Age effects on interrelationships between lung volume and heart rate during standing

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We and others (7, 26, 27) have investigated the role of the autonomic nervous system in heart rate variability. We believe that heart rate variability provides a noninvasive probe of the age-related changes in autonomic responsiveness, which have been described in many species (11, 14–16, 28–31). To further characterize the effects of aging on autonomic mediation of heart rate, lung volume, and interrelationships between lung volume and heart rate, we analyzed spectral properties of respiration and heart rate and modeled interrelationships between respiration and heart rate in healthy young and older subjects in response to movement from the supine to standing positions.

Our results demonstrating age-related changes in heart rate, respiration, and the interrelationship between respiration and heart rate in resting and supine subjects are consistent with previous findings (26, 27). We also present new information showing age-related changes in respiration and the interrelationship between respiration and heart rate in response to standing. These findings suggest quantitative differences, or blunting, of individual heart rate and lung volume time series content but preservation of qualitative postural responses. However, the data also demonstrate a delay in the transfer of information between lung volume and heart rate with aging. This time delay may contribute to the increased time required for attainment of homeostasis after stressors in aged compared with younger individuals.

METHODS

Subject selection. Men and women in two age groups (young: 20–40 yr; older: > 60 yr) were recruited. They were defined as “healthy individuals” if their medical history and physical examination showed no evidence of cardiovascular, pulmonary, hepatic, or renal disease, weight was within 1 SD of ideal body weight, and routine laboratory tests, including complete blood count, chemistry tests with liver panel, urinalysis, chest X-ray, and electrocardiogram (ECG), revealed no abnormalities. A normal response during a maximal symptom-limited treadmill examination was necessary for subjects ≥ 40 yr of age (to evaluate coronary artery disease) as was a normal echocardiogram for younger subjects. Subjects were ineligible if they were smokers, had a recent illness, or were taking medications (other than aspirin, acetaminophen, birth control pills, or estrogens) or had a recent illness. Females of childbearing age had negative tests for pregnancy.

General study protocol. After an overnight fast and refraining from caffeine, subjects were admitted to the General Clinical Research Center, Moffitt Hospital of the University of California, San Francisco. Subjects were weighed, had an intravenous catheter placed in the forearm, and were placed in the supine position for at least 30 min. Continuous ECG (Hewlett-Packard 78352A bedside monitor) and lung volume (respiratory inductive plethysmograph by Respitrace) monitoring were performed throughout the experiments. At baseline, continuous 5- to 7-min segments of lung volume and R-R
interval data were collected during spontaneous respiration (Teac RD-110T PCM data recorder) sampling at a rate of 360 Hz. Subjects then stood, and after 3 min in the standing position, all measurements were repeated. All analyses were performed using Matlab System Identification and Signal Processing Toolboxes (Mathworks, Natwick, MA) on a 486DX/50 MHz PC, unless otherwise noted.

Lung volume analysis. Lung volume data were digitally recorded (Teac RD-110T recorder) from the output of the Respicratch monitor (sampling at a rate of 360 Hz), which provides calibrated outputs corresponding to rib cage and abdominal compartment volume changes associated with respiration. The data were decimated to a 4-Hz sampling rate, corresponding to a sampling interval of 0.25 s. The mean lung volumes were removed from the data, and spectral estimates were generated using fast-Fourier analysis techniques that employ a Hamming smoothing window. Analysis of lung volume data included estimation of the mean interval between breaths (respiration interval) for each individual as well as the corresponding standard deviations (SDs) representing the variability in respiration intervals, estimation of tidal volume, estimation of the mean respiratory band by observing the concentration of power around the main respiratory frequency in the spectra, the area under the curve (AUC) for the main respiratory band and low-frequency band (0.04–0.10 Hz), and the total AUC from 0.04 to 0.4 Hz in lung volume spectra.

Heart rate analysis. Heart rate data were obtained using the Teac RD-110T recorder to digitally record the R-wave detector output of the Hewlett-Packard bedside monitor, sampling at a rate of 360 Hz. Mean R-R interval lengths as well as the corresponding SDs that are time domain representations of the variability were computed. The recorded R-wave spike trains were transformed into a signal representative of the heart rate by inverting the interval between spikes and convolving with a smoothing window (3, 5), resulting in heart rate signals at a 4-Hz sampling rate, which corresponds to a 0.25-s sampling interval. Mean heart rates were computed. The means were removed from the data, and spectral estimates were generated using fast-Fourier analysis techniques that employ a Hamming smoothing window. Analysis of heart rate spectral estimates included AUC for the respiratory frequency band associated with parasympathetic mediation, AUC for the low-frequency band (0.04–0.10 Hz) associated with baroreceptor, and β-adrenergic mediation as well as total AUC from 0.04 to 0.4 Hz of heart rate spectra.

Transfer function analysis. To examine the relationship between the lung volume and the heart rate, coherence was computed as a frequency-dependent measure of correlation (27). For the estimation procedures used, a coherence above ~0.67 was considered statistically different from zero (12). The two signals were considered coherent over a specific frequency range if the coherence measure tended to be >0.67, which typically corresponds to the frequency range with larger respiratory power. Over coherent frequency ranges, the two signals were related through a linear time-invariant transfer function, giving magnitude and phase information concerning the interrelationship between lung volume and heart rate (7, 25, 27, 31). Both mean transfer function magnitudes and phases and mean coherence were computed over statistically significant ranges of high coherence.

Statistical analysis. Data were analyzed using Statview 4.01 (Abacus Concepts, Berkeley, CA). Respiratory rates, R-R intervals, and spectral measures were analyzed for age and position effects, as well as interactions, by analysis of variance (ANOVA) for repeated measures after determining that data were normally distributed (32). Transfer function magnitudes were nearly constant over the highly correlated frequency ranges of interest. ANOVA techniques were therefore applied to test the mean magnitudes over these ranges for age and position effects and interactions. Transfer function phases were also nearly constant over the highly correlated frequency ranges of interest, but because of the circular nature of the phase information, additional statistical techniques were employed. A Watson-Williams parametric two-sample test of angles was applied to test the mean phase angles for age and position effects and interactions (34).

RESULTS

Study population. Seventeen active healthy subjects (young, n = 7; old, n = 10) gave informed consent to participate in the protocol approved by the University of California, San Francisco, Committee on Human Research. The mean age of the seven subjects in the young group was 27 ± 3 yr (range 21–31 yr), the mean weight was 62.1 ± 12.2 kg (range 47.8–81.5 kg), and the mean height was 1.67 ± 8 cm (range 154–176 cm). Three were men, and four were women; two were African-American, two were Hispanic, two were Caucasian, and one was Asian. Two women were on birth control pills, and one attended a daily aspirin. The mean age of the older group was 69 ± 6 yr (range 60–79 yr), the mean weight was 72.5 ± 12.7 kg (range 54.8–100.5 kg), and the mean height was 168.1 ± 9.9 cm (range 151–180 cm). Four were men, and six were women; one was Hispanic, and nine were Caucasian. Two women were on hormone replacement therapy, two men took a daily aspirin, and one woman was on lovastatin.

Data presented do not include measurements of some parameters in several subjects. In one young subject and one old subject (ages 21 and 75 yr), data were not included due to technical problems during data collection. Heart rate data were not included for three older women (ages 72, 72, and 66 yr) because of frequent atrial premature contractions, precluding accurate estimates of spectral content. Therefore, for heart rate variability and transfer function estimates between lung volume and heart rate, n = 6 for the older group and n = 5 for the younger group; for lung volume data, n = 9 for the older group and n = 5 for the younger group.

Lung volume data. Respiratory data and statistical comparisons are presented in Table 1. Respiratory interval increased with aging, as did the respiratory interval SD. Age effects on tidal volume were not detected. Respiratory interval and tidal volume increased with standing, so that minute ventilation had little or no change in response to standing. In subjects in the supine position, minute ventilation was 5.3 ± 1.8 and 4.5 ± 1.1 l/min in younger and older subjects, respectively. In subjects in the standing position, minute ventilation was 6.4 ± 0.7 and 5.5 ± 3.0 l/min in younger and older subjects, respectively. Age effects on minute ventilation were not detected. The slight increase in minute ventilation with standing failed to reach statistical significance (P = 0.07). Age-position interactions were not detected in respiratory interval, tidal volume, or minute ventilation.
R-R data. R-R interval data and statistical comparisons are presented in Table 1. Mean R-R intervals were not affected by age. A trend for greater SD of R-R intervals in young compared with older subjects was seen, although these differences failed to reach statistical significance (P = 0.059). R-R intervals decreased from the supine to the standing position in both age groups, but decreases were significantly greater in young subjects compared with older subjects (P < 0.0001). SD of R-R interval was unaffected by position.

Lung volume spectra. Figure 1 presents individual lung volume spectra for all subjects, and lung volume spectral AUC measurements for young and old subjects in supine and standing positions are shown in Table 2. No age effects were detected for lung volume spectral AUC measures. Going from the supine to standing position increased lung volume spectral AUC in the respiratory frequency band as well as the total AUC. Increases in low-frequency lung volume spectral AUC failed to reach statistical significance (P = 0.099). No position-age interactions were detected.

Heart rate spectra. Heart rate spectra are presented in Fig. 2, and heart rate spectral AUC data are shown in Table 2. Both low and total spectral AUC were greater in young subjects compared with older subjects. Both of these measures increased in subjects going from the supine to standing position and increased more in young than in older subjects. Postural changes in spectral content at the respiratory frequency did not reach statistical significance.

Coherence. Individual coherence data between lung volume and heart rate at all frequencies are presented in Fig. 3, and mean data are shown in Table 2. Position did not affect measures of coherence in a consistent manner. Coherence over the respiratory frequency band tended to be higher for young compared with older subjects when supine (P = 0.05, unpaired t-test), but this difference was eliminated by standing.

Transfer function estimates. Lung volume-to-heart rate transfer function magnitudes over regions of higher coherence (>0.67) are presented in Fig. 4, and mean data are shown in Table 3 and Fig. 5. Magnitude tended to be larger for young subjects than for older subjects and tended to decrease in going from the supine to the standing position. Both of these trends approached but failed to reach statistical significance (P < 0.068). Phase angle between lung volume and heart rate was smaller in young than in older subjects. Although younger subjects exhibited a mean decrease in phase angle with standing, whereas the older subjects showed a mean increase in phase angle with standing, no age-position interactions were detected.

DISCUSSION

Previous studies have utilized spectral analysis of heart rate variability to elucidate autonomically medi-
It has been demonstrated that, in response to standing, high-frequency heart rate variability due to parasympathetically mediated respiratory input decreases and low-frequency heart rate variability due to baroreflex stimulated \( \beta \)-adrenergic sympathetic input increases (11, 16–28). The present study was designed to analyze the effect of aging on the relationship between lung volume and heart rate during postural maneuvers.

As seen previously (31), older age was associated with slower and more variable respiration, but mean

### Table 2. Effects of position and aging on lung volume and heart rate spectra

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<td>Position</td>
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<td>Lung volume spectra</td>
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<td>Respiratory frequency AUC, liters(^2)</td>
<td>0.006 ± 0.006</td>
<td>0.009 ± 0.003</td>
<td>0.008 ± 0.008</td>
<td>0.021 ± 0.020</td>
<td>0.028</td>
<td>0.26</td>
<td>0.22</td>
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<td>Low-frequency AUC, liters(^2)</td>
<td>0.002 ± 0.002</td>
<td>0.002 ± 0.002</td>
<td>0.005 ± 0.008</td>
<td>0.006 ± 0.006</td>
<td>0.099</td>
<td>0.17</td>
<td>0.59</td>
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<td>Total AUC, liters(^2)</td>
<td>0.007 ± 0.007</td>
<td>0.013 ± 0.004</td>
<td>0.014 ± 0.014</td>
<td>0.029 ± 0.025</td>
<td>0.008</td>
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<td>Heart rate spectra</td>
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<td>Respiratory frequency AUC, bpm(^2)</td>
<td>1.46 ± 1.09</td>
<td>0.95 ± 0.77</td>
<td>0.65 ± 0.84</td>
<td>0.57 ± 0.44</td>
<td>0.16</td>
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<td>Low-frequency AUC, bpm(^2)</td>
<td>1.23 ± 1.63</td>
<td>4.5 ± 2.3</td>
<td>0.76 ± 0.59</td>
<td>1.17 ± 0.93</td>
<td>0.001</td>
<td>0.04</td>
<td>0.03</td>
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<td>Total AUC, bpm(^2)</td>
<td>3.31 ± 2.80</td>
<td>6.25 ± 3.18</td>
<td>1.53 ± 1.24</td>
<td>1.80 ± 1.30</td>
<td>0.02</td>
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<td>Coherence between spectra</td>
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<td>Respiratory frequency</td>
<td>0.80 ± 0.12</td>
<td>0.65 ± 0.09</td>
<td>0.68 ± 0.12</td>
<td>0.63 ± 0.16</td>
<td>0.34</td>
<td>0.21</td>
<td>0.17</td>
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<td>Low frequency</td>
<td>0.26 ± 0.17</td>
<td>0.36 ± 0.10</td>
<td>0.40 ± 0.19</td>
<td>0.34 ± 0.17</td>
<td>0.81</td>
<td>0.44</td>
<td>0.26</td>
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<td>Total</td>
<td>0.51 ± 0.11</td>
<td>0.52 ± 0.06</td>
<td>0.48 ± 0.15</td>
<td>0.53 ± 0.15</td>
<td>0.39</td>
<td>0.89</td>
<td>0.65</td>
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Data are means ± SD; for lung volume, \( n = 5 \) and 9 for young and old; for heart rate and coherence, \( n = 5 \) and 6 for young and old. AUC, area under curve of power vs. frequency spectra for lung volume and heart rate; respiratory frequency, subject-dependent respiratory frequency band; low frequency, 0.04–0.12 Hz; total, 0.04–0.40 Hz; coherence, between lung volume and heart rate over respiratory frequency band, low-frequency band, and total. bpm, Beats/min.

Fig. 2. Heart rate spectra for young (A) and older (B) subjects in supine (solid lines) and standing (dotted lines) positions. At low frequencies, spectral content is larger in standing position compared with supine. Spectral content also tends to be larger for younger than for older subjects. bpm, Beats/min.

Fig. 3. Lung volume-to-heart rate coherence for 5 young (A) and 6 older (B) subjects in supine (solid) and standing (dotted) positions. Coherence tends to be higher over main respiratory frequency band.
Tidal volume was not significantly altered by age. A number of potential mechanisms could contribute to the slower mean respiratory rates in the older subjects. These include the simple mechanical explanation that longer times are needed for inflation and/or deflation of the lungs. This is supported by the documented decrease in volumes per timed forced expirations seen in healthy aging (22). Other possibilities include age-related changes at the peripheral chemoreceptors, pulmonary or upper airway mechanoreceptors, the motor cortex, or the pontine pneumotaxic center leading to decreased afferent input to the medulla respiratory control center. Longer times for blood flow from the lungs to the carotid body could delay input to the respiratory center, and within the medulla, chemoreceptors could respond less rapidly to changes in CO₂ or oxygenation. Also in agreement with previous findings (11, 14, 16, 28, 29), supine heart rate was not affected by aging, but measures of heart rate variability were greater in young than in older subjects. We have previously shown that the age-related variability in heart rate can be abolished by double autonomic pharmacological blockade with atropine and propranolol (11).

Standing was accompanied by decreased respiration rate and increased tidal volume in both young and old, suggesting that the decreased rate of respiration is compensated for by an increased tidal volume, thereby having little or no net effect on minute ventilation. Heart rate increased with standing in both age groups, with greater heart rate increases in younger compared with older subjects. Position had no statistically significant effect on time domain measures of heart rate variability, but position effects were detected in low- and high-frequency spectral content of heart rate variability. The increased low-frequency AUC in the heart rate with standing is consistent with increased baroreflex activity with standing.

There was a qualitative difference between the lung volume spectra of the young and older subjects. The lung volume spectra of the older subjects appeared more dispersed than those of the young. These differences are difficult to further characterize because of the relatively small sample size and the considerable variance.

Table 3. Effects of position and aging on lung volume to heart rate transfer function

<table>
<thead>
<tr>
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<th>Young</th>
<th>Old</th>
<th>ANOVA (P)</th>
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<tr>
<td></td>
<td>Supine</td>
<td>Standing</td>
<td>Supine</td>
</tr>
<tr>
<td>Magnitude, bpm/l</td>
<td>18 ± 15</td>
<td>8 ± 3</td>
<td>7 ± 5</td>
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<tr>
<td>Phase, °</td>
<td>18 ± 11</td>
<td>-7 ± 7</td>
<td>44 ± 17</td>
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Data are means ± SD in both supine and standing positions over subject-dependent respiratory frequency ranges; n = 5 for young and 6 for old.
tions in spectra from subject to subject. In a number of the older subjects, power was more diffusely distributed across frequencies than in younger subjects. The respiratory spectra in subjects in both the supine and standing positions were characterized by greater content in the low- and midfrequency ranges vs. confinement to the high-frequency range as was seen in the younger subjects. This observation suggests age-related uncoupling of lung volume changes from respiratory rate and could reflect age-related alterations in peripheral or central chemoreceptor, proprioceptor, temperature, brain stem, metabolic, or lung stretch receptor function. It is in agreement with reports of greater periodic breathing in healthy elderly compared with younger subjects (9, 17, 21). Our prior work showing the lack of autonomic pharmacological blockade with atropine and propranolol to alter lung volume spectra in young or older subjects (31) suggests that pathways involving muscarinic or β-adrenergic feedback are less likely to be responsible for these differences. The lung volume spectral AUC increased with standing at all frequencies in both age groups.

We and others (11, 16, 28) have previously demonstrated the relationship between position and heart rate variability as a function of age. Heart rate variability decreases with age, and heart rate spectral AUC decreases with age in all frequency bands (11, 28). In the current study, low- and total frequency content were significantly affected by age, and age-position interactions were detected for these measures of heart rate variability. Standing also increased low-frequency and total AUC. Age-related differences in response to postural maneuvers could possibly be attributed to age-related alterations in baroreflex and/or autonomic nervous system activity. We believe that the failure to reach statistical significance in age- and position-related differences in heart rate spectral AUC at the respiratory frequency is due to the small sample size and large intersubject variability in this study.

Our main objective was to determine whether age affected relationships between lung volume and heart rate as a function of posture. As a frequency-dependent measure of correlation, we computed coherence between lung volume and heart rate, as previously described (31). As anticipated, coherence tended to be higher for the main respiratory frequency band compared with other frequencies. This was true for both the supine and standing position despite the tendency for increased lung volume spectral content at lower frequencies with standing.

As in our previous study (31), we restricted the analysis of transfer function magnitude and phase to the frequency band over which high coherence was observed. Because of this restriction, analyses were confined to the respiratory or vagally mediated frequency range. Transfer functions were qualitatively similar for young and old but tended to decrease in magnitude with age and in going from the supine to standing position. The decrease in response to standing suggests less parasympathetically mediated respiratory input in the standing compared with supine position. The decrease in magnitude with aging can possibly be attributed to age-related decreases in vagal modulation of heart rate as previously suggested (11, 14, 16, 23, 28, 33).

The analysis of transfer function phase was also restricted to the same frequency bands. Near-synchronous relationships have been reported between lung volume and heart rate in young subjects (26, 31), and slightly more delayed relationships have been reported for older subjects (31). The mean phase angle in younger subjects was significantly less than for older subjects, indicating increased time required for responses in older subjects to reflex stimulation. Standing decreased the phase angle in younger subjects, indicating an even more synchronous relationship between lung volume and heart rate in the standing state. In contrast, mean phase angle increased in older subjects. Although this possible age-position interaction for phase angle did not reach statistical significance, the lack of a decrease in mean phase angle in older subjects suggests that aging may be accompanied by fixed time delays between lung volume and heart rate information that cannot be altered by standing or mild postural stimuli.

Our study has a number of limitations. The small sample size may have led to type II statistical errors in conclusions regarding several parameters in which trends were seen. However, in general the age-related and postural effect trends were apparent. Post hoc power calculations for heart rate spectral AUC in the respiratory frequency band indicate that a sample size of 30 for each age group would reduce the probability of a type II error of detecting an age-related difference of 0.64 bpm^2/Hz (51%) to 0.20 (α = 0.05, β = 0.2), but that a sample size of ~60 would be needed to reduce the probability of a type II error in detecting a position-related difference of 0.28 bpm^2/Hz (23%) to 0.20 (α = 0.05, β = 0.2). Post hoc power calculations for transfer function magnitude indicate that a sample size between 25 and 35 for each age group would reduce the probability of a type II error in detecting a position-related difference of 5.8 bpm/l (60%) because of the large intersubject variability of these measures. With visual inspection, however, age-related differences are suggested. Post hoc power calculations for age effects on low-frequency lung volume spectral AUC indicate that for the sample size used, a type II error in failing to detect an age-related difference of 0.0044 l^2/Hz (340%) was unlikely (α = 0.05, β = 0.1).

In conclusion, we found age-related differences in respiration and respiratory variability in healthy nonmedicated subjects. Standing also significantly affected respiration but not respiratory variability. Subjects from both age groups tended to breathe more rapidly in the supine compared with standing position. Heart rate variability with standing showed increased variability associated with sympathetically mediated low-fre-
quency baroreflex influences. The effects of standing showed age-related differences, suggesting that both parasympathetic and sympathetic mediation changes with aging. Although magnitude of the transfer function between lung volume and heart rate showed a decreasing trend with age in both positions and with standing for both age groups, more marked age and posture effects were seen for the time required for transfer of information from lung volume to heart rate as measured by the transfer function phase.

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