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1 **ALTERED CORE AND SKIN TEMPERATURE RESPONSES**
2 **TO ENDURANCE EXERCISE IN HEART FAILURE**
3 **PATIENTS AND HEALTHY CONTROLS**

4
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17
18 **Short title:** Thermoregulatory responses to exercise in heart failure

19
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23
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27

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32

33 **ABSTRACT**

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

39 **Design.** Cross-sectional observational study to compare changes in core body temperature
40 (T_{core}) and skin temperature (T_{skin}) during cycling exercise between HF patients and
41 controls.

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

46 **Results.** T_{core} increased to a similar extent in both groups (controls $1.1 \pm 0.4^\circ\text{C}$, HF
47 $0.9 \pm 0.3^\circ\text{C}$, 'time*group': $P=0.149$). T_{skin} decreased during the initial phase of exercise in
48 both groups, followed by an increase in T_{skin} in controls ($1.2 \pm 1.0^\circ\text{C}$), whilst T_{skin} remained
49 low in HF patients ($-0.3 \pm 1.4^\circ\text{C}$) ('time*group': $P<0.001$). Furthermore, we found that a given
50 change in T_{core} was associated with a smaller increase in T_{skin} in HF compared to controls.
51 When comparing HF patients and controls who performed exercise at similar absolute
52 workload, between-group differences disappeared (P -values >0.05).

53 **Conclusion.** HF patients and controls show a comparable exercise-induced increase in T_{core} ,
54 whilst HF patients demonstrate altered T_{skin} responses to exercise and attenuated elevation in
55 T_{skin} per increase in T_{core} . These impaired thermoregulatory responses to exercise are, at
56 least partly, explained by the low physical fitness level in HF patients.

57

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59

60 **KEYWORDS:** body temperature, skin temperature, body temperature regulation, heart

61 failure, exercise

62 INTRODUCTION

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

70

71 In healthy subjects, core body temperature (T_{core}) rises during exercise as a result of the
72 production of heat in active muscles (7). Consequently, cutaneous perfusion, skin temperature
73 (T_{skin}) and sweat production will increase to dissipate heat (7). Studies that have examined
74 changes in T_{core} and T_{skin} in HF patients during exercise have largely focused on the initial
75 responses during exercise. During the onset of exercise, a paradoxical decrease in core body
76 temperature is observed in HF patients compared to healthy subjects (4, 6), possibly as a
77 result of redistribution of cooler blood from the skin to the core. In addition, HF patients show
78 excessive cutaneous vasoconstriction and a persistent decline in T_{skin} compared to controls
79 (4, 5). However, these exercise studies adopted a short (≤ 11 min) period of exercise at low
80 absolute intensity, leading to low heat production. As thermoregulatory responses are more
81 important during prolonged exercise, these previous studies provide only limited insight into
82 the potential impact of HF on changes in T_{core} and T_{skin} during exercise.

83

84 To date no previous study comprehensively examined the thermoregulatory responses in HF
85 patients to a typical bout of exercise training as applied in cardiac rehabilitation. Therefore,
86 the main question of our study was whether HF patients and healthy controls differ in

87 thermoregulatory responses during a moderate intensity endurance exercise bout. To study
88 this, we measured changes in Tcore and Tskin during a 45-minute cycle exercise bout at
89 comparable relative exercise intensity in HF patients and controls. We hypothesize that
90 exercise in HF patients leads to a larger increase in Tcore and lower Tskin compared to
91 healthy controls, suggesting an impaired thermoregulatory response to exercise in HF
92 patients.

93

94

95 **METHODS**

96 **Subjects**

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

109

110 **Experimental protocol**

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

122

123 **Day 1: Medical screening and maximal incremental cycling test**

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

128 The incremental maximal cycling test was performed on a cycle ergometer (Lode, Excalibur
129 v1.52, 1991, Groningen, the Netherlands/Ergoline, Ergoselect 200k, Bitz, Germany). After a
130 2-minute baseline measurement, subjects started cycling and workload was increased by 10-
131 25 Watt per minute, depending on the sex, age and height of the participant. Subjects were
132 instructed to pedal at a frequency of >60 rpm until volitional exhaustion. During the maximal
133 exercise test we continuously measured oxygen consumption (breath-by-breath, CPET
134 Cosmed v9.1b, Rome, Italy/LabManager V5.32.0), to determine peak oxygen uptake

135 ($\text{VO}_{2\text{peak}}$), which was defined as the average oxygen uptake during the last 30 seconds of the
136 exercise test.

137

138 **Day 2: Cycle exercise bout**

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

145

146 **T_{core} and T_{skin} measurements**

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

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

159 Tcore and Tskin data were analysed using custom made software (Fysitemp, Radboudumc,
160 Nijmegen, The Netherlands) based on Matlab (Matlab R2008a, MathWorks, Natick, MA).
161 Baseline values were determined from the average over 5 minutes preceding exercise. As
162 previous work found changes in thermoregulatory responses during exercise of short duration
163 (<11min) (4, 6), Tcore and Tskin values were averaged over 2-minute intervals during the
164 first 10 minutes of exercise (warm-up). Thereafter, 5-minute intervals were calculated during
165 the remainder of the exercise bout. To explore the relationship between exercise-induced
166 increases in Tcore and changes in Tskin, Tskin was plotted against changes in Tcore.

167

168 **Statistical analysis**

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

178

179

180 **RESULTS**

181 **Subject characteristics**

182 HF patients demonstrated a higher BMI and a lower VO_{2peak} compared to controls, whilst no
183 significant differences between groups were found for age, body weight, BSA, and systolic

184 and diastolic blood pressure (Table 1). We included 8 HF patients with ischemic HF and 6
185 with non-ischemic HF. Cardiovascular medication use by HF patients is presented in Table 1.
186 Both groups exercised at comparable relative intensity (%max workload) and rate of
187 perceived exertion (Table 1). Absolute workload of the cycle exercise bout was significantly
188 higher in controls compared to HF patients (Table 1).

189

190 **Thermoregulatory responses to exercise**

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

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

202 T_{skin_{forearm-finger}}. T_{skin_{forearm-finger}} was comparable between both groups at baseline. Controls
203 showed a persistent decrease in this index during exercise, indicative of an increase in
204 cutaneous blood flow, which was not present in HF patients (‘time*group’-interaction:
205 P=0.019).

206

207 Subgroup analysis. In our subanalysis, HF patients with the highest workload (male:female
208 8:0, 63±7 yrs) and control subjects with the lowest workload (male:female 3:2, 64±7 yrs)

209 were included, allowing us to correct for differences in workload. These groups exercised at
210 comparable workload ($89\pm 15\text{W}$ and $90\pm 22\text{W}$ respectively, $P=0.891$). T_{core} demonstrated a
211 comparable exercise-induced increase in HF patients and controls ('group'-effect; $P=0.830$,
212 'time*group'-interaction; $P=0.471$, Figure 1C). T_{skin} decreased during the initial phase of
213 exercise, after which T_{skin} increased to baseline values after 40 minutes of exercise ('time'-
214 effect; $P<0.001$, Figure 1D). This change was similarly present in HF patients and controls
215 ('group'-effect; $P=0.176$, 'time*group'-interaction; $P=0.307$, Figure 1D). When changes in
216 T_{skin} are plotted against exercise-induced changes in T_{core} , HF patients show a similar
217 pattern as controls (Figure 2B).

218

219

220 **DISCUSSION**

221 This study compared thermoregulatory responses to moderate intensity cycle exercise
222 between HF patients and healthy controls. First, we found that HF patients and controls show
223 a comparable increase in T_{core} when exercise is performed at comparable relative exercise
224 intensity (but lower absolute workload). Second, after an initial decrease in T_{skin} at the onset
225 of exercise, controls demonstrate an increase in T_{skin} towards baseline values, whilst T_{skin}
226 remains low in HF patients. Furthermore, when analysing the relation between T_{core} and
227 T_{skin} , HF patients consistently demonstrate an attenuated increase in T_{skin} for a given
228 increase in T_{core} during exercise. These differences in T_{core} and T_{skin} responses to exercise
229 disappear when examining a subgroup of controls and HF patients who performed cycle
230 exercise at comparable absolute workload.

231

232 When exercise is performed at similar relative exercise intensity, a comparable and gradual
233 increase in core body temperature is observed in HF patients and their controls. In line with

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

248

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

258

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

272

273 Whilst elevation in core body temperature during exercise relates to the relative exercise
274 intensity (23, 24), others have suggested an important role for the absolute level of exercise as
275 this is related to the amount of heat generation (25, 26). Given the marked differences in
276 physical fitness level between HF patients and controls, absolute workload in HF patients was
277 ~60% of that in control subjects (Table 1). Therefore, we performed a subgroup analysis in
278 subjects with comparable absolute workload. Interestingly, comparable changes in T_{core} and
279 T_{skin} were observed during exercise between these subgroups. This suggests that, at least
280 some of the differences can be explained by an a priori difference in workload, which is a
281 direct result of difference in physical fitness level. The subgroup analysis indeed included
282 relatively fit HF patients, in combination with moderately fit controls, resulting in a
283 comparison of HF patients with fitness levels of ~75% of that of the subgroup of controls

284 (rather than ~50% in the original comparison). The importance of physical fitness level in
285 thermoregulatory responses to exercise is reported in several previous reports (14, 27, 28).
286 Therefore, our additional subanalysis suggests that, at least some of the differences in
287 thermoregulation to exercise between groups, relate to differences in physical fitness level.

288

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

300

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

305

306 In conclusion, our findings demonstrate that, despite performing exercise at lower absolute
307 workload and therefore generating a smaller amount of heat, HF patients have a comparable
308 increase in core body temperature to a 45-minute moderate intensity cycle exercise bout as

309 healthy controls. These differences may relate to the distinct exercise-induced changes in skin
310 temperature, with HF patients reporting an attenuated increase in skin temperature during
311 exercise. These differences in thermoregulation can, at least partly, be explained by
312 differences in physical fitness between groups.

313

314

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318

319 **DECLARATION OF CONFLICTING INTERESTS**

320 The authors declare that there is no conflict of interest.

321

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- 399
- 400
- 401

402 **FIGURE LEGENDS**

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

408

409 **FIGURE 2.** A. Change in core body temperature related to change in skin temperature during
410 exercise in HF patients (n=5) and controls (n=12). B. Change in core body
411 temperature related to change in skin temperature during exercise in subgroup of HF
412 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. #¹data was missing for 1 control subject,

#²data was missing for 1 control subject and 1 HF patient.



