**Blunted Cardiac Autonomic Responsiveness to Hypoxemic Stress in Healthy Older Adults**

S. Deborah Lucy¹,², John M. Kowalchuk¹,³, Richard L. Hughson⁴, Donald H. Paterson³, and David A. Cunningham¹,³

**Abstract/Résumé**

Supine resting cardiac dynamics and responses to steady-state hypoxemia were investigated in six healthy older (59–72 yrs) adults using coarse-graining spectral analysis of heart rate variability (HRV) and were compared to six young (22–29 yrs) adults studied previously (Lucy et al., 2000). End-tidal carbon dioxide pressure (P$_{ET}$CO$_2$) was clamped at 1–2 mmHg above the usual resting value for 11 min of euoxia (P$_{ET}$O$_2$ 100 mmHg), followed by 22 min of hypoxia (P$_{ET}$O$_2$ 55 mmHg). During euoxia, vagally mediated harmonic and fractal power of HRV of older adults was minimal. Hypoxia induced an increase in ventilation, p < 0.01, and heart rate, p < 0.05. The heart rate increase (mean ± SE) of 0.23 ± 0.08 beats·min$^{-1}$ per 1% decrease in arterial O$_2$ saturation was 25% of that demonstrated previously by young subjects, p < 0.001. In older adults, HRV spectral power remained unchanged during hypoxia, providing further evidence of an age-related blunting of cardiac autonomic function.

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La dynamique cardiaque au repos couché et les ajustements à l’hypoxémie stable sont analysés chez six personnes âgées en bonne santé (59 à 72 ans) au moyen d’une analyse spectrale de type coarse-graining de la variabilité de la fréquence cardiaque (HRV); elles sont ensuite comparées aux valeurs obtenues chez six jeunes personnes (22 à 29 ans) rapportées dans une étude récente (Lucy et al., 2000). La Pco2 de fin d’expiration (P_{ET}CO2) est stabilisée à 1–2 mmHg au dessus des valeurs normales de repos au cours d’une période d’euxoxie (P_{ET}O2 100 mmHg) d’une durée de 11 min, suivie d’une période d’hypoxie (P_{ET}O2 55 mmHg) d’une durée de 22 min. Au cours de la période d’euxoxie, les puissances fractale et harmonique de HRV d’origine vagale des personnes âgées sont minimales. L’hypoxie provoque une augmentation de la ventilation (p < 0,01) et de la fréquence cardiaque, p < 0,05. L’augmentation de la fréquence cardiaque de 0,23 ± 0,08 bpm (moyenne ± erreur type) pour une baisse de 1% de la saturation artérielle d’oxygène correspond au quart de la valeur observée précédemment chez les jeunes adultes, p < 0,001. Chez les personnes âgées, la puissance spectrale de HRV ne varie pas au cours d’une période d’hypoxie, ce qui fournit une observation de plus à l’effet que la fonction autonome du cœur est atténuée par l’âge.

**Introduction**

Heart rate responses to autonomic provocation tests decline significantly with increasing age (O’Brien et al., 1986; Pfeifer et al., 1983; Ziegler et al., 1992). Whereas resting supine heart rate has been reported to be similar for all ages, from 9 to 80 years (Lipsitz et al., 1990; Pagani et al., 1986; Sato et al., 1981; Schwartz et al., 1991; Shannon et al., 1987; Simpson and Wicks, 1988), resting heart rate in the upright position decreases with age (Sato et al., 1981; Schwartz et al., 1991; Simpson and Wicks, 1988), suggesting a blunted responsiveness to orthostatic stress. Additionally, rhythmic variations in resting heart period, known to reflect the integrity of autonomic cardiac control, diminish with advancing age (Hellman and Stacy, 1976; O’Brien et al., 1986; Pfeifer et al., 1983; Sato et al., 1981; Ziegler et al., 1992), as does the magnitude of increase in heart rate variation during β-adrenergic blockade (Pfeifer et al., 1983). While increased cardiovascular sympathetic activity in healthy older adults has been inferred from age-related increases in blood pressure and plasma norepinephrine concentration (Pfeifer et al., 1983), β-adrenergic responsiveness reportedly diminishes (O’Brien et al., 1986).

Spectral analysis studies of heart rate variability (HRV) have been consistent with a decline in cardiac autonomic control in healthy older adults (Jarisch et al., 1987). The power (amplitude) of high-frequency (HI, >0.15 Hz) oscillations in HRV, related to respiration, is known to reflect parasympathetic outflow to the heart, while low-frequency (LO, <0.15 Hz) power, related to baroreflex and vaso-motor control, may be determined jointly by parasympathetic and sympathetic efferent cardiac activity (Pomeranz et al., 1985; Saul et al., 1989).

Frequency domain studies showing marked decreases in low- and high-frequency power, as well as total power, with age in lying (predominant parasympathetic control) and upright postures (sympathetic activation and parasympathetic withdrawal), suggest there is a decline of both parasympathetically and sympathetically mediated influences on HRV (Lipsitz et al., 1990; Schwartz et al., 1991; Shannon et al., 1987; Ziegler et al., 1992). Age-related differences have also been found in the HRV response to upright tilt (baroreceptor unloading and sympathetic
stimulation), with young subjects exhibiting a much greater increase in total and low-frequency power than older subjects (Jarisch et al., 1987; Lipsitz et al., 1990; Pagani et al., 1986; Simpson and Wicks, 1988).

Studies have implicated vagal withdrawal as the mediator of the resultant tachycardia response to moderate systemic hypoxia in young adults (Eckberg et al., 1982; Lucy et al., 2000). Information on the response of older adults, however, remains limited. Kronenberg and Drage (1973) demonstrated that the heart rate and ventilatory responses of healthy elderly men to progressive hypoxia, down to an alveolar PO2 of 40 mmHg, were reduced by approximately 66% and 50%, respectively, compared to young subjects. On the other hand, Poulin et al. (1993) used the dynamic end-tidal forcing (DEF) technique to produce square wave step changes in end-tidal oxygen pressure (PETO2) and found a significant blunting of only the cardiac response, but not the ventilatory response, of older compared to younger adults, to a 2-min exposure to isocapnic (IC) hypoxia. While the ventilatory response to sustained (20–25 min) IC hypoxia has likewise been shown to be independent of age in healthy persons (Ahmed et al., 1991; Smith et al., 1995; 2001), neither the cardiac response nor the HRV spectral characteristics of older adults have been examined under these hypoxic conditions.

Thus the purpose of this study was to examine the cardiac chronotropic response and the alterations in heart rate dynamics of healthy older adults evoked by an acute exposure to steady-state IC hypoxia. It was anticipated that the purported autonomic changes associated with physiological aging would lead to a blunting of the vagal response of older adults to hypoxic stress. Testing of older persons was therefore restricted to the supine position, in which vagal cardiac control and the beat-to-beat modulation of heart rate by respiration is maximised (Pomeranz et al., 1985; Saul et al., 1989).

Methods

Spectral analysis of heart rate variability (Yamamoto and Hughson, 1993, 1994) was used for the noninvasive investigation of cardiac dynamics and autonomic control function, while the respiratory control system was stimulated simultaneously with the DEF technique (Lucy et al., 2000; Poulin et al., 1993).

EXPERIMENTAL DESIGN

Subjects and Test Conditions. Six healthy volunteers (2 M, 4 F; mean ± SD age = 67.3 ± 5.4 yrs; height = 167.7 ± 12.3 cm; body mass = 69.1 ± 15.3 kg) participated in the study. Prior to inclusion in the study, all volunteers were screened by a physician; they underwent a brief physical examination and medical history assessment so as to exclude cardiovascular, respiratory, and metabolic diseases. The medical examination further included the recording of a 12-lead electrocardiogram (ECG) during a symptom-limited, graded treadmill exercise stress test (grade increased 1% per 30 s and speed increased 0.5 mph per 1 min) in order to screen for myocardial conduction disturbances, cardiac arrhythmias, and myocardial ischemia. One volunteer developed a ventricular tachycardia during the screening stress test and was excluded from further study.
All participants were nonsmokers, normotensive (unmedicated), and physically active, with 5 of the 6 subjects exercising for one hour 2 or 3 mornings a week as part of an exercise program, while the other subject jogged ($\approx 40 \text{ k week}^{-1}$) on a regular basis. The study requirements were fully explained in verbal and written forms to all participants, with each one giving informed consent prior to participation in the study. The research conformed to the guidelines of the Declaration of Helsinki (1996) and was approved by the university ethics committee on human research.

Subjects were asked not to eat or drink caffeinated beverages within the 4 hrs prior to the testing sessions. All studies were conducted at the same time of day (noon to 5 p.m.) in a quiet climate-controlled room with the subject supported comfortably in the supine position and listening to music. The subject was fitted with an ear oximeter (OXI; Radiometer, Copenhagen), surface ECG electrodes and leads, and a mouth-breathing face mask (Series 7900, Hans Rudolph, Kansas City, MO) connected to the gas control system, for continuous noninvasive recording of arterial oxygen saturation ($S_{\text{a}}O_2$), ECG, and ventilatory parameters throughout the experiment. Each subject underwent a 40-min practice session breathing different combinations of euoxic, hypoxic, or hyperoxic gas mixtures, administered in stepwise fashion, so as to become familiar with the required instrumentation and accustomed to the breathing apparatus. The subsequent sessions were for testing purposes according to the experimental protocol. Any session during which the subject either fell asleep or moved enough to create significant motion artefacts in the data was excluded and subsequently replicated to ensure strict adherence to standardised test conditions.

**Protocol.** The control of respired gases was achieved using a computer-controlled fast-gas-mixing system (Lucy et al., 2000; Poulin et al., 1993). Individual supine resting end-tidal CO$_2$ pressure ($P_{ET\text{CO}_2}$) was determined by having the subject breathe warm humidified air for 5 min, while end-tidal O$_2$ ($P_{ET\text{O}_2}$) was held constant at 100 mmHg, and CO$_2$ was allowed to vary spontaneously with respiration. The subject’s resting $P_{ET\text{CO}_2}$ was determined as the mean of the last 10 $P_{ET\text{CO}_2}$ values of this 5-min collection period.

A sequence of square wave steps in $P_{ET\text{O}_2}$ was then administered to subjects while maintaining $P_{ET\text{CO}_2}$ constant (isocapnia, IC) at 1–2 mmHg above the individually determined normal euoxic value. The timing and sequence of changes in $P_{ET\text{O}_2}$ replicated that which had been employed previously in the laboratory when studying the response of young adults to IC hypoxia (Lucy et al., 2000). At the start of the protocol, subjects underwent an initial 5-min habituation period to the face mask, breathing warmed and humidified room air. Upon transition to breathing on the gas control system, $P_{ET\text{O}_2}$ was clamped at 100 mmHg (euoxia) for the first 11 min. This was followed by a square wave step into hypoxia ($P_{ET\text{O}_2}$ 55 mmHg, arterial O$_2$ saturation $\approx 85\%$) for 22 min. $P_{ET\text{O}_2}$ was then returned to 100 mmHg for an 11-min recovery period. Plots of the end-tidal gas pressures recorded for a representative older subject during a single test session are shown in Figure 1. Indirect brachial artery BP determinations were made once during each stage of the protocol with the use of a digital blood pressure meter (Model UA-751, Lafayette Instrument Co., Lafayette, IN). Mean arterial pressure (MAP) was calculated as diastolic pressure (DBP) + 1/3 [systolic pressure (SBP) – DBP].
Figure 1. End-tidal gas pressures ($P_{ET}$) recorded for one older adult during a test of isocapnic (IC) hypoxia. $P_{ET}O_2$ is shown in top trace and $P_{ET}CO_2$ in bottom trace. $P_{ET}CO_2$ was held constant throughout the protocol at 1–2 mmHg above the individually determined resting value, i.e., at essentially the eucapnic level. Solid vertical lines mark the time of step changes in $P_{ET}O_2$; the first line marks the transition from room air breathing to breathing on the gas control system. An initial 11-min period of euoxia ($P_{ET}O_2$ 100 mmHg) was followed by a 22-min exposure to hypoxia ($P_{ET}O_2$ 55 mmHg). $P_{ET}O_2$ was then returned to 100 mmHg for an 11-min recovery period.
Respiratory Apparatus and Gas Analysis. Respiratory volumes were measured by having subjects breathe through a mouth-breathing face mask (separately sealed nose and mouth chambers) connected to a low resistance bidirectional turbine (Alpha Technologies VMM 110, Bellingham, WA) and volume transducer (SensorMedics VMM-2A, Yorba Linda, CA), which was calibrated daily with a syringe of known volume (3.01 L). Respiratory flows and timing were obtained with a pneumotachograph (Model 3800, Hans Rudolph Inc.) and a differential pressure transducer (Validyne MP45-871). The fractional concentrations of O₂, CO₂, and N₂ in the inspired and expired gases, sampled continuously at the mouth, were determined with a mass spectrometer (Airspec 2000, Bigginhill, Kent, UK) calibrated with precision-analysed gas mixtures. Analog signals were sampled and digitized every 20 ms by a data acquisition computer. The gas concentration signals were aligned with the inspired and expired volumes after correcting for the time delay appropriate for the instrument.

Respired gases were controlled on a breath-by-breath basis using a computer-controlled dynamic end-tidal forcing (DEF) and feedback method as detailed previously (Lucy et al., 2000). The variables used for feedback control were P<sub>ET</sub>O₂ and P<sub>ET</sub>CO₂. In brief, a control computer compares the target end-tidal gas tensions specified by the experimental protocol with the PO₂ and PCO₂ sensed at the end of each breath. The composition of the inspired gases (O₂, CO₂, and N₂) delivered on the subsequent breath is then adjusted by the control computer to force the P<sub>ET</sub>O₂ and P<sub>ET</sub>CO₂ toward the desired values. This method of gas control has been noted for the squareness of the alveolar gas steps, as well as the constancy of PET O₂ and P<sub>ET</sub>CO₂ in the face of a constantly changing ventilation (Swanson and Belleville, 1975).

Heart Rate Variability Measurement and Spectral Analysis. This study was designed to examine the profile of changes in the harmonic and fractal components of heart rate variability (HRV) invoked by exposure of spontaneously breathing older adults to sustained IC hypoxia. Similar to our prior study of hypoxia in young adults (Lucy et al., 2000), beat-to-beat variability in the instantaneous heart period was analysed with coarse-graining spectral analysis (CGSA) in order to isolate and separately quantify the contribution of these two components, i.e., harmonic and fractal, to the total variability (Yamamoto and Hughson, 1993, 1994).

The surface ECG was acquired continuously by an electrocardiograph (Harco Electronics Ltd, Winnipeg, MB) with the use of standard bipolar leads. The analog output of the electrocardiograph was differentiated in order to obtain a train of rectangular impulses corresponding to the QRS spikes. The impulse train was processed on a real-time basis with a personal computer (Packard Bell Force 486/33, NEC Group, The Netherlands) via a 12-bit analog-to-digital converter (PCL-812, Advantech Co. Ltd, Taiwan) at a sampling frequency of 1,000 Hz, and was stored sequentially for later analyses.

The time series data of cardiac interpulse (R-R) intervals were scanned and subjected to a filtering process that either deleted extra beats or inserted missing beats by interpolation, prior to performing CGSA. Following calculation of the mean R-R interval (R-R; ms) and standard deviation of R-R (SD<sub>R-R</sub>; ms), we aligned the unequal R-R intervals sequentially to obtain equally spaced samples (Yamamoto and Hughson, 1993). A linear regression method was used to eliminate linear trend from the data sets.
The total harmonic power \( (H_{tot}) \) was divided into low-frequency \( (P_l, 0.0–0.15 \text{ Hz}) \) and high-frequency \( (P_h, 0.15–1.0 \text{ Hz}) \) power \( (\text{ms})^2 \), from which indices of sympathetic (SNS) and parasympathetic (PNS) nervous system activity were derived. SNS and PNS activity were evaluated by \( P_l / P_h \) and \( P_h / P_l \), respectively (Yamamoto and Hughson, 1993, 1994), where \( P_t \) is total spectral (harmonic and fractal) power.

The fractal component was plotted in a log-power vs. log-frequency plane, with the spectral exponent \( (\beta) \) estimated as the slope \( (−\beta) \) of the linear regression of this plot. From the value of the spectral exponent, the fractal dimension \( (D_F) \) of the trail of HRV was calculated as \( D_F = 2/(\beta − 1) \) for \( 1 < \beta \leq 3 \). For \( \beta > 3 \) and \( 0 \leq \beta \leq 1 \), \( D_F \) was taken as 1 and infinity \( (\infty) \), respectively. The relationship between the spectral exponent, \( \beta \), and the calculated fractal dimension is nonlinear. Statistical analysis therefore was restricted to the linear variable \( \beta \), with the value of \( D_F \) reported from the mean of \( \beta \) (Lucy et al., 2000).

**DATA ANALYSIS**

In order to comply with Fourier analysis requirements for stationarity, we excluded the acute phase of the cardiac response to the step into hypoxia from power spectral analysis. Likewise, the prolonged delay in the cardiac off-response following relief from hypoxia precluded application of spectral analysis to the recovery period. The terminal 30-second segments of each of the three stages of the protocol (baseline euoxia, hypoxia, and recovery euoxia) were eliminated from data analysis. The 400 heartbeats immediately preceding this terminal 30-second segment in the initial (baseline) euoxic and hypoxic periods were subjected to CGSA to determine the profile of changes in the HRV power spectrum associated with the exposure to IC hypoxia during spontaneous breathing. Ventilatory parameters were analysed initially on a breath-by-breath basis, and then averaged over the corresponding terminal 400-heartbeats time intervals subjected to CGSA, as well as the terminal 400 heartbeats of the recovery period.

*Statistical Analysis.* Data were analysed using Sigma Stat (Jandel Scientific, San Rafael, CA) statistical software. Data that passed the tests of normality and equal variance were analysed with one-way repeated-measures ANOVA, while nonparametric data were assessed for significance using Friedman repeated-measures ANOVA on ranked data. Post-hoc tests of significance were done using the Student-Newman-Keuls test. Statistical significance was accepted for \( p \leq 0.05 \). Data reported in the text are the mean and the standard error of the mean \( (SEM) \), unless otherwise noted.

*Comparison of Older vs. Young Adults.* The cardiac autonomic responses to moderate steady-state IC hypoxia of 6 young adults (3 M, 3 F) had been studied previously in our laboratory under the same experimental conditions, in both the sitting and supine positions (Lucy et al., 2000). To assist with the interpretation of results of the current study, data collected earlier for young subjects in the supine position were used as a comparator for the responses of the older adults. Parametric data were assessed for statistically significant differences between the older and younger group using an unpaired \( t \)-test, while data that failed to pass either the test of normality or equal variance were analysed with the Mann-Whitney rank sum test.
Results

RESPONSES TO TESTING

Ventilatory Response to IC Hypoxia. The ventilatory and cardiac responses of a single older subject elicited by exposure to IC hypoxia are shown in Figure 2, while the average ventilatory data for all the older adults are summarized in Table 1. Ventilation was stimulated significantly by exposure to IC hypoxia (Table 1) and was biphasic (Figure 2), as has been described previously in both healthy young (Easton et al., 1986; Lucy et al., 2000) and older (Smith et al., 2001) adults. Thus there was typically a brisk initial increase in ventilation, followed by a subsequent decline to an intermediate plateau which was higher, *p* < 0.01, than the average baseline ventilation (Table 1). The increase in ventilation of these older adults...
Table 1 Ventilatory Response to Sustained Isocapnic Hypoxia While Supine

<table>
<thead>
<tr>
<th></th>
<th>Older adults (n = 6)</th>
<th>Young adults (n = 6)*</th>
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<tbody>
<tr>
<td></td>
<td>Euoxia (E1)</td>
<td>Hypoxia (Ho)</td>
</tr>
<tr>
<td></td>
<td>Euoxia (E2)</td>
<td>Euoxia (E1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypoxia (Ho)</td>
</tr>
<tr>
<td><strong>P_{ET}CO_2 (mmHg)</strong></td>
<td>39.3 ± 1.3</td>
<td>39.3 ± 1.4</td>
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<td></td>
<td>40.1 ± 1.5</td>
<td>39.8 ± 1.6</td>
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<tr>
<td><strong>S_aO_2 (%)</strong></td>
<td>94.7 ± 0.5</td>
<td>84.1 ± 1.1 b</td>
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<td></td>
<td>93.5 ± 0.9</td>
<td>96.4 ± 0.2</td>
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<td></td>
<td>96.2 ± 1.0</td>
<td>95.2 ± 1.0</td>
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<tr>
<td><strong>V_E (L·min(^{-1}))</strong></td>
<td>10.30 ± 1.41 a</td>
<td>11.60 ± 1.15 b,c</td>
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<td></td>
<td>9.70 ± 1.21</td>
<td>10.42 ± 1.61</td>
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<td></td>
<td>17.89 ± 1.61</td>
<td>18.0 ± 1.16</td>
</tr>
<tr>
<td><strong>V_T (ml)</strong></td>
<td>737 ± 36 a</td>
<td>826 ± 44 b</td>
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<td></td>
<td>697 ± 32</td>
<td>734 ± 81</td>
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<tr>
<td></td>
<td>1063 ± 116</td>
<td>116 ± 116</td>
</tr>
<tr>
<td><strong>f_B (breaths·min(^{-1}))</strong></td>
<td>15.1 ± 1.4</td>
<td>14.9 ± 1.3</td>
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<td></td>
<td>14.3 ± 1.3</td>
<td>15.2 ± 1.1</td>
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<tr>
<td></td>
<td>18.0 ± 1.3</td>
<td>1.1 ± 1.3</td>
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</table>

Note: Parameters expressed as mean ± SEM for terminal 400-heartbeat time intervals in each initial E1 and Ho period subjected to spectral analysis, as well as terminal 400 heartbeats of recovery E2 period. P_{ET}CO_2 = end-tidal CO_2; S_aO_2 = arterial O_2 saturation; V_E = minute expired ventilation; V_T = tidal volume; f_B = breathing frequency.

Significance for older adults: \( p < 0.01 \) E1 vs. Ho; \( p < 0.01 \) Ho vs. E2; \( p < 0.05 \) vs. young adults.

*Data for young adults tested using same experimental protocol from Lucy et al. (2000).

was accomplished solely by an increase in tidal volume, \( p < 0.01 \), as neither breathing frequency (Table 1) nor inspiratory airflow (baseline, 432 ± 44 ml·s\(^{-1}\) vs. hypoxia, 493 ± 29 ml·s\(^{-1}\)) changed. Following relief from hypoxia, there was a brief characteristic undershoot in ventilation (Figure 2) before returning to the baseline euoxic level.

**Resting Heart Rate and the Response to IC Hypoxia.** Figure 2 likewise depicts the cardiac response of a single older adult to hypoxic stimulation. Average group responses for all subjects are reported in Table 2. Exposure to sustained IC hypoxia induced a cardio-acceleration in 5 of the 6 older subjects, with no change in the remaining subject. While the hypoxia-induced shortening of the average R-R interval by 33 ± 10 ms (increased mean heart rate of 3 ± 1 beats·min\(^{-1}\)) was minimal (Table 2), it did reach statistical significance, \( p < 0.05 \).

In healthy adults, the increase in heart rate associated with an acute exposure to progressive IC hypoxia is known to be linearly related to the fall in oxygen saturation over the range from 100% to 70% (Sanders and Keller, 1989). Each subject’s heart rate response was thus normalised to the individual change (percent drop) in arterial oxygen saturation (S_aO_2) during hypoxia (Figure 3). In order to
better interpret the magnitude of the response in older subjects, we also calculated
the normalised cardiac responses to hypoxia for six young subjects (ages 22–29
yrs) studied earlier in our laboratory and added this data to Figure 3. The change in
heart rate (HR) normalised to change in percent $S_aO_2$ ($\Delta HR/\Delta S_aO_2$) of the older
adults averaged $0.23 \pm 0.08$ (range = $-0.02$ to $0.52$) beats·min$^{-1}$ per 1% $S_aO_2$, with
the individual responses of all but one subject being less than that of young adults
under similar hypoxic conditions (Figure 3).

**Blood Pressure and IC Hypoxia.** Neither the baseline MAP (90 ± 3.8
mmHg) nor the average DBP (76 ± 2.6 mmHg) of the older subjects was altered
during sustained IC hypoxia (MAP = 92 ± 2.8 mmHg; DBP = 76 ± 1.7 mmHg). Hypoxic exposure was associated with an increase, $p < 0.05$, in mean systolic
pressure (SBP) from 118 ± 6.5 mmHg to 124 ± 5.8 mmHg.

**Resting HRV and IC Hypoxia.** Despite being healthy and physically ac-
tive, time (SD$_{R-R}$) and frequency domain (spectral analysis) measurements
demonstrated minimal resting heart rate variability (HRV) in the older adults (Table 2). Reduced absolute spectral power was seen in the high- ($P_h$) and low-frequency
($P_l$) harmonic (10-fold reduction), as well as the fractal (7-fold reduction) components of HRV (Table 2) compared to values reported in the literature using the
CGSA technique for subjects in their 20s (Lucy et al., 2000).

### Table 2 Isocapnic Hypoxia and Heart Rate Variability Indices While Supine

<table>
<thead>
<tr>
<th></th>
<th>Older adults ($n = 6$)</th>
<th>Young adults ($n = 6$)*</th>
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<tbody>
<tr>
<td></td>
<td>Euoxia (E1)</td>
<td>Hypoxia (Ho)</td>
</tr>
<tr>
<td>R-R (ms)</td>
<td>920 ± 37$^a$</td>
<td>887 ± 41</td>
</tr>
<tr>
<td>SD$_{R-R}$ (ms)</td>
<td>39 ± 2$^b$</td>
<td>42 ± 3</td>
</tr>
<tr>
<td>$P_h$ (ms$^2$)</td>
<td>81 ± 26$^c$</td>
<td>110 ± 33</td>
</tr>
<tr>
<td>$P_l$ (ms$^2$)</td>
<td>86 ± 29$^b$</td>
<td>70 ± 21</td>
</tr>
<tr>
<td>Fractal (ms$^2$)</td>
<td>639 ± 156$^b$</td>
<td>583 ± 99</td>
</tr>
<tr>
<td>$P_t$ (ms$^2$)</td>
<td>805 ± 162$^b$</td>
<td>757 ± 109</td>
</tr>
<tr>
<td>$\beta$</td>
<td>1.33 ± 0.19</td>
<td>1.23 ± 0.29</td>
</tr>
<tr>
<td>PNS</td>
<td>0.119 ± 0.044</td>
<td>0.155 ± 0.045</td>
</tr>
<tr>
<td>SNS</td>
<td>2.681 ± 1.396</td>
<td>1.415 ± 0.845</td>
</tr>
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</table>

*Data for young adults tested using same experimental protocol from Lucy et al. (2000).

**Note:** Parameters expressed as mean ± SEM for terminal 400-heartbeat time intervals in
each initial E1 and Ho period subjected to spectral analysis. R-R = cardiac interpulse
interval; SD$_{R-R}$ = std. dev. of R-R; $P_h$ = high-freq. harmonic power; $P_l$ = low-freq.
harmonic power; $P_t$ = total spectral power; $\beta$ = spectral exponent; PNS = parasympathetic
nervous system indicator; SNS = sympathetic nervous system indicator.

Significance for older adults: $^a p < 0.05$ E1 vs. Ho; $^b p < 0.05$; $^c p < 0.01$ vs. young adults.
During the period of sustained hypoxia-induced cardio-acceleration, there were no changes in the fractal or harmonic power of HRV, the indices of PNS (P_h/P_t) and SNS (P_l/P_h) activity, or β, the spectral exponent (Table 2). Likewise, the SD_{R-R} was not altered by the hypoxic exposure (Table 2).

**Discussion**

Cardiac dynamics and autonomic control were studied in recumbent healthy older adults at rest during euoxia and sustained steady-state hypoxemia. The investigation was unique in that spectral analysis of HRV has not been used previously to assess the effects of physiological aging beyond early adulthood on autonomic function in response to a hypoxic perturbation. Furthermore, a direct comparison of the supine responses of these healthy older adults to a younger cohort (Tables 1 and 2) was possible, as we had previously examined the effect of body position (supine vs. sitting) on the nature and neural mediation of the cardiac responses of six young adults (26.3 ± 1.5 yrs) to IC hypoxia in the laboratory under the same experimental conditions, using DEF and CGSA techniques (Lucy et al., 2000). Apart from the age criteria, the young subjects met the same inclusion criteria as the older subjects, were likewise engaged in recreational physical activities, and were of similar height (168.7 ± 10.4 cm), mass (64.6 ± 13.8 kg), and ventilatory characteristics during resting euoxic conditions (Table 1).

Data from the present study and our earlier work (Lucy et al., 2000), consistent with the literature (Jennings and Mack, 1984; Lipsitz et al., 1990; Schwartz et al., 1991; Shannon et al., 1987; Simpson and Wicks, 1988; Ziegler et al., 1992), provided evidence of a marked reduction in both low- (P_l, p < 0.05) and high-
frequency ($P_h, p < 0.01$) harmonic, as well as total spectral power, $p < 0.05$, of supine resting HRV, in healthy older subjects, despite similar heart rates (Table 2). Likewise, the SD_R-R, the time domain index of total variation in heart period (Hellman and Stacy, 1976; O’Brien et al., 1986; Sato et al., 1981), was minimal in the older subjects, averaging only 40% of that recorded in our prior study of younger subjects (Lucy et al., 2000).

An additional finding, not previously documented, was the diminished absolute fractal (nonharmonic) power of HRV, but preservation of the fractal dimension, in those subjects 59 to 72 years of age (Table 2). Marked attenuation of cardiac spectral responses, as well as chronotropic responses, evoked by the older adults’ exposure to sustained IC hypoxia furnished further new evidence in support of a depression of cardiac autonomic function with healthy aging beyond 60 years of age.

RESTING CARDIAC DYNAMICS

**HRV Harmonic Component.** The age-related decreases in high- and low-frequency harmonic and fractal power recorded in the present study for supine subjects (during euoxia) are consistent with an attenuation of vagally mediated cardiac control with advancing age. The highest frequency oscillations (>0.15 Hz) of heart rate, linked to the respiratory modulation of heart rate (respiratory sinus arrhythmia, RSA), are mediated solely by cardiac vagal efferents (Pomeranz et al., 1985; Saul et al., 1989). Furthermore, while the low-frequency (<0.15 Hz) component of HRV has been shown to include contributions from both the SNS and PNS in the resting supine state, the majority of $P_1$ is related to parasympathetic tone (Pomeranz et al., 1985). Likewise, cardiac vagal (Yamamoto et al., 1995b), but not sympathetic efferent outflow (Yamamoto and Hughson, 1994), has been implicated in mediating the fractal component of HRV.

The mechanism of the reduced parasympathetic cardiac control (decreased reactivity of the sinus node to vagal activation, diminished cardiac vagal outflow, and/or diminished modulation of vagal efferent activity) remains unclear. The high-frequency harmonic components of HRV reflect modulation of vagal tone (Hedman et al., 1995) primarily by respiration, with the amplitude (power) of modulation showing a positive correlation with tidal volume and a negative correlation with breathing frequency (Hellman and Stacy, 1976; Hirsch and Bishop, 1981; Saul et al., 1989). In this study there were no differences in the average resting tidal volume ($V_T$), breathing frequency ($f_B$), or overall minute ventilation of the older adults when compared to the previously studied younger cohort. Additionally, resting inspiratory flow rate ($V_T/T_i$), which has been used as an index of central respiratory drive (Poulin et al., 1993), was comparable in both the older (432 ± 44 ml·s⁻¹) and young (437 ± 49 ml·s⁻¹, unpublished data) groups. It therefore seems unlikely that the 10-fold reduction in resting $P_h$ exhibited by the older subjects can be attributed to a reduction in the respiratory inputs known to modulate vagal efferent activity.

The low-frequency component of HRV in part reflects human sinus node responses to fluctuations of afferent arterial baroreceptor traffic (Eckberg, 1980; Elghozi et al., 1991), and aging has been suggested as being associated with a loss of baroreceptor sensitivity (Pfeifer et al., 1983). Neither tests of baroreceptor sen-
sitivity nor continuous blood pressure determinations were done in this study. Thus the contribution of the loss of baroreceptor sensitivity to the reduced $P_t$ of the older subjects cannot be excluded. However, the effect of diminished fluctuations in afferent baroreceptor traffic on the frequency power spectrum would be expected to be more prominent in the upright position, in which (a) low-frequency oscillations are amplified by sympathetic activation (Elghozi et al., 1991) in response to orthostatic stress, and (b) the mechanical effects of respiration on arterial pressure are maximised (Saul et al., 1991).

**HRV Fractal Component.** There is limited understanding of the origin of HRV fractal components (Yamamoto and Hughson, 1994; Yamamoto et al., 1995a). The fractal dimension ($D_F$) used to characterise cardiac fractal processes is thought to reflect the overall complexity of the autonomic control of heart rate (Lipsitz et al., 1990; Yamamoto et al., 1992). This study documented, for the first time, an approximate 7-fold reduction in the absolute power of the fractal component in healthy adults age 60 and over. Conversely, unlike the report of Lipsitz et al. (1990), the (calculated) fractal dimension (Table 2) was found to be comparable in our groups of supine young (Lucy et al., 2000) and older adults, suggesting a relative preservation of complexity in the underlying cardiac control.

The disparity in the results may be explained in part by the calculation of the slope of the log-frequency vs. log-power plot of total spectral power by Lipsitz and colleagues (1990), compared to the isolated fractal component in this study. On the other hand, the two investigations were not strictly equivalent, since the older adults in the present study were relatively young and physically active (age range 59 to 72 yrs), compared to the elderly subjects (71–94 yrs) of Lipsitz et al. (1990). It is possible that changes in heart rate fractal processes may occur more abruptly beyond the age of 70 years.

**RESPONSES TO HYPOXIA**

**Cardiac Chronotropic Response.** The attenuated cardiac chronotropic and spectral responses evoked by the exposure of older adults to sustained IC hypoxia in this study gave further evidence of an age-related depression of cardiac autonomic function. The change in heart rate of the older adults in response to moderate hypoxemia ($S_aO_2 \approx 84\%$) of $0.23 \pm 0.08$ beats·min$^{-1}$ per 1% $S_aO_2$ was similar in fact to the mean value ($\pm SD$) of $0.29 \pm 0.13$ beats·min$^{-1}$ per 1% $S_aO_2$ reported in the literature for five human heart transplant recipients with denervated hearts (Simon et al., 1995).

Considerable variability is recognized in the hypoxia-induced tachycardia found among human subjects (Simon et al., 1995). However, in the present study and our previous study (Lucy et al., 2000) of IC hypoxia, there was an overlap in the $\Delta HR/\Delta S_aO_2$ values (Figure 3) of only one older (0.52 beats·min$^{-1}$ per 1% $S_aO_2$) and one younger subject (0.50 beats·min$^{-1}$ per 1% $S_aO_2$), further strengthening the conclusion of a distinctly different response to hypoxic stress in older adults. Furthermore, this difference cannot be ascribed to an exaggerated response of the younger subjects, since the $\Delta HR/\Delta S_aO_2$ of $1.03 \pm 0.19$ beats·min$^{-1}$ per 1% $S_aO_2$ for the young group (Lucy et al., 2000) was consistent with the range of mean values ($0.86–0.98$ beats·min$^{-1}$ per 1% $S_aO_2$) documented in the literature for healthy young adults (Lambert et al., 1993; Sanders and Keller, 1989; Simon et al., 1995).
Two factors, baroreceptor stimulation and a lesser increase in hypoxia-stimulated ventilation, may have contributed in part to the relatively diminished hypoxia-induced tachycardia response of the older adults. In our earlier study of subjects in their 20s (Lucy et al., 2000), blood pressure remained unchanged during an acute exposure to steady-state IC hypoxemia (unpublished data). Conversely, hypoxic exposure of older adults in this study was associated with a significant increase in systolic BP. The subsequent baroreceptor stimulation would be expected to provoke a cholinergically mediated cardiac slowing. Certainly in healthy young adults, sympathetic responses to hypoxia were inhibited when baroreceptors were activated by increases in arterial pressure with phenylephrine infusion (Somers et al., 1991). Similarly in middle-aged adults, arterial baroreflex activity was depressed during acute hypobaric hypoxia (Bernardi et al., 1998). The significance of such a mechanism in diminishing the heart rate response of the older adults in this study to hypoxic stress is challenged, however, by the noted blunting of the HRV response to orthostatic stress (Jarisch et al., 1987; Lipsitz et al., 1990; Pagani et al., 1986; Simpson and Wicks, 1988) and the purported decrease in the sensitivity of the baroreceptor reflex mechanism with advancing age (Pfeifer et al., 1983).

Ventilation of recumbent older subjects was stimulated significantly by exposure to sustained IC hypoxia in this study. While consistent with the range of mean values (10.23–12.68 L·min⁻¹) previously reported for older persons evaluated under similar hypoxic conditions in the seated position (Ahmed et al., 1991; Smith et al., 1995), this ventilatory response was significantly less than we had noted previously (Lucy et al., 2000) for the young subjects in the supine position (mean plateau ventilation 17.89 L·min⁻¹). In particular, hypoxia stimulated a greater increase in the tidal volume (Vₜ) of the younger vs. the older subjects, and it has been speculated that the pulmonary inflation reflex may contribute significantly to the marked variability in the magnitude of human cardiac response to hypoxemic stress (Simon et al., 1995).

Since the Hering-Breuer reflex is relatively weak in humans, it does not normally influence respiration until lung inflation volume exceeds 1 litre (Marshall, 1994). While the Vₜ of only one older subject increased above 1 litre during hypoxia, compared to three of our younger adults, the average Vₜ of the young group was only 1063 ml (Lucy et al., 2000). Thus it seems unlikely that this mechanism alone can fully account for the marked differences in the hypoxia-induced tachycardia response between the two groups.

**The HRV Power Spectrum.** The HRV spectral characteristics of the older subjects were not altered by the hypoxic exposure. Specifically, despite hypoxia-induced increases in ventilation, blood pressure, and heart rate, it was not reflected in any change in the respiratory-related high-frequency component, the vasomotor/baroreflex-related low-frequency component of HRV, or the overall magnitude of spectral power. Conversely, the hypoxia-induced tachycardia of young subjects in our previous study was coupled with a significant loss of high-frequency harmonic and total spectral power, which had been linked to vagal withdrawal (Lucy et al., 2000). The lack of a hypoxia-related change in spectral characteristics of older individuals is perhaps not surprising, since the 10-fold reduction in resting HRV power suggested that the responsiveness of cardiac vagal efferents to modulation may be blunted. Alternatively, this lack of change might be a reflection of the minimal cardiac response to hypoxemic stress.
LIMITATIONS

The study was limited in the small number of subjects studied, particularly given the mixed gender (2 M, 4 F) of the sample, which further differed in composition (3 M, 3 F) from the younger cohort (Lucy et al., 2000) used in part as a comparator to evaluate the significance of age-related changes in cardiac function. While increased total spectral power of supine resting HRV has been noted in young women compared to young men, no significant difference was found in the PNS indicator (Gregoire et al., 1996). Similarly, despite lower resting heart rates in young men compared to young women, gender differences in long-term recordings of HRV have been reported for the jointly SNS- and PNS-mediated low-frequency harmonic power, but not the solely PNS-mediated high-frequency harmonic power (Stein et al., 1997). On the other hand, HRV indices have been found to be similar in men and women of roughly the same age (64–76 yrs) as our subjects, who likewise exhibited an age-related decline in vagal modulation of heart rate (Stein et al., 1997).

It should further be noted that the subjects in this study were a relatively young (59–72 yrs), physically active, healthy group of individuals. Consequently, the results arguably are not necessarily representative of the average older adult. Yet they may assist in delineating age-related changes in cardiac function from those secondary to the adoption of a progressively more sedentary lifestyle, or compromised health status.

Conclusion

In conclusion, the results of this study demonstrated an approximate 10-fold reduction in the total spectral power of supine resting heart rate variability in healthy older adults, when compared to a younger cohort studied previously (Lucy et al., 2000) and likewise using DEF and CGSA techniques. In addition to the previously documented loss of high- and low-frequency harmonic power, new evidence was provided in support of an age-related reduction in the power of the fractal components of HRV. The marked attenuation of hypoxia-induced tachycardia and the absence of an associated change in HRV spectral characteristics of these older adults demonstrated that cardiac responsiveness to acute hypoxemic stress and vagally mediated control are likewise depressed with advancing age, even in healthy and physically active individuals.

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