Selective reductions of cardiac autonomic responses to light bicycle exercise with aging in healthy humans

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Received 22 July 2003; received in revised form 13 October 2003; accepted 21 October 2003

Abstract

We examined on 56 (age 38 ± 2 [range: 16–60] years) healthy subjects the effects of aging on cardiovascular autonomic responses to progressive supine bicycle exercise of light intensity. Autoregressive spectral analysis of RR interval and systolic arterial pressure (SAP) variabilities provided measures of the exercise-induced changes in baroreflex gain (by index $a$) and in sympathetic and vagal modulation of the SA node (by the normalized low [LF] and high frequency [HF] component of RR interval variability, respectively), as well as of changes in sympathetic vasomotor control (LFSAP). For each hemodynamic and autonomic variable, the gain of the response was expressed both as individual step increments, and as the slope of the linear regression of the sequential data points from rest and during the three steps of exercise. Age resulted significantly correlated to changes in spectral derived markers of SA modulation (LFRR,H FRR and index $a$). Conversely, no significant relationships were found with changes in RR interval, in SAP and indices of vascular regulation (LFSAP). In addition, exercise-induced changes in indices of SA node regulation were more evident in the youngest tertile (age 25 ± 1 years), compared to the oldest tertile (age 52 ± 1 years). In conclusion, we have observed that aging progressively and selectively reduces the cardiac autonomic excitatory response to light exercise, while hemodynamic and vascular responsiveness are maintained.

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Keywords: Sympathetic nervous system; Baroreflex; Heart rate variability; Computer analysis

1. Introduction

While the concept that basal sympathetic activity increases with aging has gained a large consensus (Folkow and Svanborg, 1993), the modification in the autonomic adjustments to dynamic exercise which might occur with age are in contrast still debated. First, plasma catecholamine determinations during maximal and submaximal dynamic exercise provided inconsistent results, as the changes observed in older compared to young humans were reported either greater (Fleg et al., 1985; Taylor et al., 1992) or similar (Esler et al., 1995; Kastello et al., 1993; Mazzeo et al., 1997) or smaller (Jensen et al., 1994; Kohrt et al., 1993). Second, studies estimating total body and regional norepinephrine spillover as an indicator of sympathetic nerve activity showed no significant differences in sympathetic response to dynamic exercise between young and older subjects (Esler et al., 1995; Mazzeo et al., 1997). More recently, Tulppo et al. (1998) assessed the effects of age on vagal modulation of heart rate in resting condition and during dynamic exercise, by means of the RR interval variability using Poincaré plots. The authors reported a basal age-related difference in vagal modulation diminishing along with a progressive increase in workload, but indicators of sympathetic modulation were not provided. Some of the observed discrepancies might depend upon technical reasons, such as different type of exercise (ergometric cycling or treadmill exercise), body posture (upright or supine position) and the specific methodology employed to study autonomic neural regulation.

Most previous studies (Esler et al., 1995; Fleg et al., 1985; Jensen et al., 1994; Kastello et al., 1993; Kohrt et al., 1993; Mazzeo et al., 1997; Taylor et al., 1992; Tulppo et al., 1998) have employed work loads of moderate to heavy intensity, ranging from 50% to over 70% of maximal oxygen consumption (Bouchard et al., 1994), implying elevated or extreme levels of sympathetic activation. On the contrary,
little and conflicting information is available on age-related changes in autonomic responses to exercise of light intensity (Taylor et al., 1992; Tulppo et al., 1998), corresponding to less than 50% of maximal oxygen uptake (Bouchard et al., 1994), implying a more modest increase in noradrenergic drive (Leuenberger et al., 1993; Savard et al., 1989).

Evaluating age-related autonomic responses to light-intensity exercise might have clinical, in addition to physiological, implications. Indeed, light intensity activities, such as walking for pleasure, gardening, house work, slow dancing belong to every day life in normalcy, and have been demonstrated to produce significant long-term health benefits and to lower the risk of cardiovascular events (Fletcher et al., 1996; Manson et al., 2002). Moreover, light intensity exercise represents an important component of most clinical programs of rehabilitation (American College of Sports Medicine, 2000).

Finally, mild exercise implying only a modest increase in heart rate, associated to a relatively slight reduction in the RR interval variance, permits a sound use of spectral analysis of cardiovascular variabilities (Iellamo, 2001; Iellamo et al., 1999; Lucini et al., 1995; Pagani et al., 1988; Rimoldi et al., 1992) for a continuous non-invasive evaluation of the dynamics of autonomic adjustment to exercise.

Accordingly, the specific aim of this study was to assess whether aging modifies the cardiac and vascular autonomic nervous system responses to light dynamic exercise. Autoregressive spectral analysis of RR and systolic arterial pressure (SAP) variabilities, a non-invasive technique recently validated against human muscle sympathetic nerve recordings (Pagani et al., 1997), was used to obtain indices of autonomic regulation at rest and during exercise.

2. Materials and methods

2.1. Study population

This study involved 56 (35 male and 21 female), non-obese (BMI 23.3 ± 0.4), non-smokers, normotensive (systolic arterial pressure 115 ± 2 mm Hg, diastolic arterial pressure 76 ± 1 mm Hg, heart rate 71 ± 2 beats/min) healthy subjects (age 38 ± 2 [range: 16–60] years). Health was confirmed by a medical history and a complete physical examination. No subject was on any medication or abused alcohol or coffee. No enrolled subject was highly trained or completely inactive, as resulted by means of physical activity rating (Ross and Jackson, 1990) (PA-R = 2.6 ± 0.1) and peak oxygen uptake (VO2 peak = 37 ± 1 ml/kg/min), predicted for each subject employing the method of Jackson et al. (Jackson et al., 1990).

Recordings were performed in a quiet room, with a comfortable temperature (22–24 °C), always in the same time slot (between 8:00 and 12:00 a.m.). On the day of the study, every subject was instructed to have a light breakfast, with no caffeinated beverages (coffee or tea) and to postpone lunch till after recording was completed. All subjects were instructed to attend to their usual daily activity in the hours preceding the study, and to avoid bouts of heavy physical exercise, which might produce long lasting autonomic effects (Furlan et al., 1993). All subjects had been carefully instructed about the study procedure, and all had given their consent. The local ethics committee approved this investigation, which conforms to the principles outlined in the Declaration of Helsinki.

2.2. Protocol

Each participant was connected to a two-channel telemetry system (Marazza, Monza, Italy), which provided continuous electrocardiographic and respiratory signals (obtained with a piezoelectric transducer). Arterial pressure was continuously estimated with a non-invasive device (Finapres, Ohmeda, Englewood, USA).

After a 10-min period for stabilization, a 10-min control recording was obtained while the subject was in a recumbent position. The subjects then performed three stages of exercise, at increasing intensity (EXE1 – EXE2 – EXE3). The equation used is: \( y = mx + b \), where \( y \) is the dependent variable, \( x \) is the independent variable, \( m \) is the slope and \( b \) is the intercept. \( r \) = correlation coefficient.

![Fig. 1. Representative examples of the linear regression of the sequential data points for the LF and HF components (in normalized units, nu) of RR interval variability in resting condition and during the three steps of exercise (EXE1–EXE2–EXE3). The equation used is: \( y = mx + b \), where \( y \) is the dependent variable, \( x \) is the independent variable, \( m \) is the slope and \( b \) is the intercept. \( r \) = correlation coefficient.](image-url)
position; on the horizontal bicycle, subsequently every subject performed a three-step, progressive, supine, electronically braked, bicycle exercise (Lode, Groningen, The Netherlands). Each subject was instructed to maintain a constant pedaling rate of 60 rpm during the test. The incremental work test consisted of three 4-min exercise stages. Exercise intensity was fixed at 25, 50 and 75 W for men, and 15, 30 and 45 W for women (corresponding to a nominal average of 20%, 30% and 40 ± 2% of the estimated VO₂ peak). Finally, a 10-min recovery period was considered and the last stable 3–4 min used for analysis.

Analog signals were channeled after appropriate amplification and filtering, to an analogue to digital board (Data Translation, Marlborough, MA, USA), inserted into a PC (Compaq, Houston, TX, USA). During experimental sessions continuous acquisition at 300 samples/s per channel was performed. Data stored on the hard disk were subsequently processed off-line and saved on back up digital tape.

2.3. Data analysis

2.3.1. Spectral analysis (Malliani et al., 1991; Pagani et al., 1986; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996)

From the ECG signal a continuous RR interval series (i.e., tachogram) was initially obtained, with the peak of the R wave as the fiducial point. Tachogram sections, of adequate length and stationarity, are used to calculate simple statistics and the best autoregressive estimate of the power spectral density. The power and frequency of every spectral component are computed both in absolute (i.e., [s²]) and normalized units (i.e., [nu]) (Malliani et al., 1991; Pagani et al., 1986). Normalized units are obtained by dividing the absolute power of a given high frequency (HF) or low frequency (LF) component by total power (i.e., variance) after having subtracted from it the power of the component with a center frequency near 0 Hz (less than 0.03 Hz, i.e.,

Fig. 2. (a) Representative example of RR interval, SAP and respiratory (RESP) time series. The continuous tracings refer (in sequence) to rest, three steps of exercise (EXE1–EXE2–EXE3) and recovery period (see Section 2). X-axis represents heart beat number. AU = arbitrary units. (b) Representative example (from the same subject of Fig. 2a) of spectral analysis of RR interval, systolic arterial pressure and respiratory variability in resting condition, during three steps of exercise and in recovery period. X-axis represents frequency, expressed in hertz. Other abbreviations as in Fig. 2a.
VLF) and multiplying this ratio by 100. In this study, spectral power of RR interval variability will be presented, for simplicity, only in normalized units. Low and high frequency spectral component of RR interval variability and their ratio (LF/HF) have been proposed as markers of autonomic modulation of the SA node (Malliani et al., 1991; Pagani et al., 1986). In spite of some ongoing debate about a consistent link appears to exist between the predominance of vagal, inhibitory, or sympathetic, excitatory, modulations and predominance of HF and LF oscillations, respectively. This link is best appreciated using normalized units or the LF/HF ratio (Malliani et al., 1991; Pagani et al., 1986; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). This concept has been further supported by studies in humans (Pagani et al., 1997) showing a high degree of coherence between similar LF and HF oscillations in cardiovascular and muscle sympathetic nerve activity (MSNA) across various levels of the sympatho-vagal balance.

Spectral analysis was also performed on the SAP variability, to obtain an indirect estimate of the sympathetic vasomotor modulation by way of LF SAP (Pagani et al., 1996). This concept has been further expanded by studies in humans (Pagani et al., 1997) showing a high degree of coherence between similar LF and HF oscillations in cardiovascular and muscle sympathetic nerve activity (MSNA) across various levels of the sympatho-vagal balance.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>RR (ms)</th>
<th>VARRR (ms²)</th>
<th>LFRR (nu)</th>
<th>HFRR (nu)</th>
<th>LF/HF</th>
<th>Respiratory frequency (Hz)</th>
<th>SAP (mm Hg)</th>
<th>VARSAP (mm Hg²)</th>
<th>LF SAD (mmHg²)</th>
<th>x (ms/mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>REST</td>
<td>870 ± 19</td>
<td>2308 ± 280</td>
<td>56.6 ± 2.5</td>
<td>32.9 ± 2.3</td>
<td>3.1 ± 0.5</td>
<td>0.27 ± 0.01</td>
<td>114 ± 2.4</td>
<td>19.0 ± 2.6</td>
<td>3.0 ± 0.5</td>
<td>21.5 ± 2.3</td>
</tr>
<tr>
<td>EXE1</td>
<td>680 ± 11a</td>
<td>827 ± 109a</td>
<td>67.4 ± 2.2a</td>
<td>21.3 ± 1.7a</td>
<td>6.3 ± 1.1a</td>
<td>0.37 ± 0.01a</td>
<td>132 ± 3a</td>
<td>22.1 ± 1.9</td>
<td>5.4 ± 1.2a</td>
<td>8.7 ± 0.8a</td>
</tr>
<tr>
<td>EXE2</td>
<td>613 ± 10ab</td>
<td>481 ± 54ab</td>
<td>70.9 ± 2.5a</td>
<td>18.9 ± 2.1a</td>
<td>8.7 ± 1.8a</td>
<td>0.39 ± 0.01a</td>
<td>137 ± 3a</td>
<td>29.7 ± 5.2a</td>
<td>6.5 ± 1.5a</td>
<td>5.5 ± 0.5ab</td>
</tr>
<tr>
<td>EXE3</td>
<td>552 ± 9ab</td>
<td>249 ± 26ab</td>
<td>74.1 ± 2.2a</td>
<td>14.5 ± 1.5ab</td>
<td>12.7 ± 2.0a</td>
<td>0.40 ± 0.01ab</td>
<td>145 ± 3ab</td>
<td>35.0 ± 4.8ab</td>
<td>8.6 ± 1.8a</td>
<td>3.6 ± 0.3ab</td>
</tr>
<tr>
<td>RECOVERY</td>
<td>793 ± 17abcd</td>
<td>2576 ± 412b</td>
<td>63.5 ± 2.5</td>
<td>25.1 ± 2.1ad</td>
<td>4.5 ± 0.6d</td>
<td>0.31 ± 0.01ab</td>
<td>114 ± 2bcd</td>
<td>29.5 ± 5.2a</td>
<td>4.8 ± 0.9a</td>
<td>18.1 ± 2.4bcd</td>
</tr>
</tbody>
</table>

Abbreviations: VARRR = variance of RR interval; LFRR = low frequency component of RR interval variability; HFRR = high frequency component of RR interval variability; LF/HF = ratio of LFRR to HFRR; Resp = respiratory frequency; SAP = systolic arterial pressure by Finapres; VAR SAP = variance of SAP; LF SAD = low frequency component of SAP variability; x = index alpha; nu = normalized units; a = significant contrast vs. REST; b = significant contrast vs. EXE1; c = significant contrast vs. EXE2; d = significant contrast vs. EXE3. Data are presented as mean ± S.E.

Table 2

<table>
<thead>
<tr>
<th></th>
<th>RR (ms)</th>
<th>VARRR (ms²)</th>
<th>LFRR (nu)</th>
<th>HFRR (nu)</th>
<th>LF/HF</th>
<th>SAP (mm Hg)</th>
<th>VARSAP (mm Hg²)</th>
<th>LF SAD (mmHg²)</th>
<th>x (ms/mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXE1</td>
<td>r=0.16</td>
<td>r=0.19</td>
<td>p&lt;10⁻⁶</td>
<td>p&lt;6×10⁻²</td>
<td>p&lt;4×10⁻³</td>
<td>p&lt;3×10⁻³</td>
<td>r=0.41</td>
<td>r=0.37</td>
<td>r=0.34</td>
</tr>
<tr>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EXE2</td>
<td>r=0.17</td>
<td>r=0.25</td>
<td>p&lt;10⁻⁶</td>
<td>p&lt;6×10⁻²</td>
<td>p&lt;4×10⁻³</td>
<td>p&lt;10⁻⁶</td>
<td>r=0.53</td>
<td>r=0.44</td>
<td>r=0.39</td>
</tr>
<tr>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EXE3</td>
<td>r=0.15</td>
<td>r=0.24</td>
<td>p&lt;8×10⁻²</td>
<td>p&lt;10⁻⁶</td>
<td>p&lt;8×10⁻³</td>
<td>p&lt;10⁻⁶</td>
<td>r=0.50</td>
<td>r=0.34</td>
<td>r=0.59</td>
</tr>
</tbody>
</table>

Abbreviations: difference (Δ) and ratio (Δ%) between the value in each exercise step and the value in resting conditions; VARRR = variance of RR interval; LFRR = low frequency component of RR interval variability; HFRR = high frequency component of RR interval variability; LF/HF = ratio of LF RR to HF RR; x = index alpha; r = correlation coefficient; p = significance; ns = not significant.

2.3.2. Baroreflex gain

The simultaneous analysis of arterial pressure and R–R interval variabilities permits to derive the frequency domain index α (Pagani et al., 1988), which, like the spontaneous Baroreflex slope (BRS) (Persson et al., 2001), provides a lumped measure of baroreflex gain. The index α is usually computed both in correspondence of LF and HF oscillatory components; an average index can be obtained with the formula:

\[ α = \frac{(P_{RR}/P_{SAP})LF^{1/2} + (P_{RR}/P_{SAP})HF^{1/2}}{2} \]

where \( P_{RR} \) and \( P_{SAP} \) represent the spectral power of the RR interval and of the systolic arterial pressure components, respectively. The validity of this calculation requires that the value of the coherence function between the two variability signals is, at the relevant frequencies, greater than 0.5 and the direct (i.e., non-reflexly mediated) influence of respiration on RR period variability be minimal. More complex models are required to separate the two major components of the baroreflex, i.e., the arterial and cardiopulmonary gains (Lucini et al., 2000).

Response to exercise: A simple input–output linear model was employed to obtain estimates of individual responses to exercise. For each hemodynamic (RR, SAP, respiratory frequency) and autonomic (VAR RR, LF RR, HF RR, LF/HF ratio, VAR SAP, LF SAD) index α variable the gain of the response was expressed both as individual step increments (Δ) and normalized against control (Δ%), and as the slope of the linear regression of the sequence of data points from rest and during the three steps of exercise (see examples in Fig. 1).
2.4. Statistics

Data are presented as mean ± S.E. One-way repeated measure analysis of variance (ANOVA) or Friedman repeated measure ANOVA on ranks, as appropriate, followed by individual contrasts with Tukey test, was used to estimate significance of changes between different conditions (i.e., rest, each exercise step and recovery) in the whole study population. Relationships between age and responses to exercise were computed by the Spearman correlation analysis. Finally, to better depict the influence of age, subjects were divided into three tertiles according to age: young group (age 25 ± 1 years), middle group (age 38 ± 1 years) and old group (age 52 ± 1 years). Accordingly, differences in exercise-induced changes between the three groups were assessed by two way repeated measures ANOVA on ranks, with Tukey test for multiple comparisons. Only the extreme tertiles were employed in the illustration for greater clarity. A probability level of less than 0.05 was considered significant.

3. Results

3.1. Hemodynamics

A representative example of RR interval and of systolic arterial pressure during the overall experiment is shown in Fig. 2a. As compared to resting conditions, RR interval and

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Table 3

Spearman correlation between age and responses of SAP variability and respiratory frequency to three-step, progressive, supine bicycle exercise in 56 healthy subjects

<table>
<thead>
<tr>
<th></th>
<th>SAP (mm Hg)</th>
<th>VARSAP (mm Hg²)</th>
<th>LF₅AP (mm Hg²)</th>
<th>Resp (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Δ</td>
<td>Δ%</td>
<td>Δ</td>
<td>Δ%</td>
</tr>
<tr>
<td>EXE1</td>
<td>r=0.20 ns</td>
<td>r=0.15 ns</td>
<td>r=−0.05 ns</td>
<td>r=0.02 ns</td>
</tr>
<tr>
<td>EXE2</td>
<td>r=0.05 ns</td>
<td>r=−0.04 ns</td>
<td>r=0.16 ns</td>
<td>r=0.0002 ns</td>
</tr>
<tr>
<td>EXE3</td>
<td>r=0.08 ns</td>
<td>r=−0.05 ns</td>
<td>r=0.02 ns</td>
<td>r=0.007 ns</td>
</tr>
</tbody>
</table>

Abbreviations: difference (Δ) and ratio (Δ%) between the value in each exercise step and the value in resting conditions; SAP = systolic arterial pressure by Finapres; VARSAP = variance of SAP; LF₅AP = low frequency component of SAP variability; Resp = respiratory frequency; r = correlation coefficient; ns = not significant.

Fig. 3. Relationships, computed for all 56 subjects of the study population, by means of Spearman correlation analysis, between age and the response of autonomic variables to the entire exercise, expressed as the slope of linear regression (see Section 2). VAR₅RR = variance of RR interval; α = index alpha; LF₅RR = low frequency component of RR interval variability; HF₅RR = high frequency component of RR interval variability; nu = normalized units; r = correlation coefficient; p = significance.
its variance were progressively reduced during all three stages of exercise and RR interval remained lower also during the early recovery period (Table 1).

SAP and its variance increased progressively during all three stages of exercise and SAP, but not its variance, returned rapidly to the rest values in the recovery period (Table 1).

3.2. Spectral analysis of cardiovascular variabilities

Fig. 2b shows a representative example of spectral analysis of RR interval and of SAP variabilities during the whole experimental protocol indicating a clear reduction of total power (as expressed by the area under the spectral curve) and a leftward shift of spectral distribution. Accordingly, Table 1 shows that, as compared to resting conditions, the low frequency component of RR interval variability and the LF/HF ratio appeared to be increased during all three stages of exercise, and decreased in the recovery period, returning toward the rest values. Conversely, the high frequency component followed a reciprocal change (Table 1).

Also the low frequency component of SAP variability seemed to increase during all three stages of exercise and to return toward baseline values in the early recovery period (Table 1).

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Fig. 4. Exercise-induced changes in hemodynamic and autonomic variables in the young tertile (black circle) and in the old tertile (white circle); the middle aged tertile is not depicted for clarity. \(\Delta = \) for each variable, difference between the value in each working phase and the value in resting condition; \(\text{VAR}_{RR} = \) variance of RR interval; \(\text{LF}_{RR} = \) low frequency component of RR interval variability; \(\text{HF}_{RR} = \) high frequency component of RR interval variability; \(\text{SAP} = \) systolic arterial pressure; \(\text{VAR}_{SAP} = \) variance of SAP; \(\text{LF}_{SAP} = \) low frequency component of SAP variability; \(\alpha = \) index alpha; \(\text{nu} = \) normalized units. Data are presented as mean (circle) \(\pm\) S.E. (bar); \#global \(p < 0.05\); *\(p < 0.05\) old vs. young tertile.
The index $\alpha$ fell progressively over all three exercise stages and returned rapidly to the rest values in the recovery period (Table 1).

3.3. Respiration

As compared to resting conditions, respiratory frequency increased significantly in all three exercise steps and remained still slightly elevated during the early recovery period (Table 1).

3.4. Relationship between age and responses to exercise

Tables 2 and 3 report the relationships between age and the response to the three-step, progressive exercise of each hemodynamic (RR, SAP, respiratory frequency) and autonomic (VAR$_{RR}$, LF$_{RR}$, HF$_{RR}$, LF/HF, VAR$_{SAP}$, LF$_{SAP}$, index $\alpha$) variable, expressed both as difference ($\Delta$) and as ratio ($\Delta\%$) between the value in each working phase and the value in resting conditions. In all three stages of exercise, age resulted significantly correlated to changes in spectral derived markers of SA modulation: positively correlated to both $\Delta$ and $\Delta\%$ of VAR$_{RR}$, of HF$_{RR}$ and of index $\alpha$; negatively correlated to both $\Delta$ and $\Delta\%$ of LF$_{RR}$ and of LF/HF. Conversely, no significant relationships were found between age and simple hemodynamic changes (i.e., $\Delta$ and $\Delta\%$ of RR, and of SAP), between age and indices of vascular regulation (i.e., $\Delta$ and $\Delta\%$ of VAR$_{SAP}$ and of LF$_{SAP}$), as well as between age and both $\Delta$ and $\Delta\%$ of respiratory frequency.

Fig. 3 shows synthetically the relationships between age and the whole exercise of each autonomic (VAR$_{RR}$, LF$_{RR}$, HF$_{RR}$, index $\alpha$) variable, expressed as the slope of linear regression (i.e., gain, see Section 2). As with the step-by-step analysis, age resulted positively correlated with the slope of the linear regression of VAR$_{RR}$, HF$_{RR}$ and index $\alpha$. Conversely, we observed a negative correlation between age and the slope of the regression of LF$_{RR}$. Thus, also with this approach a significant link was observed between age and reciprocal changes in vagal and sympathetic markers of SA regulation. Likewise, we found no significant relationships between age and the response to exercise of simple hemodynamic (RR, SAP) variables nor of autonomic markers of vascular modulation (VAR$_{SAP}$, LF$_{SAP}$). Changes in respiratory frequency, as well, did not appear affected by age (data not shown for simplicity).

Aging was also associated to a significant ($p<0.005$) reduction of the goodness of fit of individual regressions in the case of LF$_{RR}$ and HF$_{RR}$.

3.5. Differences in exercise-induced changes between three age groups

As graphically represented in Fig. 4, changes in indices of SA node regulation ($\Delta$VAR$_{RR}$, $\Delta$LF$_{RR}$, $\Delta$HF$_{RR}$ and $\Delta\alpha$) to gradual exercise were more evident in the young tertile compared to the old tertile (the middle aged tertile was not included for clarity). Conversely, no significant differences were observed regarding indices of SAP regulation. Similar results were obtained with responses to exercise expressed as $\Delta\%$ (data not shown for simplicity).

4. Discussion

The main and novel finding of this study is that the aging process progressively and selectively reduces the cardiac autonomic excitatory response to light bicycle exercise, while hemodynamic and autonomic vascular responsiveness are preserved. To our knowledge, this is the first study to simultaneously assess age-related cardiac and vascular neural regulation during aerobic exercise with a fully non-invasive, unobtrusive approach, thus avoiding invasive techniques or pharmacological manipulations which would alter both the baseline vagal tone (Dauchot and Gravenstein, 1971) and heart rate response to exercise (Freyschuss, 1970), as well as baroreflex functioning (Legramante et al., 1999; Lucini et al., 1994).

This study extends to an aging population prior findings (Iellamo et al., 1999; Lucini et al., 1995) of the possibility of reliably, non-invasively assessing the dynamics of autonomic adjustment to mild exercise, employing spectral analysis of cardiovascular variabilities.

As expected, graded light exercise in the entire study population induced a progressive increase in markers of sympathetic regulation, and reduction of vagal modulation of the SA node, in addition to a clear increase in markers of sympathetic vasomotor control. To interpret these dynamic changes of autonomic cardiovascular regulation, it might be useful to consider the relatively few studies that examined the effects of light exercise with direct recordings of sympathetic efferent activity in conscious animals (O’Hagan et al., 1993; Tsuchimochi et al., 2002) or with norepinephrine spillover in humans (Leuenberger et al., 1993; Savard et al., 1989). The overall picture resulting from these investigations suggests an immediate progressive increase in sympathetic drive, supporting our indirect findings.

Regarding the effects of aging a reduced heart rate response in older populations has been clearly found at moderate (Rodeheffer et al., 1984) to high (Fleg et al., 1995) levels of exercise. Work loads of moderate to heavy intensity were also used by most previous studies assessing age-related changes in autonomic responses to dynamic exercise (Esler et al., 1995; Fleg et al., 1985; Jensen et al., 1994; Kastello et al., 1993; Kohrt et al., 1993; Mazzeo et al., 1997). The few investigations evaluating autonomic responses to light exercise (Taylor et al., 1992; Tulppo et al., 1998), reported conflicting results. Moreover, these studies only focused on selected effects of exercise: either the induced increase in plasma norepinephrine levels (Taylor et al., 1992) or the reduction in the vagal component of SA regulation (Tulppo et al., 1998). No information is available on the effects of aging on exercise-induced changes in
sympathetic regulation of both RR interval and blood pressure, nor in baroreflex gain.

In the present study, we observed that the light exercise-induced changes in spectral derived markers were significantly modified with aging, while hemodynamic responses were not affected by aging.

More in detail, we found that aging progressively reduced the responses to exercise in markers of autonomic regulation of the SA node, such as RR variance, LF_{RR} and HF_{RR} (in normalized units), and index α. Conversely, changes in markers of vascular modulation, such as SAP variance and LF_{SAP} were similar at all examined ages. This divergent behavior in markers of cardiac and vascular modulation was apparent both using a simple stepwise analysis and linear regression.

These results are in keeping with previous reports of a lesser vagal withdrawal with age during isometric (Taylor et al., 1995) or dynamic (Tulppo et al., 1998) exercise, and extend those findings to light dynamic exercise. In addition, we provide evidence that aging blunts sympathetic cardiac and baroreflex responses to light exercise, whereas sympathetic vascular regulation is largely preserved. The combination of a lesser vagal withdrawal with a reduced cardiac sympathetic activation, in addition to the relatively less baroreflex inhibition during exercise in the old as compared to the young group, might explain the similar response of RR interval observed in this study and the reduced heart rate response reported for exercises of greater intensity (Rodeheffer et al., 1984; Fleg et al., 1995). This suggests a disconnection between hemodynamic and autonomic components of the response to exercise with aging.

As to the mechanisms responsible for the age-related blunted cardiac sympathetic responses to exercise, a diminution in the number of myocardial β-adrenergic receptors and/or an impaired postreceptor adrenergic responsiveness (Lakatta, 1993; White et al., 1994) may be implicated. The present study was not designed to assess this issue, but it aimed at addressing the question of whether the aging process per se modifies the autonomic nervous system response to exercise levels that are far from maximal and in the range of those that may occur commonly during daily physical activity.

Autonomic adjustments were inferred indirectly from spectral analysis of RR and arterial pressure variability, using non-invasive, non-obtrusive methodologies, easily applicable also in a clinical setting. It should be noted that the specific protocol, focusing only on the initial, light loads of the exercise response, permitted a sound use of the spectral methodology that, conversely, cannot be applied in extreme conditions, such as severe exercise (Casadei et al., 1995). The light exercise procedure, in addition, is likely to be safely applicable also in clinical settings possibly characterized by reduced coronary or cardiac reserve (American College of Sports Medicine, 2000). Accordingly, as light exercise might have important health benefit (Fletcher et al., 1996; Manson et al., 2002), present findings bear also clinical relevance.

Finally, the approach we used to assess the baroreflex control of the sinoatrial node was not designed to analyze the full stimulus-response curve of the arterial baroreflex (i.e., threshold and saturation pressure and the linear range of the reflex), as it can be obtained with the use of drug induced pressure manipulation or the neck chamber device. However, this methodological limit would not alter our results and conclusions, since arterial pressure changes during exercise were well within the normal (linear) operational range described for the arterial baroreflex (Eckberg, 1977). In addition, baroreflex gain, as estimated with the index α from spontaneous RR and SAP variability, permitted a continuous analysis throughout the experimental protocol, from rest to recovery, and always maintaining the supine position. This latter avoided the potential bias of changing vestibular inputs or hydrostatic load on arterial baroreflexes (Ray, 2000).

In conclusion, we have observed that aging progressively and selectively reduces the cardiac autonomic excitatory response to light exercise, while hemodynamic and vascular responsiveness are maintained. This non-invasive dynamic protocol could be employed to test autonomic responsiveness in other physiological and pathological cardiovascular conditions.

Acknowledgements

Partial financial support by COFIN 2001, ASI 2001 and FIRB.

References


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