

1 **Title:**

2 Heat acclimation improves sweat gland function and lowers sweat sodium concentration in an  
3 adult with cystic fibrosis.

4 **Running Title:**

5 Heat acclimation and cystic fibrosis

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25 **Abbreviations:**  $[Na^+]$  – sodium concentration; TEM – typical error of measurement;  $\dot{V}O_{2max}$   
26 – maximal oxygen uptake; pwCF – people with cystic fibrosis; FEV<sub>1</sub> – forced expiratory  
27 volume in 1 second;  $W_{peak}$  – peak power output.

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32 Supervision; Writing - review & editing. **Rob Holliss and Adam Causer:** Data curation;  
33 Investigation; Project administration; Resources; Writing – review & editing. **Ashley Willmott:**  
34 Methodology; Formal analysis; Writing - original draft.

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36 **Highlights:**

- 37 • Heat acclimation improved sudomotor function in an adult with cystic fibrosis (CF)
- 38 • Sweat loss increased and sweat [sodium] decreased following heat acclimation.
- 39 • Adaptations were maintained for 7-days, with no evidence of heat acclimation decay.
- 40 • Heat acclimation was well tolerated and appeared to be safe in an adult with CF.
- 41 • Heat acclimation using controlled hyperthermia may benefit people with CF.

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## ABSTRACT

We present novel data concerning the time-course of adaptations and potential benefits of heat acclimation for people with cystic fibrosis (pwCF), who are at greater risk of exertional heat illness. A 25-year-old male (genotype: delta-F508 and RH117, forced expiratory volume in 1-second: 77% predicted and baseline sweat  $[Na^+]$ :  $70 \text{ mmol}\cdot\text{L}^{-1}$ ), who had previously experienced muscle cramping during exercise in ambient heat, underwent 10-sessions of heat acclimation (90-min at  $40^\circ\text{C}$  and in 40% relative humidity). Adaptations included; lower resting core temperature ( $-0.40^\circ\text{C}$ ) and heart rate ( $-6 \text{ beats}\cdot\text{min}^{-1}$ ), plasma volume expansion ( $+6.0\%$ ) and, importantly, increased sweat loss ( $+370 \text{ mL}$ ) and sweat gland activity ( $+12 \text{ glands}\cdot\text{cm}^2$ ) with decreased sweat  $[Na^+]$  ( $-18 \text{ mmol}\cdot\text{L}^{-1}$ ). Adaptations were maintained for at least 7-days, with no evidence of cramping during follow-up exercise-heat stress testing. These data suggest pwCF may benefit from heat acclimation to induce sudomotor function improvements, particularly reductions in sweat  $[Na^+]$ , however, further research is required.

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**Key words:** Heat acclimation; cystic fibrosis; sweat sodium concentration; adaptation; heat stress

## BACKGROUND

Standard care involves encouraging a physically active lifestyle for all people with cystic fibrosis (pwCF). PwCF may be at an increased risk of exertional heat illness during prolonged exercise and/or exercise in higher ambient temperatures [1]. Specifically, as mutant CF transmembrane conductance regulator proteins reduce ion reabsorption capacity within the sweat duct, pwCF produce sweat with higher sodium ( $[Na^+]$ ) and chloride ( $[Cl^-]$ ) concentrations [2]. As such, pwCF are more susceptible to electrolyte imbalances, hyponatremia and dehydration (via inadequate fluid ingestion, reduced osmotic drive for thirst and an absence/suppressed thirst sensation), which may all predispose exertional heat illness [3]. However, currently there is limited understanding regarding strategies that may help mitigate these risks.

69 One potential strategy is through physiological adaptive mechanisms (e.g. increased sweat rate and  
70 diluted sweat electrolyte concentrations), as observed in healthy individuals following repeated bouts  
71 of exercise-heat stress (i.e. heat acclimation) [4]. However, little is known concerning the effectiveness  
72 of this strategy, and the time-course and maintenance of adaptations in pwCF. Orenstein et al. [1]  
73 reported similar thermoregulatory (lower rectal temperature) and cardiovascular adaptations (lower  
74 heart rate) in pwCF versus healthy controls, following 8-days of heat acclimation. However, sudomotor  
75 function remained unchanged in pwCF, whereas healthy individuals displayed reductions in sweat  
76  $[\text{Na}^+]$  and  $[\text{Cl}^-]$ , suggesting an inability to adapt, a disparity in the time-course of adaptations and/or a  
77 sub-optimal heat acclimation protocol [1].

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79 Therefore, this case study aimed to investigate how a young man with moderate CF lung disease and a  
80 history of muscle cramping during exercise in heat stress, adapted to 10-sessions of heat acclimation,  
81 with a particular emphasis on the time-course and maintenance of heat adaptations, specifically, sweat  
82 gland function and sweat  $[\text{Na}^+]$ .

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## METHODS

85 A recreationally active 25-year-old-male (height: 169.9 cm, body mass: 77.8 kg, body fat: 19.8%) gave  
86 informed consent to participate in this study, which was approved by our Institutional Ethics Committee  
87 and complied with the principles of the Declaration of Helsinki (2013). He had moderate CF lung  
88 disease as indicated by his genotype (delta-F508 and R117H), forced expiratory volume in 1 second  
89 ( $\text{FEV}_1$ : 77% predicted) and baseline sweat  $[\text{Na}^+]$  ( $70 \text{ mmol}\cdot\text{L}^{-1}$ ). He played football thrice weekly and  
90 ran regularly but previously had reported signs and symptoms of heat-related illnesses (heat cramps and  
91 heat exhaustion) during prolonged exercise in temperate/hot environmental conditions (London and  
92 Brighton marathons).

93

94 The participant completed a maximal cardiopulmonary exercise test [5] at  $22^\circ\text{C}$  and in 40% relative  
95 humidity to determine aerobic fitness (maximal oxygen uptake  $[\dot{V}\text{O}_{2\text{max}}]$ :  $3.50 \text{ L}\cdot\text{min}^{-1}$  and  $45.0 \text{ mL}\cdot\text{kg}^{-1}$

96  $\cdot\text{min}^{-1}$  [117.4% predicted]), peak power output ( $W_{\text{peak}}$ : 261 W and  $3.4 \text{ W}\cdot\text{kg}^{-1}$  [119.7% predicted]) and  
97 to prescribe exercise intensities for his heat acclimation state test (3, 4.5 and  $6 \text{ W}\cdot\text{kg}^{-1}$ ) [4]. Heat  
98 acclimation state tests were completed at  $45^{\circ}\text{C}$  and in 20% relative humidity; 2-days pre- (PRE),  
99 midway through- (MID), 2-days post- (POST) and 7-days post-heat acclimation (POST+7-days). Heat  
100 acclimation included ten 90-min exercise sessions of controlled hyperthermia. This involved cycling at  
101  $65\% \dot{V}O_{2\text{max}}$  ( $2.2 \text{ W}\cdot\text{kg}^{-1}$ ) to achieve a target rectal temperature of  $38.5^{\circ}\text{C}$ , then using variable exercise  
102 intensities to maintain this target temperature for the remainder of the session. Heat acclimation  
103 occurred at  $40^{\circ}\text{C}$  and in 40% relative humidity, over two consecutive 5-day periods (i.e. 5-days heat  
104 acclimation, rest day, heat acclimation state test, rest day, 5-days heat acclimation).

105

106 Physiological (rectal and skin temperature, heart rate, plasma volume, whole-body sweat loss and rate,  
107 local sweat rate, sweat gland activity and sweat  $[\text{Na}^+]$ ) and perceptual measures (using fixed-point  
108 categorical scales for: rating of perceived exertion [from 6 “*No exertion*” to 20 “*Maximal Exertion*”],  
109 thermal sensation [from 0 “*Very Very Cold*” to 4 “*Neutral*” to 8 “*Very Very Hot*”] and thermal comfort  
110 [from 0 “*Very Comfortable*” to 5 “*Very Uncomfortable*”) were assessed during each visit, as described  
111 previously [4]. Briefly, whole-body sweat loss was estimated from nude body mass differences pre- to  
112 post-exercise (Adam Equipment Inc., USA), local sweat rate was estimated from technical absorbent  
113 patches (Tegaderm+Pad, 3M<sup>TM</sup>, USA) on the upper back, sweat gland activity was estimated using the  
114 modified iodine technique, and sweat  $[\text{Na}^+]$  measured using a Sweat-Chek<sup>TM</sup> analyser (Wescor Inc.,  
115 USA). Predefined analytical limits and typical error of measurements (TEM) were used to highlight  
116 meaningful adaptations following heat acclimation [4].

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## RESULTS

119 Heat acclimation intervention:

120 The participant completed all of the scheduled sessions with no adverse incident, cramping or other  
121 heat-related illness reported. The thermal forcing-function was maintained throughout, as indicated by  
122 the consistent attainment of the target rectal temperature (Table 1).

123

124 MID-heat acclimation state test:

125 After 5 exercise-heat sessions thermo-physiological adaptations were evident, including reduced resting  
126 rectal temperature ( $-0.21^{\circ}\text{C}$ ; 53% of final adaptation), resting heart rate ( $-8 \text{ beats}\cdot\text{min}^{-1}$ ; 133% of final  
127 adaptation) and peak heart rate ( $-19 \text{ beats}\cdot\text{min}^{-1}$ ; 173% of final adaptation) (Table 1). Sudomotor  
128 adaptations were also evident, including reduced sweat  $[\text{Na}^+]$  ( $-11 \text{ mmol}\cdot\text{L}^{-1}$ ; 61% of final adaptation),  
129 and increased sweat gland activity ( $+12 \text{ glands}\cdot\text{cm}^2$ ; 100% of final adaptation) and local sweat rate at  
130 the back ( $+0.36 \text{ mg}\cdot\text{min}^{-1}\cdot\text{cm}^2$ ; 78% of final adaptation). The participant perceived the MID-heat  
131 acclimation state test to be easier (peak rating of perceived exertion  $-2$  [arbitrary units]) and felt cooler  
132 (peak thermal sensation  $-1$  [arbitrary units])

133

134 POST-heat acclimation state test:

135 Further reductions in resting rectal temperature ( $-0.19^{\circ}\text{C}$  vs. MID;  $-0.40^{\circ}\text{C}$  vs. PRE) and sweat sodium  
136  $[\text{Na}^+]$  ( $-7 \text{ mmol}\cdot\text{L}^{-1}$  vs. MID;  $-18 \text{ mmol}\cdot\text{L}^{-1}$  vs. PRE) were evident. Peak rectal temperature was reduced  
137 relative to the MID-heat acclimation state test ( $-0.24^{\circ}\text{C}$ ), and a reduction in skin temperature (rest -  
138  $0.96^{\circ}\text{C}$ , peak  $-0.43^{\circ}\text{C}$ ), expansion of plasma volume ( $+6.0\%$ ) and increased whole-body sweat loss  
139 ( $+370 \text{ mL}$ ) were also evident relative to PRE-heat acclimation state test (Table 1).

140

141 POST+7-days heat acclimation state test:

142 The majority of adaptations, including sudomotor enhancements (whole-body sweat loss, sweat  $[\text{Na}^+]$   
143 and sweat gland activity), were maintained for 7-days after heat acclimation (Table 1). A strong negative  
144 correlation ( $r = 0.95$ ) was observed between sweat  $[\text{Na}^+]$  and whole-body sweat loss during the course  
145 of heat acclimation (Table 1).

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## DISCUSSION

148 We observed changes in classic markers of heat adaptation following 5 and 10-sessions of heat  
149 acclimation in an adult with moderate CF lung disease, consistent with typical responses in healthy

150 adults of a similar age [4]. Our data demonstrated a rapid time-course of adaptation in several  
151 parameters (including; heart rate, sweat gland activity, local sweat rate at the back), with ~ 75% of the  
152 final adaptation achieved after only 5-sessions; yet, other parameters required longer to evoke a  
153 substantial change. After 10-sessions of heat acclimation, we observed lower resting rectal temperature  
154 and heart rate; plasma volume expansion; increased whole-body sweat loss, sweat gland activity and  
155 local sweat rate; and reduced sweat  $[\text{Na}^+]$ .

156

157 A seminal study by Orenstein and colleagues in 1984 investigated whether pwCF could heat-acclimate  
158 using an 8-day exercise heat acclimation protocol (70-min exercise at 50%  $\dot{V}O_{2\text{max}}$ ;  $\sim 37\text{-}38^\circ\text{C}$ , 33-55%  
159 relative humidity). PwCF demonstrated some thermo-physiological adaptations, including a reduced  
160 resting rectal temperature ( $-0.2^\circ\text{C}$ ), lower peak exercise rectal temperature ( $-0.4^\circ\text{C}$ ) and heart rate ( $-15$   
161  $\text{b}\cdot\text{min}^{-1}$ ). However, it was concluded that heat acclimation did not alter sweat gland function or sweat  
162 electrolyte concentration in pwCF. Our data contrasts with Orenstein et al. [1], demonstrating for the  
163 first time, a range of important sudomotor adaptations following heat acclimation. The increased sweat  
164 loss (1.93 to 2.30 L) and reduced sweat  $[\text{Na}^+]$  (70 to 52  $\text{mmol}\cdot\text{L}^{-1}$ ) observed in the participant with  
165 moderate CF involvement are consistent with the sudomotor responses of healthy individuals following  
166 a similar heat acclimation protocol (+533 mL and  $-27 \text{ mmol}\cdot\text{L}^{-1}$  [4]). These adaptations are likely to  
167 reduce the risk of predisposing factors to exertional heat illness (e.g. electrolyte imbalance, cramping,  
168 and hyponatremia) and suggest that this individual improved his heat tolerance without reporting further  
169 cramping issues. However, further investigations are warranted to understand why this strategy has not  
170 been widely utilised by pwCF, particularly athletes, most likely due to a lack of research-informed  
171 practice and logistical challenges, with the potential for other, more time-efficient approaches (e.g.  
172 saunas/hot baths and/or pre-cooling) also requiring investigation in this population.

173

174 Another unique observation is that the adaptations were maintained for at least 7-days after heat  
175 acclimation (Table 1). This is an under-investigated area in pwCF and our data provides practical  
176 information for those interested in heat acclimation to minimise performance and/or health impairments

177 anticipated during athletic events. Future studies should investigate the effect of heat acclimation on  
178 sweat [Cl<sup>-</sup>] in pwCF (a limitation of this case report), given this prognostically-relevant outcome is  
179 known to decrease following heat acclimation in healthy individuals.

180

### 181 **CONCLUSION**

182 This case report demonstrates how heat acclimation may benefit pwCF and potentially lower the risk  
183 of exertional heat illness, which is particularly important for pwCF exercising in hot climates. Future  
184 studies to confirm these findings in a larger representative sample are needed to further understand the  
185 benefits from heat acclimation for pwCF.

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### 187 **CONFLICT OF INTEREST STATEMENT**

188 The authors declare no conflict of interest.

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192 (1,440 / 1,200 words)

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**Table 1. Mean  $\pm$  SD data for: (A) heat acclimation sessions; (B) differences in heat adaptations as evaluated by repeated heat acclimation state tests; and (C); correlation between sweat  $[Na^+]$  and whole-body sweat loss.**

(A) Heat acclimation	Session 1	1 to 5	6 to 10	1 to 10
Time to 38.5°C (min)	60	59 $\pm$ 9	57 $\pm$ 6	58 $\pm$ 7
Peak rectal temperature (°C)	38.62	38.62 $\pm$ 0.12	38.65 $\pm$ 0.06	38.63 $\pm$ 0.09
Change in rectal temperature (°C)	1.49	1.51 $\pm$ 0.14	1.61 $\pm$ 0.06	1.56 $\pm$ 0.12
Mean heart rate (b·min <sup>-1</sup> )	159	151 $\pm$ 8	143 $\pm$ 3	147 $\pm$ 7
Peak heart rate (b·min <sup>-1</sup> )	176	175 $\pm$ 5	174 $\pm$ 3	174 $\pm$ 4
Whole-body sweat loss (mL)	1830	1892 $\pm$ 167	2156 $\pm$ 132	2024 $\pm$ 199
Whole-body sweat rate(L·hr <sup>-1</sup> )	1.22	1.26 $\pm$ 0.11	1.44 $\pm$ 0.09	1.35 $\pm$ 0.13
Peak rating of perceived exertion	19	19 $\pm$ 1	18 $\pm$ 0	18 $\pm$ 1
Peak thermal sensation	7	8 $\pm$ 0	7 $\pm$ 0	8 $\pm$ 0
Peak thermal comfort	4	5 $\pm$ 0	5 $\pm$ 0	5 $\pm$ 0

  

(B) Heat acclimation state tests	PRE	PRE to MID	MID to POST	PRE to POST	PRE to POST+7-days	POST to POST+7-days	Criteria ( $\pm$ )	Adapted			Maintained
								1 to 5	6 to 10	1 to 10	
Rest rectal temperature (°C)	37.25	-0.21	-0.19	-0.40	-0.36	+0.04	0.20	✓	✗	✓	✓
Peak rectal temperature (°C)	38.30	+0.10	-0.24	-0.14	-0.16	-0.02	0.20	✗	✓	✗	✓
Rest skin temperature (°C)	31.86	+0.94	-1.90	-0.96	-1.40	-0.45	0.24	✗	✓	✓	✓
Peak skin temperature (°C)	37.53	+0.92	-1.35	-0.43	-0.21	+0.21	0.24	✗	✓	✓	✓
Rest heart rate (b·min <sup>-1</sup> )	71	-8	+2	-6	-16	-10	5	✓	✗	✓	✓
Peak heart rate (b·min <sup>-1</sup> )	191	-19	+8	-11	-26	-15	5	✓	✓	✓	✓
Plasma volume (%)	-	+0.7	+5.3	+6.0	+4.4	-1.6	5	✗	✓	✓	✓
Sweat setpoint (°C)	37.67	-0.13	-0.05	-0.18	-0.04	+0.14	0.21	✗	✗	✗	✓
Sweat gain (g·sec <sup>-1</sup> ·°C <sup>-1</sup> )	0.50	-0.09	+0.08	-0.01	+0.01	+0.02	0.09	✗	✗	✗	✓
Whole-body sweat loss (mL)	1930	+110	+260	+370	+310	-60	200	✗	✓	✓	✓
Sweat $[Na^+]$ (mmol·L <sup>-1</sup> )	70	-11	-7	-18	-18	0	2	✓	✓	✓	✓
Sweat gland activity (gland·cm <sup>2</sup> )	113	+12	0	+12	+16	+4	5	✓	✗	✓	✓
Local sweat rate (mg·min <sup>-1</sup> ·cm <sup>2</sup> )	0.52	+0.36	+0.10	+0.46	+0.44	-0.02	0.13	✓	✗	✓	✓
Peak rating of perceived exertion	20	-2	+1	-1	-3	-2	1	✓	✗	✓	✓
Peak thermal sensation	8	-1	0	-1	-2	-1	1	✓	✗	✓	✓
Peak thermal comfort	5	0	0	0	-1	-1	1	✗	✗	✗	✓

  

Note: ✓ - yes; ✗ - no.

