Changes in Autonomic Regulation Induced by Physical Training in Mild Hypertension

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SUMMARY The adaptive effects of physical training on cardiovascular control mechanisms were studied in 11 subjects with mild hypertension. In these subjects we assessed the gain of the heart period-systolic arterial pressure relationship in the unfit and the fit state by using 1) an open loop approach, whereby the gain is expressed by the slope of the regression of heart period as a function of systolic arterial pressure, during a phenylephrine-induced pressure rise and 2) a closed loop approach with proper simplification, whereby the gain is expressed by the index $\alpha$, obtained through simultaneous spectral analysis of the spontaneous variabilities of heart period and systolic arterial pressure. Both methods indicated that training significantly increased the gain of the relationship between heart period and systolic arterial pressure at rest and reduced arterial pressure and increased heart period significantly. This gain was drastically reduced during bicycle exercise both in the unfit and fit state. In a second group of normotensive ($n = 7$; systolic pressure, $133 \pm 3$ mm Hg) and hypertensive ($n = 1$; systolic pressure, $180 \pm 10$ mm Hg) subjects undergoing 24-hour diagnostic continuous electrocardiographic and high fidelity arterial pressure monitoring, the index $\alpha$ was significantly reduced in the hypertensive group at rest. Furthermore, when analyzed continuously over the entire 24-hour period, this index underwent minute-to-minute changes with lower values during the day and higher values during the night. We propose the index $\alpha$ as a quantitative indicator of the changes in the gain of baroreceptor mechanisms occurring with physical training in mild hypertension and during a 24-hour period in ambulatory subjects. (Hypertension 12: 600-610, 1988)

KEY WORDS • baroreceptor reflex mechanisms • exercise • 24-hour direct arterial blood pressure • neural control of circulation • power spectrum analysis

PHYSICAL training induces bradycardia and a modest reduction in arterial pressure.1,2 This raises the possibility of recommending physical training as part of the nonpharmacological treatment of hypertension.1,2 The mechanisms underlying the observed cardiovascular changes are not yet understood but are likely to be quite complex; they may include metabolic, cardiovascular, and neural factors in addition to changes in skeletal muscle fiber type. Our study explored the hypothesis that training induces new operating conditions in the neural regulatory mechanisms. We compared two different methods of measuring some indices of this autonomic regulation.

Several techniques are available to detect sudden changes in sympathetic outflow in humans (e.g., the level of circulating catecholamines3 or direct electrical recording of the impulse activity from sympathetic fibers4). However, long-term adaptive changes in parasympathetic outflow, such as those produced by physical training, cannot be assessed by similar techniques. It is possible to gain some insight into vagal and sympathetic control of the heart by measuring the reflex bradycardia that results from the arterial pressure rise induced by intravenous injection of a pressor drug5; with this approach the baroreceptor reflex control of heart rate is quantified by calculating the slope of the regression of heart period (RR interval) on systolic arterial pressure (SAP) during the blood pressure rise induced by phenylephrine. A reduction in this slope occurs temporarily during physical exercise6,7 or chronically in hypertension or in older subjects8.
In the present study, carried out in a selected population of patients with mild arterial hypertension undergoing an intense physical training program, we had the opportunity of comparing the gain of the reflex bradycardia induced by i.v. injection of phenylephrine with other recently described indices obtained by power spectral analysis. It has long been known that beat-by-beat, spontaneous fluctuations of RR and arterial pressure (Figure 1) give rise to definite rhythms. We found that these rhythms can be well quantified by spectral analysis, as shown in Figure 2, and that the powers of the two major oscillations can be used as markers of short-term and long-term changes in cardiovascular neural control activities. In particular, the high frequency (HF) respiratory component (at 0.25 Hz) seems to reflect mostly vagal modulation while the power of the low frequency (LF) oscillation (0.1 Hz), although amplified by vagal activity seems mainly to provide an index of sympathetic modulation and its changes.

In the present study, we used an automatic bivariate parametric spectral analysis to obtain the gain of the relationship existing between spontaneous RR and SAP oscillations. The two methods (phenylephrine injection and spectral analysis) furnish complementary information and both suggest that important changes in the neural regulatory mechanisms are induced by physical training.

**Subjects and Methods**

**Study of the Effects of Training**

This part of the study was composed of 11 subjects (age, 32 ± 2 years; three women, eight men) with uncomplicated mild hypertension without target organ damage. They participated in a research project in the Department of Cardiologic Medicine, John Radcliffe Hospital (Oxford, UK), designed to assess the systemic arterial blood pressure-lowering effect of physical training. The study was approved by the ethics committee of the hospital and all the subjects gave informed consent. These patients were allocated to one of two groups.

In the first group (n = 7), a first hemodynamic study was performed with subjects in the unfit state, and then after a 6-month training period they were studied again. The other group of subjects (n = 4) underwent a 6-month training period before the first hemodynamic study. They were studied again after a 4-month period during which they avoided physical activity as much as possible (i.e., the "detraining" period). Thus, with this pseudo-crossover design all subjects underwent two sessions of direct arterial pressure recording.

The training period consisted of a daily routine of 22 minutes of calisthenics followed by 20 minutes of jogging at least five times a week. The training period was supervised by one of the authors (V.S.). The hemodynamic study was performed at the Oxford Center. After a light breakfast, with no coffee or alcohol then or in the previous 12 hours, the subjects, who were not taking any medication, arrived in the laboratories at about 1000. A Teflon cannula (internal diameter, 1 mm) was placed in the brachial artery of the nondominant arm by the Seldinger technique and was connected to a pressure transducer (Statham Gould, Oxnard, CA, USA). The catheter-manometer system had a frequency response flat (±5%) to at least 8 Hz, with maximum resonance at 14 Hz and the -3dB point at 26 Hz.

An indwelling catheter was also positioned in the basilar vein of the same arm for injecting phenylephrine (40–60 μg) just prior to the end of the rest and exercise periods. The electrocardiogram (ECG; lead II) was also recorded. Data were fed to a laboratory frequency-modulated tape recorder (Racal, Southampton, England) for later analysis.

After a period of equilibration, patients were studied at rest for 20 minutes. They were then asked to pedal for 10 minutes on a bicycle ergometer at 100 W work load (see Figure 1).

The subjects included in this study all had pressure recordings adequate for computer analysis and free of artifacts throughout. Only 10 subjects satisfied these criteria during exercise.

**Study of the Effects of Hypertension**

An additional group of 18 subjects, without evidence of any disease and with arterial pressure levels ranging from normotension to hypertension was used for this section of the study. These subjects were part of an ongoing study of blood pressure variability originating at the Ospedale L. Sacco (Milan, Italy). As part of the protocol, prepared in accordance with institutional guidelines, these subjects underwent a 24-hour direct high fidelity blood pressure recording that employed a miniature (diameter, 3F) catheter tip transducer (Millar, Houston, TX, USA), which was introduced into the radial artery of the non-dominant arm by the Seldinger technique. The transducer has a high degree of constancy in gain and stability and a wide
Figure 2. Example of the simultaneous computer analysis of the RR interval and systolic arterial pressure (SAP) variabilities. As explained in the text, after appropriate analog-to-digital conversion of the ECG and arterial pressure signals, the RR interval and SAP series are obtained (top and middle left panels). Then, the corresponding spectra (power spectral density [PSD]) are computed (top and middle right panels). The bottom left panel shows the cross spectrum (Cross); the bottom right panel shows the phase relationship ($\Phi$) and the squared coherence ($K^2$, curve with two major peaks).

Data Analysis

Off-line analysis was performed in Milan. Data were played back from Racal tape at real time and analog-to-digital (A/D) conversion was performed at 300 samples/sec per channel on a Minc 23 computer (Digital Equipment, Maynard, MA, USA). In the case of the 24-hour recordings, playback was performed at 64 times real time, thus allowing acquisition of the entire recording in about 22 minutes. At this speed, A/D conversion (PDP 11/24, Digital Equipment) is performed with 19,200 samples/sec per channel in order to achieve 300 samples/sec for channel real time. Spectral and cross-spectral analysis was performed using a PDP 11/24 and a VAX 750 computer (Digital Equipment). The principles of the software for data acquisitions and analysis have been described previously. Schematically (see Figure 2), the computer first calculates the interval tachogram (i.e., the series of consecutive RR intervals) as well as the systogram (i.e., the series of systolic values synchronized to the beat at the beginning of each RR interval). The length of the tachogram and systogram was usually 512 beats. From these series the computer program automatically calculates simple statistics (mean and variance) as well as the autoregressive coefficients necessary to define the estimate of the power spectral density.

An important feature of the program is that it also calculates the model that provides the best statistical estimate of the power spectrum (maximum entropy spectrum) and prints out the power and frequency of each component. Every spectral component is presented in absolute units and also in a normalized form obtained by dividing it by the total power minus any DC component. Normalized values allow comparisons among subjects when large interindividual variability exists. Only stationary (steady state) sections of recordings were analyzed. Stationarity was defined as a difference of less than 5% in the spectral components calculated in two successive 256-beat series, with the subject in a steady state. It should be pointed out that with this technique the duration of the periodical phenomena in the variability signal was measured as a function of cardiac beats rather than seconds. However, this frequency can be converted into its Hertz equivalent without producing harmonic effects by dividing it by the average RR interval. Accordingly, the units for frequency in this paper will be indicated by the abbreviation Hz. In the case of the 24-hour recordings, a recursive version of the program is used.

Assessment of the RR Interval–Systolic Arterial Pressure Relationship

As previously described, the slope of the linear regression of RR interval as a function of SAP
during the pressor rise produced by the i.v. injection of phenylephrine was computed using a Data General Eclipse 200 computer (Westborough, MA, USA). This value provides an estimate of the gain of the open loop model of the RR-SAP relationship as schematically depicted below.

\[
\begin{align*}
\begin{array}{c}
\text{s} \\
\text{t}
\end{array}
\end{align*}
\]

\[
\begin{align*}
\begin{array}{c}
H_u
\end{array}
\end{align*}
\]

According to this model \( s \) and \( t \) are intended as beat-to-beat SAP and RR duration values, respectively, \( H_u \) is the transfer function between \( s \) and \( t \). It should be noted that \( s \) and \( t \) values (small signal representation) are the difference between individual SAP (and RR interval) values and the mean of the respective series. In order to get a mathematical equation that describes the input-output relationship of the model in terms of its transfer function, it is necessary to transform the input and output signals into the frequency \( f \) domain, thus obtaining \( T(f) = H_u \cdot S(f) \) where \( T \) and \( S \) are the Fourier transforms of \( t \) and \( s \), respectively. In the particular case considered above, we have \( H_u = k \) (where \( k \) is the constant slope of the regression straight line between \( s \) and \( t \) values), and therefore the input-output relation between the RR/SAP magnitudes becomes \( T(f) = k \cdot S(f) \) or \( t = k \cdot s \).

However, changes in \( t \) could also induce changes in \( s \). For example, an increase in RR, and hence in the filling period of the heart, will tend to produce a greater stroke volume, and hence a higher SAP and aortic runoff. On the other hand, \( s \) could affect \( t \) through various neural reflexes operating with both positive and negative feedback mechanisms. To account for these effects, a closed loop model appears more appropriate (Figure 3).

The two transfer functions \( H_{st} \) and \( H_{ts} \) describe the simultaneous effect of \( t \) on \( s \) and of \( s \) on \( t \), respectively. The interactions under study are relevant to variability phenomena that are small in respect to the set point values (mean values) and are well suited to be described by linear equations, at least as a first order approximation. \( H \)'s are generally complex operators (commonly expressed under the form of gain and phase) that are functions of frequency \( f \). Two noises, \( n_t \) and \( n_s \), are also intended to describe the external inputs to the system, such as mechanical disturbances, respiration, and small adjustments by central command, to take into account all the possible sources that can cause variability of the \( t \) or \( s \) signal independently of \( s \) or \( t \), respectively.

Experimental measurement of the gain of the neural feedback from SAP to the RR period is possible in two essentially equivalent ways: 1) by forcing a change in SAP and consequently measuring the relevant variations in RR duration (this modeling technique is equivalent to the experimental increase in SAP produced by an intravenously administered vasoconstrictor agent, implying a virtually open loop at the level of \( s \)); 2) by analyzing the simultaneous variabilities of SAP and RR duration, which are actually interacting in a closed loop. Using the latter approach, it should be noted that a complete solution of the system shown in Figure 3 is impossible without additional a priori hypotheses. The problem involves the computation of \( H_u \), \( H_{st} \), \( n_t \), and \( n_s \) spectral and cross-spectral characteristics. In general, \( n_t \) and \( n_s \) are colored processes (i.e., they present power peaks in specific bands) and are correlated (i.e., they affect RR duration and SAP but not independently). These interactive effects on RR and SAP variability could otherwise be erroneously attributed to effects of the loop.

One possible way to solve this problem, as suggested by Akselrod et al. for the LF components, starts from the simplified hypothesis that all disturbances enter the system (or are generated) only at a level through \( n_t \) (let us suppose that \( n_t = 0 \)). In this way, when \( n_t \) tends to zero, it is possible to compute the transfer function of the closed loop model. Hence, it is easy to obtain the gain of \( H_u \) (i.e., its modulus \( |H_u| \)) as a function of frequency \( f \) (see also Appendix) from the power spectra \( P(f) \) of \( t \) and \( s \) following the formula below.

\[
|H_u| = \left| \frac{P_t(f)P_s(f)}{P_t(f)} \right|^{1/2}
\]

In particular, the modulus \( |H_u| \) is calculated in the two major bands: those centered at 0.1 Hz (LF) and at the respiratory frequency (HF). This parameter is indicated as \( \alpha_{LF} \) and \( \alpha_{HF} \) for LF and HF bands, respectively. Therefore, under the hypothesis discussed above, in the closed loop model the index \( \alpha_{LF} \) is the gain of the relationship between SAP variability and RR interval variability at about 0.1 Hz; \( \alpha_{HF} \) is the same index relative to the respiratory frequency. The correct interpretation of \( \alpha \) requires that there is high coherence in these bands (see also

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**Figure 3.** Schematic representation of the closed loop model of the relationship between tachogram (t) and systogram (s), with the indication of the two noises \( n_t \) and \( n_s \).
Appendix); therefore the calculation of \( \alpha \) was made after verification of a high value (>0.5) of coherence in the LF and HF bands (see Figure 2).

**Statistics**

Results are presented as means ± SE. The significance of the effects of training and exercise, as well as the difference between the changes produced by exercise in the fit and unfit states, was assessed by the two-tailed paired \( t \) test. The unpaired \( t \) test was used to assess the difference between normotensive and hypertensive subjects. Multiple correlation analysis of \( \alpha_{HF} \), \( \alpha_{LF} \), and the phenylephrine slopes in the fit and unfit states, with the training bradycardia and training hypotension, was used to assess the effects of training. A probability level below 0.05 was considered significant.21

**Results**

**Effects of Training on the Gain of the Heart Period—Systolic Arterial Pressure Relationship**

In the 11 subjects with mild hypertension, arterial pressure and heart rate, both at rest and during steady state exercise, always showed spontaneous beat-by-beat oscillations around their mean values (see Figure 1). Spectral analysis provided a quantitative assessment of their nonrandom components (Table 1; see Figure 2). Consistently, two major components were observed at ~0.1 (LF) and 0.25 (HF) Hz, respectively; the LF component had greater power in both RR and SAP variability (see Figure 2 and Table 1) than the HF (respiration-linked) component. Cross-spectral analysis indicated that only at these two frequencies was the coherence value greater than 0.5.

Physical training significantly increased the average resting heart period (RR) from 796 ± 77 to 923 ± 39 msec, thus producing a training bradycardia as well as modifying the powers of both the LF and HF components of RR variability. LF was reduced and the respiration-linked component (HF) increased; however, there was some overlap in the distribution of data. SAP was significantly reduced by 10 ± 2 from 147 ± 4 mm Hg and diastolic arterial pressure (DAP) by 7 ± 1 from 82 ± 3 mm Hg as a result of training.

Training significantly increased the gain of the RR-SAP relationship at rest (see Table 1). This effect was assessed in two ways: from the slope of the regression of the RR period during a pressure rise produced by i.v. injection of phenylephrine and by the index \( \alpha \) (i.e., by the square root of the ratio between spectral components of RR and SAP variabilities). This index was computed for both LF and HF components (see Subjects and Methods and the Appendix), and there was a significant correlation \((p < 0.001)\) between both these indices and the phenylephrine RR-SAP slopes in the population studied (Figure 4). Thus, the phenylephrine slope and both the \( \alpha_{LF} \) and \( \alpha_{HF} \) at rest were significantly greater after physical training (see Table 1). Furthermore, for both \( \alpha_{LF} (r = 0.82) \) and \( \alpha_{HF} (r = 0.80) \) this increase was positively correlated with the attendant increase in resting RR. On the other hand, the magnitude of the fall in arterial pressure with training was not significantly correlated with either the changes in \( \alpha \) or the phenylephrine slope.

During 100 W bicycle exercise (Table 2), the RR interval was reduced significantly: by 274 ± 23 msec in the untrained state and by 372 ± 31 msec in the trained state; training significantly reduced the a HF, a LF, correlation analysis of

<p>| Table 1. Effects of Training on RR and Arterial Pressure Variabilities at Rest in 11 Subjects with Mild Hypertension |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Group</th>
<th>Slope (msec/mm Hg)</th>
<th>( \alpha_{LF} )</th>
<th>( \phi ) (sec)</th>
<th>( \phi ) (degrees)</th>
<th>( \alpha_{HF} )</th>
<th>( \phi ) (sec)</th>
<th>( \phi ) (degrees)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untrained</td>
<td>14.7±2.5</td>
<td>10.4±1.3</td>
<td>2.7±0.2</td>
<td>-95±3</td>
<td>12.2±0.7</td>
<td>0.53±0.10</td>
<td>-50±9</td>
</tr>
<tr>
<td>Trained</td>
<td>19.5±2.7*</td>
<td>15.4±3.0*</td>
<td>3.3±0.3</td>
<td>-104±7</td>
<td>21.5±3.2*</td>
<td>0.38±0.04</td>
<td>-36±3</td>
</tr>
<tr>
<td>RR (interval msec)</td>
<td>796±27</td>
<td>1831±270</td>
<td>65±2</td>
<td>0.11±0.01</td>
<td>24±2</td>
<td>0.28±0.01</td>
<td></td>
</tr>
<tr>
<td>Untrained</td>
<td>923±39*</td>
<td>5465±1853</td>
<td>57±3*</td>
<td>0.10±0.01</td>
<td>31±3*</td>
<td>0.27±0.01</td>
<td></td>
</tr>
<tr>
<td>Trained</td>
<td>147±4</td>
<td>19±3</td>
<td>7.4±1.5</td>
<td>0.10±0.01</td>
<td>1.6±0.3</td>
<td>0.28±0.01</td>
<td></td>
</tr>
<tr>
<td>SAP (mm Hg)</td>
<td>138±3*</td>
<td>18±2</td>
<td>6.1±0.9</td>
<td>0.09±0.01</td>
<td>1.6±0.3</td>
<td>0.27±0.01</td>
<td></td>
</tr>
<tr>
<td>DAP (mm Hg)</td>
<td>82±3</td>
<td>12±2</td>
<td>5.7±0.9</td>
<td>0.10±0.01</td>
<td>0.6±0.1</td>
<td>0.28±0.01</td>
<td></td>
</tr>
<tr>
<td>Values are means ± SE. Slope = slope of the regression of RR as a function of systolic arterial pressure (SAP) during the pressure rise produced by i.v. injection of phenylephrine; ( \alpha_{LF}, \alpha_{HF} ) = gain of the RR-SAP relationship, closed-loop model; ( \phi ) = phase angle of the cross spectrum between RR and SAP variability. The negative sign indicates that pressure oscillations lead RR interval oscillations. LF = low frequency component; HF = high frequency component; ( nu ) = normalized units; DAP = diastolic arterial pressure. *( p &lt; 0.05 ) compared with untrained value.</td>
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</table>
trained state. The variance of RR was drastically reduced by exercise both before and after training to 640 ± 142 and 828 ± 252 msec², respectively. In the fit state, the LF component of RR variability increased by 22 ± 4 normalized units from the value observed at rest (Figure 5).

During exercise in the unfit state, SAP and DAP increased significantly (by 27 ± 4 and 6 ± 2 mm Hg), together with their total variance (by 37 ± 5 and 14 ± 2 mm Hg²), from the values observed at rest. Furthermore, the LF component of both SAP and DAP variability was markedly augmented during exercise: by 11 ± 3 and 5 ± 2 mm Hg², respectively.

In the trained state, similar changes in SAP and DAP (29 ± 4 and 4 ± 1 mm Hg, respectively) were observed during exercise; however the increases in the LF component of both SAP and DAP (22 ± 6 and 11 ± 3 mm Hg²) were more evident than in the unfit state.

Finally, 100 W bicycle exercise in the unfit state drastically reduced from the resting values the phenylephrine slope (by 12 ± 3 msec/mm Hg) as well as $\alpha_{LF}$ and $\alpha_{HF}$ (by 8 ± 1 and 9 ± 1 msec/mm Hg, respectively). Similar changes were observed in the fit state (i.e., the slope was reduced by 17 ± 5 msec/mm Hg, $\alpha_{LF}$ by 13 ± 3 msec/mm Hg, and $\alpha_{HF}$ by 19 ± 3 msec/mm Hg).

**Cross-spectral analysis** allowed a quantification of the phase angle between RR and SAP beat-by-beat variabilities. At rest (see Figure 2), there was a lag of about 50 degrees, corresponding to 0.5 seconds, at the respiratory frequency, with pressure leading. The lag was greater in the case of the LF component (i.e., about 100 degrees corresponding to 5 seconds).

<table>
<thead>
<tr>
<th>Group</th>
<th>Slope (msec/mm Hg)</th>
<th>$\alpha_{LF}$ (msec/mm Hg)</th>
<th>$\Phi$ (sec)</th>
<th>$\Phi$ (degrees)</th>
<th>$\alpha_{HF}$ (msec/mm Hg)</th>
<th>$\Phi$ (sec)</th>
<th>$\Phi$ (degrees)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Untrained</strong></td>
<td>2.8±0.6</td>
<td>1.8±0.6</td>
<td>2.8±0.3</td>
<td>$-97±11$</td>
<td>2.2±0.5</td>
<td>0.6±0.1</td>
<td>$-72±13$</td>
</tr>
<tr>
<td></td>
<td>2.6±0.5</td>
<td>2.0±0.4</td>
<td>3.4±0.4</td>
<td>$-108±8$</td>
<td>2.8±0.6</td>
<td>0.5±0.1</td>
<td>$-77±15$</td>
</tr>
<tr>
<td><strong>Trained</strong></td>
<td>526±35</td>
<td>640±142</td>
<td>69±8</td>
<td>0.11±0.01</td>
<td>23±4</td>
<td>0.34±0.02</td>
<td>0.36±0.03</td>
</tr>
<tr>
<td></td>
<td>555±26</td>
<td>828±252</td>
<td>77±6</td>
<td>0.11±0.01</td>
<td>19±6</td>
<td>0.36±0.02</td>
<td></td>
</tr>
<tr>
<td><strong>Untrained</strong></td>
<td>177±5</td>
<td>56±6</td>
<td>19±3</td>
<td>0.10±0.01</td>
<td>6±1</td>
<td>0.34±0.02</td>
<td></td>
</tr>
<tr>
<td></td>
<td>167±6</td>
<td>66±11</td>
<td>29±5*</td>
<td>0.10±0.01</td>
<td>6±1</td>
<td>0.36±0.02</td>
<td></td>
</tr>
<tr>
<td><strong>Trained</strong></td>
<td>86±3*</td>
<td>28±4</td>
<td>11±2</td>
<td>0.10±0.01</td>
<td>3±0.4</td>
<td>0.34±0.02</td>
<td></td>
</tr>
<tr>
<td></td>
<td>78±3</td>
<td>29±5</td>
<td>13±3</td>
<td>0.10±0.01</td>
<td>2±0.4</td>
<td>0.36±0.02</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SE. Slope = slope of the regression of RR as a function of systolic arterial pressure (SAP) during the pressure rise produced by i.v. injection of phenylephrine; $\alpha_{LF}$, $\alpha_{HF}$ = gain of the RR-SAP relationship, closed-loop model; $\Phi$ = phase angle of the cross spectrum between RR and SAP variability. The negative sign indicates that pressure oscillations lead RR interval oscillations. LF = low frequency component; HF = high frequency component; nu = normalized units; DAP = diastolic arterial pressure.

*p < 0.05 compared with untrained value.
FIGURE 5. Spectral analysis of simultaneous RR (top panels) and systolic arterial pressure (bottom panels) variabilities in a trained subject, at rest and during exercise (inset in lower left panel: X10 magnification of amplitude). Note the marked predominance of the low frequency component in both spectra during exercise.

to 3 seconds). This lag was not significantly modified by exercise or by training.

Day-Night Variations in RR-SAP Relationship

The short-term changes in the gain of the relationship between the RR period and SAP, as reflected by both $\alpha_{LF}$ and $\alpha_{HF}$, were assessed from continuous recordings of ECG and high fidelity arterial pressure for 24 hours in six ambulatory Milan subjects (Table 3). Figure 6 illustrates this analysis. The well known day-night differences in RR and SAP can easily be appreciated, with maximum RR and minimum pressure occurring during the night hours. Similarly, both $\alpha_{LF}$ and $\alpha_{HF}$ demonstrate higher values during the night and lower values during the waking hours. The slow trends in day-night oscillations can be well represented by hourly averages, as shown in Figure 6 (right panels). However, only a continuous representation of the data throughout the recording period can depict the fast oscillations that are superimposed on the slow day-night changes (see Figure 6, left panels).

RR-SAP Relationship in Normotensive and Hypertensive Subjects at Rest

In the nine hypertensive subjects SAP and variance were greater than in the nine controls, while the difference in RR interval and variance was not. Furthermore, in hypertensive subjects the gain of the RR-SAP relationship (i.e., $\alpha_{LF}$ and $\alpha_{HF}$) was significantly smaller (Table 4). However, the age of the normotensive subjects was lower, although not significantly, than the age of hypertensive subjects (see Table 4); thus, age may in part account for the differences in $\alpha_{LF}$ and $\alpha_{HF}$ that we have observed.

Discussion

In this study we employed methods based on control theory to investigate with a simplified closed loop model the relationships between heart period (RR interval) and arterial pressure. To this purpose, we assessed: 1) the gain of the RR-SAP relationship using the phenylephrine method during rest and exercise, both before and after physical training; 2) the gain of the RR-SAP relationship using the index $\alpha$ obtained, under the same conditions, with simultaneous spectral analysis of RR and SAP variabilities. Furthermore we assessed continuous variability of the index $\alpha$ through the analysis of 24-hour, direct high fidelity arterial pressure recordings in ambulatory patients as well as the difference between normotensive and hypertensive subjects at rest.

RR-SAP Relationship

In this study the RR-SAP relationship was evaluated in two ways. First, we calculated the slope of the regression of RR intervals as a function of SAP during the pressor rise produced by an i.v. bolus injection of phenylephrine. This approach, developed and tested at the Oxford Center since 1969 has the advantage of requiring only a simple linear relationship between the two variables (i.e., RR period and SAP). According to this technique, the slope of the regression provides an index of the gain of the reflex arc, the afferent limb from the baroreceptors, projecting to the medulla, and the efferent limbs in both the cardiac vagal and sympathetic nerves. This approach revealed that the gain of the baroreceptor reflex control of heart rate was affected by a variety of pathophysiological situations. Myocardial infarction, hypertension, exercise, and sympathetic activation all reduce, while sleep increases, the gain of the relationship.

Table 3. 24-Hour Changes in Arterial Pressure, Pulse Interval, and $\alpha$ Values in Six Ambulatory Subjects

<table>
<thead>
<tr>
<th>Measured values</th>
<th>Systolic (mm Hg)</th>
<th>Mean (mm Hg)</th>
<th>Diastolic (mm Hg)</th>
<th>RR interval (msec)</th>
<th>$\alpha_{LF}$ (msec/mm Hg)</th>
<th>$\alpha_{HF}$ (msec/mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average</td>
<td>138±3</td>
<td>108±3</td>
<td>86±4</td>
<td>791±21</td>
<td>7.9±1.5</td>
<td>8.4±1.3</td>
</tr>
<tr>
<td>Variance*</td>
<td>139±21</td>
<td>75±10</td>
<td>56±9</td>
<td>16921±4473</td>
<td>53.6±20.8</td>
<td>45.3±13.4</td>
</tr>
<tr>
<td>Maximum</td>
<td>162±5</td>
<td>122±4</td>
<td>99±5</td>
<td>1040±55</td>
<td>28.6±6.5</td>
<td>22.5±5.1</td>
</tr>
<tr>
<td>Minimum</td>
<td>123±3</td>
<td>97±3</td>
<td>76±5</td>
<td>525±31</td>
<td>2.3±0.3</td>
<td>3.2±0.4</td>
</tr>
</tbody>
</table>

Values are means ± SE. LF = low frequency; HF = high frequency; $\alpha_{LF}$, $\alpha_{HF}$ = gain of the RR-systolic arterial pressure relationship, closed loop model.

*Variance units = SD$^2$. 
reported with physical training in both conscious dogs and patients trained after a prior myocardial infarction.

Experimental evidence indicates that other factors modify the gain of this reflex mechanism and should be included in the analysis of the RR-SAP relationship (e.g., the central command and the role played by other sensory inputs, such as that subserved by the cardiovascular sympathetic afferent fibers). An additional problem in the assessment of RR-SAP relationship is provided by the mechanical effects of changes in the RR interval on the following SAP value. Therefore, a closed loop model, as already suggested by Akselrod et al., seems more appropriate to describe the complex interaction between beat-by-beat changes in RR (i.e., the tachogram) and SAP (i.e., the systogram; see Subjects and Methods and the Appendix). Hence, we employed an approach to the study of the RR-SAP relationship that is based on the analysis of beat-by-beat spontaneous changes in RR and SAP and does not require a disturbance in the pressure from outside the system such as that produced by i.v. administration of a pressor drug.

This problem has also been addressed by others, although with different methods. De Boer et al., using stationary recordings of several minutes, computed the regression of the difference between successive RR values of SAP. The slope of that regression was considered analogous to the phenylephrine slope. Bertinieri et al. selected short episodes of 3 to 5 successive beats, in which changes in SAP and RR period were directionally similar, and computed a baroreceptorlike slope. Robbe et al. used spectral analysis to compute the modulus of the relationship between SAP and RR variability in the band 0.07 to 0.14 Hz in order to quantify the gain of the RR-SAP relationship.

In the present study a two-way autoregressive bivariate model provides an index of the gain of the closed loop relationship between tachogram and systogram as a whole. The gain of the relationship is equal to the square root of the ratio, at any given frequency, of the RR and SAP variabilities, provided the coherence value between the two signals approaches unity (see the Appendix and Subjects and Methods). In this way two indices are obtained (\( \alpha_{LF} \) and \( \alpha_{HF} \)) that indicate the gain of the relationship between tachogram and systogram, from which the possible frequency dependency is also analyzed. It is interesting to observe that essentially the same gain is observed both at LF and HF, in keeping with the simplified hypothesis of considering \( n_t \) negligible not only at the LF but also at the HF components. On the contrary, the phase difference between tachogram and systogram occurring during fast respiration-linked oscillations (HF) is smaller than that measured during the slow oscillations (LF). This finding could explain the variable latency reported for baroreceptor heart rate reflexes in humans. In the present study, both the slope and

**TABLE 4. Relationship of RR and Systolic Arterial Pressure in Normotensive and Hypertensive Subjects at Rest**

<table>
<thead>
<tr>
<th>Measured variables</th>
<th>Normotensive (n=9)</th>
<th>Hypertensive (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>41±6</td>
<td>49±3</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>7:2</td>
<td>3:6</td>
</tr>
<tr>
<td>SAP (mm Hg)</td>
<td>133±3</td>
<td>177±9*</td>
</tr>
<tr>
<td>Variance (mm Hg²)</td>
<td>20±2</td>
<td>44±8*</td>
</tr>
<tr>
<td>RR interval (msec)</td>
<td>828±37</td>
<td>799±27</td>
</tr>
<tr>
<td>Variance (msec²)</td>
<td>601±223</td>
<td>1123±189</td>
</tr>
<tr>
<td>( \alpha_{LF} ) (msec/mm Hg)</td>
<td>10±2</td>
<td>4±1*</td>
</tr>
<tr>
<td>( \Phi ) (sec)</td>
<td>-2.67±0.35</td>
<td>-2.24±0.27</td>
</tr>
<tr>
<td>( \Phi ) (degrees)</td>
<td>-90±9</td>
<td>-75±8</td>
</tr>
<tr>
<td>( \alpha_{HF} ) (msec/mm Hg)</td>
<td>9±2</td>
<td>4±1*</td>
</tr>
<tr>
<td>( \Phi ) (sec)</td>
<td>-0.37±0.29</td>
<td>-0.00±0.22</td>
</tr>
<tr>
<td>( \Phi ) (degrees)</td>
<td>-28±19</td>
<td>-22±12</td>
</tr>
</tbody>
</table>

Means are values ± SE. SAP = systolic arterial pressure. \( \alpha_{LF} \), \( \alpha_{HF} \) = gain of the RR-SAP relationship, closed loop model; \( \Phi \) = phase angle of the cross spectrum between RR and SAP variabilities. The negative sign indicates that pressure oscillations lead RR interval oscillations.

*p < 0.05, compared with normotensive subjects.
the spectral analysis method indicate that training increases the gain of the tachogram-systogram relationship while exercise drastically reduces it. Furthermore, the results obtained employing either method were significantly correlated (see Figure 4).10

The mechanisms responsible for the changes that we have observed cannot be specifically identified because of the complexity of the neural circuitry, which is composed of arterial baroreceptive, vagal and sympathetic afferent fibers, together with the integration within the central nervous system of the reflex mechanisms that they mediate (Figure 7).18

This modeling approach can only indicate a change in the net gain of the complex interaction without providing information on the changes in the tonic activity of the major constituents of the sympathovagal balance, which can instead be inferred from the study of RR and arterial pressure variabilities with spectral techniques.11 However, the present approach is useful in showing that the net gain (α) of the neural circuitry undergoes fast minute-to-minute changes, as indicated by the analysis of 24-hour recordings of ECG and direct arterial pressure in ambulatory subjects.

As to the possible hemodynamic consequences of changes in the gain of the RR-SAP relationship, we could consider the importance of higher values of α in promoting a buffering of the beat-by-beat variations in arterial pressure by way of changes in the RR period when the system is operating toward stability.32 Conversely, lower values of α, as observed in hyperension, may be important in promoting sudden changes when the system is shifting toward instability.18

Effects of Physical Training and Exercise on RR and Arterial Pressure Variabilities

In this study we have used spectral analysis to quantify the beat-by-beat oscillations present in the heart rate and arterial pressure signals, in accordance with the concept that these oscillations reflect the interaction between sympathetic and vagal control.11 The HF respiratory component of RR variability has consistently been considered to reflect modulation of vagal efferent activity on the basis of experiments on vagotomized, decerebrated cats,19 conscious dogs,13 and humans with muscarinic receptor blockade.14 In prior studies the power of the LF component has been attributed to both vagal and sympathetic mechanisms.19

We consistently correlated the presumed changes in sympathetic activity with changes in the normalized power of LF. This correlation was observed in both the RR and arterial pressure variability signals.11 However, the possibility of a vagal modulation of the power of the LF oscillations of RR variability was suggested by experiments with vagotomy12 or muscarinic receptor blockade13 in conscious dogs. The LF oscillations in arterial pressure, with a 10 second rhythmicity (i.e., Mayer waves), which have long been recognized in short-term animal experiments,15 have more recently been observed in normal humans.36 Using high fidelity blood pressure recording techniques in humans37 in various conditions, we found that Mayer waves follow the gradual increase of sympathetic activity from rest, through tilt,11 to treadmill exercise38 or the decrease of activity during sleep.37 We should note, however, that spectral markers of autonomic control cannot distinguish between efferent nerve activity and target organ response; instead, they provide a quantitative indication of the complex interaction between the various neural and nonneural components.

The major effects of physical training at rest, were represented by an increase in average RR (i.e., bradycardia), together with a significant reduction in SAP and DAP. Bradycardia at rest is a well-known consequence of physical training and has been attributed to changes in neural control of the heart,39 either an increase in vagal activity40 or a decrease in sympathetic activity,41 or else to a reduced intrinsic heart rate.42 In this group of subjects with mild hypertension spectral markers of autonomic activity controlling heart rate suggested, during resting conditions after training, a simultaneous reduction of sympathetic modulation and increase of vagal modulation, as LF was reduced and HF was increased.

Thus, a readjustment of sympathovagal balance, with an increase in the gain of baroreceptor reflex mechanisms and the attendant enhancement of vagal modulation, appears, at rest, to be the major adaptive change in neural regulation produced by physical training. As to spectral markers of sympathetic activation, LF components of RR and SAP and DAP variabilities during exercise were markedly increased in the fit state. This finding should be interpreted within the context of the substantial role played by the sympathetic nervous system in increasing cardiovascular performance with training.44,45

![Figure 7. Schematic representation of the closed loop model of the relationship between tachogram (t) and systogram (s). In this scheme the neural block contains both negative (H_{st}^-) and positive (H_{st}^+) feedback mechanisms. Thus, the gain of transfer function depends on the complex interaction between these functional components and the central command.](image-url)
Appendix

The original ECG and arterial blood pressure signals are first digitized as described in Subjects and Methods, and the discrete series t and s are obtained automatically, where t is the RR duration and s is the value of systolic blood pressure relative to the i-th cardiac cycle. The model of the signal generation mechanism is supposed to be a linear, time-invariant system, which "colors" with repeatable features a white (completely random) noise. For example, the value of t_i at the i-th cardiac cycle is

\[ t(i) = a_d(i-1) + a_d(i-2) + \ldots + a_d(i-N) + w(i) \]

That is, it is a linear combination of the t values in the N preceding cycles through N constant coefficients \((a_1 \ldots a_N)\) and the random value \(w(i)\), which is the i-th sample of the white noise \(w(i)\) and is characterized by a null mean value and \(\lambda^2\) as a variance. As already described\(^1\) it is possible to verify whether the starting autoregressive (AR) modeling hypothesis is satisfied or not by the actual signal. To this end, a test of whiteness of the prediction error is performed. The autocorrelation function of the prediction error (defined as the difference between the values of the identified model and the actual ones) is calculated and Anderson's test\(^14\) is applied (confidence limit of 5%). The calculation of \((a_1 \ldots a_N)\) coefficients and of \(\lambda^2\) is performed by a least squares method (Levinson-Durbin recursive algorithm).\(^6\) All the nonrandom information of the signal is therefore contained in these parameters and the residual information is white noise.

Parametric auto- and cross-spectral analysis of the variability signals\(^47\) may be used to estimate some parameters in the closed loop model depicted in Figure 3. The model reported, which is derived from a control theory approach, cannot be solved without additional a priori information. Therefore, modifying further a recent suggestion by Akselrod et al.,\(^19\) we have introduced the hypothesis that \(n_i = 0\) (i.e., all the external disturbances enter the loop only at s level), as described in Subjects and Methods. Thus, the relationship between the power density spectra \((P)\) of input/output signals of the block reported in Figure 3 is

\[ P_s = \left| H_{ss} \right|^2 \cdot P_t \]

Hence, the gain of the transfer function is expressed by

\[ |H_{ss}| = (P_t/P_s)^{1/2} \]

where \(H_{ss}\), \(P_s\), and \(P_t\) are functions of s. \(H_{ss}\) is computed only at those bands that present a high squared coherence value (>0.5), which usually occurs at LF and HF bands. The program of power spectral density estimation of \(P_s\) and \(P_t\) is implemented using a least squares method (Levinson-Durbin recursive algorithm).\(^6\) All the nonrandom information of the signal is therefore contained in these parameters and the residual information is white noise.

Spectral decomposition of AR processes (described in Reference 47) provides the LF and HF components of \(P_s\) and \(P_t\). From these data, the gain \(|H_{ss}|\) in the two bands is obtained with

\[ |H_{ss}\text{LF}| = (P_{s\text{LF}}/P_{s\text{HF}})^{1/2} = \alpha_{\text{LF}} \text{ and} \]

\[ |H_{ss}\text{HF}| = (P_{s\text{HF}}/P_{s\text{HF}})^{1/2} = \alpha_{\text{HF}} \]

In the present article the gain \(|H_{ss}|\) is indicated by the index \(\alpha\) (i.e., \(\alpha_{\text{LF}}\) and \(\alpha_{\text{HF}}\)).

In summary, the calculation of \(\alpha\) values requires the following steps: 1) calculation of the AR power spectrum and coherence of \(t\) and \(s\); 2) automatic determination of LF and HF components through AR spectral decomposition; and 3) calculation of the square root ratio of \(P_s\) and \(P_t\) in two major bands, provided that coherence is more than 0.5.

References

17. de Trafford JC, Lafferty K, Kitney RI, Cotton, LT, Roberts VC. Modelling of the human vasomotor control system and its application to the investigation of arterial disease. IEE Proc 1987;129:646-650


33. Chess GF, Tam RMK, Calaresu FR. Influence of cardiac neural inputs on rhythmic variations of heart period in the cat. Am J Physiol 1975;228:775-780


Changes in autonomic regulation induced by physical training in mild hypertension.
M Pagani, V Somers, R Furlan, S Dell'Orto, J Conway, G Baselli, S Cerutti, P Sleight and A Malliani

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