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# Journal Pre-proof

Exercise-induced cardiac fatigue after a 45-minute bout of high-intensity running exercise is not altered under hypoxia

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# 1       **Exercise-induced cardiac fatigue after a 45-minute bout of high-** 2       **intensity running exercise is not altered under hypoxia**

3                   **Brief title: Exercise-induced cardiac fatigue under hypoxia**

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32 **ABSTRACT**

33 **Background.** Acute exercise promotes transient exercise-induced cardiac fatigue (EICF), which affects  
34 the right ventricle (RV) and to a lesser extent the left ventricle (LV). Hypoxic exposure induces an  
35 additional increase in RV afterload. Therefore, exercise in hypoxia may differently affect both  
36 ventricles.

37 **Aim.** Investigate the acute effects of a bout of high-intensity exercise under hypoxia *versus* normoxia  
38 in healthy individuals on right- and left-sided cardiac function and mechanics.

39 **Methods.** 21 healthy individuals (22.2±3.0 years, fourteen men) performed a 45-minute high-  
40 intensity running exercise, under hypoxia (fraction of inspired oxygen [FiO<sub>2</sub>] 14.5%) and normoxia  
41 (FiO<sub>2</sub> 20.9%) in a randomized order. Pre- and post-exercise echocardiography, at rest and during low-  
42 to-moderate intensity recumbent exercise ('stress'), was performed to assess RV and LV cardiac  
43 function and mechanics. RV structure, function and mechanics were assessed using conventional 2D,  
44 Doppler, tissue Doppler, speckle tracking echocardiography and novel strain-area loops.

45 **Results.** Indices for RV systolic function (RVFAC, TAPSE, RVS', RV free wall strain) as well as LV  
46 function (LV ejection fraction, LV global longitudinal strain)) significantly reduced after high-intensity  
47 running exercise ( $p < 0.01$ ). These exercise-induced changes were more pronounced when  
48 echocardiography was examined during stress compared to baseline. These responses in RV or LV  
49 were not altered under hypoxia ( $p > 0.05$ ).

50 **Conclusion.** There was no impact of hypoxia on the magnitude of EICF in the RV and LV after a bout  
51 of 45-minute high-intensity exercise. This finding suggests that any potential increase in loading  
52 conditions does not automatically exacerbate EICF in this setting.

53

54 **Keywords:** athlete's heart; exercise-induced cardiac fatigue; hypoxia; echocardiography; speckle

55 tracking echocardiography

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56 **INTRODUCTION**

57 It is well established that exercise is associated with potent cardioprotective effects<sup>1-3</sup>, however,  
58 acute exercise can lead to a paradoxical short-term increase in cardiac events.<sup>4-6</sup> One potential  
59 explanation is that exercise performed under demanding conditions (i.e. exercise at high-intensity  
60 and/or during prolonged duration) may lead to an acute reduction in cardiac function.<sup>7-13</sup> This  
61 transient decline in cardiac function after strenuous exercise is typically referred to as exercise-  
62 induced cardiac fatigue (EICF). EICF may affect both left (LV) and right ventricles (RV), with possibly a  
63 larger impact on the RV due to the disproportionately higher wall stress experienced by the RV  
64 relative to the LV during exercise.<sup>11, 14, 15</sup>

65 Previous studies have demonstrated that hypoxia increases the demands on the cardiovascular  
66 system.<sup>16</sup> Specifically, acute exposure to hypoxia induces a decrease in systemic vascular resistance  
67 at rest, which may contribute to a decrease in LV afterload.<sup>17, 18</sup> In contrast, hypoxia leads to a resting  
68 increase in pulmonary artery resistance, and subsequently to an increase in pulmonary vascular  
69 resistance (PVR) and pulmonary artery pressure (PAP).<sup>19</sup> Exercise in normoxic conditions results in  
70 additional load challenges and an increased PAP secondary to the mismatch of elevated stroke  
71 volume to inadequate pulmonary vascular distension.<sup>20</sup> This is exacerbated when exercising in  
72 hypoxic conditions, leading to an even greater PAP and RV wall stress and potentially further  
73 increasing the risk of RV EICF.<sup>19-23</sup>

74 To non-invasively examine right heart haemodynamics, studies have examined conventional and  
75 Doppler based echocardiographic indices at rest and during exercise.<sup>24-26</sup> Recently, the strain-area  
76 loop has been introduced assessing simultaneous structure and strain across the cardiac cycle.<sup>5</sup>  
77 Previously, we found that RV loop characteristics relate to PVR in patients with pulmonary arterial  
78 hypertension (PAH) whilst also demonstrating value in the assessment of EICF.<sup>27, 28</sup> Therefore, these  
79 non-invasive characteristics may provide additional insight in understanding exercise-induced  
80 changes in hypoxia.

81 In view of this, the aim of this study, was to investigate the acute effects of a bout of high-intensity  
82 exercise under hypoxia *versus* normoxia in healthy individuals on right- and left-sided cardiac  
83 function and mechanics (i.e. longitudinal strain and strain-area loops). Based on the presumed higher  
84 workload of the RV during hypoxic *versus* normoxic exercise, we hypothesize that exercise under  
85 hypoxia exaggerates RV to a greater extent than LV compared to exercise under normoxia. To  
86 investigate EICF, we examined pre- and post-exercise echocardiography at rest, but also during a  
87 standardized low-to-moderate-intensity recumbent exercise challenge ('stress'). As the post-exercise  
88 recovery period is associated with persistent sympathoexcitation and peripheral vasodilation<sup>17, 18</sup>,  
89 evaluation of EICF could be confounded when evaluated solely at rest. Therefore, evaluation during  
90 stress echocardiography may better reflect cardiac function *during* exercise and offsets the key  
91 limitation of (para)sympathetic imbalance associated with echocardiographic assessment in  
92 recovery.<sup>14</sup>

93

## 94 **METHODS**

### 95 **Study population**

96 Twenty-one participants (22.2±0.6 years, fourteen men, 24.0±0.6 kg/m<sup>2</sup>, VO<sub>2</sub>max/kg/min 52.4±1.8  
97 mL/min/kg) completed the study. Baseline characteristics are shown in **Table 1**. Participants were  
98 eligible to take part in this study if they were able to run on a treadmill and if they trained <2 hours a  
99 week at moderate-to-high-intensity for the last six months. Exclusion criteria were a body mass index  
100 (BMI) <18 or >30 kg/m<sup>2</sup>, active smoker, any possibility of pregnancy, personal history of  
101 cardiovascular disease, positive family history of cardiovascular death (<55y), exercise-limiting  
102 respiratory disease, physical (i.e. musculoskeletal) complaints making completion of a bout of high-  
103 intensity running exercise impossible, abnormal resting 12-lead electrocardiogram (ECG) and  
104 abnormalities observed on resting transthoracic echocardiography. The procedures were in  
105 accordance with institutional guidelines and conformed to the declaration of Helsinki. The study was



106 approved by the Ethics Research Committee of Liverpool John Moores University (18/SPS/065).  
107 Participants gave full written and verbal informed consent before participation.

108

### 109 **Study design**

110 In this randomized crossover trial, participants attended the laboratory on three separate occasions  
111 (**Figure 1**). During the first visit, a medical screening was performed to determine eligibility of the  
112 potential participants. After signing informed consent, baseline measurements were performed.  
113 Visits two and three included performance of a bout of 45-minute high-intensity running exercise  
114 under normobaric hypoxia or normoxia, which were performed in a randomized order. Participants  
115 were blinded for the order of test days and abstained from exercise for a minimum of 48 hours, and  
116 from alcohol and caffeine consumption 24 hours before the test days.

117 *Baseline measurements.* Participants were examined for height (SECA stadiometer, SECA GmbH,  
118 Germany), weight (SECA scale, SECA GmbH, Germany), oxygen saturation (SpO<sub>2</sub>, pulse oximetry; Ana  
119 Pulse 100, Ana Wiz Ltd., UK), 12-lead ECG (Cardiovit MS-2010, Schiller, Switzerland) and maximal  
120 oxygen consumption (VO<sub>2</sub>max). Resting heart rate (HR, Polar, Kempele, Finland) and resting blood  
121 pressure (BP, Dinamap V100, GE Medical, Norway) were determined at the end of ten minutes of  
122 quiet rest in a supine position. A standardized maximal cardiopulmonary exercise test (CPET, Oxycon  
123 pro, CareFusion, VS) for VO<sub>2</sub>max assessment was conducted on a motorized treadmill (HP Cosmos,  
124 Nussdorf, Germany) after a 10-min warm-up and familiarization. VO<sub>2</sub>max was defined as the highest  
125 value of a 30-s average<sup>29</sup>, and attainment was verified according to previous recommended criteria.<sup>30</sup>

126 *Test days.* **Figure 1** outlines the details of a single test day. One of the test days was performed at  
127 normoxia (sea level, equivalent to fraction of inspired oxygen [FiO<sub>2</sub>] 20.9%) and the other at  
128 normobaric hypoxia (FiO<sub>2</sub> 14.5%; equivalent to a simulated altitude of 3,000m), separated by at least  
129 48 hours of rest. Participants were subjected to 30 minutes of acclimation in a seated position  
130 followed by 45-minute of high-intensity (85% of maximum achieved HR during CPET) endurance

131 running exercise on a motorized treadmill (HP Cosmos, Nussdorf, Germany) and 60 minutes of  
132 recovery in seated position. HR was measured continuously throughout (Polar, Kempele, Finland),  
133 and rate of perceived exertion (RPE) was monitored during the 45-minutes high-intensity running  
134 exercise.<sup>31</sup>

135 In total four echocardiographic assessments were performed per test day. After acclimation and  
136 prior to the 45-minute exercise, echocardiography was performed under resting conditions ('rest')  
137 and during recumbent cycling to elevate heart rate to directly assess cardiac function during exercise  
138 ('stress', target HR 110-120 bpm). The 'stress' echocardiogram was repeated directly after the 45-  
139 minute exercise, to prevent sympathetic withdrawal (i.e. a drop in BP and HR).<sup>32</sup> Finally, images were  
140 obtained at the end of the 60 minutes of recovery in a resting state. During every echocardiography  
141 assessment, BP measurements were performed. Measurements were performed at the same time  
142 on both days to control for diurnal variation. Fluid intake was controlled by providing the same  
143 amount of water to participants during both testing days.

144 *Environmental chamber and safety.* All exercise tests were conducted in an environmental chamber  
145 (TISS, Alton, UK; Sportingedge, Basingstoke, UK). Normobaric hypoxia was achieved by a nitrogen  
146 dilution technique. Ambient temperature, carbon dioxide (CO<sub>2</sub>) and oxygen (O<sub>2</sub>) levels were  
147 controlled in all sessions (20°C; FiO<sub>2</sub> 14.5%; CO<sub>2</sub> 0.03%), whilst a Servomex gas analysis system  
148 (Servomex MiniMP 5200, Servomex Group Ltd., UK) was used inside the chamber to provide the  
149 researcher continuous information regarding O<sub>2</sub> and CO<sub>2</sub> levels. Acute mountain sickness symptoms  
150 (AMS, measured by Lake Louise Score<sup>33</sup> (LLS)) were monitored during testing and training sessions  
151 every 20 minutes. The subject was removed from the environmental chamber if oxygen saturation  
152 levels dropped below 80% or severe AMS was suspected (LLS≥6).

### 153 **Echocardiographic measurements**

154 Rest and stress echocardiography were performed in the left lateral decubitus position on a supine  
155 cycle ergometer (Lode B.V.; Groningen, The Netherlands) by one highly experienced sonographer  
156 (DO) using a Vivid E95 ultrasound machine (GE Medical, Horton, Norway), equipped with a 1.5-4.5

157 MHz transducer. Images were stored in raw digital imaging and communication in medicine (DICOM)  
158 format and were exported to an offline workstation (EchoPac, version 203, GE Medical, Horton,  
159 Norway). Data-analysis, from three stored cycles, was performed by a single observer with  
160 experience in echocardiography (GK) using commercially available software (EchoPac, version 203,  
161 GE Medical, Horton, Norway). The observer was blinded for the timing (pre vs. post) and condition  
162 (normoxia vs. hypoxia) under which echocardiography was performed. For stress echocardiography,  
163 low-to-moderate-intensity (target HR 110-120 bpm) exercise consisted of recumbent cycling at a  
164 cadence of ~60 revolutions per minute with watts manually adjusted to stabilise at target HR.

165 *Conventional measurements.* Cardiac structural and functional measurements were made according  
166 to the current guidelines for cardiac chamber quantification.<sup>34</sup> Regarding the right heart, we  
167 examined the following structural and functional indices: basal and mid-cavity end-diastolic  
168 diameters, RV end-diastolic area (RVEDA), RV end-systolic area (RVESA), RV outflow tract (RVOT)  
169 diameter at the proximal level in the parasternal long-axis (PLAX) and parasternal short-axis (PSAX)  
170 view, right atrial (RA) area, RV fractional area change (RVFAC), tricuspid annular plane systolic  
171 excursion (TAPSE), tissue Doppler imaging (TDI) of the tricuspid annulus (RV 's, e', a') and pulmonary  
172 artery Doppler acceleration time (PAT). Tricuspid regurgitation velocity was not obtainable in the  
173 major part of the participants and therefore was unable to be utilized in this study.

174 Regarding the left heart, the following structural and functional indices were determined: LV end-  
175 diastolic volume (LVEDV), LV end-systolic volume (LVESV), LA diameter, LA volume, modified  
176 Simpson's left ventricular ejection fraction (LVEF), tissue Doppler imaging (TDI) of the mitral annulus  
177 (LV 'e', e' and a') and trans-mitral Doppler (E, A and E/A ratio). Doppler A and RV and LV TDI a' were  
178 not measurable on account of e'/a' and E/A fusion during stress echocardiography at higher heart  
179 rates.

180 *Mechanics.* Images were acquired and optimized for STE. This involved maintaining frame rates  
181 between 40 and 90 frames s<sup>-1</sup>, depth to ensure adequate imaging of the chamber of interest and

182 compression and reject to ensure endocardial delineation. The RV focused and the apical two-  
183 chamber, four-chamber and long-axis view were utilized for the RV and LV global longitudinal strain,  
184 respectively. Pulmonary and aortic valve closure times were determined from the respective pulsed  
185 wave Doppler signals. For both the RV and LV views the myocardium was manually traced to include  
186 the septum and adjusted so that the region of interest (ROI) incorporated all of the wall thickness  
187 while avoiding the pericardium.<sup>35, 36</sup> The region of interest was divided into six myocardial segments,  
188 providing segmental strain curves and a longitudinal strain curve as an average of all six segments for  
189 the LV views and as an average of the 3 segments of the RV free wall. LV global longitudinal strain  
190 (LVGLS) was obtained by averaging the single strain measurements of the three separate apical LV  
191 views. If inappropriate tracking of segments was observed visually or detected by the system,  
192 retracing was performed until all segments were considered acceptable.

193 *RV strain-area loops.* The longitudinal strain-area relationship (detailed methods of derivation see,  
194 Supplemental 1, Oxborough *et al.*<sup>5</sup> and Hulshof *et al.*<sup>37</sup>) was assessed using the following parameters  
195 (**Figure 2**): (I) the linear strain-area slope (Sslope) and early strain-area slope during first 5% of  
196 volume ejection in systole (ESslope); (II) end-systolic peak longitudinal strain (peak strain); (III) the  
197 early linear strain-area slope during first 5% (EDslope) and late linear strain-area slope (LDslope)  
198 during last 5% of volume increase in diastole; and (IV) diastolic uncoupling (i.e. difference in strain  
199 between systole and diastole at any given area), divided into uncoupling during early (Uncoupling ED)  
200 and late diastole (Uncoupling LD).<sup>5, 28</sup> Based on previous work from our laboratory, we found that  
201 PAH patients with higher PVR have a lower Sslope and a decreased Uncoupling LD. Therefore, these  
202 may serve as markers of an increased PVR and consequently PAP.<sup>28</sup>

203 In order to obtain intra-observer variability, strain-area loops were re-analysed in 20 randomly  
204 selected echocardiograms (n=10 rest, n=10 stress). For all strain-area loop characteristics intra-class  
205 correlation coefficient (ICC) and Bland-Altman limits of agreement (LOA) analysis were performed.<sup>38</sup>

206

## 207 **Statistical analysis**

208 Statistical analysis was performed using SPSS Statistics 25 (SPSS Inc., Chicago, IL, VS). All parameters  
209 were visually inspected for normality and tested with Shapiro-Wilk normality tests. Continuous  
210 variables were reported as mean  $\pm$  standard error of the mean (SEM) and categorical variables were  
211 presented as proportions. Linear mixed models analysis for repeated measurements were performed  
212 to test the acute effects of a bout of 45-minutes high-intensity exercise on cardiac function and  
213 mechanics (Exercise), and whether this effect was influenced when echocardiography was performed  
214 at rest or during stress (Exercise\*Stress). Furthermore, linear mixed models were used to test the  
215 effect of hypoxia *versus* normoxia (Hypoxia) and the effect of rest *versus* stress echocardiography  
216 (Stress) on cardiac structure and function. To examine our primary objective, linear mixed models  
217 analysis was used to examine whether hypoxia impacted the effect of exercise on cardiac function  
218 (Exercise\*Hypoxia), and how this was affected by testing condition rest *versus* stress  
219 (Exercise\*Hypoxia\*Stress). For all tests, we assumed statistical significance at  $p < 0.05$ .

220

## 221 **RESULTS**

222 Both the right and left heart had normal geometry and all structural measurements were within  
223 normal ranges (**Table 2**). There were no abnormal 12-lead ECG findings.

224 *Exercise characteristics.* HR during exercise was matched between exercise under hypoxia and  
225 normoxia ( $172 \pm 1$  bpm,  $173 \pm 2$  bpm respectively,  $p = 0.23$ ). Body mass loss (hypoxia  $-410 \pm 70$ g vs.  
226 normoxia  $-410 \pm 43$ g  $p = 0.99$ ) and water intake (hypoxia  $373 \pm 60$ ml vs. normoxia  $336 \pm 44$ ml,  $p = 0.24$ )  
227 during exercise did not differ between testing sessions. Mean distance covered during exercise was  
228 significantly higher in normoxia ( $6,655 \pm 351$ m) compared to hypoxia ( $5,797 \pm 308$ m,  $p < 0.001$ ), whilst  
229 there was no significant difference in subjective ratings of perceived exertion (RPE normoxia  
230  $12.5 \pm 0.3$ , RPE hypoxia  $13.3 \pm 0.3$ ;  $p = 0.07$ ).  $SpO_2$  during exercise was significantly lower in hypoxia  
231 ( $82 \pm 0.8$ ) compared to normoxia ( $95 \pm 0.4$ ).

232

233 **Right ventricular structure, function and mechanics**

234 All RV structural, functional and mechanicals indices pre- and post- 45-minute high-intensity running  
235 exercise are displayed in **Table 2**. Indices of RV systolic function (RVFAC, TAPSE, RVS', RV free wall  
236 strain (**Figure 3A**)) significantly reduced following 45-minute high-intensity exercise (Exercise:  
237  $p < 0.01$ ). The decline in indices of RV function and mechanics after exercise were not different  
238 between rest and stress echocardiography, except for a more pronounced reduction in RV free wall  
239 strain during stress (Exercise\*Stress:  $p = 0.01$ , **Table 2, Figure 3A**). Related to the strain-area loop,  
240 following 45-minute high-intensity exercise there was a reduction in RV longitudinal strain,  
241 uncoupling and uncoupling LD (Exercise:  $p < 0.05$ ) without a rightward shift (RVEDA Exercise:  $p > 0.05$ )  
242 (**Table 2 Figure 4A,B**).

243 *Exercise under hypoxia.* Under hypoxia, PAT was significantly shorter, RA size significantly larger, late  
244 diastolic uncoupling (Uncoupling LD) significantly lower, and a trend was found for a lower systolic  
245 slope (Sslope) compared to normoxic conditions (Hypoxia:  $p = 0.04$ ,  $p = 0.04$ ,  $p < 0.001$ ,  $p = 0.07$ ,  
246 respectively, **Table 2, Figure 4A,B**). Importantly, hypoxia did not alter the impact of exercise and/or  
247 stress on indices of RV function (Hypoxia\*Exercise and Exercise\*Hypoxia\*Stress: all  $p > 0.05$ , **Table 2**).

248 *Intra-observer variability.* ICC and LOA for RV strain-area loop characteristics were as follows: RV free  
249 wall strain ICC 0.95 (0.89-0.98), LOA 0.33 (-1.55, 2.21); Sslope ICC 0.91 (0.80-0.97), LOA -0.05 (-0.30,  
250 0.20); ESslope ICC 0.60 (0.23-0.82), LOA 0.60 -0.17 (-1.20, 0.86); EDslope ICC 0.93 (0.84-0.97), LOA  
251 0.19 (-0.37, 0.75); LDslope ICC 0.95 (0.87-0.98), LOA -0.30 (-0.93, 0.32); Uncoupling ICC 0.88 (0.73-  
252 0.95), LOA -0.27 (-2.36, 1.81); Uncoupling\_ED ICC 0.86 (0.68-0.94), LOA -0.31 (-2.63, 2.01);  
253 Uncoupling\_LD ICC 0.88 (0.72-0.95), LOA -0.20 (-2.25, 1.86).

254

255 **Left ventricular structure, function and mechanics**

256 All LV structural, functional and mechanicals indices pre- and post- 45-minute high-intensity running  
257 exercise are displayed in **Table 3**. With the exception of LVS' (Exercise:  $p=0.78$ ), indices of LV systolic  
258 function (LVEF, LVGLS) significantly reduced following high-intensity exercise (Exercise:  $p<0.001$ ). The  
259 reduction in LVEF and LVGLS was more pronounced in stress *versus* rest echocardiography  
260 (Exercise\*Stress: both  $p<0.05$ , **Figure 3B**).

261 *Exercise under hypoxia*. Changes in LV indices in response to exercise, either examined at rest and/or  
262 during stress, were not different when performed under hypoxic conditions (Hypoxia\*Exercise and  
263 Exercise\*Hypoxia\*Stress:  $p>0.05$ , **Table 3**). Blood pressure response patterns did not significantly  
264 differ between hypoxic and normoxic conditions (Hypoxia and Hypoxia\*Exercise: all  $p>0.05$ , **Table 3**).

265

## 266 **DISCUSSION**

267 The aim of our study was to investigate the impact of a bout of high-intensity exercise under hypoxia  
268 *versus* normoxia on EICF on both ventricles. The main findings were 1) a bout of 45-minute high-  
269 intensity exercise induced a reduction in functional indices of right- and left-sided cardiac function  
270 and mechanics in healthy individuals, 2) the reduction in right- and left-sided cardiac function was  
271 more pronounced when echocardiography was performed during a standardized low-to-moderate-  
272 intensity recumbent exercise challenge and 3) there was no impact of hypoxia on exercise-induced  
273 reduction in right- or left-sided cardiac function and mechanics, either under rest or under stress.  
274 Taken together, these data indicate that EICF after short-term high-intensity exercise is not  
275 exaggerated under hypoxia, suggesting that an additional cardiac load (induced by hypoxia) on the  
276 RV does not necessarily relate to an exaggerated EICF in this setting.

277

278 **High-intensity exercise-induced cardiac fatigue**

279 A bout of 45-minute high-intensity running exercise induced a reduction of both RV and LV function  
280 indicative for EICF, which was mainly expressed during a low-to-moderate-intensity exercise  
281 challenge ('stress') compared to resting conditions. Earlier studies primarily investigated EICF after  
282 prolonged exercise (>180minutes)<sup>4, 27</sup>, however, recent research has revealed a dose-response  
283 relationship between EICF and the duration and intensity of exercise.<sup>14, 39</sup> Our study adds the novel  
284 knowledge that EICF also occurs after relatively short periods of high-intensity exercise in both the  
285 RV and LV. Interestingly, in contrast to other short-term high-intensity EICF studies<sup>10, 14, 39</sup>, we showed  
286 also marked reductions in LV function which may be due to the different type of exercise (running vs.  
287 cycling). An explanation for our ability to detect EICF after a relatively short duration of exercise may  
288 relate to the post-exercise assessment of cardiac function during 'stress', i.e. low-to-moderate-  
289 intensity exercise-Indeed, some of the indices for systolic function were primarily/only reduced when  
290 echocardiography was performed during the low-to-moderate-intensity exercise challenge. For  
291 example, a reduction in RVLS post-exercise was only apparent during the low-to-moderate-intensity  
292 exercise challenge (**Figure 4A**). We believe the echocardiography assessment under low-to-  
293 moderate-intensity exercise is more likely to detect EICF. The recovery phase post-exercise is  
294 associated with a change in autonomic tone and vasodilation, which may result in post-exercise  
295 tachycardia and hypotension, respectively. These (para)sympathetic imbalance factors likely  
296 influence cardiac function measurements such as strain, and therefore potentially mask the presence  
297 of EICF. Evaluation of cardiac function *during* the high-intensity exercise, therefore, is preferred.  
298 However, one should consider the practical aspects (e.g. echocardiography is impossible during  
299 running) and that reliable speckle tracking is extremely challenging with higher heart rates (i.e. 70%  
300 of maximum HR).<sup>40</sup> Low-to-moderate intensity cycling exercise at a semi-recumbent bike is both  
301 feasible and reliable, and allows to examine cardiac function during exercise. Utilising this approach,  
302 our data indicates that, with short durations of high-intensity exercise, EICF occurs when assessment  
303 of cardiac function is performed during an exercise challenge.

304



**305 Impact of exercise under hypoxia**

306 Under hypoxic conditions, less oxygen is bound to haemoglobin, and will, therefore, increase the  
307 demand on the cardiovascular system. In our population, this was reflected by a higher resting HR  
308 under hypoxia *versus* normoxia and the less distance covered under hypoxia *versus* normoxia during  
309 the exercise despite it being matched for relative intensity. More importantly, hypoxia has been  
310 shown to induce vasoconstriction of the pulmonary vasculature, leading to higher relative PVR  
311 resulting in a higher PAP, and consequently a higher RV wall stress. Elevated PAP has been previously  
312 demonstrated at conditions at 3000m altitude.<sup>23</sup> Although we were unable to directly measure PAP,  
313 we demonstrated shorter PAT and a larger RA size which indirectly supports the presence of an  
314 increase in PAP and, therefore potentially wall stress. Also, the strain-area loop showed less  
315 uncoupling in late diastole and a trend for a less steep systolic slope under hypoxia. In line with a  
316 previous study in PAH patients, these changes are associated with a higher PVR at rest.<sup>28</sup> Although  
317 we adopted a non-invasive approach and one should consider alternative explanations (i.e. related to  
318 the assessment), these findings support the presence of an elevated wall stress in our study under  
319 hypoxia. That aside, our hypothesis was rejected as the 45-minute high-intensity running exercise  
320 under hypoxia did not exaggerate RV EICF compared to exercise under normoxia. This suggests that  
321 changing cardiac workload does not necessarily change the magnitude of RV EICF and may not be the  
322 principle mechanism for RV EICF. One potential explanation for the lack of an impact of hypoxia on  
323 EICF may be that the exaggerated loading conditions under hypoxia were not sufficient enough at  
324 3000m of simulated altitude, and/or the exposure time to the raised afterload of the RV was not long  
325 enough to contribute to the EICF magnitude. There are also indications that hypoxia itself may induce  
326 cardiac dysfunction due to sustained low oxygen availability, however, this seems mainly during  
327 prolonged exposure.<sup>41</sup>

328 Our hypothesis originated from the accepted phenomenon of disproportionately higher relative wall  
329 stress in the RV compared to the LV during exercise, but also based on observations suggesting a

330 larger magnitude of EICF in the RV compared to the LV.<sup>11, 14, 15</sup> For example, Stewart *et al.* examined  
331 the influence of high-intensity exercise on RV free wall and segmental LV strain EICF following 90  
332 minutes cycling<sup>10</sup>, and found that the reduction in strain was more profound in the RV than in the LV.  
333 In their study they demonstrated a relative reduction in RV strain of -17.5% compared to -9.8% in our  
334 study, which supports a dose-response relationship. Our study is the first to our knowledge to  
335 directly compare normoxic and hypoxic conditions on EICF, and demonstrated similar changes in  
336 both RV and the LV. Although mechanical changes in the RV and LV are independent of each other<sup>27</sup>,  
337 and likely differ during exercise, our work suggests that (after)load dependency may be a less  
338 contributing factor to EICF as previously suggested. Alternatively, intrinsic myocardial factors such as  
339  $\beta$ -adrenergic receptor desensitization<sup>7, 42</sup> and oxidative stress<sup>43</sup> may play a more substantial role. Our  
340 study, however, is unable to provide further insight into these other possible mechanisms.

341 It is also of interest that following the 45-minute high-intensity exercise, this study showed a lack of  
342 any RV dilation (no rightward shift strain-area loop, **Figure 4**) as previously demonstrated following  
343 prolonged exercise.<sup>27</sup> Previous studies have demonstrated a serial and parallel impact from  
344 ventricular interdependence on LV filling secondary to RV volume / pressure overload.<sup>27, 44</sup> This  
345 finding is consistent with other studies of high-intensity exercise of relative short durations rather  
346 than is seen in EICF studies of prolonged exercise highlighting a possible dose response related to  
347 both intensity and duration.<sup>10, 14, 27</sup> In the shorter duration exercise intervention studies, the  
348 reduction in LV size occurs irrespective of changes in RV size which provides additional support for an  
349 intrinsic mechanism independent to both the right and left side of the heart. Moreover, the  
350 decreased uncoupling in the strain-area loop (**Figure 4**), indicating less longitudinal contribution to  
351 area change, in combination with a lack of RV dilatation, supports that the reduction in peak  
352 longitudinal strain post-exercise (i.e. EICF) is more likely representative of intrinsic dysfunction.

353

354 **Perspectives**

355 The mechanisms underlying EICF are likely multifactorial, and importantly may differ between the RV  
356 and LV. Previous research has proposed several influencing factors varying from  $\beta$ -adrenergic  
357 receptor desensitization, oxidative stress, impaired calcium metabolism to altered post-exercise  
358 loading. The influence of afterload conditions on RV EICF have rarely been explored. This study  
359 demonstrated that, under hypoxic conditions at 3000m altitude ( $\text{FiO}_2$  14.5%), the magnitude of EICF  
360 is not augmented and thus it may be less likely that a role for elevated RV wall stress is relevant.  
361 Although knowledge about the clinical long-term consequences of these temporary post-exercise  
362 reductions in cardiac function is lacking, it has been hypothesized that this may be associated with  
363 myocardial damage and worse clinical outcome. The absence of an effect in EICF between exercising  
364 at sea level (normoxia) and 3000m altitude (hypoxia) is interesting, but long-term studies that link  
365 these findings to prolonged follow-up is needed to better understand these findings. The novel  
366 strain-area loop, introduced to assess haemodynamics non-invasively, provided substantial added  
367 value in this study where it was sensitive enough to detect changes due to hypoxia. This novel  
368 technique seems promising in providing physiological and pathophysiological insight and might be of  
369 added value in clinical practice.<sup>5, 27, 28, 37, 45-48</sup>

370

### 371 **Limitations**

372 This study implemented a standardized exercise challenge to prevent a pre- and post-exercise  
373 (para)sympathetic imbalance during echocardiographic evaluation. Instead of the methodology of  
374 Stewart *et al.*<sup>14</sup> (aiming at 100 bpm), we set our target HR at 110-120 bpm during the exercise  
375 challenge, to better mimic cardiac function during exercise. This higher HR may impede speckle  
376 tracking quality. With current frame rates used, we experienced that tracking was still good to  
377 excellent for LV global longitudinal strain and RV free wall strain. A further limitation is that we did  
378 not obtain direct measures of RV wall stress as this would require invasive procedures. Alternatively,  
379 we used only non-invasive echocardiographic, indirect measures to estimate any potential difference

380 in RV wall stress under hypoxia *versus* normoxia. When considering these indirect indices, some  
381 studies have demonstrated value of PAT during stress to estimate PAP in PAH patients whilst others  
382 have questioned the outside of the normal heart rate range (<60 or >100 bpm).<sup>24, 26</sup> It is clear that a  
383 more robust assessment of PAP would provide added support to the well-established physiological  
384 concepts and understanding of hypoxia and pulmonary haemodynamics. Previous studies have  
385 applied strain-area loops to PAH patients and demonstrated an association between PVR and the late  
386 diastolic uncoupling and the Sslope during rest only.<sup>28</sup> Further work should aim to validate the strain-  
387 area loops during stress. Finally, for technical reasons we only evaluated right heart function and  
388 haemodynamics during low-to-moderate stress echocardiography rather than during the high-  
389 intensity running exercise.

390

## 391 **CONCLUSION**

392 There was no impact of hypoxia on the magnitude of EICF in the RV and LV after a bout of 45-minute  
393 high-intensity exercise. This finding suggests that any potential increase in loading conditions does  
394 not automatically exacerbate EICF in this setting.

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526

527 **FIGURE LEGENDS**

528 **Figure 1.** Overview of study design, where the dotted panel is highlighting visit 2 and 3 (test days).

529

530 **Figure 2.** Schematic overview of the RV strain-area loop and the derived characteristics.

531 The black line represents the strain-area loop, the thick part represents the systolic phase and the thin line the  
532 systolic phase. EDA, end-diastolic area. ESA, end-systolic area. ESslope, early systolic slope. Sslope, systolic  
533 slope. Uncoupling ED, uncoupling end-diastolic. Uncoupling LD, uncoupling late diastolic.

534

535

536 **Figure 3.** Right ventricular longitudinal strain (A) and left ventricular longitudinal strain (B) prior to  
537 and post 45-minutes high intensity running exercise. Error bars reflect the standard error of the  
538 mean.

539 Linear mixed models factors:

540 E, Exercise: Comparison between all echocardiographic measurements performed pre vs. post 45-minutes high  
541 intensity exercise.

542 H, Hypoxia: Comparison between all echocardiographic measurements performed under hypoxic vs. normoxic  
543 conditions.

544 S, Stress: Comparison between all echocardiographic measurements performed during rest vs. during stress.

545 H\*E, Hypoxia\*Exercise: Comparison whether the change pre- vs. post-exercise (EICF) is different during hypoxic  
546 vs. normoxic conditions.

547 E\*S, Exercise\*Stress: Comparison whether the change pre- vs. post-exercise is different measured during rest  
548 vs. stress echocardiography.

549 E\*H\*S, Exercise\*Hypoxia\*Stress: comparison whether the change pre- vs. post-exercise under hypoxic vs.  
550 normoxic conditions was different when observed using rest vs. stress echocardiography.

551

552 **Figure 4.** Right ventricular strain-area loops prior to and post 45-minute high intensity running  
553 exercise during rest (A) and stress (B). Red and blue lines indicating normoxic and hypoxic exercise,  
554 respectively. Solid and dotted lines reflecting pre- and post-exercise, respectively.



## TABLES

**Table 1.** Subject characteristics

Sex (m/f)	14/7
Age (yr)	22.2±0.6
Height (cm)	170±2
Body Mass (kg)	70±2
BMI (kg/m <sup>2</sup> )	24.0±0.6
BSA (m <sup>2</sup> )	1.8±0.04
Resting HR (bpm)	65±2
Resting SBP (mmHg)	119±1
Resting DBP (mmHg)	69±2
Resting MAP (mmHg)	85±1
resting SpO <sub>2</sub> (%)	98.4±0.3
VO <sub>2</sub> max (L/min)	3.6±0.1
VO <sub>2</sub> max/kg (mL/min/kg)	52±2
VE (L/min)	138±6
HRmax (bpm)	199±2

555 *Data are expressed as means±SEM. m, male. f, female. BMI, body mass index. BSA, body surface area. HR, heart*  
 556 *rate. SBP, systolic blood pressure. DBP, diastolic blood pressure. MAP, mean arterial pressure. SpO<sub>2</sub>, oxygen*  
 557 *saturation. VO<sub>2</sub>max, maximal oxygen uptake. VE, ventilation.*

**Table 2.** Right ventricular function and mechanics during rest and stress pre- and post-exercise under normoxia and hypoxia

	Rest echocardiography				Stress echocardiography				p-values					
	Normoxia		Hypoxia		Normoxia		Hypoxia		H	E	S	H*E	E*S	E*H*S
	Pre	Post	Pre	Post	Pre	Post	Pre	Post						
<i>Structure</i>														
RV basal diameter (mm)	36.8±0.9	37.4±0.7	36.9±0.7	37.8±0.7	36.4±0.7	35.6±0.8	36.9±.7	37.1±0.6	0.13	0.45	<b>0.03</b>	0.25	0.10	0.36
RV mid-cavity diameter (cm)	28.9±0.8	29.4±0.6	29.4±0.9	29.9±0.7	28.8±0.7	28.2±0.8	28.9±.7	28.8±0.8	0.19	0.9	0.07	0.61	0.22	0.65
RVEDA (cm <sup>2</sup> )	20.4±0.7	20.3±0.6	20.7±0.7	21.4±0.7	19.9±0.6	19.7±0.8	20.3±0.6	20.3±0.7	<b>0.01</b>	0.56	<b>0.01</b>	0.14	0.38	0.46
RVESA (cm <sup>2</sup> )	10.8±0.5	11.2±0.4	11.0±0.4	11.8±0.4	9.8±0.3	10.3±0.5	9.9±0.4	10.8±0.5	0.14	<b>0.001</b>	<b>&lt;0.001</b>	0.14	0.65	0.99
RVOTplax (mm)	24.0±0.7	24.4±0.8	25.5±0.6	25.6±0.5	24.2±0.7	23.0±0.7	24.6±0.7	24.1±0.7	0.07	0.22	<b>0.006</b>	0.55	<b>0.04</b>	0.21
RVOT1psax (mm)	24.8±0.8	25.6±0.7	26.1±0.7	25.9±0.6	25.2±0.6	24.2±0.6	25.9±0.9	25.1±0.7	0.15	0.34	0.15	0.36	0.08	0.11
RVOT2psax (mm)	16.6±0.4	16.7±0.4	17.3±0.4	16.8±0.4	17.0±0.5	16.6±0.5	17.1±0.4	17.0±0.5	0.17	0.28	0.62	0.75	0.82	0.21
RA area (cm <sup>2</sup> )	14.5±0.5	13.8±0.5	14.8±0.6	14.4±0.6	13.4±0.4	13.1±0.5	14.0±0.5	13.4±0.4	<b>0.04</b>	<b>0.001</b>	<b>0.001</b>	0.98	0.8	0.28
<i>Function and mechanics</i>														
RVFAC (%)	47±1	45±1	47±1	45±1	50±1	48±1	51±1	47±1	0.93	<b>0.007</b>	<b>&lt;0.001</b>	0.49	0.43	0.36
TAPSE (cm)	27±1	26±1	28±1	26±1	30±1	28±1	30±1	28±1	0.89	<b>&lt;0.001</b>	<b>&lt;0.001</b>	0.52	0.20	0.9
TDI s' (cm/sec)	15±1	14±1	15±1	15±1	19±1	17±1	20±1	18±1	<b>0.02</b>	<b>0.002</b>	<b>&lt;0.001</b>	0.55	0.11	0.73
TDI e' (cm/sec)	17±1	16±1	18±1	17±1	28±1	28±1	29±1	27±1	0.20	<b>0.02</b>	<b>&lt;0.001</b>	0.45	0.61	0.45
TDI a' (cm/sec)	13±1	12±1	13±1	13±1	-	-	-	-	0.19	0.33	-	0.24	-	-
RV free wall strain (%)	-28.0±1	-27±1	-28±1	-28±1	-33±1	-30±1	-32±1	-30±1	0.90	<b>&lt;0.001</b>	<b>&lt;0.001</b>	0.58	<b>0.01</b>	0.86
RV time of peak (sec)	0.36±0.01	0.37±0.01	0.37±0.01	0.36±0.01	0.28±0.01	0.32±0.01	0.29±0.01	0.31±0.01	0.51	<b>&lt;0.001</b>	<b>&lt;0.001</b>	0.09	<b>0.004</b>	0.57
PAT (ms)	152±3	151±3	139±4	134±3	122±4	120±3	106±4	105±3	<b>&lt;0.001</b>	<b>0.008</b>	<b>&lt;0.001</b>	0.60	0.36	0.30
<i>Strain-area loop characteristics</i>														
Uncoupling (%)	2.0±0.2	1.0±0.4	1.4±0.3	0.6±0.4	1.4±0.5	1.2±0.5	0.7±0.4	0.3±0.5	0.07	0.05	0.32	0.99	0.23	0.66
Uncoupling ED (%)	2.0±0.3	1.0±0.4	1.4±0.3	0.6±0.4	1.4±0.5	1.3±0.5	0.7±0.5	0.4±0.6	0.10	0.10	0.40	0.92	0.14	0.7
Uncoupling LD (%)	2.0±0.2	1.1±0.3	1.3±0.3	0.6±0.4	1.5±0.4	1.0±0.5	0.8±0.4	0.1±0.5	<b>0.04</b>	<b>0.01</b>	0.22	0.96	0.67	0.62
Sslope (%/cm <sup>2</sup> )	2.5±0.1	2.5±0.1	2.4±0.1	2.4±0.1	2.8±0.1	2.7±0.1	2.6±0.1	2.6±0.1	0.07	0.53	<b>0.003</b>	0.8	0.35	0.33
Esslope (%/cm <sup>2</sup> )	2.4±0.2	2.6±0.1	2.4±0.1	2.6±0.1	2.9±0.2	2.7±0.2	2.9±0.2	2.7±0.2	0.85	0.97	<b>0.05</b>	0.87	<b>0.04</b>	0.88
Edslope (%/cm <sup>2</sup> )	1.4±0.1	1.9±0.2	1.7±0.1	1.8±0.2	1.8±0.2	1.8±0.2	1.7±0.2	2.2±0.3	0.41	0.08	0.29	0.73	0.82	<b>0.03</b>
Ldslope (%/cm <sup>2</sup> )	3.3±0.2	3.0±0.2	3.1±0.2	2.8±0.2	3.6±0.3	3.5±0.3	3.4±0.3	3.1±0.3	0.11	0.18	<b>0.02</b>	0.77	0.73	0.34

Data are expressed as means±SEM. ED, Early diastole. ES, Early systole. LD, Late Diastole. PAT, pulmonary acceleration time. PLAX, Parasternal long axis. PSAX, parasternal short axis. RA, Right atrium. RV, Right ventricle. RVFAC, RV fractional area change. RVEDA, Right ventricular end-diastolic area. RVESA, Right ventricular end-systolic area. RVOT, Right ventricular outflow tract. TAPSE, Tricuspid annular plane systolic excursion. TDI, Tissue Doppler imaging.

Linear mixed models factors:

H, Hypoxia: Comparison between all echocardiographic measurements performed under hypoxic vs. normoxic conditions.

E, Exercise: Comparison between all echocardiographic measurements performed pre vs. post 45-minutes high intensity exercise.

S, Stress: Comparison between all echocardiographic measurements performed during rest vs. during stress.

E\*S, Exercise\*Stress: Comparison whether the change pre- vs. post-exercise is different measured during rest vs. stress echocardiography.

H\*E, Hypoxia\*Exercise: Comparison whether the change pre- vs. post-exercise (EICF) is different during hypoxic vs. normoxic conditions.

E\*H\*S, Exercise\*Hypoxia\*Stress: comparison whether the change pre- vs. post-exercise under hypoxic vs. normoxic conditions was different when observed using rest vs. stress echocardiography.

**Table 3.** Haemodynamics and left ventricular function and mechanics during rest and stress pre- and post-exercise under normoxia and hypoxia

	Rest echocardiography				Stress echocardiography				p-values					
	Normoxia		Hypoxia		Normoxia		Hypoxia		H	E	S	H*E	E*S	E*H*S
	Pre	Post	Pre	Post	Pre	Post	Pre	Post						
<i>Haemodynamics</i>														
Heart rate (bpm)	68±2	71±3	74±2	79±3	113±1	112±1	111±1	113±1	<b>0.03</b>	0.07	<b>&lt;0.001</b>	0.18	0.10	0.41
Systolic blood pressure (mmHg)	121±2	118±2	124±2	117±2	143±3	120±3	141±4	125±3	0.38	<b>&lt;0.001</b>	<b>&lt;0.001</b>	0.56	<b>&lt;0.001</b>	<b>0.03</b>
Diastolic blood pressure (mmHg)	70±2	69±2	70±2	67±2	75±2	60±1	73±2	60±1	0.47	<b>&lt;0.001</b>	0.16	0.98	<b>&lt;0.001</b>	0.19
Mean arterial pressure (mmHg)	87±1	85±2	88±2	84±2	98±2	80±2	96±2	82±1	0.99	<b>&lt;0.001</b>	0.08	0.75	<b>&lt;0.001</b>	<b>0.04</b>
SpO2 (%)	98±0.2	98±0.3	90±0.5	90±0.7	94±0.8	95±0.6	82±1.0	83±0.9	<b>&lt;0.001</b>	0.17	<b>&lt;0.001</b>	0.36	0.86	0.68
<i>Structure</i>														
LVEDV (ml)	120±7	113±7	123±6	113±6	114±6	109±6	117±7	110±6	0.30	<b>&lt;0.001</b>	<b>0.004</b>	0.46	0.55	1.0
LVESV (ml)	50±2	52±3	50±3	49±3	42±2	45±2	42±2	43±2	0.24	0.06	<b>&lt;0.001</b>	0.17	0.12	0.76
LA diameter (mm)	30±1	29±1	30±1	28±1	31±1	27±1	30±1	27±1	0.79	<b>&lt;0.001</b>	0.34	0.72	0.06	0.25
LA volume (ml)	38±2	34±0.3	39±2	34±2	38±1	35±1	39±1	36±1	0.21	<b>&lt;0.001</b>	0.18	0.13	0.12	0.50
<i>Function and mechanics</i>														
LVEFbip (%)	58±1	56±1	59±1	56±1	63±1	58±1	65±1	60±1	<b>0.008</b>	<b>&lt;0.001</b>	<b>&lt;0.001</b>	0.69	<b>0.005</b>	0.44
TDI s' (cm/sec)	10±0.4	11±0.4	11±0.3	11±0.4	14±0.5	13±0.5	14±0.4	14±0.4	<b>0.04</b>	0.78	<b>&lt;0.001</b>	0.98	0.24	0.19
TDI e' (cm/sec)	18±0.5	17±0.6	19±0.4	16±0.4	22±1.1	19±0.7	21±0.6	20±0.5	0.89	<b>&lt;0.001</b>	<b>&lt;0.001</b>	0.45	0.52	0.09
TDI a' (cm/sec)	8±0.4	9±0.3	9±0.3	10±0.3	-	-	-	-	<b>0.001</b>	0.054	-	0.60	-	-
E (cm/sec)	1.02±0.03	0.85±0.04	1.06±0.03	0.86±0.03	1.28±0.05	1.14±0.03	1.32±0.04	1.16±0.04	0.09	<b>&lt;0.001</b>	<b>&lt;0.001</b>	0.30	0.37	0.80
A (cm/sec)	0.56±0.02	0.57±0.02	0.55±0.02	0.62±0.03	-	-	-	-	<b>0.004</b>	0.39	-	0.18	-	-
E/A ratio	1.86±0.06	1.6±0.10	1.83±0.07	1.41±0.06	-	-	-	-	<b>0.048</b>	<b>&lt;0.001</b>	-	0.15	-	-
LV longitudinal strain (%)	-20±0.3	-20±0.3	-21±0.3	-20±0.2	-23±0.3	-21±0.4	-24±0.4	-22±0.2	0.01	<b>&lt;0.001</b>	<b>&lt;0.001</b>	0.08	<b>0.05</b>	0.86
LV time of peak (sec)	0.36±0.01	0.36±0.01	0.35±0.01	0.34±0.01	0.28±0.01	0.29±0.01	0.28±0.01	0.29±0.01	0.14	<b>0.03</b>	<b>&lt;0.001</b>	0.22	<b>&lt;0.001</b>	0.88

*Data are expressed as means±SEM. ES, Early systole. LA, Left atrium. LVEDV, Left ventricular end-diastolic volume. LVESA, Left ventricular end-systolic volume. S, Stress. TDI, Tissue Doppler imaging.*

Linear mixed models factors:

H, Hypoxia: Comparison between all echocardiographic measurements performed under hypoxic vs. normoxic conditions.

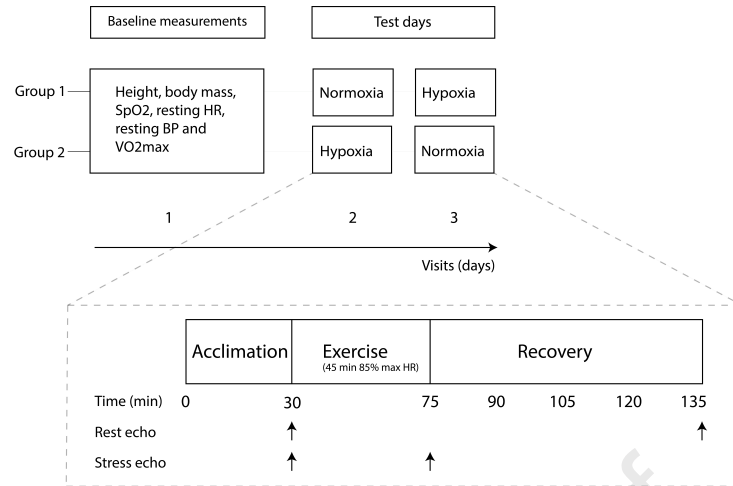
E, Exercise: Comparison between all echocardiographic measurements performed pre vs. post 45-minutes high intensity exercise.

S, Stress: Comparison between all echocardiographic measurements performed during rest vs. during stress.

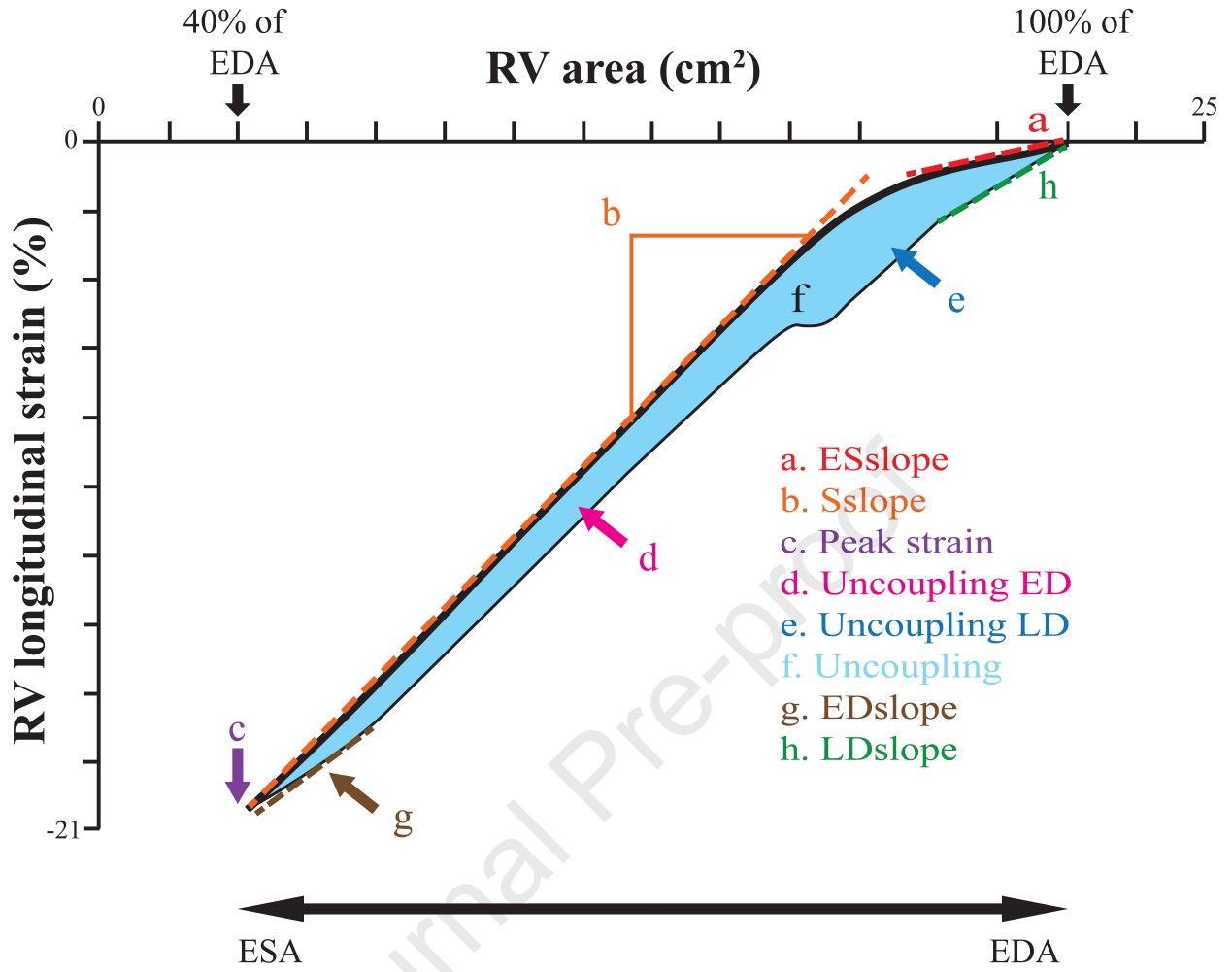
E\*S, Exercise\*Stress: Comparison whether the change pre- vs. post-exercise is different measured during rest vs. stress echocardiography.

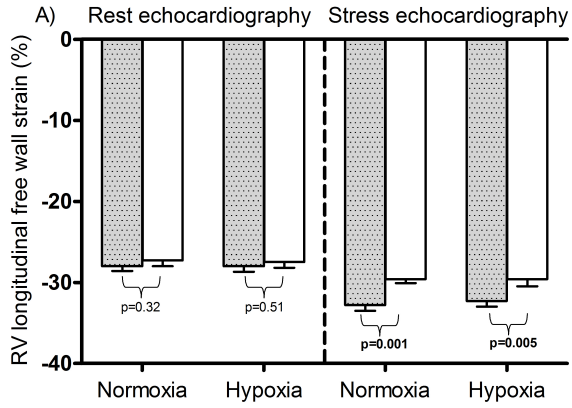
H\*E, Hypoxia\*Exercise: Comparison whether the change pre- vs. post-exercise (EICF) is different during hypoxic vs. normoxic conditions.

E\*H\*S, Exercise\*Hypoxia\*Stress: comparison whether the change pre- vs. post-exercise under hypoxic vs. normoxic conditions was different when observed using rest vs. stress echocardiography.

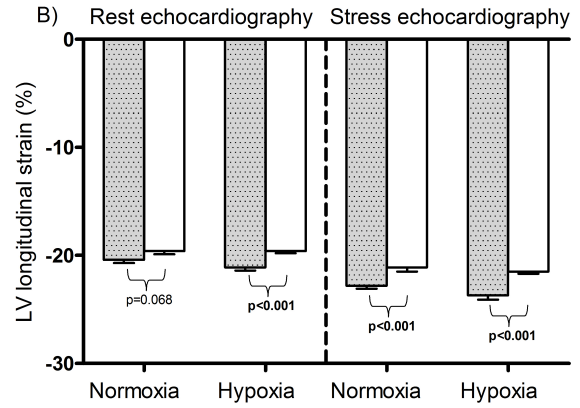


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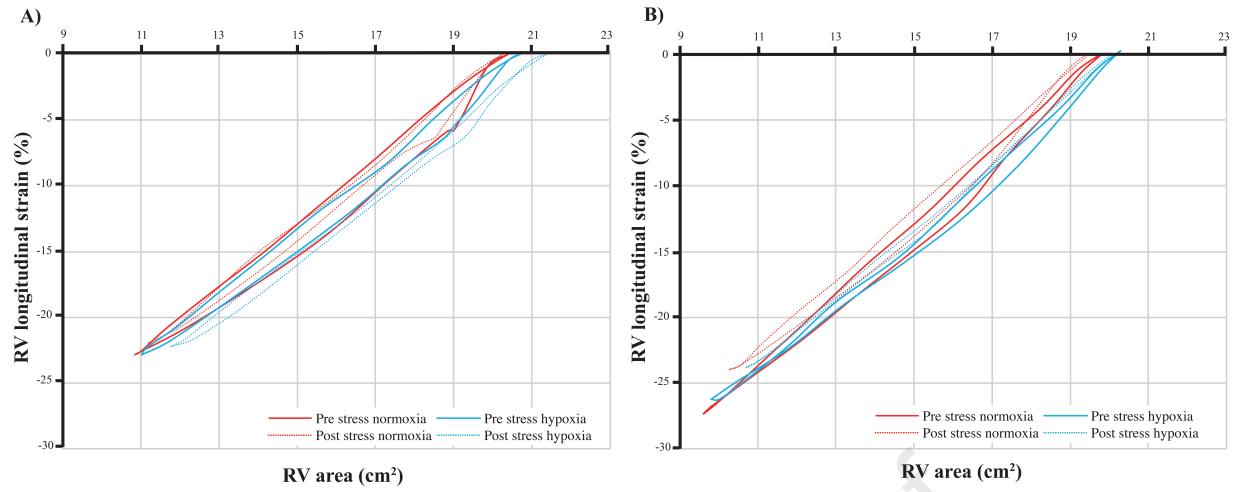


E:  $p < 0.001$ ; H:  $p = 0.90$ ; S:  $p < 0.001$ ;  
 H\*E: 0.58; E\*S: 0.01; E\*H\*S:  $p = 0.86$



E:  $p < 0.001$ ; H:  $p = 0.01$ ; S:  $p < 0.001$ ;  
 H\*E: 0.08; E\*S:  $p = 0.05$ ; E\*H\*S:  $p = 0.86$

Pre exercise (hatched bar)  
 Post exercise (white bar)





## HIGHLIGHTS

- 45-minutes high-intensity exercise induces right- and left-sided cardiac fatigue
- Exercise-induced cardiac fatigue is more pronounced during stress echocardiography
- Exercise under hypoxia does not exaggerate exercise-induced cardiac fatigue

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