

# The inflammatory response to a wheelchair half-marathon in people with a spinal cord injury - the role of autonomic function

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32 **Abstract**

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3 33 This study investigates the relationship between autonomic function and the inflammatory  
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6 34 response to a wheelchair half-marathon in people with a spinal cord injury (SCI). Seventeen  
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8 35 wheelchair athletes with a cervical SCI (CSCI, N=7) and without CSCI (NON-CSCI, N=10)  
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10 36 participated in a wheelchair half-marathon. Blood was taken prior, post and 1 h post-race to  
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12 37 determine the concentrations of adrenaline, noradrenaline, extracellular heat shock protein 72  
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14 38 (eHsp72) and interleukin-6 (IL-6). A sit-up tilt test was performed to assess autonomic  
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16 39 function at rest. CSCI showed a lower supine ratio of the low and high frequency power of  
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18 40 the variability in RR intervals (LF/HF RRI,  $p=0.038$ ), total and low frequency power of the  
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20 41 systolic blood pressure variability (TP SBP,  $p<0.001$ ; LF SBP,  $p=0.005$ ) compared to NON-  
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22 42 CSCI. Following the race, catecholamine concentrations increased only in NON-CSCI  
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24 43 ( $p<0.036$ ). The increase in IL-6 post-race was larger in NON-CSCI ( $p=0.040$ ). Post-race  
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26 44 catecholamine levels explained 60% of the variance in the IL-6 response ( $r=0.77$ ,  $p=0.040$ ),  
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28 45 which was further increased when the resting autonomic function indices were added to the  
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30 46 regression model ( $R^2>81\%$ ,  $p<0.012$ ). In summary, the dampened acute inflammatory  
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32 47 response to a wheelchair half-marathon in CSCI was strongly associated with the autonomic  
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34 48 dysfunction present in this group.  
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## 54 Introduction

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3 55 Chronic low-grade inflammation, characterised by elevated resting levels of pro-  
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6 56 inflammatory proteins (e.g. interleukin-6 (IL-6) and extracellular heat shock protein 72  
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8 57 (eHsp72)) and strongly associated with chronic diseases such as type 2 diabetes mellitus and  
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10 58 cardiovascular disease, is more prevalent in people with a spinal cord injury (SCI) compared  
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12 59 to members of the able-bodied population (Bauman & Spungen, 2008). This might be the  
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14 60 consequence of a physically inactive lifestyle and the physiological changes accompanying  
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16 61 the injury (Martin Ginis et al., 2010). Exercise training is widely recognised as a means to  
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18 62 combat chronic low-grade inflammation (Petersen & Pedersen, 2005), partly as a result of the  
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20 63 acute inflammatory response induced by each bout. Although transiently elevating pro-  
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22 64 inflammatory proteins such as IL-6, the subsequent longer lasting anti-inflammatory response  
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24 65 can lower resting levels of these proteins when engaging in exercise on a regular basis  
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26 66 (Petersen & Pedersen, 2005). During and shortly after exercise, the primary source of  
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28 67 circulating IL-6 concentrations is skeletal muscle (Steensberg et al., 2000). Despite a smaller  
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30 68 active muscle mass involved, upper-body exercise has been shown effective in the induction  
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32 69 of an acute inflammatory response (Sasaki et al., 2014; Umemoto et al., 2011). However, this  
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34 70 response might be attenuated in people with a cervical SCI (CSCI) (Paulson et al., 2013).

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43 71 Persons with CSCI have a smaller muscle mass and impaired autonomic function  
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45 72 compared to able-bodied individuals and people with paraplegia, both impacting on their  
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47 73 exercise capacity (West et al., 2015). There is limited research into the influence of these  
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49 74 factors on the acute inflammatory response to exercise. Paulson et al. (2013) reported an  
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51 75 attenuated IL-6 response to a strenuous bout of exercise in CSCI compared to SCI; a finding  
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53 76 that was replicated in a wheelchair racing setting (Ogawa et al., 2014). Together with the  
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55 77 attenuated IL-6 response, both studies reported a blunted adrenaline and noradrenaline  
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78 response to the exercise bout in the CSCI group (Ogawa et al., 2014; Paulson et al., 2013),  
79 suggesting a major role of catecholamines in the dampened acute inflammatory response to  
80 exercise present in people with CSCI. Indeed, adrenaline infusion in resting able-bodied  
81 individuals results in increased plasma IL-6 concentrations (Sondergaard et al., 2000;  
82 Steensberg et al., 2001), potentially via the increase of intracellular cyclic adenosine  
83 monophosphate (cAMP) following the stimulation of  $\beta$ -receptors on skeletal muscle with  
84 adrenaline (Sondergaard et al., 2000).

85           Apart from resulting in lower resting and exercise-induced plasma catecholamine  
86 concentrations, CSCI can lead to the disruption of sympathetic innervation of the heart, as  
87 well as the skin and blood vessels below the lesion (Krassioukov, 2009). Consequently,  
88 members of this population have an impaired blood pressure regulation and heart rate (HR)  
89 attained during maximal exercise does often not exceed ~130 bpm (West et al., 2015).  
90 Therefore, although an attenuated catecholamine response to exercise is a characteristic of  
91 autonomic dysfunction, the latter affects a plethora of other physiological processes that may  
92 influence the acute inflammatory response to exercise. As autonomic completeness of a  
93 spinal injury varies between people as a result of the potential sparing of autonomic fibres  
94 below the lesion (Krassioukov, 2009), the impact of autonomic dysfunction on the  
95 inflammatory response to exercise may also differ between people with SCI.

96           For a more comprehensive assessment of autonomic function than using exercise-  
97 induced plasma catecholamine concentrations alone (Paulson et al., 2013; Ogawa et al., 2014),  
98 additional tests exist (Krassioukov, 2009). The sit-up tilt test, for instance, can be used to  
99 detect abnormal changes in HR and blood pressure in response to a passive tilt manoeuvre  
100 (Claydon & Krassioukov, 2008). Moreover, Claydon & Krassioukov (2008) reported that  
101 frequency blood pressure and heart rate variability measures taken in a supine position are

102 predictive of a range of clinical measures of autonomic dysfunction, such as for instance  
103 orthostatic hypotension.

104 The present study therefore extends on previous research (Ogawa et al., 2014;  
105 Paulson et al., 2013) by incorporating autonomic function indices measured at rest in addition  
106 to the assessment of the catecholamine response following exercise to investigate the  
107 association of autonomic function with the inflammatory response to a wheelchair half-  
108 marathon. In addition, this study investigates the potential of upper-body exercise in SCI to  
109 acutely elevate eHsp72 concentrations, a relatively novel marker implicated in chronic low-  
110 grade inflammation (Johnson & Fleshner, 2006). Together, this can provide further insight  
111 into factors that influence the acute inflammatory response to exercise and inform strategies  
112 to reduce chronic low-grade inflammation in people with CSCI.

## 114 **Methods**

115 Participants were seventeen male recreational wheelchair athletes with CSCI (N=7) or  
116 without CSCI (NON-CSCI, N=10), the latter group including individuals with a spinal lesion  
117 below the cervical level (N=6), spina bifida (N=2), polio (N=1) and myotonia congenita (N=1)  
118 (Table 1). Participants took part in the wheelchair half-marathon of Oita 2016. The study was  
119 approved by the local ethics committees of Loughborough University (United Kingdom) and  
120 Wakayama University (Japan) and participants gave informed consent prior to participation.

### 122 *Sit-up tilt test*

124 One to 2 days prior to the race, a sit-up tilt test was conducted in 16 of the 17 athletes  
125 for the assessment of autonomic function. All tests were performed using the same

126 wheelchair with adjustable back rest and in a room set at 25°C. Participants were rested for 5  
127 minutes in a supine position and were then elevated into the sitting position, which they  
128 maintained for another 5 minutes. Participants were instructed to breathe at a frequency of  
129 0.25 Hz. Blood pressure was measured beat-by-beat at the wrist (MUB101-50, MediSense  
130 Inc., Tokyo, Japan) whilst a brachial blood pressure cuff (STBP-780, Colin, Komaki, Japan)  
131 was used for the calibration. Both cuffs were situated at the level of the heart for the full  
132 duration of the test. Heart rate was continuously monitored using a 7-lead electrocardiogram  
133 (PhysioFlow Lab-1, Manatec Biomedical, Paris, France). Following the test, participants  
134 reported their height, body mass, wheelchair racing experience and average time spent  
135 training.

136 To obtain HR and blood pressure variability measures in the frequency domain, beat-  
137 to-beat mean arterial pressure and HR were obtained by integrating the respective signals  
138 within each cardiac cycle. Cardiac cycles were determined based on the diastolic intervals of  
139 the beat-to-beat blood pressure signal. Beat-to-beat mean arterial pressure and HR were first  
140 linearly interpolated and resampled at 2Hz and then detrended by subtracting their third  
141 polynomial. Subsequently, the beat-to-beat time series were used for the spectral analyses  
142 based on the Welch algorithm. Each time series was subdivided into successive 256-point  
143 Hann windows that overlapped by 50% before fast Fourier transform analysis (Van der  
144 Scheer et al., 2018). Outcome measures used to reflect autonomic function were: the largest  
145 drop in blood pressure following the onset of the sitting position (to detect orthostatic  
146 hypotension (OH), defined as a drop in SBP>20 mmHg or DBP>10 mmHg (Freeman et al.,  
147 2011)), the ratio of the power in the low (power = 0.07 – 0.20 Hz) and high frequency (power  
148 = 0.20 – 35 Hz) domain of the heart rate variability (LF/HF RRI), total power and power in  
149 the low frequency domain of systolic blood pressure variability (TP SBP and LF SBP,  
150 respectively) in the supine position (Claydon & Krassioukov, 2008). These variability

151 measures were chosen as they have been shown reliable in people with SCI (Ditor et al., 2005)  
152 and to strongly correlate with clinical symptoms of autonomic dysfunction (Claydon &  
153 Krassioukov, 2008). Additionally, the root mean square differences of successive R-R  
154 intervals in the supine position (RMSSD) was included as a time domain autonomic function  
155 index.

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### 157 *Wheelchair half-marathon*

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159 The Oita wheelchair half-marathon is a 21.1 km race on relatively flat terrain in the  
160 city centre. The race started at 10am in relatively mild conditions (23°C, 56% relative  
161 humidity). Participants had refrained from exercise in the 24 hours prior to the race. While  
162 food and liquid ingestion were not controlled due to the potential interference with the race  
163 practices of the athletes, these were reported using a food diary. All participants reported to  
164 have consumed a carbohydrate-rich breakfast in the morning of the race and to have  
165 consumed a sports drink during the race. Heart rate was continuously measured using a  
166 Garmin monitor (Garmin Edge 500, US). Blood was drawn from an antecubital vein prior to  
167 the warm-up for the race (pre), directly after finishing the race (post) and 1 h post-race (1 h  
168 post) into a glass serum separation and a K<sub>3</sub>EDTA tube of which respectively serum and  
169 plasma were extracted and stored at -80 °C until analysis. These time-points were chosen  
170 based on previous studies on the acute inflammatory response to endurance-type exercise in  
171 able-bodied (Fehrenbach et al., 2005; Fischer, 2006) and individuals with disability (Ogawa  
172 et al., 2014). Interleukin-6 (High sensitivity; R&D systems, UK) and eHsp72 (Amp`d high  
173 sensitivity; Enzo life sciences, US) were analysed in serum using a quantitative sandwich-  
174 type enzyme-linked immunosorbent assay (CV: 8.2% and 6.3%, respectively), while  
175 adrenaline and noradrenaline were analysed in plasma by high-performance liquid

176 chromatography. Haemoglobin and haematocrit were determined using an automated cell  
177 counter (MEK-6400, Nihon Kodan, Tokyo, Japan) and were used to correct the outcome  
178 markers for changes in plasma volume resulting from the race (Dill and Costil, 1964).

179

### 180 *Statistical analyses*

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182 The participants were divided into two groups based on lesion level (regardless of  
183 completeness), resulting in a CSCI and NON-CSCI group. All data were checked for  
184 normality with the Shapiro-Wilk test, after which the data were log-transformed when this  
185 assumption was violated. Data were checked for sphericity using Levene`s test. Comparisons  
186 of athlete characteristics and responses to the sit-up tilt test between CSCI and NON-CSCI  
187 were assessed using independent student T-tests. Two-way repeated measures ANOVAs  
188 were used to assess changes in IL-6, eHsp72, adrenaline and noradrenaline in CSCI and  
189 NON-CSCI following the race. 95% confidence intervals of the difference in participants`  
190 characteristics between both groups were computed, while effect sizes (ES) Cohen`s d were  
191 calculated where appropriate, whereby an ES of 0.20, 0.5 and 0.80 refers to a small, moderate  
192 or large effect, respectively (Cohen, 1992). The ES for a time x group interaction was  
193 calculated by comparing the pre-post change scores in each group. Using GPower 3.1.9.2, we  
194 calculated we would need six participants in both groups to detect a difference in the acute  
195 IL-6 response to exercise between the groups, with 90% power, an  $\alpha$  of 5% and an effect size  
196 of 2.0 based on data reported by Ogawa et al. (2014).

197 To further assess the relationship of catecholamines and the autonomic function  
198 indices with the inflammatory response following the race, simple and multiple linear  
199 regression analysis using the whole sample was performed. Adrenaline and noradrenaline  
200 were entered into the model both together and individually and the  $R^2$  was used to describe



201 the explained variance of the dependent variable. The same was done for LF/HF RRI,  
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2 202 RMSSD, LF SBP and TP SBP. Finally, adrenaline and noradrenaline together with a heart  
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4 203 rate and blood pressure variability measure were entered into the regression model and the  
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7 204 change in  $R^2$  as compared to the model with the catecholamines or sit-up tilt test indices only  
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10 205 was tested using ANOVA. Collinearity among the predictor variables was tested using  
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12 206 Tolerance and the Condition Index, whereby values higher than 1 and 15 respectively were  
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15 207 considered concerning (Midi et al., 2010). All analyses were performed using the 23<sup>rd</sup> version  
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17 208 of SPSS and statistical significance was defined as  $p < 0.05$ .

## 20 209 **Results**

### 24 210 *Sit-up tilt test*

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29 212 Five participants demonstrated OH in response to the tilt manoeuvre, four of which  
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31 213 were in the CSCI group and one in NON-CSCI. Athletes in the CSCI group showed a larger  
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34 214 drop in SBP in response to the tilt manoeuvre compared to NON-CSCI ( $p=0.017$ ; ES: 1.36).  
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36 215 LF/HF RRI ( $p=0.038$ ; ES: 1.30), LF SBP ( $p=0.005$ ; ES: 1.86) and TP SBP ( $p < 0.001$ ; ES:  
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38 216 2.37) differed significantly between the two groups, with NON-CSCI showing larger values.  
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41 217 The RMSSD did not differ between both groups ( $p = 0.87$ ) (Table 1). As such, the remaining  
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43 218 of this manuscript focusses on the frequency rather than time domain autonomic function  
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46 219 indices at rest.

48 220 \*\*\*\*\*Table 1 near here\*\*\*\*\*

### 51 221 *Wheelchair half-marathon*

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56 223 At rest, CSCI had lower levels of adrenaline ( $p=0.003$ ; ES: 1.62) and noradrenaline  
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58 224 ( $p < 0.001$ ; ES: 3.20) compared to NON-CSCI. While there was no difference in baseline IL-6

225 serum concentrations ( $p=0.519$ ), a strong trend for higher resting eHsp72 concentrations for  
226 CSCI compared to NON-CSCI was present ( $p=0.055$ ; ES: 1.04) (Fig. 1).

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228 The NON-CSCI group took significantly less time to complete the race than the CSCI  
229 athletes (1.06 (0.21) versus 1.43 (0.38) h,  $p=0.026$ ; ES: 1.21). The average HR during the  
230 race was significantly higher for NON-CSCI compared to CSCI (145 (32) versus 103 (20) bpm,  
231  $p=0.029$ ; ES: 1.43). There was a trend for a higher peak HR in the NON-CSCI group (166  
232 (41) versus 129 (18) bpm,  $p=0.087$ ; ES: 1.04).

233  
234 Following the race, plasma adrenaline and noradrenaline concentrations were  
235 increased in NON-CSCI ( $p<0.036$ ; ES: 1.60 and 1.58 for adrenaline and noradrenaline,  
236 respectively), but not in CSCI ( $p>0.113$ ; ES: 0.63 and 0.84 for adrenaline and noradrenaline,  
237 respectively). The increase in serum IL-6 concentrations in response to the race was larger in  
238 NON-CSCI compared to CSCI ( $p=0.040$ ; ES: 0.71), although the latter group showed a  
239 significant increase in IL-6 as well ( $p=0.033$ ; ES: 1.03). Extracellular heat shock protein 72  
240 did not increase in either of the groups (NON-CSCI:  $p=0.338$  and CSCI:  $p=0.116$ ) (Fig. 1).  
241 Since both IL-6 and eHsp72 concentrations did not change from post to 1 h post ( $p>0.391$ ),  
242 further analyses were performed using the serum concentrations of both markers immediately  
243 following the race only.

244

245 \*\*\*\*\* Figure 1 near here\*\*\*\*\*

246 *Association of autonomic function with the inflammatory response*

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248 The relationship between the autonomic function indices, catecholamines and the  
249 inflammatory response to the race is illustrated in Table 2 and Figure 2. Post-race levels of

250 adrenaline and noradrenaline combined explained 60% of the variance in the IL-6  
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2 251 concentrations following to the race ( $p=0.04$ ), while adrenaline alone explained 44% of the  
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5 252 variance ( $p=0.007$ ). The LF/HF RRI and TP SBP both individually explained a significant  
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7 253 proportion of the variance in post-race plasma adrenaline concentrations (29% and 33%,  
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10 254 respectively;  $p<0.042$ ). The model including combination of LF/HF RRI with LF SBP or TP  
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12 255 SBP did not significantly explain the adrenaline response ( $p>0.08$ ). The variance in the IL-6  
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15 256 response could not be explained by one of the autonomic function indices in isolation (LF/HF  
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17 257 RRI:  $R^2 = 8\%$ ,  $p=0.37$ ; RMSSD:  $R^2 = 11\%$ ,  $p=0.28$ ; LF SBP:  $R^2 = 12\%$ ,  $p=0.27$ ; TP SBP:  $R^2$   
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19 258  $= 29\%$ ,  $p=0.07$ ). The same was true for the combination of LF/HF RRI together with either of  
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22 259 the two variability measures of systolic blood pressure ( $p>0.281$ ). The regression model  
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24 260 including adrenaline, noradrenaline, LF/HF RRI and one of the systolic blood pressure  
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27 261 variability measures (i.e. LF SBP or TP SBP) increased the explained variance of post-race  
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29 262 IL-6 concentrations in comparison to the model including catecholamines only ( $R^2>81\%$ ,  
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32 263  $p<0.012$ ). The change in  $R^2$  compared with the model including catecholamines only was  
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34 264 significant (adrenaline, noradrenaline, LF/HF RRI, TP SBP;  $p=0.036$ ), or showed a trend  
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36 265 towards significance (adrenaline, noradrenaline, LF/HF RRI, LF SBP;  $p=0.07$ ). Of note,  
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39 266 Tolerance and the Condition Index were  $<0.54$  and  $<8.87$ , respectively, indicating no  
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41 267 substantial collinearity among the predictor variables. Finally, athletes that presented with  
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44 268 OH during the sit-up tilt test showed lower levels of adrenaline (104 (131) mmol/L versus  
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46 269 265 (243) mmol/L) and IL-6 (4.34 (1.08) pg/ml versus 10.21 (6.84) pg/ml) post-race,  
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49 270 although only the difference in IL-6 reached statistical significance ( $p=0.192$ ; ES: 0.66 and  
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51 271  $p=0.026$ ; ES: 0.96, respectively).

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56 273 \*\*\*\*\*Table 2 and Figure 2 near here\*\*\*\*\*

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275 **Discussion**

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4 276 This study showed that the acute IL-6 response to a wheelchair half-marathon is  
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6 277 attenuated in CSCI compared to NON-CSCI athletes, predominantly associated with the  
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8 278 blunted catecholamine response observed in this group. Although autonomic function indices  
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11 279 assessed at rest do not seem to be strong independent predictors for the IL-6 response to  
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13 280 exercise, when used in combination with catecholamines they enhanced the predictive value  
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16 281 of autonomic function assessments. This suggests that the influence of autonomic dysfunction  
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18 282 on the dampened IL-6 response in people with CSCI is mediated by more than  
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21 283 catecholamines only. Finally, eHsp72 was not elevated after the wheelchair half-marathon,  
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23 284 suggesting that more intense or longer duration upper-body exercise is needed to increase its  
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26 285 release into the circulation.

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29 286 The resting autonomic function indices in the frequency domain (i.e. LF/HF RRI, LF  
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31 287 SBP and TP SBP) differed between CSCI and NON-CSCI, indicating a difference in  
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34 288 autonomic function between the two groups. Importantly, Claydon and Krassioukov (2008)  
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36 289 observed a strong correlation between those measures and clinical outcomes of autonomic  
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39 290 dysfunction (e.g. the catecholamine, HR and blood pressure response to the tilt manoeuvre as  
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41 291 well as the sympathetic skin responses). As suggested by these authors, this may provide  
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43 292 practitioners with an easy-to-use and non-invasive tool to assess autonomic function in  
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46 293 people with SCI (Claydon & Krassioukov, 2008). Further indicating a difference in  
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49 294 autonomic function between NON-CSCI and CSCI, the latter showed lower plasma  
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51 295 concentrations of adrenaline and noradrenaline at rest and in response to exercise.

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54 296 Previous research using only catecholamines as an indication of autonomic function  
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56 297 has highlighted the importance of an intact sympathetic nervous system for the elevation of  
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59 298 IL-6 following exercise (Ogawa et al., 2014; Paulson et al., 2013). Indeed, in the current  
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299 study catecholamines explained 60% of the variance in serum IL-6 levels post-race. Studies  
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2 300 infusing adrenaline in persons at rest support the notion that adrenaline can independently  
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5 301 elevate circulating IL-6 concentrations (Sondergaard et al. 2000; Steensberg et al. 2001).  
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7 302 Animal studies using adrenergic receptor antagonists suggest that adrenaline stimulates IL-6  
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10 303 production by the activation of  $\beta$ -receptors (De Rijk et al. 1994), which in turn leads to an  
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12 304 increase in intracellular cAMP (Langfort et al., 2003). This can directly stimulate IL-6  
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15 305 production (Zhang et al., 1988). Additionally, the impact of adrenaline on muscle glycogen  
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17 306 breakdown may mediate its stimulating effect on IL-6 production (Jensen et al., 1999).  
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19 307 Indeed, exercise in a glycogen depleted state leads to an exacerbated acute IL-6 response  
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22 308 (Bishop et al., 2001). However, the infusion of similar adrenaline levels as observed during  
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24 309 exercise results in a much lower elevation in IL-6 when compared to exercise (Steensberg et  
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27 310 al., 2001), suggesting that exercise provides additional stressors that cause the elevation of  
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29 311 circulating IL-6 concentrations.

32 312 As circulating catecholamines seem to only partly explain the acute IL-6 response to  
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35 313 exercise (Steensberg et al., 2001), other consequences of autonomic dysfunction such as the  
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37 314 altered vascular tone and sympathetic innervation of the heart might further impact on the  
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40 315 capacity to induce an inflammatory response through exercise (Paulson et al., 2013).  
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42 316 Autonomic function indices taken at rest are associated with clinical symptoms of autonomic  
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45 317 dysfunction (Claydon & Krassioukov, 2008), but also exercise performance (West et al.,  
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47 318 2015). In the present study, the predictive value of the individual autonomic function indices  
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50 319 measured at rest seems to be limited with regards to the inflammatory response. However, the  
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52 320 addition of these measures to the regression model with catecholamines significantly  
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55 321 enhanced the explained variance of post-race serum IL-6 concentrations. This suggests that a  
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57 322 combination of exercise-induced (catecholamines) and resting autonomic function indices  
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59 323 (supine LF/HF RRI, LF SBP and TP SBP) can provide additional insight into the role of

1 324 sympathetic dysfunction in the acute IL-6 response to exercise in people with SCI. This may  
2 325 be used to inform individual exercise prescription as well as the creation of additional  
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4 326 strategies to promote health in people with SCI (Leicht et al., 2015). From a mechanistic  
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7 327 perspective, the added predictive value of autonomic function indices at rest suggests that the  
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10 328 impact of autonomic dysfunction on the dampened acute inflammatory response to exercise is  
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12 329 indeed mediated by other factors than blunted circulating catecholamine concentrations only.

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14 330 The close link between autonomic function and the catecholamine response to  
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17 331 exercise makes it difficult to suggest what is accounted for by the resting autonomic function  
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19 332 indices that is not accounted for by post-race catecholamine concentrations. In this respect it  
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21  
22 333 is noteworthy that athletes with autonomic complete CSCI might still experience autonomic  
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24 334 reflexes below the lesion, resulting in spill-over of noradrenaline into the circulation (Leicht  
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26 335 et al., 2013). Interestingly, one participant with CSCI showed a 4-fold and 2.5-fold increase  
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29 336 in adrenaline and noradrenaline post-race respectively, despite being classified with a  
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32 337 complete lesion and showing OH during the sit-up tilt test. Moreover, this was accompanied  
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34 338 by an almost 4-fold increase in IL-6 following the race. Therefore, the impact of sympathetic  
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36 339 reflexes and additional consequences of autonomic dysfunction other than lowered  
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39 340 catecholamine concentrations on the acute inflammatory response to exercise would be an  
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41 341 intriguing subject for future research.

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44 342 While there is now sufficient evidence for the ability of upper-body exercise to induce  
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47 343 an IL-6 response (e.g. Kouda et al., 2012; Paulson et al., 2013), this is not yet the case for  
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49 344 eHsp72. In the current study no elevation of eHsp72 concentrations was detected in either  
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52 345 CSCI or NON-CSCI. In a study investigating able-bodied participants, Leicht et al. (2016)  
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54 346 reported an increase in eHsp72 after 45 min of arm-cranking at 60-65% peak power output in  
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57 347 a non-permeable suit as opposed to the absence of an eHsp72 response after the same bout of  
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59 348 exercise in conventional sport clothes. Since the exercise bout in the non-permeable suit

349 resulted in increased heat storage, the results of this study suggest an important role of body  
1  
2 350 temperature in the eHsp72 response. Since studies on lower-body exercise have shown  
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5 351 increases in eHsp72 levels following relatively moderate bouts of exercise (Walsh et al.,  
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7 352 2001), the reason for the attenuated eHsp72 response following upper-body exercise might  
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10 353 partly lie in the limited muscle mass involved, inducing smaller increases in core temperature  
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12 354 during exercise (Price, 2006). On the other hand, thermoregulation during exercise is  
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14 355 impaired in individuals with SCI, possibly resulting in higher attained core temperatures  
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17 356 (Price & Campbell, 2003). Future research in applied settings should therefore attempt to  
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19 357 monitor core temperature during competition to shed more light on this measure as a potential  
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22 358 mediator of the inflammatory response (Laing et al., 2008; Whitham et al., 2007).

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25 359         Some limitations of this study need consideration. First, we were not able to monitor  
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27 360 sleep, warm-up practices, psychological stress prior and during the race, nor control food and  
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30 361 liquid intake on the day of the race. These factors may have impacted on the acute  
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32 362 inflammatory response following the race. Furthermore, the physiological underpinning of  
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35 363 heart rate and blood pressure variability measures in the frequency domain have been the  
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37 364 subject of debate (Billman, 2013). While it is indeed questionable whether LF HRV and LF  
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40 365 SBP reflect solely sympathetic activation (Billman, 2013), the measures included in the  
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42 366 present study strongly correlate with more clinical outcomes of autonomic dysfunction  
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45 367 (Claydon & Krassioukov, 2008). Moreover, these measures have been shown reliable in  
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47 368 people with SCI (Ditor et al., 2005). Nevertheless, they should be considered as autonomic  
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50 369 function indices, rather than measures of sympathetic activation (Esco et al., 2018).

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52 370 Additionally, the present study has assessed the relationship between autonomic function  
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54 371 indices and the acute inflammatory response to strenuous exercise such as a wheelchair half-  
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57 372 marathon. Therefore, caution needs to be applied when translating the findings to shorter,  
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1 373 moderate-intensity exercise prescribed to promote health in the general population with SCI  
2 374 (Martin Ginis et al., 2018).

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4 375 Notwithstanding its limitations, appreciating the scarcity of available data on the  
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7 376 effects of exercise and autonomic dysfunction on health in people with SCI (Buker et al.,  
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10 377 2018), the present field study in recreational wheelchair athletes may be used to inform future  
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12 378 research in this area. For instance, the positive effect of chronic exercise training on  
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14 379 autonomic balance (Buker et al., 2018) provides rationale for research into its impact on the  
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17 380 acute inflammatory response to exercise, while further study is also needed to determine the  
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19 381 most appropriate measures to indicate autonomic function in people with SCI (El-Kotob et al.,  
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22 382 2017). Furthermore, there is increasing evidence for the anti-inflammatory effect of  
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24 383 resistance training (Strasser et al., 2012). To further inform exercise prescription, future  
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27 384 research could investigate the effectiveness of different types of (standardised) exercise in  
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29 385 inducing an acute inflammatory response to people with SCI.  
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31 386 In summary, the strong association between post-race serum IL-6 and catecholamine  
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34 387 concentrations suggests a major role for the latter in the acute inflammatory response to a  
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37 388 wheelchair half-marathon. While autonomic function indices assessed at rest were not  
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39 389 predictive of the IL-6 response to the race when used in isolation, they enhanced the  
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42 390 predictive value of autonomic function assessments when added to a predictive model with  
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44 391 catecholamines alone. Therefore, the dampened acute IL-6 response to a wheelchair half-  
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46 392 marathon observed in people with CSCI may be influenced by more factors associated with  
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49 393 autonomic dysfunction than solely blunted circulating catecholamine concentrations. Taking  
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51 394 a wide range of factors associated with autonomic dysfunction into account may hence be of  
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54 395 use to inform health promoting strategies to reduce chronic low-grade inflammation in  
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56 396 individuals with CSCI.

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398 *Disclosure of interest*

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5 400 The authors report no conflict of interest.

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423 Table 1. Characteristics of the participants with (CSCI) compared to the participants without (NON-CSCI) a  
1 424 cervical spinal cord injury. Values are given in mean (SD).  
2 425  
3  
4 426 Table 2. Regression analyses with autonomic function indices and the inflammatory response to the wheelchair  
5 427 half-marathon. Reported as R<sup>2</sup> (r)  
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7 428 Fig. 1 Changes in circulating concentrations of IL-6, eHsp72, adrenaline and noradrenaline in response to the  
8 429 wheelchair half-marathon. Connected dots represent the individual responses, whilst horizontal lines represent  
9 430 the mean difference of the group between pre-and post-race, including the positive standard deviation of the  
10 431 difference. \* Significant difference between pre- and post-race. ^ Significant time x group interaction between  
11 432 NON-CSCI and CSCI (*p*<0.05). Graphs created using the template provided by Weissgerber et al. (Weissgerber,  
12 433 Milic, Winham, & Garovic, 2015).  
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14 434  
15 435 Fig. 2 Individual relationships between post-race concentrations of adrenaline, noradrenaline and eHsp72 with  
16 436 post-race IL-6 concentrations for CSCI (O) and NON-CSCI (+). \* Variable significantly explains variance in  
17 437 post-race IL-6 concentrations (*p*<0.05).  
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Table 1. Characteristics of the participants with (CSCI) compared to the participants without (NON-CSCI) a cervical spinal cord injury. Values are given in mean (SD).

Parameter	NON-CSCI (N=10)	CSCI (N=7)	NON-CSCI vs. CSCI mean (95% CI) difference
Age (yrs)	43.5 (12.1)	43.4 (15.0)	-0.7(-14.1 to 13.9)
Height (cm)	155.3 (23.3)	172.6 (7.8)	17.3(-2.4 to 37.0)
Body mass (kg)	53.8 (11.4)	60.0 (15.8)	6.2(-8.4 to 20.8)
Wheelchair racing experience (yrs)	15.1 (9.6)	16.3 (10.2)	1.2(-11.0 to 13.4)
Training per week (min)	313 (245)	307 (193)	-5(-273 to 262)
Lesion level SCI	<Thoracic 5	>Cervical 8	NA
Sensory and motor complete/incomplete SCI	N=4/1	N=3/4	-1/3
Orthostatic hypotension	N=1	N=4	3
Change in SBP/DBP following tilt (mmHg)	-2 (12) / -4 (7)	-21 (10)/-5 (11)	-18.1(-32.3 to -3.7)* / -0.9(-11.0 to 9.2)
Supine LF/HF RRI	1.65 (1.22)	0.34 (0.20)	-1.31(-2.53 to -0.36) *
Supine LF SBP (Hz)	7.54 (3.71)	1.39 (1.95)	-6.15(-10.07 to -2.22) *
Supine TP SBP (Hz)	5.96(3.74)	36.34(11.27)	-30.3(-41.9 to -18.9)*
Supine RMSSD (ms)	42.6(11.1)	46.6(23.1)	3.95(-46.0 to 53.9)

Abbreviations: SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate; LF/HF RRI = ratio of the power in the low and high frequency domain of the heart rate variability; LF SBP = power in the low frequency domain of systolic blood pressure variability; TP SBP = total power of systolic blood pressure variability. Orthostatic hypotension is defined as a drop in SBP>20 mmHg or DBP>10 mmHg following the onset of the sitting position. \* Significant difference between NON-CSCI and CSCI ( $p<0.05$ ).

Table 2. Regression analyses with autonomic function indices and the inflammatory response to the wheelchair half-marathon. Reported as R<sup>2</sup> (r)

Predictor variable	IL-6 post-race	Adrenaline post-race	Noradrenaline post-race
A	44% (0.66)*	N/A	67% (0.82)*
N	8% (0.29)	67% (0.82)*	N/A
LF/HF RRI	8% (0.28)	29% (0.54)*	11% (0.33)
LF SBP	12% (0.35)	19% (0.44)	34% (0.58)*
TP SBP	29% (0.54)	33% (0.58)*	28% (0.53)
RMSSD	11% (0.33)	5% (0.23)	3% (0.18)
A + N	60% (0.77)*	N/A	N/A
LF/HF RRI + LF SBP	14% (0.36)	33% (0.58)	34% (0.59)
LF/HF RRI + TP SBP	27% (0.52)	38% (0.61)	25% (0.50)
RMSSD + LF SBP	6% (0.24)	21% (0.46)	34% (0.58)
RMSSD + TP SBP	34% (0.58)	36% (0.60)	30% (0.55)
A + N + LF/HF RRI + LF SBP	81% (0.90)*	N/A	N/A
A + N + LF/HF RRI + TP SBP	88% (0.94)*	N/A	N/A
A + N + RMSSD + LF SBP	64% (0.80)	N/A	N/A
A + N + RMSSD + TP SBP	72% (0.85)*	N/A	N/A

Abbreviations: IL-6 = interleukin-6; A = adrenaline post-race; N = noradrenaline post-race; LF/HF RRI = ratio of the power in low and high frequency of the heart rate variability; LF SBP = power in the low frequency of systolic blood pressure variability; TP SBP = total power of systolic blood pressure variability; RMSSD = root mean square differences of successive R-R intervals.

\* Regression model significantly explains variance in dependent variable ( $p < 0.05$ )



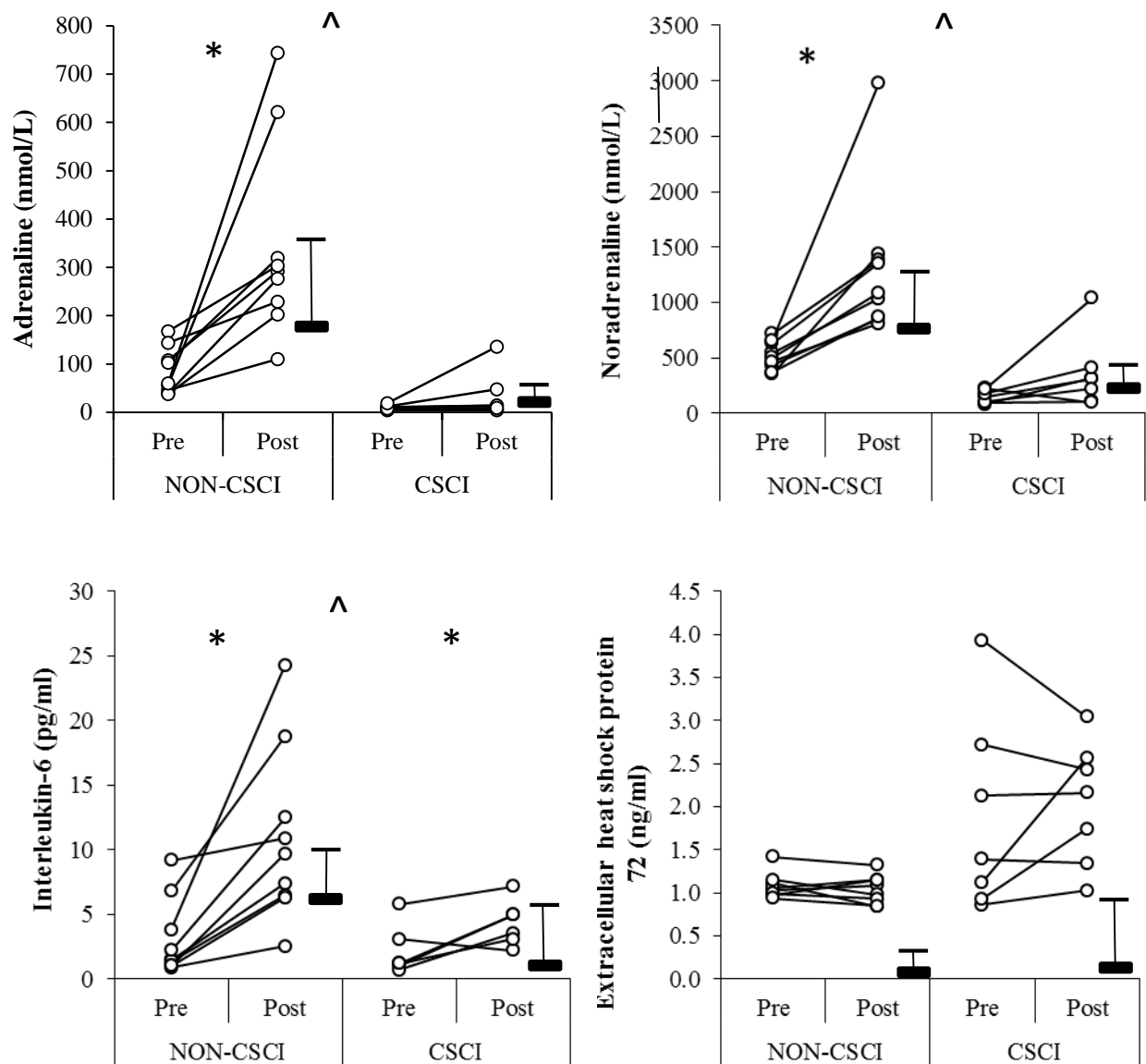


Fig. 1 Changes in serum concentrations of IL-6, eHsp72, adrenaline and noradrenaline in response to the wheelchair half-marathon. Connected dots represent the individual responses, whilst horizontal lines represent the mean difference of the group between pre- and post-race, including the positive standard deviation of the difference. \* Significant difference between pre- and post-race. ^ Significant time x group interaction between NON-CSCI and CSCI ( $p < 0.05$ ). Graphs created using the template provided by Weissgerber et al. (Weissgerber, Milic, Winham, & Garovic, 2015).

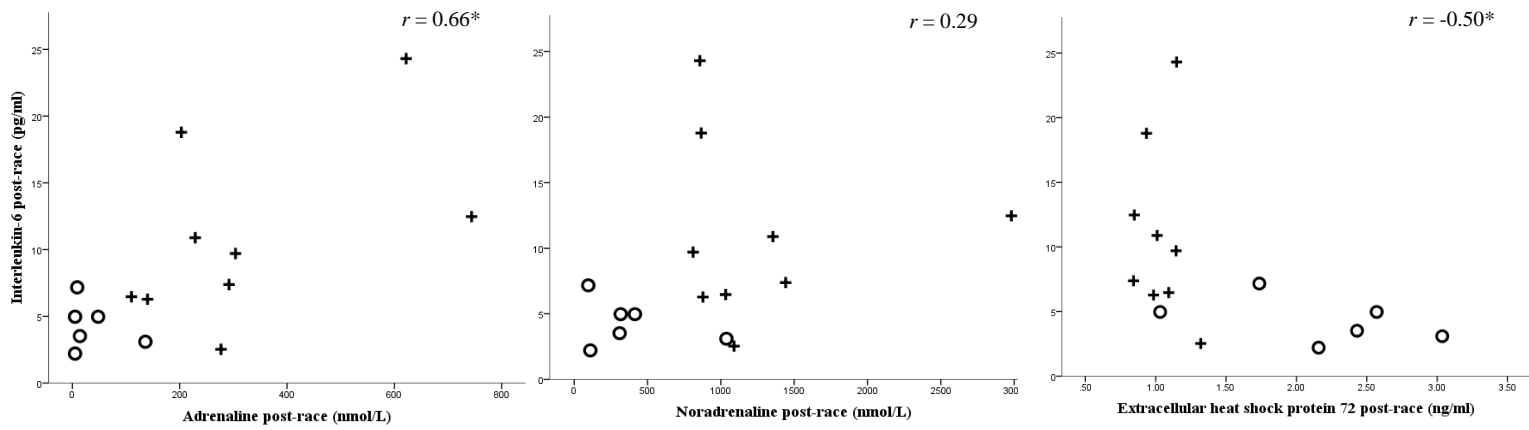


Fig. 2 Individual relationships between post-race serum concentrations of adrenaline, noradrenaline and eHsp72 with post-race IL-6 serum concentrations for CSCI (O) and NON-CSCI (+). \* Variable significantly explains variance in post-race IL-6 serum levels ( $p < 0.05$ ).