Hypoxia increases exercise heart rate despite combined inhibition of β-adrenergic and muscarinic receptors

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Siebenmann C, Rasmussen P, Sørensen H, Bonne TC, Zaar M, Aachmann-Andersen NJ, Nordsborg NB, Secher NH, Lundby C. Hypoxia increases exercise heart rate despite combined inhibition of β-adrenergic and muscarinic receptors. Am J Physiol Heart Circ Physiol 308: H1540–H1546, 2015. First published April 17, 2015; doi:10.1152/ajpheart.00861.2014.—Hypoxia increases the heart rate response to exercise, but the mechanism(s) remains unclear. We tested the hypothesis that the tachycardic effect of hypoxia persists during separate, but not combined, inhibition of β-adrenergic and muscarinic receptors. Nine subjects performed incremental exercise to exhaustion in normoxia and hypoxia (fraction of inspired O2 = 12%) after intravenous administration of 1) no drugs (Cont), 2) propranolol (Prop), 3) glycopyrrolate (Glyc), or 4) Prop + Glyc. HR increased with exercise in all drug conditions (P < 0.001) but was always higher at a given workload in hypoxia than normoxia (P < 0.001). Averaged over all workloads, the difference between hypoxia and normoxia was 19.8 ± 13.8 beats/min during Cont and similar (17.2 ± 7.7 beats/min, P = 0.095) during Prop but smaller (P < 0.001) during Glyc (9.8 ± 9.6 and 8.1 ± 7.6 beats/min, respectively). Cardiac output was enhanced by hypoxia (P < 0.002) to an extent that was similar between Cont, Glyc, and Prop + Glyc (2.3 ± 1.9, 1.7 ± 1.8, and 2.3 ± 1.2 l/min, respectively, P > 0.4) but larger during Prop (3.4 ± 1.6 l/min, P = 0.004). Our results demonstrate that the tachycardic effect of hypoxia during exercise partially relies on vagal withdrawal. Conversely, sympatheoxication either does not contribute or increases heart rate through mechanisms other than β-adrenergic transmission. A potential candidate is α-adrenergic transmission, which could also explain why a tachycardic effect of hypoxia persists during combined β-adrenergic and muscarinic receptor inhibition.

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MATERIALS AND METHODS

Ethical approval. The study was approved by the Ethical Board of the University of Copenhagen (Ref. H-3-2011-101) and conducted in accordance with the Declaration of Helsinki. Written and oral consent was obtained from all subjects.

Subjects. Twelve healthy, male lowlanders volunteered to participate in the study, but three withdrew before completion of the study. The analysis was based on the remaining nine subjects (26 ± 5 yr old, 1.80 ± 0.07 m height, 80 ± 7 kg body wt).

Design. The subjects performed a familiarization session on an electronically braked cycle ergometer (Monark, Varberg, Sweden). Four experimental days, each separated by ~1 wk, were then scheduled. Subjects refrained from vigorous exercise for 24 h prior to these days. On each day, they received 1) no drug (Cont), 2) Prop, 3) Glyc, or 4) Prop + Glyc. The order was randomized, but neither subjects nor investigators were blinded to the drug that was used. The evaluation included two maximal exercise tests, one in normoxia and one in hypoxia (fraction of inspired O2 = 12%; Altitrainer, SMTEC, Nyon, Switzerland), in a randomized order.

DURING EXERCISE IN ACUTE HYPOXIA, arterial O2 content decreases due to a diminished alveolar PO2 and reduced alveolar-capillary O2 diffusion (15). Hypoxia triggers a compensatory acceleration of heart rate (HR), which depends convective O2 delivery by increasing cardiac output (Q̇) (29, 31). This HR response is generally attributed to the sympatheoxcitatory effect of hypoxia, which is evidenced by elevated levels of catecholamines (24) and muscle sympathetic nerve activity (18) evoked by a given workload. It is, however, unclear whether the parasympathetic nervous system is involved in the elevated HR during hypoxic exercise. Although hypoxic stimulation of peripheral chemoreceptors potentiates vagal nervous drive to the heart, this appears to be counteracted by input from pulmonary stretch receptors when ventilation is high, resulting in vagal withdrawal (19). Furthermore, hypoxia accelerates accumulation of fatigue-related metabolites in exercising muscles (13, 30), which may reinforce vagal withdrawal through activation of the muscle metaboreflex (10).

To determine the contributions of sympatheoxication and vagal withdrawal to the elevated HR during hypoxic exercise, Hopkins et al. (14) pharmacologically inhibited β-adrenergic or muscarinic receptors. Surprisingly, the interventions decreased (β-adrenergic inhibition) or increased (muscarinic inhibition) HR in normoxia and hypoxia to the same extent and, thus, did not attenuate the tachycardic effect of hypoxia. Thus an alternative mechanism seemed to be involved, at least when the main pathways were inhibited. On the other hand, it could be that inhibition of one arm of the autonomic nervous system was met by a compensatory adjustment of the other arm (14). These two explanations can be tested by simultaneous inhibition of β-adrenergic and muscarinic receptors.

The purpose of the present study was to determine the HR response to acute hypoxia during incremental cycling exercise after administration of 1) no drug (Cont), 2) the β-antagonist propranolol (Prop), 3) the muscarinic receptor antagonist glycopyrrolate (Glyc), or 4) Prop + Glyc. We hypothesized that the tachycardic effect of hypoxia would not be affected by Prop or Glyc but would be abolished by Prop + Glyc.
The subjects reported to the laboratory in the early morning. A catheter was inserted into the brachial arterial part of the nondominant arm. A second catheter was inserted into the median cubital vein and advanced toward the right atrium until an atrial pattern in the pressure trace was observed using a transducer (Edwards Life Sciences, Irvine, CA) located at the level of the heart. This catheter was intended for the collection of central venous blood; however, the quality of the results was insufficient for presentation, since the catheter could not be properly advanced in some subjects and the pressure signal indicated that the catheter tip was displaced from the atrium during exercise in several cases. After 30 min of rest, the study drugs were applied intravenously. Resting measurements were then performed with the subjects in the supine position. The first exercise trial started ~1 h after administration of the study drugs. After 2 h of supine recovery the second trial was started.

Exercise. Subjects exercised for 5 min at 20, 30, and 40% of the highest workload achieved in the familiarization trial; thereafter the workload was increased by 10% every 90 s until exhaustion. The initial workloads and the increments were reduced by 30% in hypoxia. Ventilatory variables were measured breath-by-breath (Innocor M400, Innovision, Odense, Denmark), and the median over the last 20 breaths within each workload was used for the analysis. PaO₂ was measured by inert gas rebreathing (Innocor) at rest, at the end of the three initial workloads, and thereafter at the end of every second workload. After each workload, blood was collected anaerobically in heparinized syringes (Pico 50, Radiometer, Copenhagen, Denmark) and analyzed without temperature correction in a hemoximeter (ABL 800, Radiometer) for arterial O₂ saturation, arterial Pao₂, arterial O₂ content, and lactate concentration. Intra-arterial pressure was monitored by a transducer (Edwards Life Sciences) connected to the arterial catheter and placed at the level of the heart. HR was derived from this signal by a peak detection algorithm included in the recording software (Labchart, ADInstruments, Dunedin, New Zealand). All signals were converted from analog to digital (DI-720, Datalq Instruments, Akron, OH) and sampled at 100 Hz.

Drug administration. Prop was administered in 2-mg boluses. When the injection induced no further drop in HR, one additional bolus was administered. A further 2-mg bolus was injected immediately prior to both exercise trials. Glyc was injected in 0.2-mg boluses until no further increase in HR was evoked; then an additional bolus was injected. Prior to both exercise trials, another 0.2-mg bolus was administered. For administration of Prop + Glyc, the drugs were applied as specified, with the order balanced between subjects.

The total doses were 18.7 ± 1.9 mg of Prop, 2.2 ± 0.4 mg of Glyc, and 20.5 ± 2.3 mg of Prop + 2.6 ± 0.4 mg of Glyc, corresponding to 0.24 ± 0.02, 0.28 ± 0.006, and 0.26 ± 0.02 and 0.034 ± 0.007 mg/kg, respectively.

Statistical analysis. We used a repeated-measures approach throughout; i.e., subject was entered as a random effect in all tests. To establish the effect of hypoxia on HR, Q, and stroke volume (SV) within the drug conditions, we calculated the difference between the individual HR evoked by a workload in hypoxia and HR predicted for the same subject and workload in normoxia by regression analysis. The hypoxia-induced differences in HR were compared between drug conditions by two-way mixed-model repeated-measures ANOVA, with exercise intensity and drug as factors and following a significant F-test, Tukey’s test, post hoc for pairwise comparison.

Other variables were compared at rest, at a submaximal workload corresponding to 50% of the highest individual workload achieved throughout the study (W₅₀), and at maximal exercise (Wmax) by repeated-measures ANOVA with hypoxia and the drugs as factors. We applied Tukey’s post hoc test for pair-wise comparison if a significant main effect was observed. SAS Enterprise Guide 6 (SAS Institute, Cary, NC) was used for the analysis. P < 0.05 was considered significant, and values represent means ± SD.

RESULTS

Exercise capacity. Maximal O₂ uptake (V˙O₂ max) and Wmax were reduced by hypoxia in all drug conditions (P < 0.001; see Table 2). Furthermore, Glyc (P = 0.03) and Prop + Glyc (P < 0.001) reduced V˙O₂ max in normoxia.

Heart rate. At rest the HR response to hypoxia depended on the type of receptor inhibition (P = 0.02), with HR increasing by ~12 min⁻¹ during Cont, Prop, and Glyc and decreasing by ~5 min⁻¹ during Prop + Glyc (P > 0.05 for all in post hoc testing; Table 1).

Exercise increased HR in all conditions (P < 0.001; Fig. 1). The individual differences between the HR evoked by a given workload in hypoxia and that in normoxia are presented in Fig. 2. In all drug conditions, HR was higher in hypoxia (P < 0.001; Fig. 2A), and since the difference between hypoxia and normoxia was not affected systematically by exercise intensity (P = 0.23), the difference was averaged over all subjects and

Table 1. Cardiorespiratory variables during supine rest

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cont</th>
<th>Prop</th>
<th>Glyc</th>
<th>Prop + Glyc</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, beats/min</td>
<td>71 ± 9</td>
<td>83 ± 14</td>
<td>55 ± 148</td>
<td>68 ± 75</td>
</tr>
<tr>
<td>Q, l/min</td>
<td>8.1 ± 2.1</td>
<td>7.9 ± 1.6</td>
<td>6.0 ± 1.5</td>
<td>6.9 ± 1.4</td>
</tr>
<tr>
<td>SV, ml</td>
<td>117 ± 43</td>
<td>87 ± 42</td>
<td>106 ± 20</td>
<td>100 ± 13</td>
</tr>
<tr>
<td>V˙O₂, l/min</td>
<td>0.36 ± 0.13</td>
<td>0.47 ± 0.12</td>
<td>0.35 ± 0.10</td>
<td>0.45 ± 0.10</td>
</tr>
<tr>
<td>Vt, l/min</td>
<td>16 ± 6</td>
<td>20 ± 16</td>
<td>13 ± 4</td>
<td>15 ± 2</td>
</tr>
<tr>
<td>RER</td>
<td>0.90 ± 0.15</td>
<td>1.13 ± 0.28</td>
<td>0.86 ± 0.16</td>
<td>1.04 ± 0.07</td>
</tr>
<tr>
<td>Pao₂, mmHg</td>
<td>137 ± 17</td>
<td>137 ± 15</td>
<td>123 ± 19</td>
<td>121 ± 18</td>
</tr>
<tr>
<td>Pao₂, mmHg</td>
<td>69 ± 4</td>
<td>67 ± 6</td>
<td>70 ± 15</td>
<td>63 ± 5</td>
</tr>
<tr>
<td>Sao₂, %</td>
<td>98 ± 1</td>
<td>81 ± 9</td>
<td>98 ± 1</td>
<td>87 ± 8</td>
</tr>
<tr>
<td>Pao₂, mmHg</td>
<td>112 ± 17</td>
<td>41 ± 17#</td>
<td>109 ± 14</td>
<td>40 ± 4#</td>
</tr>
<tr>
<td>Cao₂, ml/dl</td>
<td>197 ± 12</td>
<td>161 ± 20##</td>
<td>195 ± 12</td>
<td>145 ± 18##</td>
</tr>
<tr>
<td>Lactate, mmol/l</td>
<td>1.9 ± 1.1</td>
<td>1.1 ± 0.2</td>
<td>1.2 ± 0.4</td>
<td>1.2 ± 0.3</td>
</tr>
</tbody>
</table>

Values are means ± SD. Cont, control; Prop, propranolol; Glyc, glycopyrrolate; HR, heart rate; Q, cardiac output; SV, cardiac stroke volume; V˙O₂, pulmonary O₂ uptake; Vt, pulmonary ventilation; RER, respiratory exchange ratio; Pao₂, and Pao₂, systolic and diastolic blood pressures; Sao₂, arterial O₂ saturation; Pao₂, partial pressure of O₂ in arterial blood; Cao₂, arterial O₂ content; lactate, arterial lactate concentration. #P < 0.05 vs. normoxia in the same drug condition. $P < 0.05 vs. Cont in the same environment.
workloads for comparison between drug conditions (Fig. 2B). This approach indicated that the tachycardic effect of hypoxia was not changed by Prop ($P = 0.95$) but was decreased to a similar extent by Glyc and Prop + Glyc ($P < 0.001$).

Maximal HR was reduced by hypoxia during Cont ($P < 0.001$), but not in any other drug condition (Table 2).

Cardiac output. At rest neither hypoxia nor the drugs affected $Q$ (Table 1). Exercise increased $Q$ under all conditions ($P < 0.001$; Fig. 3). Similar to HR, $Q$ was elevated by hypoxia for a given workload in each drug condition (Fig. 4A), and since the difference between hypoxia and normoxia was not systematically affected by exercise intensity ($P = 0.38$), it was averaged over all subjects and workloads (Fig. 4B). The hypoxia-induced increase in $Q$ was similar to Cont during Glyc ($P = 0.64$) and Prop + Glyc ($P = 0.99$) but higher ($P = 0.004$) during Prop.

Because of the stressful conditions (catheters, hypoxia, study drugs), it was difficult for most subjects to perform the Innocor rebreathing maneuvers during exercise, and it was necessary to exclude several measurements (Figs. 3 and 4). Accordingly, we cannot present average values for $Q$ and SV at specific workloads, i.e., at $W_{50}$ and $W_{max}$ (Table 2).
SV increased during exercise (P < 0.001) and was not affected by hypoxia during Cont (P = 0.94). However, hypoxia increased SV for a given workload during Prop (P < 0.001), Glyc (P = 0.02), and Prop + Glyc (P < 0.001) by 10.4 ± 10.2, 5.1 ± 9.1, and 12.1 ± 6.8 ml, respectively.

Ventilatory and hematologic variables. Tables 1 and 2 further summarize variables at rest (Table 1) and during submaximal exercise (W50) and Wmax (Table 2). Hypoxia increased minute ventilation at W50, but this effect was attenuated by Prop and Prop + Glyc. Furthermore, a main effect indicated that hypoxia decreased minute ventilation at Wmax (P < 0.001), but this was not significant in the post hoc test. Similarly, main effects indicated that hypoxia increased respiratory exchange ratio at rest, at W50, and at Wmax (P < 0.001), but this only reached significance in the post hoc test at W50 and at Wmax during Glyc. Arterial pressures were not system-

![Cardiac output during incremental exercise in normoxia (●) and hypoxia (○).](image-url)
attractively affected by hypoxia or the drugs at rest or at W\textsubscript{max}. However, at W\textsubscript{50}, Prop, Glyc, and Prop + Glyc reduced systolic pressure. All indexes of arterial oxygenation were reduced by hypoxia (P < 0.001) but were not affected by the drugs. Arterial lactate concentration was not affected by hypoxia or the drugs at rest. At W\textsubscript{50}, hypoxia increased lactate concentration, and this effect was attenuated by Prop + Glyc. At W\textsubscript{max}, Prop and Glyc reduced arterial lactate concentration in normoxia (P = 0.02), whereas Prop + Glyc reduced arterial lactate concentration (P < 0.001) in normoxia and hypoxia (P < 0.001).

**DISCUSSION**

Contrary to our hypothesis, the combined inhibition of \(\beta\)-adrenergic and muscarinic receptors did not prevent the tachycardic response to hypoxia during exercise. While the tachycardic response was unaffected by Prop, it was blunted to a similar extent by Glyc and Prop + Glyc. Exercise Q was elevated in hypoxia, and this effect was unchanged (Glyc and Prop + Glyc) or increased (Prop) by the autonomic antagonists.

In studies using autonomic antagonists, the HR response to exercise is blunted, but not abolished, by combined inhibition of \(\beta\)-adrenergic and muscarinic receptors (9, 17, 20, 27). This raises the question whether pharmacological receptor inhibition is incomplete, and, indeed, Prop has failed to fully prevent the effect of electrical stimulation of cardiac sympathetic fibers in greyhounds (6). The relevance for natural stimuli is, however, questioned, and adequate doses of Prop prevent the HR response to \(\beta\)-agonists in humans (16). Experiments in animals furthermore demonstrate that exercise may increase HR independent of \(\beta\)-adrenergic or muscarinic transmission. When the blood of exercising dogs with cardiac denervation was perfused into isolated canine hearts, tachycardia proportional to the work intensity was observed (7). Inhibition of \(\beta\)-adrenergic receptors to prevent an impact of circulating catecholamines abolished tachycardia in isolated, but not donor, hearts. Changes in perfusion temperature were ruled out as an explanation (8). The preload-dependent increase in HR demonstrated by Bainbridge (1) is excluded, since it relies on vagal transmission. Potentially, \(\alpha\)-adrenergic receptors, which possess tachycardic function in young animals and humans (28), preserve the HR response to exercise when \(\beta\)-adrenergic and muscarinic receptors are inhibited. Alternatively, stretching of sinoatrial fibers, as induced during exercise by a higher preload, may increase their depolarization rate by activation of ion channels (5), but that remains to be established in humans.

Tachycardia is among the earliest observed responses to hypoxia, but its regulation is unclear, particularly during exercise, where only separate inhibition of \(\beta\)-adrenergic and muscarinic transmission has been performed (2, 3, 14, 34) and compensatory adjustment of the antagonistic arm could not be ruled out (14). Combined inhibition of both receptor types has, however, been applied in resting humans, where it abolished the \(\sim 20\) beats/min increase in HR induced by hypoxia corresponding to 6,000 m (21). This was also the case in the present study, although the HR increase during Cont was less pronounced, likely due to milder hypoxia, and it did not reach significance in the post hoc test. Adjustment of the balance between \(\beta\)-adrenergic and muscarinic transmission thus appears to account for the hypoxia-induced increase in resting HR, although the individual contributions are difficult to establish. During exercise, the tachycardic effect of hypoxia was attenuated by Glyc, indicating that the increase in HR during hypoxia partially relies on vagal withdrawal. This may result from activation of the muscle metaboreflex (26), since hypoxia accelerates the occurrence of fatigue-related metabolites (13, 30), as illustrated by the arterial lactate concentrations at W\textsubscript{50}. Furthermore, the increased ventilation may activate pulmonary stretch receptors and promote vagal withdrawal through the Hering-Breuer reflex (12, 19). Hopkins et al. (14) did not observe this effect of Glyc, which could have been related to \(\sim 50\%\) lower doses applied or to different statistical approaches.
Although hypoxia increases the sympathetic activity evoked by a given workload (23), the inhibition of β-adrenergic receptors did not reduce the tachycardic effect. Together with the finding that hypoxia-induced tachycardia persisted during Prop + Glyc, this supports the idea that cardiac α-adrenergic receptors may respond to increased sympathetic neural drive and/or circulating catecholamines (14).

Hypoxia reduces maximal HR, as illustrated during Cont (22). Incomplete vagal withdrawal has been identified as the underlying mechanism in chronic hypoxia (3). The observation that maximal HR during hypoxic Glyc was similar to normoxic Cont supports the same explanation in acute hypoxia. The reduced maximal HR did not contribute to the hypoxia-induced decrease in $V_{\text{O}2\text{max}}$, since Glyc induced no improvements. Furthermore, although hypoxia reduces maximal Q (4, 33), this is not related to the blunted maximal HR, since restoration of the latter by Glyc leads to reciprocal changes in SV (2, 3). Vagal withdrawal during exercise is governed by the increases in central command and exercise pressor reflex activity (26); hence, incomplete withdrawal in hypoxia is likely an effect, rather than a cause, for the reduced maximal exercise capacity.

During submaximal exercise, the accelerated HR in hypoxia augmented Q, which counteracted the effect of hypoxemia on systemic O$_2$ delivery. The importance of this response is limited, since in experiments at 4,300 m a decrease in systemic O$_2$ delivery induced by Prop was compensated by a reduction in mixed venous O$_2$ content, indicating a reserve in muscular O$_2$ extraction (34). During Prop, Glyc, and Prop + Glyc, a slight increase in SV contributed to the hypoxia-induced increase in Q. SV is determined by cardiac preload, afterload, and contractility (32), and since it is unclear how they were affected by the combination of hypoxia and the drugs, the mechanisms underlying the increases in SV are difficult to establish. Nevertheless, the combination of the increased SV and the preserved tachycardic response explains why the hypoxia-induced increase in Q was enhanced during Prop.

We could not confirm the expected decrease in maximal Q in hypoxia mentioned above (4, 33), since most subjects were unable to perform an adequate rebreathing maneuver during maximal exercise. It is debated whether the reduced maximal Q affects $V_{\text{O}2\text{max}}$ in hypoxia. While one study attributed 30% of the hypoxia-induced loss in $V_{\text{O}2\text{max}}$ to reductions in maximal Q (4), a mathematical analysis indicates that the importance of maximal Q for $V_{\text{O}2\text{max}}$ decreases in hypoxia, whereas O$_2$ diffusion limitations become more important (33).

During submaximal exercise, Prop and Glyc reduced systolic blood pressure, which is consistent with results from studies in which autonomous antagonists were applied (9, 17, 20, 27, 34). Since diastolic pressure remained unchanged, the reduced systolic pressure was likely related to a decreased SV. We cannot provide reliable values for SV at W$_{50}$, but a reduction could have occurred during Prop due to blunted ventricular contractility, whereas during Glyc the accelerated HR could have decreased end-diastolic volumes. As a further side effect, Prop blunted the ventilatory response to hypoxia during submaximal exercise, supporting a role of β-adrenergic receptors in chemoreceptor O$_2$ sensing (11, 25). Another explanation could be reduced activation of anaerobic metabolism, as indicated by the lower arterial lactate concentrations. Prop reduces lactate concentration during exercise in hypoxia (35), suggesting that the acceleration of lactate formation by hypoxia is related to circulating epinephrine acting on β-adrenergic receptors.

In contrast to earlier studies (2, 3, 14), Glyc reduced normoxic $V_{\text{O}2\text{max}}$. A likely explanation is that we used higher doses, which may have amplified its side effects, i.e., inability to sweat, headache, and dry mouth, and may thus have led to an earlier abortion of exercise, as supported by the lower lactate concentrations. This limitation was accepted, since complete receptor inhibition was judged of higher importance than unrestrained maximal effort. In this context, it has to be considered whether the doses of Prop and Glyc were adequate, particularly since they were not challenged by agonists. We injected 18.7 ± 1.9 mg of Prop, 2.2 ± 0.4 mg of Glyc, and 20.5 ± 2.3 mg of Prop + 2.6 ± 0.4 mg of Glyc, which are about twice the doses used in related studies (2, 3, 14) and conform to the doses that provide complete receptor inhibition (16). To prevent a time-dependent loss, we administered an additional 2 mg of Prop and/or 0.2 mg of Glyc immediately before exercise.

A limitation to this study is that we cannot present Q and SV at specific workloads because of missing measurement points. It should also be considered whether the small sample size may have led to a type I error. We find this unlikely, since the P value for the tachycardic effect of hypoxia was <0.001 in each drug condition.

In conclusion, the results demonstrate that mechanisms beyond β-adrenergic stimulation and vagal withdrawal can mediate the tachycardic effect of hypoxia during exercise. Future studies are encouraged to investigate the function of cardiac α-adrenergic receptors in this regard.

**GRANTS**

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**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the authors.

**AUTHOR CONTRIBUTIONS**

C.S., P.R., N.B.N., N.S., and C.L. developed the concept and designed the studies. N.J.A.-A., N.B.N., N.S., and C.L. approved the final version of the manuscript. C.S., P.R., N.B.N., N.S., and C.L. formed the experiments; C.S., P.R., and H.S. analyzed the data; C.S., P.R., H.S., T.C.B., M.Z., N.J.A.-A., N.B.N., and N.S. performed the experiments; C.S., P.R., and H.S. analyzed the data; C.S., P.R., N.S., and C.L. interpreted the results of the experiments; C.S. and P.R. prepared the figures; C.S. drafted the manuscript; C.S., P.R., N.B.N., N.S., and C.L. edited and revised the manuscript; C.S., P.R., H.S., T.C.B., M.Z., N.J.A.-A., N.B.N., N.S., and C.L. approved the final version of the manuscript.

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H1546 REGULATION OF HYPOXIA-INDUCED TACHYCARDIA DURING EXERCISE