isometric exercise conducted 50 min following the application of capsaicin cream in Dawson, Walser, Jafarzadeh and Stebbins [7]) since the resting phase "started immediately upon patch application" in the former study [61]. Similar to the forearm–fingertip temperature difference, the heat-induced reduction in total peripheral resistance serves the thermoregulatory as well as the cardiovascular function of the human body; the former by augmenting convective cutaneous heat loss and thereby offsetting the gain in core temperature, and the latter by counteracting the exercise-induced rise in SBP. Interestingly, three participants (all selected for the HRE group) requested to terminate the CA-HT trial early in the recovery phase with excessive symptoms of discomfort such as pain-induced tremor or inability to remain seated and still. In contrast to the HRE group, CON individuals displayed an augmented sweating response in HT. Given the response being observed specifically in HT, the possibility that the superposition of heat facilitated the activation of muscle metaboreflex during a short bout of isometric exercise (a nonthermal stimuli) should be investigated [64,65]. Nevertheless, the brevity of the exercise protocol, the low exercise intensity (together with the limited degree of occlusion) and the fact that whole-body sweat rate was assessed using changes in body mass in the end of the experimental protocol (lasting ~2 h) render this hypothesis difficult to evaluate.

3.3. Limitations

The non-invasive photoplethysmograph (Finometer, FMS, 2003, Enschede, The Netherlands) that was used to record arterial blood pressure parameters has been shown to measure mean arterial pressure reliably at rest and during exercise [66]. Reconstruction of intrabrachial artery pressure from finger artery pressure attained using the corrective methods of waveform filtering and height correction (use of external arm cuff) as implemented in the Finometer device reduces the pressure differences substantially [67]. The exclusive use of arm cuffs is not recommended as it would substantially reduce the sampling rate (minute values as opposed to beat-by-beat values, cf. [68]) and would result in low accuracy levels [69]. In view of the marginal changes in hemodynamic parameters, we acknowledge that the statistical power might have been benefited from the inclusion of additional participants in both (CON and HRE) groups.

The hypertensive response to exercise of dynamic [31] or isometric [40] type has been related to high 24 h SBP levels. As such, we opted for recruiting healthy young individuals that demonstrate a hypertensive response to dynamic exercise. The hypertensive response to dynamic exercise has been described as an exaggerated SBP response to exercise of submaximal [70,71] or maximal intensity [72,73]. To date, consensus is lacking regarding the definition criterion of such a phenomenon. More specifically, the hypertensive response for males undertaking maximal exercise has been defined as systolic arterial blood pressure exceeding higher (214 mmHg in Allison, et al. [74], 210 mmHg in Lorbeer, Ittermann, Volzke, Glaser, Ewert, Felix and Dorr [28] or lower [181 mmHg in Jae, Franklin, Choo, Choi and Fernhall [32]] thresholds. Since the non-invasive determination of the limited DBP response to incremental dynamic exercise lacks reliability [75,76], a rather high value of SBP was selected as the cut-off threshold for inclusion in the group of hypertensive responders to exercise. As the cycling mode of exercise allows for isometric contractions of the trunk and the upper part of the body during later stages of the trial, the expected higher values of systolic pressure were to be detected sufficiently using the photoplethysmograph (as compared to intra-arterial monitoring) at least in laboratory measurements [77]. Even with the potential confounding factors of body mass index, fitness level, W_{peak} and maximal voluntary contraction eventually matched across groups (Table 3), the HRE group demonstrated higher maximal SBP values during dynamic as well as isometric (condition: PL-TN) exercise. Taken collectively, we are quite confident that the applied experimental design enabled us to differentiate between individuals of an exaggerated (HRE group) or a modest (CON group) exercise-induced rise in blood pressure; the former group deemed susceptible to develop arterial hypertension at a later stage of life. Future studies are warranted to de-

lineate whether a rise in end-exercise blood pressure exceeding a "critical" limit [30] could further serve alternatively to enhance aerobic performance; the hypertensive response to exercise would emerge as an adaptive response to training rather than a pathological outcome [78].

Table 3. Participants' baseline characteristics.

Group	HRE, n = 8	CON, n = 9	p-Value
Age (years)	20 ± 1	25 ± 2	<0.001
Height (cm)	174 ± 8	181 ± 8	0.043
Body mass (kg)	71.6 ± 7.5	83.8 ± 7.6	0.003
Body mass index ($kg \cdot m^{-2}$)	25.3 ± 1.0	23.6 ± 1.7	0.053
Baseline SBP (mmHg)	130 ± 10	128 ± 12	0.73
Baseline DBP (mmHg)	73 ± 8	74 ± 6	0.72
End-dynamic SBP (mmHg)	234 ± 14	209 ± 8	0.002
End-isometric SBP (mmHg)	187 ± 6	165 ± 16	0.026
VO_{2peak} ($mL \cdot kg^{-1} \cdot min^{-1}$)	46.4 ± 5.8	43.3 ± 9.1	0.43
W_{peak} (W)	292 ± 57	317 ± 51	0.36
Maximal voluntary contraction (kg)	49.3 ± 8.9	51.3 ± 10.8	0.71

Values are means ± SD. Abbreviations: HRE: hypertensive responders to exercise, CON: control group, SBP: systolic arterial blood pressure, DBP: diastolic arterial blood pressure, VO_2: oxygen uptake, W_{peak}: peak power output.

The participants were requested to replicate their meals during the days preceding the experimental trials but that does not preclude their adherence to the diet. Given that even small fluctuations in salt and potassium intake could affect the hydration status of the participants, our inability to account for mineral intake poses another limitation in the results presented herein. We are quite confident though that circadian-rhythm-related hormonal imbalances are of minor concern since our experimental design involved trials scheduled for the same time of the day within each individual (see Materials and Methods). The participants' emotional status should not have affected skin temperature to an extent expected to interfere with the internal validity of the study since their weighted mean skin temperature was ~3 °C higher when performing in the hot environment.

4. Materials and Methods

4.1. Participants

In total, 42 volunteers completed the preliminary visits. Seventeen healthy young male volunteers [age = 22.8 ± 3.4 years, body mass = 78.1 ± 9.3 kg, stature = 178 ± 8 cm, peak oxygen uptake ($VO_{2\,peak}$) = 44.8 ± 7.7 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$, peak power output ($W_{peak}$) = 306 ± 49 Watts] were recruited to participate in the study. Inclusion criteria included male participants between 18 and 35 years of age, non-smokers, physically active and medication-free. Confounding variables of caffeine and alcohol consumption 24 h prior to testing and prolonged exposure/acclimation to hot conditions (>30 °C) in the 30 days preceding testing, were all controlled for, in line with our previous work involving capsaicin skin application [13,61]. Participants were also instructed to record their diet the night before the first trial and they were requested to consume the same meals during the nights preceding the remaining exercise trials. Following institutional ethics approval and a detailed description of experimental procedures, all participants completed medical questionnaires (to explore inter alia parental history of arterial hypertension [79]) and provided written informed consent following the principles outlined by the declaration of Helsinki of 1975, as revised in 2013. Participants were informed that the aim of the study was to investigate the effects of capsaicin skin application and environmental temperature on cardiovascular responses during isometric exercise. However, they were blinded to the fact that the data would be analyzed in groups according to their arterial blood pressure response to exercise.

4.2. Preliminary Trials

During the screening procedure, the participants were informed of the procedures to be followed, familiarized themselves with the laboratory equipment and were tested for an allergic reaction to capsaicin; a capsaicin patch was applied on their right forearm skin area. As a surrogate measure of body composition, the body mass index (BMI) was calculated as: BMI = body mass $\times$ eight^{-2} [kg·m^{-2}]. The maximal isometric handgrip strength was assessed with the participants on a seated position holding the dynamometer (Jamar Hydraulic Hand Dynamometer, Sammons Preston, Bolingbrook, IL, USA) with their self-reported dominant hand and their back held upright. Shoulder and elbow were flexed at 45° and 90°, respectively. On instruction, participants performed maximal isometric handgrip twice for 5 s with a 60 s rest between the exertions. Strong verbal encouragement was provided throughout both trials. The participant's maximum handgrip strength was determined as the highest force (kg) obtained in the two trials. For the participants who were included in the study, the measured maximal voluntary contraction (MVC) was used to determine the individual workloads performed during the exercise tests (20% of the MVC attained during the preliminary test).

On a separate occasion, individuals completed an incremental exercise test to exhaustion on a cycle ergometer (Lode, Groningen, The Netherlands) to establish their arterial pressure responses as well as VO_{2peak} and W_{peak}. As a warm-up procedure, and following a 5 min resting period, the participants were requested to cycle at the initial workload for 3 min. The initial workload was set at 30 W or 60 W depending on the estimated fitness level of the participant. During exercise, each participant pedalled at a preferred cadence (between 60 and 90 rpm), which they maintained via visual and verbal feedback throughout the trial. A metabolic cart (MedGraphics, CPX-D, Saint Paul, MN, USA) was used to obtain the breath-by-breath respiratory responses. Before each trial, the O_2 and CO_2 analyzers were calibrated using two different gas mixtures (atmospheric air and gas made up of 15% O_2 and 5% CO_2) and the pneumotachograph was calibrated with a 3 L syringe, in accordance with the manufacturer's recommendation. Attainment of VO_{2peak}, defined as the highest VO_2 averaged over 30 s, was confirmed when participants met the following criteria: (a) inability to maintain exercise at a given workload reflected in a cycling cadence lower than 60 rpm; (b) a plateau in VO_2, as indicated by breath-by-breath values, despite an increase in power output; and (c) end-exercise respiratory quotient > 1.10. W_{peak} was calculated according to the following equation: W_{peak} = work rate of last stage completed + [(work rate increment) $\times$ (time into current stage/60)]. All graded tests were held under thermoneutral (23 °C) normoxic (FiO_2 = 0.21) conditions at a laboratory located ~80 m above sea level (Daphne, Athens, Greece).

Arterial blood pressure parameters were continuously recorded non-invasively using a photoplethysmograph with the cuff attached to the middle finger of the left hand (Finometer, FMS, 2003, Enschede, The Netherlands). The device was automatically calibrated for pressure, distance of finger sensor from the heart level and detection of sound derived from "return to arm flow", according to the manufacturer's standards. Further information on the software used to measure accompanying cardiovascular parameters is given in the section 'Experimental Trials'.

4.3. Study Design

The experimental protocol is summarized in Figure 4. Participants were separated into two groups that were characterized by the arterial blood pressure response to dynamic exercise. The hypertensive response to exercise was defined based on end-exercise SBP. An end-exercise SBP lower than 215 mmHg or higher than 220 mmHg was deemed as a prerequisite for the participation in the group observed with the typical (CON) or hypertensive (HRE) response to exercise, respectively, in agreement with values reported in previous studies [28,74]. Ten individuals were considered as hypertensive responders to exercise. Another ten individuals were selected from those that demonstrated a typical response and were thereby included in the control group. By design, the two groups were

matched for body mass index, maximal voluntary contraction, VO_{2peak} and W_{peak}. As such, 20 participants commenced the experiment; however, three (n = 2, hypertensive responders to exercise; n = 1, control group) withdrew having completed two/three experimental visits for reasons unrelated to the experiment. Participants' baseline characteristics are presented in Table 3.

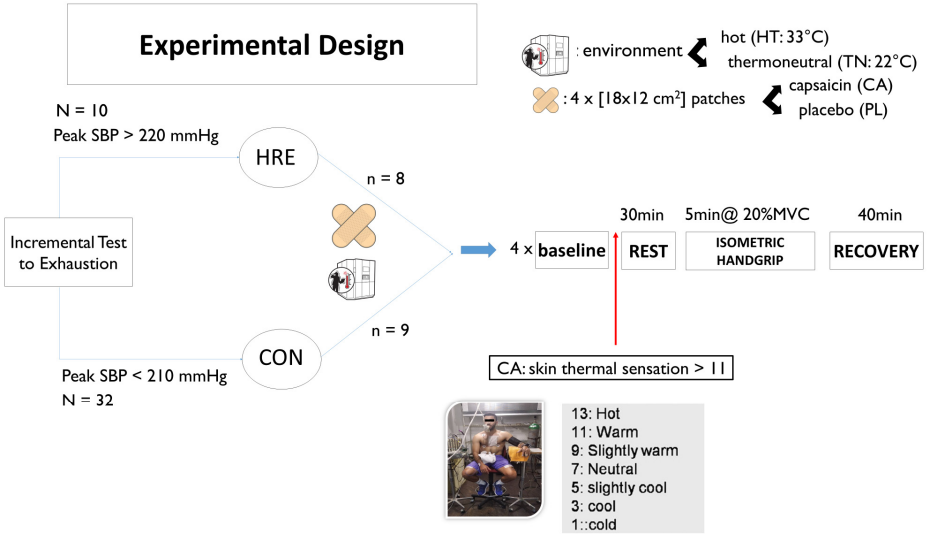


Figure 4. Overview of the study design. Abbreviations: HRE: hypertensive responders to exercise, CON: control group, MVC: maximal voluntary contraction, SBP: systolic arterial blood pressure.

Following inclusion into the experimental groups, the participants completed four experimental trials in a randomized incomplete Latin square design. The independent variables were environmental condition [hot (HT: 33 °C)/thermoneutral (TN: 22 °C)] and patch application [capsaicin (CA)/placebo (PL)].

4.4. Experimental Trials

Participants completed four experimental trials that were each separated by 2–5 days. They were requested to record and replicate their diet, hydration and physical activity levels as well as avoid strenuous exercise for the 36 h preceding each trial. To exclude the effect of the circadian rhythm on variables under investigation, individuals were scheduled to attend the laboratory at the same time of day (±1 h). Upon arrival, participants had their body mass measured (Bilance Salus, Milan, Italy) and rested at a sitting position for 15 min. To enable the measurement of core temperature, they were administered and self-inserted a rectal thermistor (MSR 145, Henggart, Switzerland) ~10 cm beyond the anal sphincter according to the manufacturer's instructions. Skin temperature was measured at four sites (chest, calf, forearm, and fingertip) using thermistors (MSR 147WD, Henggart, Switzerland) attached to the skin with a single piece of adhesive tape with the participants resting in a seated position. The assessment of calf, chest, and forearm skin temperature enabled the calculation of weighted mean skin temperature (Tsk) [80]. The forearm–fingertip temperature difference (T_{f-f}) has been validated as an index of skin vasomotor tone, even during exercise [81]. Followingly, participants entered the thermal chamber and their position was set at the cycle ergometer (Lode, Groningen, The Netherlands) and noted for all subsequent visits. Similar to the preliminary trials, the cardiovascular parameters of arterial blood pressure, total peripheral resistance, cardiac output, stroke volume and heart rate were recorded non-invasively using a photoplethysmograph with the cuff attached to the middle finger of the left hand (Finometer, FMS, 2003, Enschede, The Netherlands). The exact derivation of cardiovascular parameters has been extensively described in our previous work [13,61]. Briefly, the Modelflow technique computes stroke volume values from the (peripheral) arterial pressure waveform using a nonlinear three-element [(a) impedance of

the aorta, (b) total arterial compliance (c) peripheral vascular resistance] model of the aortic input impedance. The first two nonlinear elements depend on the elastic properties of the aorta while the third element is calculated for each beat by model simulation. Cardiac output is calculated as the product of stroke volume and heart rate. Participants were then connected to a metabolic cart (MedGraphics, Saint Paul, MN, USA) so that oxygen uptake can be measured. The pneumotachograph, the metabolic cart and the photoplethysmograph were calibrated before each session as described in the "Preliminary Trials" section.

Following instrumentation, 5 min baseline values were collected at a thermoneutral environment (~22 °C). Four capsaicin (C:4.8 mg·patch^{-1}) or placebo (PL) patches of similar colour and size (12 × 18 cm^2) were subsequently applied to the two quadriceps, left pectoralis major and left scapula. These sites were selected to represent body regions of varying thermosenitivity [82]. All application sites had been previously shaved. The thermal chamber was set to mimic a hot (33 °C) or thermoneutral environment (22 °C). From the baseline period onwards, the participants reported subjective ratings of whole-body and regional (under the patches) thermal sensation on a 1–13 numeric scale (1, cold; 3, cool; 5, slightly cool; 7, neutral, 9; slightly hot, 11; hot, 13; very hot) (ASHRAE, 1966, modified) at 5 min intervals. Immediately after the patch application on the skin, pain sensation was reported on a 0–10 numeric pain scale (0, none; 1–3, mild; 4–6, moderate; 7–10, severe), again at 5 min intervals. As soon as the regional thermal sensation reported was $\geq$ 11 (31 ± 11 min following patch application), a rest period of 30 min was initiated and preceded the 5 min isometric handgrip exercise. This was the case for all capsaicin trials. With regard to the placebo trials, the onset of the resting period was delayed not to imply to the participants the nature of the patch (placebo vs. active substance). The elapsed time between the 5 min baseline and the 30 min rest periods was 21 ± 11 min for the placebo trials. In contrast to the 5 min baseline period (whereby no patches had been applied and the environment was kept thermoneutral), the 30 min period was included to outline the effects of each specific condition on resting individuals. The body position of the participants during exercise was rather similar to the position they held during the determination of their MVC. In order to ensure that the participants would tolerate a rather lengthy bout of isometric exercise (and the concomitant rise in arterial blood pressure), the intensity was set at 20% of the individuals' MVC as assessed during the preliminary trial. The absolute workload of the isometric exercise remained unaltered across experimental trials. Cardiovascular data as well as ratings of perceived exertion (RPE; 6–20 [83]) were collected at the end of each minute and at the end of isometric exercise, respectively. In order to investigate potential post-exercise hypotension episodes, the participants were requested to stay seated and motionless during the 40 min recovery period. Data for the recovery period are not presented here. Body mass was measured again at the end of the recovery period. Whole-body sweat rate was calculated as the difference between body mass values collected pre- and post-trial (rounded to the nearest 0.05 kg), as the individuals were not provided with fluids throughout the ~2 h experimental trial.

4.5. Data Analysis

Statistical analyses were performed using Statistica 5.0 (StatSoft, Tulsa, OK, USA). The effects of the non-repeated factor of group (two levels: CON and HRE) and the repeated factors of environmental condition (two levels: TN and HT) and patch (two levels: PL and CA) on the dependent thermoregulatory and cardiovascular parameters were detected using a mixed three-way ANOVA. When ANOVA revealed a significant F-ratio for interaction and/or main effect, pairwise comparisons were performed with Tukey's honestly significant difference post hoc test. In the event that the statistical analysis revealed a non-normal distribution of the data, a nonparametric test was performed. Such was the case for local and environmental thermal sensation ratings and RPE, as well as pain sensation, which were analyzed using the Friedman nonparametric test. Planned comparisons were carried out using Kruskal–Wallis or Wilcoxon tests to locate specific differences. When failing to demonstrate statistically different levels between groups,

values were grouped together into a single group. Linear regression was also used to determine the Pearson's product-moment correlation coefficient (r) between peak values as measured during (a) incremental dynamic exercise and (b) constant-work isometric exercise (condition: PL-TN). Data are presented as means ± standard deviation unless indicated otherwise. The α-level of significance was set a priori at 0.05.

5. Conclusions

The findings of the present study suggest that heat exposure but not capsaicin application alleviates the hypertensive response to exercise by virtue of lower values of arterial blood pressure observed during moderate isometric exercise. Environmental temperature, application sites as well as the temporal characteristics of capsaicin action stand out as factors that should be controlled for when assessing the ability of capsaicin patches to attenuate exercise-induced hypertension.

Author Contributions: Conceptualization, A.S. and N.D.G.; methodology, A.S., M.D.K. and N.D.G.; formal analysis, A.S.; investigation, A.S., A.M. and M.D.K.; resources, A.S., M.D.K. and N.D.G.; data curation, A.S.; writing—original draft preparation, A.S.; writing—review and editing, A.S., A.M., M.D.K. and N.D.G.; visualization, A.S.; supervision, M.D.K. and N.D.G.; project administration, N.D.G.; funding acquisition, A.S. All authors have read and agreed to the published version of the manuscript.

Funding: This research is co-financed by Greece and the European Union (European Social Fund-ESF) through the Operational Programme «Human Resources Development, Education and Lifelong Learning» in the context of the project "Reinforcement of Postdoctoral Researchers—2nd Cycle" (MIS-5033021), implemented by the State Scholarships Foundation (IKϒ, number of grant: 2019-050-0503-17832).

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of School of Physical Education and Sports Science, National and Kapodistrian University of Athens (protocol code: 1188/13-05-2020).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data are not publicly available due to privacy and ethical concerns.

Acknowledgments: We are grateful to the study participants. We are further indebted to Charalambos Dardamanis-Aidonas, Konstantinos Papastathis and Dionysios-Ermis Geladas that contributed to data collection.

Conflicts of Interest: The authors declare no conflicts of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

References

1. Williams, B.; Mancia, G.; Spiering, W.; Agabiti Rosei, E.; Azizi, M.; Burnier, M.; Clement, D.L.; Coca, A.; de Simone, G.; Dominiczak, A.; et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur. Heart J.* **2018**, *39*, 3021–3104. [CrossRef] [PubMed]
2. Stergiou, G.S.; Menti, A.; Kalpourtzi, N.; Gavana, M.; Vantarakis, A.; Chlouverakis, G.; Hajichristodoulou, C.; Trypsianis, G.; Voulgari, P.V.; Alamanos, Y.; et al. Prevalence, awareness, treatment and control of hypertension in Greece: EMENO national epidemiological study. *J. Hypertens.* **2021**, *39*, 1034–1039. [CrossRef] [PubMed]
3. Kannel, W.B. Framingham study insights into hypertensive risk of cardiovascular disease. *Hypertens. Res.* **1995**, *18*, 181–196. [CrossRef] [PubMed]
4. Petrie, J.R.; Guzik, T.J.; Touyz, R.M. Diabetes, Hypertension, and Cardiovascular Disease: Clinical Insights and Vascular Mechanisms. *Can. J. Cardiol.* **2018**, *34*, 575–584. [CrossRef]
5. Tso, M.O.; Jampol, L.M. Pathophysiology of hypertensive retinopathy. *Ophthalmology* **1982**, *89*, 1132–1145. [CrossRef] [PubMed]
6. de Oliveira, A.A.; Nunes, K.P. Hypertension and Erectile Dysfunction: Breaking Down the Challenges. *Am. J. Hypertens.* **2021**, *34*, 134–142. [CrossRef]
7. Dawson, A.N.; Walser, B.; Jafarzadeh, M.; Stebbins, C.L. Topical analgesics and blood pressure during static contraction in humans. *Med. Sci. Sports Exerc.* **2004**, *36*, 632–638. [CrossRef]

8. Kawada, T.; Suzuki, T.; Takahashi, M.; Iwai, K. Gastrointestinal absorption and metabolism of capsaicin and dihydrocapsaicin in rats. *Toxicol. Appl. Pharmacol.* **1984**, *72*, 449–456. [CrossRef]
9. Rollyson, W.D.; Stover, C.A.; Brown, K.C.; Perry, H.E.; Stevenson, C.D.; McNees, C.A.; Ball, J.G.; Valentovic, M.A.; Dasgupta, P. Bioavailability of capsaicin and its implications for drug delivery. *J. Control Release* **2014**, *196*, 96–105. [CrossRef]
10. Chaiyasit, K.; Khovidhunkit, W.; Wittayalertpanya, S. Pharmacokinetic and the effect of capsaicin in Capsicum frutescens on decreasing plasma glucose level. *J. Med. Assoc. Thai* **2009**, *92*, 108–113.
11. O'Neill, J.; Brock, C.; Olesen, A.E.; Andresen, T.; Nilsson, M.; Dickenson, A.H. Unravelling the mystery of capsaicin: A tool to understand and treat pain. *Pharmacol. Rev.* **2012**, *64*, 939–971. [CrossRef] [PubMed]
12. Hammer, J.; Vogelsang, H. Characterization of sensations induced by capsaicin in the upper gastrointestinal tract. *Neurogastroenterol. Motil.* **2007**, *19*, 279–287. [CrossRef] [PubMed]
13. Botonis, P.G.; Miliotis, P.G.; Kounalakis, S.N.; Koskolou, M.D.; Geladas, N.D. Effects of capsaicin application on the skin during resting exposure to temperate and warm conditions. *Scand. J. Med. Sci. Sports* **2019**, *29*, 171–179. [CrossRef] [PubMed]
14. Chalacheva, P.; Khaleel, M.; Sunwoo, J.; Shah, P.; Detterich, J.A.; Kato, R.M.; Thuptimdang, W.; Meiselman, H.J.; Sposto, R.; Tsao, J.; et al. Biophysical markers of the peripheral vasoconstriction response to pain in sickle cell disease. *PLoS ONE* **2017**, *12*, e0178353. [CrossRef] [PubMed]
15. Nordin, M.; Fagius, J. Effect of noxious stimulation on sympathetic vasoconstrictor outflow to human muscles. *J. Physiol.* **1995**, *489*, 885–894. [CrossRef] [PubMed]
16. Anand, P.; Bley, K. Topical capsaicin for pain management: Therapeutic potential and mechanisms of action of the new high-concentration capsaicin 8% patch. *Br. J. Anaesth.* **2011**, *107*, 490–502. [CrossRef] [PubMed]
17. Yang, D.; Luo, Z.; Ma, S.; Wong, W.T.; Ma, L.; Zhong, J.; He, H.; Zhao, Z.; Cao, T.; Yan, Z.; et al. Activation of TRPV1 by dietary capsaicin improves endothelium-dependent vasorelaxation and prevents hypertension. *Cell Metab.* **2010**, *12*, 130–141. [CrossRef]
18. Wong, B.J.; Fieger, S.M. Transient receptor potential vanilloid type-1 (TRPV-1) channels contribute to cutaneous thermal hyperaemia in humans. *J. Physiol.* **2010**, *588*, 4317–4326. [CrossRef]
19. Stephens, D.P.; Charkoudian, N.; Benevento, J.M.; Johnson, J.M.; Saumet, J.L. The influence of topical capsaicin on the local thermal control of skin blood flow in humans. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2001**, *281*, R894–R901. [CrossRef]
20. Rowell, L.B. Human cardiovascular adjustments to exercise and thermal stress. *Physiol. Rev.* **1974**, *54*, 75–159. [CrossRef]
21. Crandall, C.G.; Wilson, T.E. Human cardiovascular responses to passive heat stress. *Compr. Physiol.* **2015**, *5*, 17–43. [CrossRef] [PubMed]
22. Brunt, V.E.; Howard, M.J.; Francisco, M.A.; Ely, B.R.; Minson, C.T. Passive heat therapy improves endothelial function, arterial stiffness and blood pressure in sedentary humans. *J. Physiol.* **2016**, *594*, 5329–5342. [CrossRef] [PubMed]
23. Giorgini, P.; Di Giosia, P.; Petrarca, M.; Lattanzio, F.; Stamerra, C.A.; Ferri, C. Climate Changes and Human Health: A Review of the Effect of Environmental Stressors on Cardiovascular Diseases Across Epidemiology and Biological Mechanisms. *Curr. Pharm. Des.* **2017**, *23*, 3247–3261. [CrossRef] [PubMed]
24. Low, D.A.; Keller, D.M.; Wingo, J.E.; Brothers, R.M.; Crandall, C.G. Sympathetic nerve activity and whole body heat stress in humans. *J. Appl. Physiol.* **2011**, *111*, 1329–1334. [CrossRef] [PubMed]
25. Rowell, L.B.; Brengelmann, G.L.; Murray, J.A. Cardiovascular responses to sustained high skin temperature in resting man. *J. Appl. Physiol.* **1969**, *27*, 673–680. [CrossRef] [PubMed]
26. Schultz, M.G.; Sharman, J.E. Exercise Hypertension. *Pulse* **2014**, *1*, 161–176. [CrossRef] [PubMed]
27. Kim, D.; Ha, J.W. Hypertensive response to exercise: Mechanisms and clinical implication. *Clin. Hypertens.* **2016**, *22*, 17. [CrossRef]
28. Lorbeer, R.; Ittermann, T.; Volzke, H.; Glaser, S.; Ewert, R.; Felix, S.B.; Dorr, M. Assessing cutoff values for increased exercise blood pressure to predict incident hypertension in a general population. *J. Hypertens.* **2015**, *33*, 1386–1393. [CrossRef]
29. American College of Sports Medicine. *ACSM's Guidelines for Exercise Testing and Prescription*, 6th ed.; Lippincott Williams & Wilkins: Philadelphia, PA, USA, 2000.
30. Cherouveim, E.D.; Miliotis, P.G.; Koskolou, M.D.; Dipla, K.; Vrabas, I.S.; Geladas, N.D. The Effect of Skeletal Muscle Oxygenation on Hemodynamics, Cerebral Oxygenation and Activation, and Exercise Performance during Incremental Exercise to Exhaustion in Male Cyclists. *Biology* **2023**, *12*, 981. [CrossRef]
31. Lima, E.G.; Spritzer, N.; Herkenhoff, F.L.; Bermudes, A.; Vasquez, E.C. Noninvasive ambulatory 24-hour blood pressure in patients with high normal blood pressure and exaggerated systolic pressure response to exercise. *Hypertension* **1995**, *26*, 1121–1124. [CrossRef]
32. Jae, S.Y.; Franklin, B.A.; Choo, J.; Choi, Y.H.; Fernhall, B. Exaggerated Exercise Blood Pressure Response During Treadmill Testing as a Predictor of Future Hypertension in Men: A Longitudinal Study. *Am. J. Hypertens.* **2015**, *28*, 1362–1367. [CrossRef] [PubMed]
33. Gupta, M.P.; Polena, S.; Coplan, N.; Panagopoulos, G.; Dhingra, C.; Myers, J.; Froelicher, V. Prognostic significance of systolic blood pressure increases in men during exercise stress testing. *Am. J. Cardiol.* **2007**, *100*, 1609–1613. [CrossRef] [PubMed]
34. Seals, D.R. Influence of force on muscle and skin sympathetic nerve activity during sustained isometric contractions in humans. *J. Physiol.* **1993**, *462*, 147–159. [CrossRef] [PubMed]
35. Smolander, J.; Aminoff, T.; Korhonen, I.; Tervo, M.; Shen, N.; Korhonen, O.; Louhevaara, V. Heart rate and blood pressure responses to isometric exercise in young and older men. *Eur. J. Appl. Physiol. Occup. Physiol.* **1998**, *77*, 439–444. [CrossRef]
36. Vianna, L.C.; Fernandes, I.A.; Barbosa, T.C.; Teixeira, A.L.; Nobrega, A.C.L. Capsaicin-based analgesic balm attenuates the skeletal muscle metaboreflex in healthy humans. *J. Appl. Physiol.* **2018**, *125*, 362–368. [CrossRef]

37. Mitchell, J.H.; Kaufman, M.P.; Iwamoto, G.A. The exercise pressor reflex: Its cardiovascular effects, afferent mechanisms, and central pathways. *Annu. Rev. Physiol.* **1983**, *45*, 229–242. [CrossRef] [PubMed]
38. Nelson, A.J.; Ragan, B.G.; Bell, G.W.; Ichiyama, R.M.; Iwamoto, G.A. Capsaicin-based analgesic balm decreases pressor responses evoked by muscle afferents. *Med. Sci. Sports Exerc.* **2004**, *36*, 444–450. [CrossRef]
39. Fusco, B.M.; Giacovazzo, M. Peppers and pain. The promise of capsaicin. *Drugs* **1997**, *53*, 909–914. [CrossRef]
40. Koletsos, N.; Dipla, K.; Triantafyllou, A.; Gkaliagkousi, E.; Sachpekidis, V.; Zafeiridis, A.; Douma, S. A brief submaximal isometric exercise test 'unmasks' systolic and diastolic masked hypertension. *J. Hypertens.* **2019**, *37*, 710–719. [CrossRef]
41. Shibasaki, M.; Secher, N.H.; Johnson, J.M.; Crandall, C.G. Central command and the cutaneous vascular response to isometric exercise in heated humans. *J. Physiol.* **2005**, *565*, 667–673. [CrossRef]
42. Joyner, M.J. Muscle chemoreflexes and exercise in humans. *Clin. Auton. Res.* **1992**, *2*, 201–208. [CrossRef] [PubMed]
43. Zsiboras, C.; Matics, R.; Hegyi, P.; Balasko, M.; Petervari, E.; Szabo, I.; Sarlos, P.; Miko, A.; Tenk, J.; Rostas, I.; et al. Capsaicin and capsiate could be appropriate agents for treatment of obesity: A meta-analysis of human studies. *Crit. Rev. Food Sci. Nutr.* **2018**, *58*, 1419–1427. [CrossRef] [PubMed]
44. Ludy, M.J.; Moore, G.E.; Mattes, R.D. The effects of capsaicin and capsiate on energy balance: Critical review and meta-analyses of studies in humans. *Chem. Senses* **2012**, *37*, 103–121. [CrossRef] [PubMed]
45. Shirani, F.; Foshati, S.; Tavassoly, M.; Clark, C.C.T.; Rouhani, M.H. The effect of red pepper/capsaicin on blood pressure and heart rate: A systematic review and meta-analysis of clinical trials. *Phytother. Res.* **2021**, *35*, 6080–6088. [CrossRef] [PubMed]
46. Grgic, J.; Memon, A.R.; Chen, S.; Ramirez-Campillo, R.; Barreto, G.; Haugen, M.E.; Schoenfeld, B.J. Effects of Capsaicin and Capsiate on Endurance Performance: A Meta-Analysis. *Nutrients* **2022**, *14*, 4531. [CrossRef] [PubMed]
47. Mantysaari, M.J.; Antila, K.J.; Peltonen, T.E. Circulatory effects of anticipation in a light isometric handgrip test. *Psychophysiology* **1988**, *25*, 179–184. [CrossRef]
48. Voets, T.; Droogmans, G.; Wissenbach, U.; Janssens, A.; Flockerzi, V.; Nilius, B. The principle of temperature-dependent gating in cold- and heat-sensitive TRP channels. *Nature* **2004**, *430*, 748–754. [CrossRef]
49. Caterina, M.J.; Schumacher, M.A.; Tominaga, M.; Rosen, T.A.; Levine, J.D.; Julius, D. The capsaicin receptor: A heat-activated ion channel in the pain pathway. *Nature* **1997**, *389*, 816–824. [CrossRef]
50. Gifford, J.R.; Ives, S.J.; Park, S.Y.; Andtbacka, R.H.; Hyngstrom, J.R.; Mueller, M.T.; Treiman, G.S.; Ward, C.; Trinity, J.D.; Richardson, R.S. alpha1- and alpha2-adrenergic responsiveness in human skeletal muscle feed arteries: The role of TRPV ion channels in heat-induced sympatholysis. *Am. J. Physiol. Heart Circ. Physiol.* **2014**, *307*, H1288–H1297. [CrossRef]
51. Ives, S.J.; Park, S.Y.; Kwon, O.S.; Gifford, J.R.; Andtbacka, R.H.I.; Hyngstrom, J.R.; Richardson, R.S. TRPV(1) channels in human skeletal muscle feed arteries: Implications for vascular function. *Exp. Physiol.* **2017**, *102*, 1245–1258. [CrossRef]
52. Joyner, M.J.; Charkoudian, N.; Wallin, B.G. A sympathetic view of the sympathetic nervous system and human blood pressure regulation. *Exp. Physiol.* **2008**, *93*, 715–724. [CrossRef] [PubMed]
53. Wilson, T.E.; Crandall, C.G. Effect of thermal stress on cardiac function. *Exerc. Sport Sci. Rev.* **2011**, *39*, 12–17. [CrossRef]
54. Pizzey, F.K.; Smith, E.C.; Ruediger, S.L.; Keating, S.E.; Askew, C.D.; Coombes, J.S.; Bailey, T.G. The effect of heat therapy on blood pressure and peripheral vascular function: A systematic review and meta-analysis. *Exp. Physiol.* **2021**, *106*, 1317–1334. [CrossRef]
55. Caldwell, A.R.; Robinson, F.B.; Tucker, M.A.; Arcement, C.H.; Butts, C.L.; McDermott, B.P.; Ganio, M.S. Effect of passive heat stress and exercise in the heat on arterial stiffness. *Eur. J. Appl. Physiol.* **2017**, *117*, 1679–1687. [CrossRef] [PubMed]
56. Victor, R.G.; Secher, N.H.; Lyson, T.; Mitchell, J.H. Central command increases muscle sympathetic nerve activity during intense intermittent isometric exercise in humans. *Circ. Res.* **1995**, *76*, 127–131. [CrossRef] [PubMed]
57. Smith, S.A.; Mitchell, J.H.; Garry, M.G. The mammalian exercise pressor reflex in health and disease. *Exp. Physiol.* **2006**, *91*, 89–102. [CrossRef]
58. Vanhoutte, P.M. Adjustments in the peripheral circulation in chronic heart failure. *Eur. Heart J.* **1983**, *4* (Suppl. A), 67–83. [CrossRef]
59. Spranger, M.D.; Kaur, J.; Sala-Mercado, J.A.; Krishnan, A.C.; Abu-Hamdah, R.; Alvarez, A.; Machado, T.M.; Augustyniak, R.A.; O'Leary, D.S. Exaggerated coronary vasoconstriction limits muscle metaboreflex-induced increases in ventricular performance in hypertension. *Am. J. Physiol. Heart Circ. Physiol.* **2017**, *312*, H68–H79. [CrossRef]
60. Julius, S. Transition from high cardiac output to elevated vascular resistance in hypertension. *Am. Heart J.* **1988**, *116*, 600–606. [CrossRef]
61. Botonis, P.G.; Miliotis, P.G.; Kounalakis, S.N.; Koskolou, M.D.; Geladas, N.D. Thermoregulatory and cardiovascularеffects of capsaicin application on human skin during dynamic exercise to temperate and warm conditions. *Physiol. Rep.* **2019**, *7*, e14325. [CrossRef]
62. Fujii, N.; Meade, R.D.; Alexander, L.M.; Akbari, P.; Foudil-Bey, I.; Louie, J.C.; Boulay, P.; Kenny, G.P. iNOS-dependent sweating and eNOS-dependent cutaneous vasodilation are evident in younger adults, but are diminished in older adults exercising in the heat. *J. Appl. Physiol.* **2016**, *120*, 318–327. [CrossRef] [PubMed]
63. Welch, G.; Foote, K.M.; Hansen, C.; Mack, G.W. Nonselective NOS inhibition blunts the sweat response to exercise in a warm environment. *J. Appl. Physiol.* **2009**, *106*, 796–803. [CrossRef] [PubMed]
64. Kondo, N.; Tominaga, H.; Shibasaki, M.; Aoki, K.; Koga, S.; Nishiyasu, T. Modulation of the thermoregulatory sweating response to mild hyperthermia during activation of the muscle metaboreflex in humans. *J. Physiol.* **1999**, *515*, 591–598. [CrossRef] [PubMed]

65. Shibasaki, M.; Kondo, N.; Crandall, C.G. Evidence for metaboreceptor stimulation of sweating in normothermic and heat-stressed humans. *J. Physiol.* **2001**, *534*, 605–611. [CrossRef] [PubMed]
66. Waldron, M.; David Patterson, S.; Jeffries, O. Inter-Day Reliability of Finapres ((R)) Cardiovascular Measurements During Rest and Exercise. *Sports Med. Int. Open* **2018**, *2*, E9–E15. [CrossRef]
67. Guelen, I.; Westerhof, B.E.; van der Sar, G.L.; van Montfrans, G.A.; Kiemeneij, F.; Wesseling, K.H.; Bos, W.J. Validation of brachial artery pressure reconstruction from finger arterial pressure. *J. Hypertens.* **2008**, *26*, 1321–1327. [CrossRef] [PubMed]
68. Mlinar, T.; Jaki Mekjavic, P.; Royal, J.T.; Valencic, T.; Mekjavic, I.B. Intraocular pressure during handgrip exercise: The effect of posture and hypercapnia in young males. *Physiol. Rep.* **2021**, *9*, e15035. [CrossRef]
69. Shinohara, T.; Tsuchida, N.; Seki, K.; Otani, T.; Yamane, T.; Ishihara, Y.; Usuda, C. Can blood pressure be measured during exercise with an automated sphygmomanometer based on an oscillometric method? *J. Phys. Ther. Sci.* **2017**, *29*, 1006–1009. [CrossRef]
70. Miyai, N.; Arita, M.; Miyashita, K.; Morioka, I.; Shiraishi, T.; Nishio, I. Blood pressure response to heart rate during exercise test and risk of future hypertension. *Hypertension* **2002**, *39*, 761–766. [CrossRef]
71. Schultz, M.G.; Otahal, P.; Cleland, V.J.; Blizzard, L.; Marwick, T.H.; Sharman, J.E. Exercise-induced hypertension, cardiovascular events, and mortality in patients undergoing exercise stress testing: A systematic review and meta-analysis. *Am. J. Hypertens.* **2013**, *26*, 357–366. [CrossRef]
72. Kayrak, M.; Bacaksiz, A.; Vatankulu, M.A.; Ayhan, S.S.; Kaya, Z.; Ari, H.; Sonmez, O.; Gok, H. Exaggerated blood pressure response to exercise—A new portent of masked hypertension. *Clin. Exp. Hypertens.* **2010**, *32*, 560–568. [CrossRef] [PubMed]
73. Wilson, M.F.; Sung, B.H.; Pincomb, G.A.; Lovallo, W.R. Exaggerated pressure response to exercise in men at risk for systemic hypertension. *Am. J. Cardiol.* **1990**, *66*, 731–736. [CrossRef] [PubMed]
74. Allison, T.G.; Cordeiro, M.A.; Miller, T.D.; Daida, H.; Squires, R.W.; Gau, G.T. Prognostic significance of exercise-induced systemic hypertension in healthy subjects. *Am. J. Cardiol.* **1999**, *83*, 371–375. [CrossRef] [PubMed]
75. Mancia, G.; Fagard, R.; Narkiewicz, K.; Redon, J.; Zanchetti, A.; Bohm, M.; Christiaens, T.; Cifkova, R.; De Backer, G.; Dominiczak, A.; et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J. Hypertens.* **2013**, *31*, 1281–1357. [CrossRef] [PubMed]
76. Mitchell, J.H. Abnormal cardiovascular response to exercise in hypertension: Contribution of neural factors. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2017**, *312*, R851–R863. [CrossRef] [PubMed]
77. Parati, G.; Casadei, R.; Groppelli, A.; Di Rienzo, M.; Mancia, G. Comparison of finger and intra-arterial blood pressure monitoring at rest and during laboratory testing. *Hypertension* **1989**, *13*, 647–655. [CrossRef]
78. Richard, N.A.; Hodges, L.; Koehle, M.S. Elevated peak systolic blood pressure in endurance-trained athletes: Physiology or pathology? *Scand. J. Med. Sci. Sports* **2021**, *31*, 956–966. [CrossRef]
79. Molineux, D.; Steptoe, A. Exaggerated blood pressure responses to submaximal exercise in normotensive adolescents with a family history of hypertension. *J. Hypertens.* **1988**, *6*, 361–365. [CrossRef]
80. Burton, A.C. The Application of the Theory of Heat Flow to the Study of Energy Metabolism: Five Figures. *J. Nutr.* **1934**, *7*, 497–533. [CrossRef]
81. Keramidas, M.E.; Geladas, N.D.; Mekjavic, I.B.; Kounalakis, S.N. Forearm-finger skin temperature gradient as an index of cutaneous perfusion during steady-state exercise. *Clin. Physiol. Funct. Imaging* **2013**, *33*, 400–404. [CrossRef]
82. Luo, M.; Wang, Z.; Zhang, H.; Arens, E.; Filingeri, D.; Jin, L.; Ghahramani, A.; Chen, W.; He, Y.; Si, B. High-density thermal sensitivity maps of the human body. *Build. Environ.* **2020**, *167*, 106435. [CrossRef]
83. Borg, G. Perceived exertion as an indicator of somatic stress. *Scand. J. Rehabil. Med.* **1970**, *2*, 92–98. [CrossRef] [PubMed]