CARDIAC RESPONSES DURING HYPOXEMIA FOLLOWING TWO-WEEK EXPOSURES TO NORMOBARIC INTERMITTENT-HYPOXIA

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Introduction. Acute hypoxic hypoxemia stimulates chemoreflex-mediated tachycardia (1,4). However, it was unknown whether chronic, cyclic intermittent hypoxia (IH) exposures would alter the hypoxia-stimulated chemoreflex control of tachycardia response to acute, cyclic hypoxic hypoxemia. We hypothesized that the magnitude of the tachycardiac response to hypoxia would be diminished as a result of acclimatization to chronic IH exposures.

Methods. Eight healthy non-smokers (5 men and 3 women, 24.8± 1.2 years old, 24.1±1.1 kg/m^2 BMI) voluntarily participated in the study, which was reviewed and approved by the IRB at UNT Health Science Center. All subjects underwent and passed a graded exercise stress test on a cycle ergometer and were confirmed to be free of cardiovascular or pulmonary diseases. No subject had previously participated in a hypoxia study, or had lived ≥3,000 feet above sea level.

Normobaric-poikilocapnic intermittent-hypoxia exposures were induced with inhalation of medical gas with 10.0±0.2% O_2 (balance nitrogen) for 5 to 6 min interspersed with 4 min inhalation of room air, repeated 5 to 10 times for 14 days. The cumulative duration of IH exposures was 11 hours and 49 minutes in 14 sessions. No subjects reported discomfort during the hypoxic exposures.

All measurements were made with the subject in the supine position and wearing a disposable face mask. The subject's heart rate (HR) was monitored from an electrocardiogram. Brachial arterial systolic and diastolic blood pressures (SBP and DBP) were measured by an automatic recording system. Systemic arterial O_2 saturation was measured will an oximeter on the subject's earlobe. Breath-by-breath partial pressures of end-tidal O_2 ($P_{ET}O_2$) was continuously monitored by a mass spectrometer and considered a proxy for arterial PO_2.

The HR responses to acute, cyclic hypoxic hypoxemia during the 1st and 5th hypoxic bouts on Days 1 and 14 IH were compared. After supine rest for ≥20 min, baseline HR, R-R intervals (RRI), and $P_{ET}O_2$, were recorded for ~5 min. SBP and DBP were read every ~75 to 90 sec at baseline and throughout the IH exposures

RRI were analyzed using power spectral analysis after fast Fourier transform. Low-frequency power (0.04 – 0.14 Hz) and high-frequency power (0.15 – 0.40 Hz) of RRI variability were compared for respective conditions. Tachycardia responses to decreases in $P_{ET}O_2$ during hypoxic hypoxemia were analyzed by linear regression. Analysis of covariance was used to test for differences in

slopes during the 1st and 5th hypoxic bouts on Day 1 and Day 14. Three-factor analysis of variance (ANOVA) was applied to test the significance of Hypoxic Time (factor A), Bout (factor B) and Day (factor C). Data are reported as group means and standard errors (SE). Significance level was set at $P \leq 0.05$.

Results and Discussion. Baseline, normoxic values $P_{ET}O_2$ and SaO_2 were significantly lower prior to the 5th hypoxic bout than prior to the 1st hypoxic bout. On Day 14, baseline HR prior to either the 1st or the 5th hypoxic bout was significantly lower compared with corresponding values on Day1. However, baseline, normoxic SBP and DBP were stable during the daily IH exposures and did not differ from Day 1 to Day 14. Two-weeks of IH exposures significantly increased baseline, normoxic RRI variability in both low-frequency (0.04 – 0.14 Hz) and high-frequency (0.15 – 0.40 Hz) power spectra [Day 1 vs Day 14: 393±128 vs 899±235 ms^2 (P = 0.020) and 622±193 vs 1071±247 ms^2 (P = 0.014) for low-frequencies and high-frequencies, respectively].

Although arterial blood pressure was not significantly changed by normobaric-poikilocapnic hypoxia, HR significantly increased during cyclic hypoxia (Figure 1). Acute cyclic hypoxic exposures augmented the magnitude of this tachycardiac response (P = 0.001) as indicated by the slopes of $HR/P_{ET}O_2$, which were greater for the 5th bout than for the 1st bout on Day 1 [-1.46±0.06 vs -0.46±0.04 bpm/mmHg, P <0.0001] and on Day 14 [-1.14 ±0.16 vs -0.40 ±0.06 bpm/mmHg, P =0.0013]. Chronic IH exposures significantly attenuated the rate of tachycardiac responses, since the slopes of $HR/P_{ET}O_2$ were consistently less (P = 0.049) on Day 14 than on Day 1 (Figure 1). However, there was no significant different in the slopes of $HR/P_{ET}O_2$ between Day 1 and Day 14 after stratification for the Bout factor.

The present data confirmed that acute cyclic hypoxic exposures caused a rapid reset of the tachycardiac responses on both Day 1 and Day 14 (4). This rapidly augmented chemoreflex control of the HR response could be related to greater decreases in systemic O_2 content during repeated cyclic hypoxic exposures. However, the overall tachycardiac responses during the 1st and 5th hypoxic bouts were consistently smaller following 14-day IH exposures. This supports our hypothesis that acclimatization to chronic IH blunts the tachycardiac response to hypoxia.

We postulate that chronic IH conditioning-enhanced parasympathetic nerve activity (1) is primarily responsible for the diminished tachycardia in response to decreases in $P_{ET}O_2$ during hypoxic hypoxemia observed in the current study. This is supported by the lower baseline HR and enhanced R-R interval variability in both low-frequency and high-frequency spectra following 14-day IH exposures. This improved vagal-cardiac function may partially explain the cardiac protection against ischemia and arrhythmia observed in dogs (2,3,5) and in rats (3) following chronic IH conditioning.

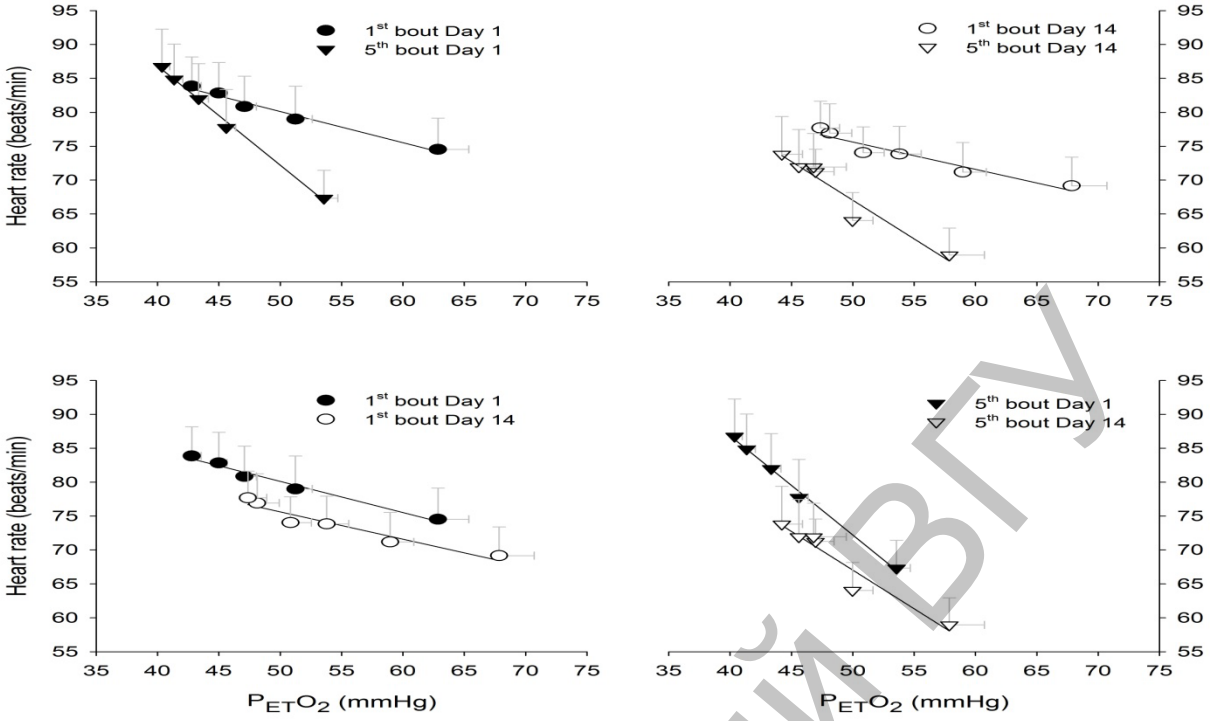

Figure 1. Heart rate plotted as a function of $P_{ET}O_2$ during IH exposures. Top panels illustrate acute responses to cyclic hypoxia on Day 1 (left top) and on Day 14 (right top). Bottom panels illustrate adaptive responses to 14 days of cyclic hypoxic exposures for the 1st hypoxic bout (bottom left) and the 5th bout (bottom right).

References

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