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Altered core and skin temperature responses to endurance exercise in heart failure patients and healthy controls.

ALTERED CORE AND SKIN TEMPERATURE RESPONSES TO ENDURANCE EXERCISE IN HEART FAILURE PATIENTS AND HEALTHY CONTROLS

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Short title: Thermoregulatory responses to exercise in heart failure

WORD COUNT: 4182
FIGURES: 2
TABLES: 1

D.H.J.T. was supported by the Netherlands Heart Foundation [E Dekker-stipend, 2009T064] and T.M.H.E. was supported by the Netherlands Organisation for Scientific Research [Rubicon Grant 825.12.016].

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ABSTRACT

Background. Exercise training represents a central aspect of rehabilitation of heart failure (HF) patients. Previous work on passive heating suggests impaired thermoregulatory responses in HF patients. However, no previous study directly examined thermoregulatory responses to an exercise bout, i.e. active heating, as typically applied in rehabilitation settings in HF.

Design. Cross-sectional observational study to compare changes in core body temperature (Tcore) and skin temperature (Tskin) during cycling exercise between HF patients and controls.

Methods. Fourteen HF subjects (65±7 yrs, 13:1 male:female) and 14 healthy controls (61±5 yrs, 12:2 male:female) were included. Tcore (telemetric temperature pill) and Tskin (skin thermistors) were measured continuously during a 45-minute cycle exercise bout at comparable *relative* exercise intensity.

Results. Tcore increased to a similar extend in both groups (controls 1.1±0.4°C, HF 0.9±0.3°C, 'time*group': P=0.149). Tskin decreased during the initial phase of exercise in both groups, followed by an increase in Tskin in controls (1.2±1.0°C), whilst Tskin remained low in HF patients (-0.3±1.4°C) ('time*group': P<0.001). Furthermore, we found that a given change in Tcore was associated with a smaller increase in Tskin in HF compared to controls. When comparing HF patients and controls who performed exercise at similar absolute workload, between-group differences disappeared (P-values >0.05).

Conclusion. HF patients and controls show a comparable exercise-induced increase in Tcore, whilst HF patients demonstrate altered Tskin responses to exercise and attenuated elevation in Tskin *per* increase in Tcore. These impaired thermoregulatory responses to exercise are, at least partly, explained by the low physical fitness level in HF patients.

ABSTRACT WORD COUNT: 249

KEYWORDS: body temperature, skin temperature, body temperature regulation, heart failure, exercise

INTRODUCTION

Physical fitness is an important factor in the progression and prognosis of heart failure (HF) patients (1). Therefore, exercise programs are increasingly important in cardiac rehabilitation and HF patients are recommended to perform regular physical activity (2). However, HF patients are limited in their exercise performance, as a result of a reduced myocardial function and abnormalities of peripheral tissues that prevent sufficient blood supply to active muscles during exercise (3). Furthermore, disturbed thermoregulatory responses during exercise may limit performance in HF patients (4-6).

In healthy subjects, core body temperature (Tcore) rises during exercise as a result of the production of heat in active muscles (7). Consequently, cutaneous perfusion, skin temperature (Tskin) and sweat production will increase to dissipate heat (7). Studies that have examined changes in Tcore and Tskin in HF patients during exercise have largely focused on the *initial* responses during exercise. During the onset of exercise, a paradoxical decrease in core body temperature is observed in HF patients compared to healthy subjects (4, 6), possibly as a result of redistribution of cooler blood from the skin to the core. In addition, HF patients show excessive cutaneous vasoconstriction and a persistent decline in Tskin compared to controls (4, 5). However, these exercise studies adopted a short (≤11 min) period of exercise at low absolute intensity, leading to low heat production. As thermoregulatory responses are more important during prolonged exercise, these previous studies provide only limited insight into the potential impact of HF on changes in Tcore and Tskin during exercise.

To date no previous study comprehensively examined the thermoregulatory responses in HF patients to a typical bout of exercise training as applied in cardiac rehabilitation. Therefore, the main question of our study was whether HF patients and healthy controls differ in thermoregulatory responses during a moderate intensity endurance exercise bout. To study this, we measured changes in Tcore and Tskin during a 45-minute cycle exercise bout at comparable *relative* exercise intensity in HF patients and controls. We hypothesize that exercise in HF patients leads to a larger increase in Tcore and lower Tskin compared to healthy controls, suggesting an impaired thermoregulatory response to exercise in HF patients.

METHODS

Subjects

Fourteen patients with HF (65±7 yrs, 13:1 male:female) NYHA class II/III and a left ventricular ejection fraction (LVEF) lower than 45% were recruited from the departments of Cardiology of the Radboud university medical center and the Canisius Wilhelmina hospital (Nijmegen, The Netherlands) (Table 1). Furthermore, we recruited 14 healthy controls (61±5 yrs, 12:2 male:female) from the local population (Table 1). We included patients who were in a pharmacologically and clinically stable situation for at least one month. One patient increased the dosage of fosinopril one week prior to the measurements. Control subjects had to be free of cardiovascular diseases and medication affecting the cardiovascular system. All subjects were non-diabetic. This study was approved by the Medical Ethical Committee of the Radboud university medical center (CMO Arnhem-Nijmegen, 2012/355) and complies with the Declaration of Helsinki. Written informed consent was obtained from each subject before participation in this study.

Experimental protocol

Subjects reported to the laboratory twice. On day 1, a medical screening was performed after which subjects underwent a maximal incremental cycling test to determine physical fitness. On day 2, subjects were instructed to ingest the telemetric temperature pill six hours prior to testing to ensure stable and valid recording of Tcore (8). The measurements were performed in a temperature-controlled room (21.9 ± 0.8 ºC). After instrumentation, subjects rested in the supine position for 10 minutes, followed by measurement of blood pressure and heart rate. Subsequently, subjects were positioned on the cycle ergometer for moderate intensity cycling exercise. The exercise protocol started with a 10-minute warm-up, followed by 30 minutes of moderate intensity exercise, and concluded by a 5-minute cooling down. During the study protocol we continuously measured: 1. Tcore, 2. average Tskin (4-point measurement), 3. skin temperature gradient between forearm and finger ($Tsk_{forearm-finger}$), and 4. heart rate.

Day 1: Medical screening and maximal incremental cycling test

Medical screening consisted of a medical history and a physical examination in which blood pressure and heart frequency were obtained. Furthermore, body weight and height were measured to calculate body mass index (BMI) and body surface area (BSA) using the Du Bois formula, and skin fold thickness was measured to estimate body fat percentage.

The incremental maximal cycling test was performed on a cycle ergometer (Lode, Excalibur v1.52, 1991, Groningen, the Netherlands/Ergoline, Ergoselect 200k, Bitz, Germany). After a 2-minute baseline measurement, subjects started cycling and workload was increased by 10-25 Watt per minute, depending on the sex, age and height of the participant. Subjects were instructed to pedal at a frequency of >60 rpm until volitional exhaustion. During the maximal exercise test we continuously measured oxygen consumption (breath-by-breath, CPET Cosmed v9.1b, Rome, Italy/LabManager V5.32.0), to determine peak oxygen uptake

(VO_{2peak}), which was defined as the average oxygen uptake during the last 30 seconds of the exercise test.

Day 2: Cycle exercise bout

A 10-minute warm-up at a heart frequency corresponding with 40% of VO_{2peak} was performed, followed by 30-minute moderate intensity exercise at 65% of VO_{2peak}. A 5-minute cooling down at 30% of VO_{2peak} concluded each session. To verify exercise intensity, heart rate was registered continuously using a heart rate monitor (Polar Electro Oy, Kempele, Finland). At the end of the warm-up and at 10-minute intervals, we assessed the rate of perceived exertion using the Borg score (scale 6-20) (9).

Tcore and Tskin measurements

To measure Tcore, subjects ingested a telemetric temperature pill (CorTemp Wireless Monitoring System, HQ Inc., Palmetto, USA). Tcore was recorded every 30 seconds and transmitted to a receiver which was worn in a pouch around the waist. Previous studies demonstrated that this method is reliable and valid in rest and during exercise (8).

Tskin was measured every 30 seconds using iButtons (Thermochron iButton DS1291H, Maxim, Dallas, United States). Skin thermistors were attached to the skin using medical tape at the left hand (dorsal side), right scapula, right shin (at the fibula head) and neck to calculate mean Tskin according to the ISO 9886 guidelines; a weighted average of the neck (0.28), left hand (0.16), right scapula (0.28) and right shin (0.28) (10). Moreover, Tskin was also registered at the right lower arm and middle fingertip (ventral side) to calculate $Tskin_{forearm-finger}$, a qualitative index of peripheral perfusion during steady state exercise (11). This is a validated index of peripheral cutaneous vasomotor tone during steady-state exercise (11).

Tcore and Tskin data were analysed using custom made software (Fysitemp, Radboudumc, Nijmegen, The Netherlands) based on Matlab (Matlab R2008a, MathWorks, Natick, MA). Baseline values were determined from the average over 5 minutes preceding exercise. As previous work found changes in thermoregulatory responses during exercise of short duration (<11min) (4, 6), Tcore and Tskin values were averaged over 2-minute intervals during the first 10 minutes of exercise (warm-up). Thereafter, 5-minute intervals were calculated during the remainder of the exercise bout. To explore the relationship between exercise-induced increases in Tcore and changes in Tskin, Tskin was plotted against changes in Tcore.

Statistical analysis

Baseline characteristics of HF patients and controls were compared using independent Student's *t* tests. A 2-way repeated measures ANOVA was used to examine whether exercise-induced changes in Tcore and Tskin across time ('time'; within-subject factor) differed between HF patients and healthy controls ('group'; between-subject factor, 'time*group'; interaction effect). When a significant main or interaction effect was observed, Least Square Difference post-hoc tests were used to identify differences. Due to a potential difference in absolute workload between the HF patient and control group, we included a subgroup analysis with comparable absolute workloads. Data were presented as mean±SD unless stated otherwise. Significance level was set at $P \leq 0.05$.

RESULTS

Subject characteristics

HF patients demonstrated a higher BMI and a lower VO_{2peak} compared to controls, whilst no significant differences between groups were found for age, body weight, BSA, and systolic and diastolic blood pressure (Table 1). We included 8 HF patients with ischemic HF and 6 with non-ischemic HF. Cardiovascular medication use by HF patients is presented in Table 1. Both groups exercised at comparable relative intensity (%max workload) and rate of perceived exertion (Table 1). Absolute workload of the cycle exercise bout was significantly higher in controls compared to HF patients (Table 1).

Thermoregulatory responses to exercise

Tcore. Tcore measurements were performed in 5 HF patients and 12 controls due to specific contra-indications of the telemetric pill (e.g. pacemaker) (12). Tcore was comparable for HF patients and controls at baseline (P=0.901). After the onset of exercise, Tcore gradually increased in both groups to a similar extend (controls 1.1±0.4°C, HF 0.9±0.3°C, 'time*group'-interaction: P=0.149, Figure 1A).

Tskin. At baseline, Tskin was comparable between groups (P=0.477). Tskin decreased during the initial phase of exercise in both groups (Figure 1B). In control subjects, Tskin returned to baseline values after 30 minutes, whilst in HF patients Tskin remained low throughout the exercise period ('time*group'-interaction: P<0.001, Figure 1B). When exercise-induced changes in Tskin are plotted against changes in Tcore, control subjects showed a larger increase in Tskin for a given increase in Tcore compared to HF patients (Figure 2A).

$Tskin_{forearm\text{-}finger}$. $\mathrm{Tskin_{forearm\text{-}finger}}$ was comparable between both groups at baseline. Controls showed a persistent decrease in this index during exercise, indicative of an increase in cutaneous blood flow, which was not present in HF patients ('time*group'-interaction: P=0.019).

Subgroup analysis. In our subanalysis, HF patients with the highest workload (male:female 8:0, 63±7 yrs) and control subjects with the lowest workload (male:female 3:2, 64±7 yrs) were included, allowing us to correct for differences in workload. These groups exercised at comparable workload (89±15W and 90±22W respectively, P=0.891). Tcore demonstrated a comparable exercise-induced increase in HF patients and controls (‘group’-effect; P=0.830, ‘time*group’-interaction; P=0.471, Figure 1C). Tskin decreased during the initial phase of exercise, after which Tskin increased to baseline values after 40 minutes of exercise (‘time’-effect; P<0.001, Figure 1D). This change was similarly present in HF patients and controls (‘group’-effect; P=0.176, ‘time*group’-interaction; P=0.307, Figure 1D). When changes in Tskin are plotted against exercise-induced changes in Tcore, HF patients show a similar pattern as controls (Figure 2B).

DISCUSSION

This study compared thermoregulatory responses to moderate intensity cycle exercise between HF patients and healthy controls. First, we found that HF patients and controls show a comparable increase in Tcore when exercise is performed at comparable *relative* exercise intensity (but lower absolute workload). Second, after an initial decrease in Tskin at the onset of exercise, controls demonstrate an increase in Tskin towards baseline values, whilst Tskin remains low in HF patients. Furthermore, when analysing the relation between Tcore and Tskin, HF patients consistently demonstrate an attenuated increase in Tskin for a given increase in Tcore during exercise. These differences in Tcore and Tskin responses to exercise disappear when examining a subgroup of controls and HF patients who performed cycle exercise at comparable *absolute* workload.

When exercise is performed at similar relative exercise intensity, a comparable and gradual increase in core body temperature is observed in HF patients and their controls. In line with previous work (4, 6), these changes in core body temperature are accompanied by distinct changes in skin temperature between HF and controls at the start of exercise. However, we importantly extend these previous findings by demonstrating that these differences in skin temperature responses to exercise remain present when continuing exercise. More specifically, similar to previous literature we found that healthy subjects demonstrate skin temperature to return to (or even exceed) baseline skin temperature after the initial drop (4, 13). In contrast, HF patients demonstrate a consistent decreased skin temperature throughout the exercise bout. The absence of a normalization of skin temperature may relate to an inability to increase skin perfusion. As an index of cutaneous vasomotor function during exercise, we measured $Tskin_{forearm\text{-}finger}$ (11). In line with previous work in healthy volunteers using laser-Doppler (14), the decrease in $Tskin_{forearm\text{-}finger}$ index in healthy controls reflects forearm skin vasodilation during cycling exercise. In contrast, exercise in HF patients did not evoke a change in $Tskin_{forearm\text{-}finger}$ index, suggesting an impaired skin perfusion in response to moderate intensity cycle exercise in HF patients.

To provide further insight into the impact of exercise on thermoregulation, we examined the relation between a change in core body temperature and change in skin temperature, and observed that a given increase in Tcore was associated with an attenuated increase in Tskin. Similar comparisons were performed in previous studies that have examined changes in core and skin temperature in HF patients and controls during passive heating (15). In agreement with our exercise-based study, these previous studies suggest the presence of an attenuated increase in skin perfusion for a given increase in Tcore in HF patients. Accordingly, these observations support the presence of impaired thermoregulatory responses to passive heat exposure as well as exercise-related heat generation in HF patients.

The impaired thermoregulatory responses during exercise in HF patients may relate to impairment of cutaneous vascular function, which has been described in several previous reports (16, 17). These vascular impairments may lead to the attenuated exercise-induced skin vasodilation. A second explanation for our observations may relate to the enhanced sympathetic tone in HF (18). Skin sympathetic nerve activity is found to contribute to thermoregulatory responses in humans (19). The increased sympathetic tone in HF patients under resting conditions, but also the exaggerated sympathetic activation during exercise (20, 21), may interfere with the normal skin blood flow and temperature responses to exercise. Another explanation is that the impaired cardiac output reserve in HF patients is a limiting factor, since this may lead to an attenuated blood supply to the skin (as HF patients need to centralize their circulatory volume to increase cardiac output). This latter hypothesis is supported by the observation of preserved thermoregulatory responses to prolonged walking exercise in cardiac patients with preserved left ventricle ejection fraction (22).

Whilst elevation in core body temperature during exercise relates to the relative exercise intensity (23, 24), others have suggested an important role for the absolute level of exercise as this is related to the amount of heat generation (25, 26). Given the marked differences in physical fitness level between HF patients and controls, absolute workload in HF patients was ~60% of that in control subjects (Table 1). Therefore, we performed a subgroup analysis in subjects with comparable absolute workload. Interestingly, comparable changes in Tcore and Tskin were observed during exercise between these subgroups. This suggests that, at least some of the differences can be explained by an *a priori* difference in workload, which is a direct result of difference in physical fitness level. The subgroup analysis indeed included relatively fit HF patients, in combination with moderately fit controls, resulting in a comparison of HF patients with fitness levels of ~75% of that of the subgroup of controls (rather than ~50% in the original comparison). The importance of physical fitness level in thermoregulatory responses to exercise is reported in several previous reports (14, 27, 28). Therefore, our additional subanalysis suggests that, at least some of the differences in thermoregulation to exercise between groups, relate to differences in physical fitness level.

Clinical relevance. Impaired thermoregulatory responses to exercise may place HF patients at increased risk to develop heat-related problems, but may also contribute to the relative exercise intolerance in HF patients. Therefore, the altered thermoregulation in HF should be kept in mind when HF patients are exposed to more challenging thermoregulatory conditions, such as passive exposure to extreme heat or performing exercise in the heat. Nonetheless, it should be emphasized that, despite the impaired thermoregulatory responses to exercise, HF patients were well capable of performing moderate intensity exercise and showed no severe hyperthermia. Furthermore, a lower physical fitness, in addition to HF *per* se, contributes to the impaired thermoregulation during exercise. This may suggest that improving physical fitness levels (through exercise training) may improve thermoregulatory responses to exercise in HF patients. Future studies are warranted to explore this clinically relevant hypothesis.

Limitations. An important limitation is that, as a direct consequence of the exclusion criteria for the use of the telemetry pill, we were only able to measure Tcore in 5 HF patients. Nonetheless, comparisons in Tcore within and between groups demonstrate significant changes during exercise.

In conclusion, our findings demonstrate that, despite performing exercise at lower absolute workload and therefore generating a smaller amount of heat, HF patients have a comparable increase in core body temperature to a 45-minute moderate intensity cycle exercise bout as healthy controls. These differences may relate to the distinct exercise-induced changes in skin temperature, with HF patients reporting an attenuated increase in skin temperature during exercise. These differences in thermoregulation can, at least partly, be explained by differences in physical fitness between groups.

ACKNOWLEDGEMENTS

We would like to thank Lisette Baltussen for her help recruiting participants and Dirk van Lier for his practical assistance during the measurements.

DECLARATION OF CONFLICTING INTERESTS

The authors declare that there is no conflict of interest.

FUNDING ACKNOWLEDGEMENT

D.H.J.T. was supported by the Netherlands Heart Foundation [E Dekker-stipend, 2009T064] and T.M.H.E. was supported by the Netherlands Organisation for Scientific Research [Rubicon Grant 825.12.016].

REFERENCES

1. Cahalin LP, Chase P, Arena R, Myers J, Bensimhon D, Peberdy MA, et al. A meta-analysis of the prognostic significance of cardiopulmonary exercise testing in patients with heart failure. Heart Fail Rev. 2013;18(1):79-94.

2. Piepoli MF, Conraads V, Corra U, Dickstein K, Francis DP, Jaarsma T, et al. Exercise training in heart failure: from theory to practice. A consensus document of the Heart Failure Association and the European Association for Cardiovascular Prevention and Rehabilitation. Eur J Heart Fail. 2011;13(4):347-57.

3. Brubaker PH. Exercise intolerance in congestive heart failure: a lesson in exercise physiology. J Cardiopulm Rehabil. 1997;17(4):217-21.

4. Griffin MJ, O'Sullivan JJ, Scott A, Maurer BJ. Core and peripheral temperature response to exercise in patients with impaired left ventricular function. Br Heart J. 1993;69(5):388-90.

5. Zelis R, Mason DT, Braunwald E. Partition of blood flow to the cutaneous and muscular beds of the forearm at rest and during leg exercise in normal subjects and in patients with heart failure. Circ Res. 1969;24(6):799-806.

6. Shellock FG, Rubin SA, Ellrodt AG, Muchlinski A, Brown H, Swan HJ. Unusual core temperature decrease in exercising heart-failure patients. J Appl Physiol Respir Environ Exerc Physiol. 1983;54(2):544-50.

7. Kenney WL, Johnson JM. Control of skin blood flow during exercise. Med Sci Sports Exerc. 1992;24(3):303-12.

8. Byrne C, Lim CL. The ingestible telemetric body core temperature sensor: a review of validity and exercise applications. Br J Sports Med. 2007;41(3):126-33.

9. Borg G, Hassmen P, Lagerstrom M. Perceived exertion related to heart rate and blood lactate during arm and leg exercise. Eur J Appl Physiol Occup Physiol. 1987;56(6):679-85.

10. <ISO9886.pdf>.

11. Keramidas ME, Geladas ND, Mekjavic IB, Kounalakis SN. Forearm-finger skin temperature gradient as an index of cutaneous perfusion during steady-state exercise. Clin Physiol Funct Imaging. 2013;33(5):400-4.

12. Veltmeijer MT, Eijsvogels TM, Thijssen DH, Hopman MT. Incidence and predictors of exertional hyperthermia after a 15-km road race in cool environmental conditions. J Sci Med Sport. 2014.

13. Torii M, Nakayama H, Sasaki T. Thermoregulation of exercising men in the morning rise and evening fall phases of internal temperature. Br J Sports Med. 1995;29(2):113-20.

14. Fritzsche RG, Coyle EF. Cutaneous blood flow during exercise is higher in endurance-trained humans. J Appl Physiol (1985). 2000;88(2):738-44.

15. Cui J, Sinoway LI. Cardiovascular Responses to Heat Stress in Chronic Heart Failure. Curr Heart Fail Rep. 2014.

16. Edvinsson ML, Uddman E, Andersson SE. Deteriorated function of cutaneous microcirculation in chronic congestive heart failure. J Geriatr Cardiol. 2011;8(2):82-7.

17. Andersson SE, Edvinsson ML, Edvinsson L. Cutaneous vascular reactivity is reduced in aging and in heart failure: association with inflammation. Clin Sci (Lond). 2003;105(6):699-707.

18. Triposkiadis F, Karayannis G, Giamouzis G, Skoularigis J, Louridas G, Butler J. The sympathetic nervous system in heart failure physiology, pathophysiology, and clinical implications. J Am Coll Cardiol. 2009;54(19):1747-62.

19. Cui J, Boehmer JP, Blaha C, Lucking R, Kunselman AR, Sinoway LI. Chronic heart failure does not attenuate the total activity of sympathetic outflow to skin during whole-body heating. Circ Heart Fail. 2013;6(2):271-8.

20. Chidsey CA, Harrison DC, Braunwald E. Augmentation of the plasma nor-epinephrine response to exercise in patients with congestive heart failure. N Engl J Med. 1962;267:650-4.

21. Kinugawa T, Ogino K, Kitamura H, Miyakoda H, Saitoh M, Hasegawa J, et al. Response of sympathetic nervous system activity to exercise in patients with congestive heart failure. Eur J Clin Invest. 1991;21(5):542-7.

22. Walsh J, Prpic R, Goodman C, Dawson B, Hung J. Thermoregulatory responses in post-coronary artery bypass surgery and healthy males during moderate exercise in warm and cool environments. J Cardiopulm Rehabil. 2002;22(1):31-7.

23. Greenhaff PL. Cardiovascular fitness and thermoregulation during prolonged exercise in man. Br J Sports Med. 1989;23(2):109-14.

24. Saltin B, Hermansen L. Esophageal, rectal, and muscle temperature during exercise. J Appl Physiol. 1966;21(6):1757-62.

25. Jay O, Bain AR, Deren TM, Sacheli M, Cramer MN. Large differences in peak oxygen uptake do not independently alter changes in core temperature and sweating during exercise. Am J Physiol Regul Integr Comp Physiol. 2011;301(3):R832-41.

26. Cramer MN, Jay O. Selecting the correct exercise intensity for unbiased comparisons of thermoregulatory responses between groups of different mass and surface area. J Appl Physiol (1985). 2014;116(9):1123-32.

27. Wang JS. Effects of exercise training and detraining on cutaneous microvascular function in man: the regulatory role of endothelium-dependent dilation in skin vasculature. Eur J Appl Physiol. 2005;93(4):429-34.

28. Roberts MF, Wenger CB, Stolwijk JA, Nadel ER. Skin blood flow and sweating changes following exercise training and heat acclimation. J Appl Physiol Respir Environ Exerc Physiol. 1977;43(1):133-7.

FIGURE LEGENDS

FIGURE 1. A. Core body temperature during exercise in HF patients (n=5) and controls (n=12). B. Skin temperature during exercise in HF patients (n=14) and controls (n=14). C. Core body temperature during exercise in subgroup of HF patients (n=4) and controls (n=5). D. Skin temperature during exercise in subgroup of HF patients (n=8) and controls (n=5). Error bars represent SE.

FIGURE 2. A. Change in core body temperature related to change in skin temperature during exercise in HF patients (n=5) and controls (n=12). B. Change in core body temperature related to change in skin temperature during exercise in subgroup of HF patients (n=4) and controls (n=5). Error bars represent SE.

Table 1: Subject characteristics, cardiovascular medication use and exercise characteristics in HF patients (n=14) and healthy controls (n=14). Data is presented as mean±SD.

	HF patients	**Controls**	**P-value**
Subject characteristics			
Age (yrs)	65±7	61±5	0.06
Sex (male:female)	13:1	12:2	0.54[§]
Weight (kg)	91±21	79±16	0.12
Height (cm)	175±5	179±5	0.04
BMI (kg/m^2)	29.4±6.7	24.7±4.6	0.04
BSA (m^2)	2.06±0.20	1.97±0.18	0.27
Waist-to-hip ratio[#1]	1.00±0.07	0.92±0.07	0.01
Fat percentage (%)[#2]	29±6	25±7	0.17
Systolic blood pressure (mmHg)	130±17	129±15	0.87
Diastolic blood pressure (mmHg)	81±10	85±9	0.29
Resting heart rate (beats/min)	59±8	60±10	0.76
CPET			
Peak heart rate (beats/min)	132±18	166±18	<0.001
Peak workload (Watt)	138±31	248±66	<0.001
Peak oxygen uptake (mlO_2/min/kg)	19.9±4.1	38.6±11.4	<0.001
Medication use			
ACE-inhibitors	9 (64%)		
Angiotensin II receptor	5 (36%)		

antagonists			
Aldosteron antagonists	10 (71%)		
Diuretics	8 (57%)		
β-blockers	13 (93%)		
Coumarin derivatives	9 (64%)		
Antiplatelet drugs	5 (36%)		
Statins	11 (79%)		
Characteristics exercise bout			
Absolute Workload (Watt)	73±23	122±29	<0.001
Relative workload (% of max)	53±12	50±6	0.37
Heart rate (beats/min)	94±15	129±17	<0.001
Heart rate (% of peak)	72±8	78±7	0.04
Relative oxygen uptake (%VO_{2peak})	65±14	65±12	0.91
RPE (Borg 6-20), 10min	12±2	12±2	0.54
RPE (Borg 6-20), 20min	13±2	13±2	0.62
RPE (Borg 6-20), 30min	14±3	14±2	0.59

BMI; body mass index. BSA; body surface area. CPET; cardiopulmonary exercise test. ACE; angiotensine converting enzyme. RPE; rate of perceived exertion. [§]Chi-square test was used to compare the sex distribution between groups. [#1]data was missing for 1 control subject, [#2]data was missing for 1 control subject and 1 HF patient.

Figure
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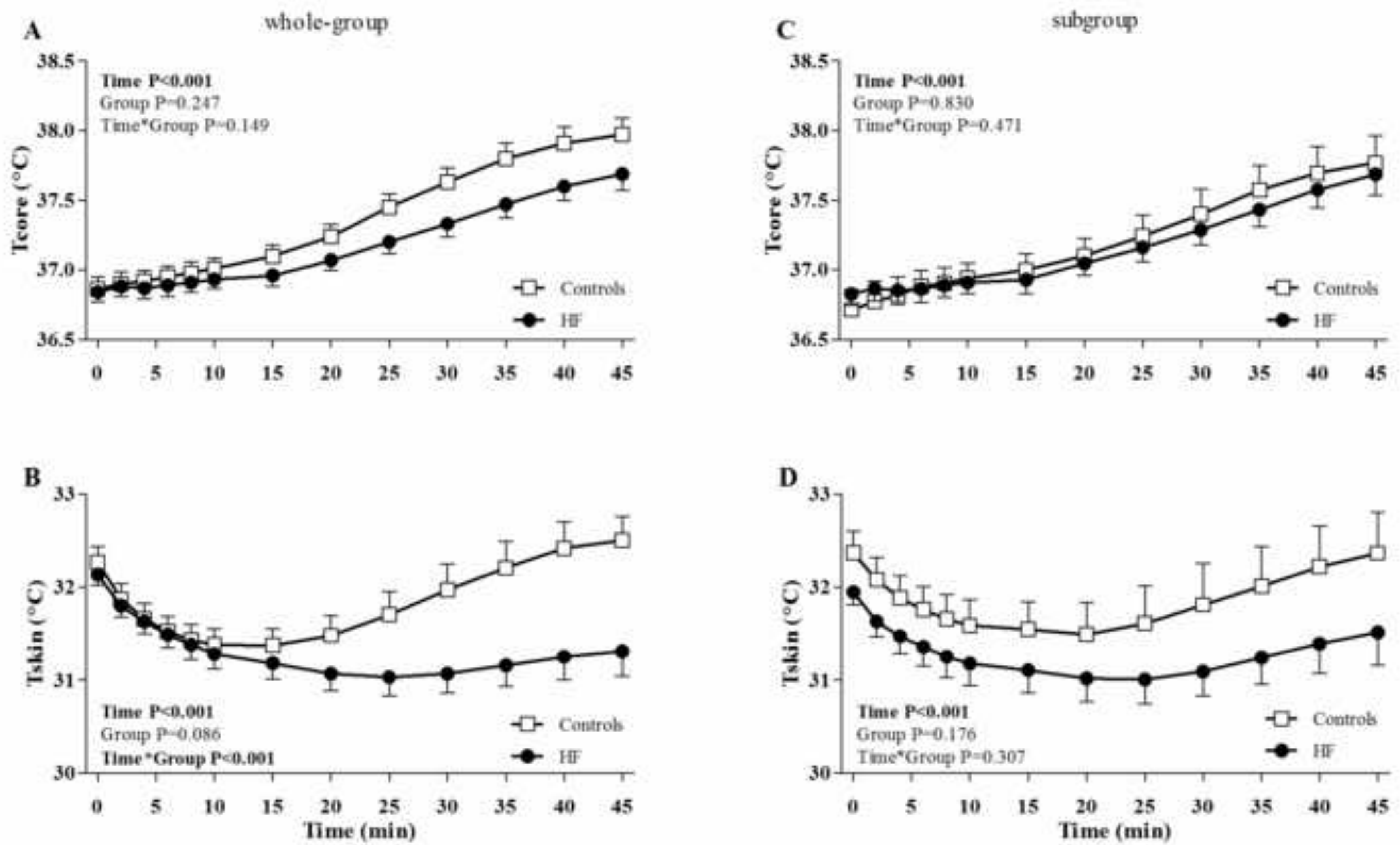

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