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ORIGINAL ARTICLE

Heart rate recovery after maximal exercise is impaired in healthy young adults born preterm

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Abstract

Purpose The long-term implications of premature birth on autonomic nervous system (ANS) function are unclear. Heart rate recovery (HRR) following maximal exercise is a simple tool to evaluate ANS function and is a strong predictor of cardiovascular disease. Our objective was to determine whether HRR is impaired in young adults born preterm (PYA).

Methods Individuals born between 1989 and 1991 were recruited from the Newborn Lung Project, a prospectively followed cohort of subjects born preterm weighing < 1500 g with an average gestational age of 28 weeks. Age-matched term-born controls were recruited from the local population. HRR was measured for 2 min following maximal exercise testing on an upright cycle ergometer in normoxia and hypoxia, and maximal aerobic capacity (VO_{2max}) was measured.

Results Preterms had lower VO_{2max} than controls (34.88 ± 5.24 v 46.15 ± 10.21 ml/kg/min, respectively, $p < 0.05$), and exhibited slower HRR compared to controls after 1 and 2 min of recovery in normoxia (absolute drop of 20 ± 4 v 31 ± 10 and 41 ± 7 v 54 ± 11 beats per minute (bpm), respectively, $p < 0.01$) and hypoxia (19 ± 5 v 26 ± 8 and 39 ± 7 v 49 ± 13 bpm, respectively, $p < 0.05$). After adjusting for VO_{2max}, HRR remained slower in preterms at 1 and 2 min of recovery in normoxia (21 ± 2 v 30 ± 2 and 42 ± 3 v 52 ± 3 bpm, respectively, $p < 0.05$), but not hypoxia (19 ± 3 v 25 ± 2 and 40 ± 4 v 47 ± 3 bpm, respectively, $p > 0.05$).

Conclusions Autonomic dysfunction as seen in this study has been associated with increased rates of cardiovascular disease in non-preterm populations, suggesting further study of the mechanisms of autonomic dysfunction after preterm birth.

Keywords Preterm birth · Autonomic function · Heart rate recovery · Cardiovascular disease · Autonomic dysfunction · Prematurity · Premature birth · Exercise testing · Maximal aerobic capacity

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Abbreviations

ANS	Autonomic nervous system
GPAQ	Global Physical Activity Questionnaire
HR	Heart rate
HR_{max}	Maximal heart rate
HRR	Heart rate recovery
MET	Metabolic equivalent
P_{max}	Maximal power
T_{max}	Maximal time to exhaustion
VO_{2max}	Maximal aerobic capacity
VT_{VO2}	Oxygen consumption per kg of body weight at ventilatory threshold

Introduction

One in every ten infants born in the USA is born preterm, or before 37 completed weeks of gestation (Centers for Disease Control and Prevention 2015). Premature birth can lead to a number of acute and chronic cardiovascular comorbidities. Young adult survivors of prematurity are more likely to develop hypertension (Norman 2010), right ventricular (RV) and left ventricular hypertrophy, and lower RV ejection fraction compared to term-born controls (Lewandowski et al. 2013). Given the known long-term effects of prematurity on the cardiovascular system, a better understanding of chronic alterations in other regulators of cardiovascular function is of substantial importance for identifying the cardiovascular risk in young adults with a history of preterm birth.

While evidence in the literature is growing about long-term cardiovascular effects of prematurity, relatively little is known about cardiac autonomic regulation in this population. The autonomic nervous system (ANS) is made up of the sympathetic and parasympathetic branches, each working in tandem with the other in regulating several internal body processes to maintain equilibrium, and plays a significant role in regulating blood pressure, heart rate and ventilation (Joyner et al. 2010; Kleiger et al. 2005). The ANS develops significantly in the third trimester of pregnancy (Porges and Furman 2011), and cardiovascular autonomic development is temporarily disrupted by preterm birth, which has lasting effects on autonomic regulation of heart rate during infancy (de Meautsart et al. 2016; Patural et al. 2004; Yiallourou et al. 2013). While ANS development continues after birth (Porges and Furman 2011), preterm infants have lower parasympathetic modulation of the heart compared to term-born controls (Yiallourou et al. 2013), and children born preterm have lower heart rate variability compared to term born controls (Yiallourou et al. 2017). Autonomic function regulates a number of physiologic responses to reductions in arterial oxygen tension during hypoxic exposure, including increased ventilation and increases in heart rate (Amann and Kayser 2009). Young adults born preterm have a blunted ventilatory response to inhaled hypoxic air (Bates et al. 2014). The blunted ventilatory response to hypoxic air suggests long-term alterations in the autonomic response to changes in blood gas tensions in adults born preterm. Globally, deficient vagal tone (parasympathetic regulation) is associated with all-cause mortality and cardiovascular disease (Thayer and Lane 2007), and evidence that vagal tone in particular may be reduced in this population is cause for further investigation.

Heart rate recovery (HRR) following maximal exercise is primarily due to the reactivation of the parasympathetic nervous system and sympathetic withdrawal (Savin et al. 1982; Pierpont et al. 2013) and is recognized as a marker of autonomic function (Davrath et al. 2006). Slower HRR following exercise has been shown to be a predictor of cardiovascular disease, pulmonary arterial hypertension severity (Minai et al. 2012), insulin resistance (Kuo and Gore 2015), heart failure (Bilsel et al. 2006), and all-cause mortality (Cole et al. 1999; Watanabe et al. 2001).

In this study, we sought to determine whether young adults born preterm exhibit abnormal autonomic function by assessing HRR following maximal exercise, and whether this autonomic response is affected by hypoxia. We hypothesized that preterm adults would exhibit slower HRR in normoxia compared to term-born controls, and that hypoxia would further blunt their HRR compared to controls.

Methods

Ethical approval

The protocol was approved by the Institutional Review Boards at the University of Wisconsin–Madison. Each subject was informed of the purpose and risks associated with the study and written consent was obtained from all subjects in accordance with the standards set by the Declaration of Helsinki. All study procedures were approved by the University of Wisconsin–Madison Institutional Review Board.

Participants

Preterm participants were recruited from the Newborn Lung Project (Palta et al. 1994, 1998, 2000, 2001; Weinstein et al. 1994), a cohort established at the University of Wisconsin (Madison, WI) that enrolled individuals born preterm with very low birth weight (< 1500 g) between 1988 and 1991 in Wisconsin and Iowa. Control subjects were recruited from the local community and were born full-term from 1988 to 1991. Inclusion criteria for all participants was ability to complete a maximal exercise test, non-smoking, being free of mental, physical, visual or neurological disabilities, and no diagnosed adult cardiovascular or respiratory disease. Subjects' height was measured using a mechanical measuring rod to the nearest 0.5 cm (Seca; Hamburg, Germany), and weight was measured using a digital scale to the nearest 0.1 kg (Taylor; Oak Brook, IL) and recorded at the beginning of the study visit.

Baseline physical activity questionnaire

Subjects verbally completed a baseline physical activity questionnaire, the Global Physical Activity Questionnaire (GPAQ) (Bull et al. 2009). The GPAQ consists of 16 questions that assess the participants' physical activity in three main domains: work, transport, and leisure time, and how much time is spent in sedentary behavior. The scores from the questionnaire were calculated and used to determine subjects' metabolic equivalent (MET) minutes per week.

Graded exercise testing

Participants performed two incremental exercise tests on an upright cycle ergometer (Velotron; RacerMate; Seattle, WA) while breathing room air (0.21 F_IO_2, AirGas; Radnor, PA) during the first test and hypoxic air (0.12 F_IO_2, AirGas; Radnor, PA) during the second test. Participants rested for a minimum of 45 min between exercise tests, or until HR returned to pre-exercise resting values preceding the maximal exercise test in normoxia. There was a wash-in period preceding the hypoxia exercise test where participants breathed the hypoxic gas at rest for 8 min to obtain resting HR and metabolic measurements (Kennedy et al. 2008). Participants cycled at 60–70 revolutions per minute (rpm) starting at 65 W for 1 min, and wattage was increased by 15W every minute until subjects were no longer able to maintain 55 rpm for more than 5 s. Heart rate was continuously monitored using forehead pulse oximetry (OxiMax N-595; Nellcor, Mansfield, MA), expired gases were collected in a breath-by-breath manner (Gemini; CWE, Ardmore, PA), and ventilatory and metabolic parameters were continuously recorded and analyzed in PowerLab (ADInstruments; Colorado Springs, CO). Maximal power (P_{max}) was determined as the wattage of the highest stage maintained for more than 30 s. Time to exhaustion (T_{max}) was calculated as total time from the start of the incremental test to the start of recovery. Maximal aerobic capacity (VO_{2max}) was determined using a 30-s rolling average of the VO_2 (ml O_2/kg/min). For a test to be a VO_{2max}, the primary criteria of a plateau in VO_2 defined as a change of < 2 mL/kg/min in O_2 consumption over the last 60 s of the test had to be met, in addition to one of the following secondary criteria: (1) a maximal heart rate (HR_{max}) of more than 90% age-predicted HR_{max} (220-age) or (2) a respiratory exchange ratio (V_{CO2}/V_{O2}) of ≥ 1.1 (Midgley et al. 2007).

Ventilatory threshold

To account for fluctuations in breath-by-breath measurements of minute ventilation, a 30-s rolling average of minute ventilation was used to determine the ventilatory threshold (VT). VT was determined as the time at which an upward deflection was noted in the slope of total ventilation over time, and oxygen consumption at VT was determined for each subject.

Heart rate recovery

After reaching maximal volitional exhaustion, subjects were instructed to stop pedaling and sit completely still and quietly on the bicycle while HR was recorded for 2 min. HRR was calculated as the absolute drop in HR (bpm) from HR_{max} for 2 min at 10-s intervals (HRR_{abs}).

Statistical analysis

Data were initially evaluated for normality using descriptive statistics and histogram analysis. Wilcoxon rank sum tests were used to compare demographic and metabolic variables between the control and preterm groups. Given the unequal distribution of sex between the groups and to account for the influence of sex on metabolic variables, VO_{2max}, P_{max}, $T_{max,}$ and VT_{VO2} were compared between groups using least square means from linear regression models including birth status and sex as covariates in the model. Cohen's d was calculated to determine the effect size between the preterm and control groups (Cohen 1988), where a higher number indicates a greater effect size.

HRR_{abs} and HR_{abs} were compared between groups at each 10-s interval using least square means from separate linear regression models. To evaluate the effect of cardiorespiratory fitness on the difference in HRR between the groups, similar comparisons of least square means at each time point were made using separate linear models including birth status and VO_{2max} as covariates. For both the unadjusted and adjusted comparisons of least square means, p values were adjusted for multiple pairwise comparisons using the method previously described by Holm (Holm 1979). Finally, for both the control and preterm groups separately, HRR at each time point was compared between the normoxia and hypoxia conditions with paired t tests with adjustment for multiple comparisons. Two-way ANOVAs were used to evaluate the interaction of sex and birth status on VO_{2max}, P_{max}, and T_{max}. Data analyses were conducted with R (R Development Core Team 2010). All tests were two-tailed and $p < 0.05$ was used to define statistical significance.

Results

Characteristics of the subjects at baseline

Twelve preterm (28.5 ± 2.7 weeks gestation at birth) and 16 term-born (39.5 ± 0.6 weeks gestation at birth) subjects completed the study in normoxia. Due to pre-syncopal symptoms while breathing hypoxic air, four preterm subjects (one male and three females) were unable to complete the hypoxia portion of the study. Controls were slightly younger than preterm subjects and had greater gestational age compared to control subjects, but otherwise the two groups were well matched (Table 1).

Physical activity

There was no difference in MET min/week in control compared to preterm subjects as assessed by the GPAQ (Table 1).

Exercise capacity

Preterm subjects attained significantly lower VO_{2max} than controls, expressed absolutely and relative to body weight in both normoxia and hypoxia, and a lower oxygen consumption relative to body weight at VT in normoxia and hypoxia. Similarly, P_{max} and T_{max} were significantly lower and shorter, respectively, in preterm adults compared to controls in both normoxia and hypoxia (Table 2).

HRR in normoxia

HR_{max} was not different between the groups (Table 2). Absolute HR during recovery in normoxia was not significantly different between groups ($p > 0.05$). HRR was slower in preterm subjects throughout the 2-min recovery period, with the difference achieving statistical significance at 30 s through 2 min (Fig. 1a). To evaluate the effect of differences in VO_{2max} on HRR, VO_{2max} was included as a covariate in a secondary analysis of HRR. After adjustment for VO_{2max}, HRR was slower in preterm subjects compared to controls at 1 and 2 min of recovery in normoxia (21 ± 2 v 30 ± 2 and 42 ± 3 v 52 ± 3 bpm, respectively, $p < 0.05$, Fig. 1b). Although the differences in least square means between the groups appeared to be attenuated slightly by the inclusion of VO_{2max} within the model, VO_{2max} was not a significant predictor of HRR at any time point ($p > 0.05$ for all).

Table 1 Physical characteristics

	Control ($n = 16$)	Preterm ($n = 12$)	p value	Cohen's d
Sex (n, % female)	6, 38%	6, 50%	0.379	
Age (years)	25.6 ± 0.7	26.9 ± 1.1	< 0.001	1.86
Height (cm)	176.1 ± 8.6	171.1 ± 9.8	0.109	0.50
Weight (kg)	77.6 ± 14.9	70.0 ± 13.3	0.123	0.57
BMI (kg/m^2)	24.9 ± 3.0	23.8 ± 3.3	0.340	0.32
Gestational age (weeks)	39.5 ± 0.6	28.5 ± 2.7	< 0.001	20.6
G-PAQ (MET-min/week)	3515 ± 2707	3282 ± 1953	0.875	0.10

Data are expressed as mean ± SD

BMI body mass index, *G-PAQ* Global Physical Activity Questionnaire, *MET* metabolic equivalent

Table 2 Aerobic fitness and metabolic and heart rate variables

	Normoxia ($F_IO_2 = 0.21$)				Hypoxia ($F_IO_2 = 0.12$)			
	Control ($n = 16$)	Preterm ($n = 12$)	p value	Cohen's d	Control ($n = 16$)	Preterm ($n = 8$)	p value	Cohen's d
VO_{2max} (L/min)[a]	3.46 ± 0.62	2.43 ± 0.70	< 0.001	1.63	2.58 ± 0.50	1.79 ± 0.70	0.002	1.79
VO_{2max} (mL/kg/min)[a]	45.79 ± 8.71	34.88 ± 9.26	0.003	2.15	34.47 ± 7.52	26.49 ± 10.52	0.029	1.25
P_{max} (W)[a]	231 ± 40	175 ± 45	0.002	1.42	186 ± 28	154 ± 39	0.020	1.53
T_{max} (min)[a]	13.48 ± 4.16	9.79 ± 3.36	0.021	0.99	9.06 ± 1.75	6.98 ± 2.45	0.016	0.94
HR_{rest} (bpm)	70 ± 11	80 ± 16	0.115	0.74	97 ± 12	113 ± 11	0.008	1.39
HR_{max} (bpm)	182 ± 12	182 ± 8	0.953	0.10	179 ± 10	180 ± 6	0.851	0.15
HRR_{1min} (bpm)	31 ± 10	20 ± 4	0.001	2.55	26 ± 8	19 ± 5	0.039	1.47
HRR_{2min} (bpm)	54 ± 11	41 ± 7	0.001	1.88	49 ± 13	39 ± 7	0.028	1.47
VT_{VO2} (ml/kg/min)[a]	37.86 ± 5.82	28.50 ± 6.60	< 0.001	0.274	28.23 ± 6.51	21.88 ± 9.11	0.043	0.081

Data are expressed as mean ± standard deviation (SD)

VO_{2max} Maximal aerobic capacity expressed absolutely (l/min) and relative to body weight (ml/kg/min), P_{max} maximal wattage attained for more than one-half of final stage of incremental maximal exercise test, T_{max} time to exhaustion during maximal exercise test, HR_{max} maximal HR attained during maximal exercise testing, HRR_{1min} HRR at 1 min of resting recovery, HRR_{2min} HRR at 2 min of resting recovery, VT_{VO2} *(ml/kg/min)* oxygen consumption per kg of body weight at ventilatory threshold

[a]Sex-adjusted estimates

HRR in hypoxia

Comparing control and preterm-born adults in hypoxia, preterm subjects had slower HRR compared to controls (Fig. 2a). After adjusting for VO_{2max} in hypoxia, HRR was slower in preterm subjects, but was only significantly different at early time points in recovery (Fig. 2b). As in normoxia, however, VO_{2max} was not a significant predictor of HRR at any time point ($p > 0.05$ for all).

Among control subjects, HRR was slower in hypoxia compared to normoxia throughout the recovery period (Fig. 3a). HRR in preterm adults was slower in hypoxia early on in recovery, but no significant differences were identified later during recovery at individual time points (Fig. 3b).

Effects of sex on VO_{2max}, P_{max}, and HRR

Consistent with the NIH goal to evaluate sex as an independent biologic variable, we also evaluated the effect of sex on multiple parameters. Preterm females and males had significantly lower HRR_{1min} compared to control females and males (Fig. 4a). There was no difference between preterm

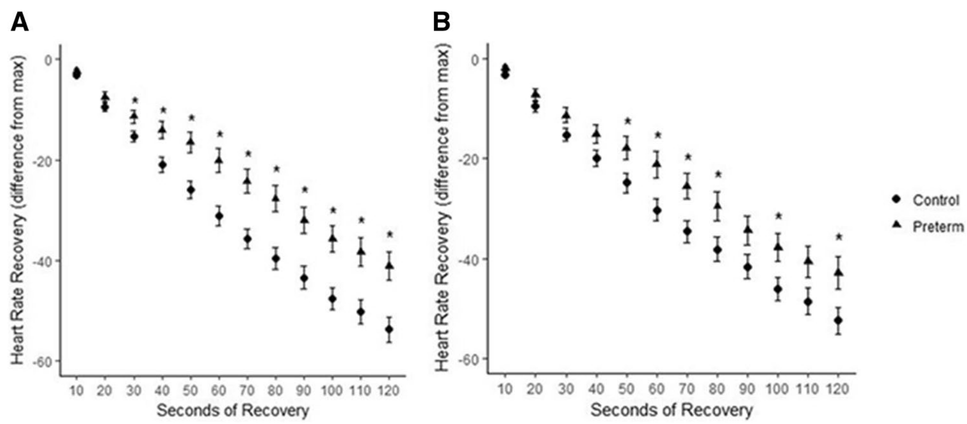

Fig. 1 Heart rate recovery in normoxia. **a** HRR (bpm; absolute drop in HR from max) in control (circles) and preterm (triangles) subjects. **b** HRR adjusted for VO_{2max} in control and preterm subjects. Data are expressed as mean ± SEM. *$p < 0.05$ adjusted for pairwise comparison between control and preterm groups at each time point

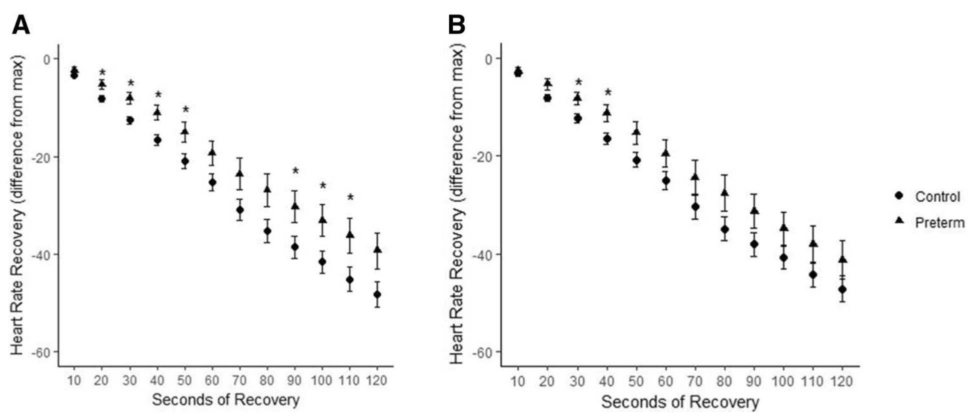

Fig. 2 Heart rate recovery in hypoxia. **a** HRR (bpm; absolute drop in HR from max) in control (circles) and preterm (triangles) subjects. **b** HRR adjusted for VO_{2max} in control and preterm subjects. Data are expressed as mean ± SEM. *$p < 0.05$ adjusted for pairwise comparison between control and preterm groups at each time point

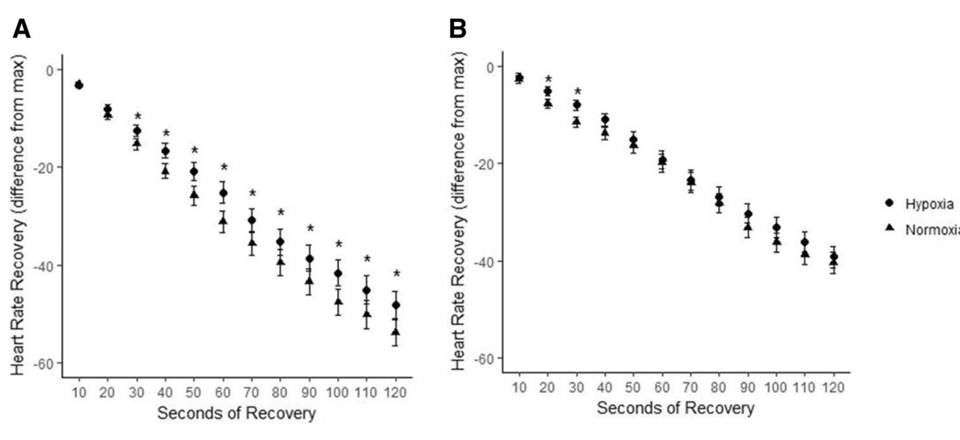

Fig. 3 Heart rate recovery response between normoxia and hypoxia in control and preterm subjects. **a** HRR (bpm; absolute drop in HR from max) in normoxia (triangles) and hypoxia (circles) in control subjects. **b** HRR in normoxia (triangles) and hypoxia (circles) in preterm subjects. Data are expressed as mean ± SEM. *$p < 0.05$ adjusted for pairwise comparison between hypoxia and normoxia conditions at each time point

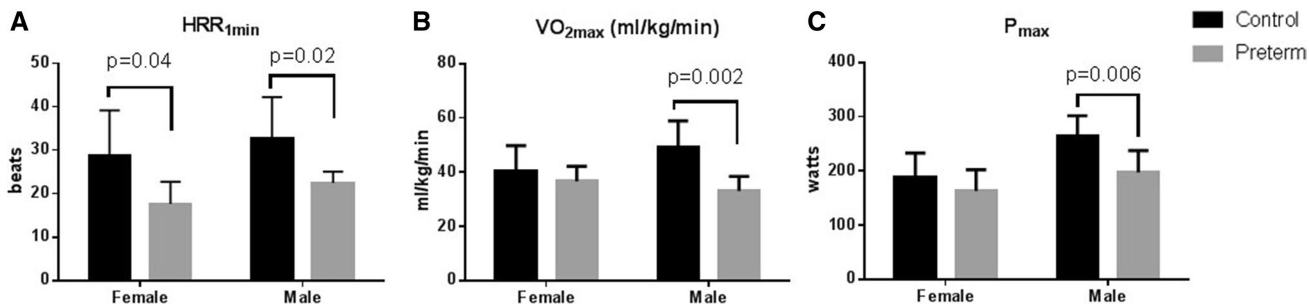

Fig. 4 Sex effects on HRR, VO_{2max}, and P_{max}. **a** HRR_{1min} (bpm; absolute drop in HR from max after 1 min of recovery) sex–birth status interaction, $p=0.91$; **b** VO_{2max} sex–birth status interaction, $p=0.06$; **c** P_{max} sex–birth status interaction, $p=0.21$. Data are expressed as mean ± SD. HRR_{1min}, heart rate recovery after 1 min of recovery; VO_{2max}, maximal aerobic capacity (ml/kg/min); P_{max}, maximal power attained during maximal exercise test

and control females in VO_{2max} and P_{max}, but preterm males had significantly lower VO_{2max} and P_{max} compared to controls ($p<0.01$ for both). There was no interaction between birth status and sex in HRR_{1min}, P_{max}, or VO_{2max}.

Discussion

In this study, we sought to determine whether young adults born preterm exhibit signicantly different autonomic function by assessing HRR following maximal exercise, and whether this autonomic response is affected by hypoxia. The key finding in this study is that HRR following maximal exercise is slower in healthy young adults born preterm compared to term-born controls in normoxia and hypoxia. This suggests that autonomic function is impaired in healthy young adults with a history of preterm birth free of known cardiovascular disease or neurological impairment. With strong evidence in the literature suggesting a correlation between slow HRR and cardiovascular disease risk (Cole et al. 1999; Qiu et al. 2017), our results suggest that otherwise healthy young adults born preterm may be at an increased risk of developing cardiovascular disease.

To our knowledge, this is the first study to investigate autonomic function in young adults born preterm using HRR following maximal exercise. Much of ANS development, particularly the parasympathetic branch, occurs in the third trimester of pregnancy (Gagnon et al. 1987). As the average gestational age in the preterm group in our study was 28.5 ± 2.7 weeks (range 24–31 weeks), this critical window of development was largely completed out of the womb in our preterm adult group. Although the effects of such altered autonomic development on cardiovascular function in adults born preterm are not fully understood, autonomic dysfunction is correlated with several negative cardiovascular outcomes (Florea and Cohn 2014; Evrengul et al. 2006; Kishi 2012).

Adolescents and young adults born preterm have lower heart rate variability at rest, suggesting altered autonomic regulation, particularly lower high-frequency heart rate variability, which is a marker of reduced parasympathetic regulatory capacity (Mathewson et al. 2015; Haraldsdottir et al. 2018). HR response to exercise is mediated by the ANS, where initiation of exercise signals vagal withdrawal followed by increased sympathetic activation, and exercise cessation conversely signals parasympathetic reactivation and sympathetic withdrawal (Mitchell 1985; Savin et al. 1982). Failure of HR to fall quickly during recovery following exercise has been identified as an independent predictor of all-cause mortality, clinical worsening of pulmonary arterial hypertension, carotid atherosclerosis, and higher risk of cardiovascular disease and coronary heart disease (Cole et al. 1999, 2000; Morshedi-Meibodi et al. 2002; Minai et al. 2012; Ramos et al. 2012; Jae et al. 2008; Watanabe et al. 2001).

The use of HRR as an indicator of disease or mortality risk is appealing due to its non-invasive nature, and there is emerging evidence that there is a threshold for HRR and adverse health outcomes. HRR after 1 min of recovery (HRR_{1min}) of ≤ 18 beats following peak exercise has been described as an independent predictor of all-cause mortality in older patients referred for exercise stress echocardiography (Watanabe et al. 2001) and for those with pulmonary arterial hypertension (Ramos et al. 2012). In our study, HRR_{1min} in the control group was similar to that seen in healthy young adults in other studies (Hautala et al. 2006; Hargens et al. 2008), but was strikingly lower in young adults born preterm.

We also found that preterm adults had a lower exercise capacity compared to controls in both normoxia and hypoxia, including lower VO_{2max}, VT_{VO2}, P_{max}, and T_{max}, which is consistent with previously published reports in the literature (Farrell et al. 2015; Duke et al. 2014). While VO_{2max} is positively correlated with HRR in endurance athletes (Ostojic et al. 2010), it is also affected by autonomic function and disease status, and HRR is faster in athletes and slower in patients with heart failure (Imai et al. 1994). While there is data to suggest that lower cardiorespiratory fitness is correlated with slower HRR (Watson et al. 2017; Imai et al. 1994), after adjusting HRR in normoxia and hypoxia for VO_{2max}, HRR was still found to be significantly slower in preterm subjects compared to control adults. Furthermore, physical activity levels in the preterm group were similar to those in the control group, and the GPAQ has been shown to have a strong correlation with accelerometer data and moderate-to-vigorous activity levels (Cleland et al. 2014). Therefore, we do not believe that fitness status is primarily responsible for the blunted HRR in the preterm group.

We found that preterm males had significantly lower VO_{2max} and P_{max} compared to control males, whereas there was no significant difference between females. To our knowledge, this is the first report of sex-specific effects on VO_{2max} after preterm birth. This is not altogether surprising though, given that males born preterm often have worse neonatal outcomes (Peacock et al. 2012). Despite this sex-specific difference in VO_{2max}, in the current study we found that HRR was equally impaired in males and females born preterm. The finding that HRR_{1min} is similarly impaired in both preterm males and females, while maximal aerobic capacity is impaired more in males than females born preterm, supports our hypothesis that there is an intrinsic impairment in autonomic function in young adults born prematurely, irrespective of fitness or sex.

To our knowledge, this is also the first study to compare HRR following maximal exercise in both normoxia and hypoxia in healthy young adults. HR response to hypoxia is well documented at rest, where exposure to hypoxia results in a drop in arterial oxygen content (Amann et al. 2007), resulting in a physiological response to reverse the hypoxemia. The sympathetic nervous system is activated to combat the drop in arterial oxygen content and results in an increase in HR, greater cardiac contractility, hyperpnea, and peripheral vasoconstriction (Amann and Kayser 2009).

Interestingly, we found that HRR was not significantly different in preterm young adults between normoxic and hypoxic conditions at the 1 min of recovery, a time point with clinical implications in the literature (Watanabe et al. 2001; Cole et al. 1999). The lack of difference in HRR_{1min} in preterm adults between normoxia and hypoxia is curious, and suggests that the autonomic response to to hypoxia is blunted in this group. In conjunction with the impaired HRR in normoxia, this suggests a blunted parasympathetic reactivation and impaired sympathetic withdrawal following maximal exercise in adults born preterm. Interestingly, young adults born preterm also have a blunted ventilatory response in hypoxia compared to term-born controls (Bates et al. 2014), suggestive of a dysfunctional autonomic ventilatory response. Though the mechanism is unknown, it has been suggested that desensitized carotid bodies become insensitive to hypoxia, resulting in blunted hypoxic ventilatory sensitivity (Prabhakar and Peng 2004). Prior data from this same cohort of young adults born preterm demonstrate evidence of a blunted ventilatory response to hypoxia (Bates et al. 2014) and our current findings of an impaired HRR recovery following maximal exercise suggest that young adults born preterm may have autonomic dysfunction that affects both respiratory and cardiac autonomic innervation.

In the preterm group, only 8 of the 12 participants were able to complete maximal exercise testing in hypoxia, while all full-term control subjects were able to complete exercise testing in both conditions. The participant dropout was due to inability to tolerate the wash-in period of hypoxic gas as a result of symptoms including dizziness, lightheadedness, or presyncope. While the low number in the preterm hypoxia group is admittedly a limitation in the study, it provides additional insight into the autonomic dysfunction in this population. Our laboratory has previously shown that young adults born preterm exhibit a blunted ventilatory drive during hypoxic exposure (Bates et al. 2014) and significantly lower Sp_{O2} and Sa_{O2} at maximal exercise in hypoxia compared to controls (Farrell et al. 2015). This evidence, combined with the inability of 33% of the preterm participants to tolerate 8 min of hypoxia wash-in, supports the notion that young adults born preterm have an inadequate autonomic response to hypoxic conditions.

The mechanisms driving a slower HRR in this population of young adults born preterm are beyond the scope of this study. Past research investigating autonomic function in subjects with a history of prematurity have focused mainly on measurements taken at rest. Children born preterm have augmented sympathoadrenal activity at rest as determined by elevated urinary catecholamines (Johansson et al. 2007), and young adults born preterm have reduced high-frequency heart rate variability, indicative of lower parasympathetic activity (Mathewson et al. 2015). Our finding that HRR, which is due to a combination of sympathetic withdrawal and vagal reactivation, is slower in preterm adults supports the notion that they may have imbalanced autonomic function, suggesting less effective sympathetic withdrawal and/or blunted parasympathetic reactivation during recovery.

This study had several strengths including a true resting period immediately following maximal exercise, use of two types of physiologic stress: hypoxia and exercise, and inclusion of groups with similar physical activity and BMI, both of which can affect HRR. Furthermore, our adjustment of HRR for VO_{2max} gave us the ability to control for a variable that can be a significant confounder in the measurement of HRR. Our study was limited by the relatively homogeneous populations in the groups, where the experimental cohort was based out of Iowa and Wisconsin, and may not be representative of a more diverse population. Furthermore, we included a moderate to severe preterm-born population, and whether these results will be applicable to young adults born mildly premature remains unknown. Because the study was conducted at a single location, there may have been biases with respect to subject recruitment, where those from the local area were enrolled. Our analysis of autonomic function only studied HRR, and additional studies evaluating resting heart rate variability and muscle sympathetic nervous activity, an overall marker of sympathetic outflow (Joyner et al. 2010), would be helpful. Furthermore, our study design did not allow us to differentiate between the mechanisms altering HRR from maximal exercise in this population.

In conclusion, our study demonstrates that HRR is significantly slower in healthy young adults born preterm compared to age-matched, term-born controls. Although preterm adults demonstrated lower aerobic fitness, the difference in HRR persisted after adjusting for differences in VO_{2max}. Autonomic dysfunction as seen in this study is associated with significantly increased rates of cardiovascular disease and mortality. With nearly half a million preterm births annually in the USA and improving neonatal survival rates, there are a growing number of adults born premature in the general population who may lack typical cardiovascular risk factors, yet present with autonomic dysfunction reflected by slower HRR following maximal exercise. Further study into the mechanisms of autonomic dysfunction following preterm birth is warranted.

Author contributions KH, AMW, KNG, and MWE conceptualized and designed the study and are the guarantor of the content of the manuscript, including the data and analysis. KH, AMW, KNG, AGB, DFP, LHT, MDB, RMC, and MWE assisted with data collection. KH, AMW, KNG, AGB, MP, LHT, MDB, RMC, and MWE contributed to the analysis and interpretation of data. AMW conducted statistical analysis. KH and AMW prepared figures. KH drafted the initial manuscript. All authors reviewed, revised, and approved the final manuscript as submitted.

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