Effects of Hydrophilic and Lipophilic β-Blockers on Heart Rate Variability and Baroreflex Sensitivity in Normal Subjects

MARIA VITTORIA PITZALIS, FILIPPO MASTROPASQUA,* FRANCESCO MASSARI,* CINZIA FORLEO, ANDREA PASSANTINO,* ROBERTO COLOMBO,** PAOLO TOTARO,* and PAOLO RIZZON

From the Institute of Cardiology, University of Bari, Bari, the *Department of Cardiology, "Salvatore Maugeri" Foundation IRCCS, Cassano Medical Centre, Cassano, and the **Bioengineering Service, "Salvatore Maugeri" Foundation IRCCS, Veruno Medical Centre, Veruno, Italy

PITZALIS, M.V., ET AL.: Effects of Hydrophilic and Lipophilic β-Blockers on Heart Rate Variability and Baroreflex Sensitivity in Normal Subjects. To evaluate the effect of a hydrophilic and a lipophilic β-blocker on the autonomic nervous system, 20 normal subjects were studied under baseline conditions and 7 days after being randomly assigned to metoprolol (200 mg/day), nadolol (80 mg/day), and placebo. Under each condition, the time-domain parameters were analyzed by means of 24-hour ECG monitoring and the frequency-domain parameters by means of the autoregressive method using 10-minute ECGs during rest, controlled respiration, and after a head-up tilt test. The alpha index (the gain in the relationship between the RR period and systolic arterial pressure variability) was also calculated. Both nadolol and metoprolol significantly increased all of the time-domain parameters except the standard deviation of the RR intervals; they also modified the frequency-domain parameters. Both blunted the significant reduction in the high frequency (HF) component and alpha index during tilt. In normal subjects, hydrophilic and lipophilic β-blockers similarly modify the time- and frequency-domain parameters that are particularly evident when high sympathetic tone is present (during daytime and tilt). The value of the alpha index was increased by both β-blockers in the HF, but not in the low frequency band; this difference might be due to the fact that the former is a measure of the vagal component of the baroreflex control and the latter a measure of the sympathetic component. The effects of hydrophilic and lipophilic β-blockers on the time- and frequency-domain parameters of heart rate variability are similar. (PACE 1998; 21:559–567)

time-domain analysis, frequency-domain analysis, metoprolol, nadolol, controlled breathing, head-up tilt test, alpha index

Introduction

Heart rate variability (HRV) represents a promising method to study sympathovagal balance in man. Although β-adrenergic blockers are known to modify sympathovagal balance, the studies performed so far in humans have shown discordant effects of these class of drugs on HRV parameters. In fact, some authors have reported in normal subjects an increase in the low frequency (LF) component, while others did not. Such a discordant effect of β-blocker administration also has been reported as far as the high frequency (HF) component and baroreflex sensitivity are concerned.

β-blockers represent a heterogeneous class of drugs that have the one common characteristic of slowing down heart rate. They are characterized by different capacities to pass the blood-brain barrier and block brain β1 receptors. The analysis of trials in which β-blockers have been administered to postmyocardial infarction patients seems to show that the beneficial effect of reducing mortality is a characteristic of lipophilic β-blockers.
this hypothesis is supported by the results of experimental studies showing the protective role of β-blockers capable of passing the blood-brain barrier,15,16 two studies11,12 were undertaken to evaluate whether there were any differences in the modification of autonomic nervous system activity when hydrophilic or lipophilic β-blockers were administered to coronary artery disease patients. However, neither of these studies proved to be capable of detecting any significant difference between the effects of the two β-blockers.

In our opinion, to understand the effects of β-blockers on autonomic nervous system activity, they should first be analyzed in normal subjects to avoid the possibility that the effect of the disease on autonomic tone might lead to misinterpretation of the results.

The present study was designed to analyze the effects of two β-blockers characterized by a hydrophilic and a lipophilic nature on time- and frequency-domain measurements of HRV, as well as on baroreflex sensitivity in normal volunteers.

Patients and Methods

Patient Characteristics

We studied 22 normal, young volunteers (10 males and 10 females, mean age 28 ± 2 years), all of whom were screened by a full medical history, physical examination, standard laboratory tests, 12-lead ECG, 24-hour ECG monitoring, blood pressure measurements, and two-dimensional echocardiography to rule out the presence of any cardiac or noncardiac disease. None of the volunteers had an incidence of more than 200 premature supraventricular contractions or more than 100 premature ventricular contractions during the 24-hour ECG monitoring period.

Two subjects were excluded from the study because of the occurrence of dizziness (one during nadolol and one during metoprolol administration).

Study Protocol

This was a randomized, single-blind, placebo controlled, two period crossover trial. All of the subjects underwent time- and frequency-domain measurements of HRV under baseline conditions as well as during the administration of a hydrophilic β-blocker (nadolol 80 mg/day), a lipophilic β-blocker (controlled release metoprolol 200 mg/day),13 and placebo.

After baseline evaluation, the subjects were randomly assigned to nadolol or metoprolol treatment for 1 week; the second β-blocker was administered after a 14-day washout period. Placebo was given for 1 week after a washout period of 14 days following the second β-blocker administration. The time- and frequency-domain analyses were made during the last 2 days of each treatment period.

None of the subjects was a habitual cigarette smoker, and, in any case, smoking was not permitted during the 48 hours preceding the recordings.

Data Collection

The time-domain measurements were obtained by means of two-channel 24-hour ECG recordings (model 445A, Del Mar Avionics, Irvine, CA, USA), which were always begun between 8:00 a.m. and 9:00 a.m. During the day, the subjects were allowed to undertake all of their usual activities except those requiring intense physical effort; no coffee, tea, or alcohol consumption was permitted and the subjects had to go to sleep at their usual time.

The frequency-domain analyses were performed by the autoregressive method, using 10-minute ECGs and systolic blood pressure measurements recorded under three different conditions: rest; controlled respiration (16 breaths/min); and after a passive head-up tilt test at 70°.

Both the resting and controlled respiration tests were performed with the subjects in a supine position.

Time-Domain Analysis of HRV

The ECG signals obtained from the 24-hour recordings were first analyzed in term of beat classification and RR intervals by means of a Del Mar Avionics Innovator 750 Electrocardioscanner whose output, together with all of the information concerning the RR cycle and the characteristics of the beats (normal or ventricular), was recorded on a floppy disk. Premature supraventricular contractions, premature ventricular contractions, arti-
facts, and general cycle lengths that were 20% longer or shorter than the mean of the eight previous normal beats were excluded, and the final analysis was made on segments with > 95% of qualifying RR intervals. All of the recordings used for the study were independently judged to be of either good or optimal quality by two different operators.

Each file was subsequently analyzed using a computer program that measured the mean normal RR cycle length (NN), the standard deviation of normal RR intervals (SDNN), and the root mean square successive difference of normal RR intervals (rMSSD). To analyze the effect of the drugs in different situations of autonomic nervous system activity, the parameters were not only evaluated over 24 hours but also over 6-hour daytime (from 10:00 a.m. to 4:00 p.m.) and 6-hour nighttime periods (from midnight to 6:00 a.m.).

**Frequency-Domain Analysis of Heart Rate and Systolic Blood Pressure Variabilities**

The following equipment was used for the recordings: a tilt-up test table (with mattress and footrest); a conventional bedside monitor (HP 78354C) (Hewlett-Packard, Andover, MA, USA) providing a three-lead ECG signal and a respiratory signal obtained by measuring the changing impedance between two leads; a noninvasive finger blood pressure monitor based on the Penaz method (Finapres, Ohmeda); and a personal computer with signal conditioning, an antialiasing low pass filter, and a 12-bit A/D interface.

The last meal before each evaluation consisted of a light breakfast without coffee or tea, which had to have been taken at least 2 hours before the evaluations. Before the recordings, the subjects were asked to rest comfortably for at least 30 minutes. The room was quiet and care was taken to avoid repetitive external auditory or visual stimuli; the lighting was soft and the temperature was kept between 23°C and 25°C.

Continuous ECG and respiratory waveforms and blood pressure measurements were obtained throughout all of the recordings. The ECG signal was acquired at a sampling rate of 1 kHz and the other signals at a sampling rate of 250 Hz. A real-time program detected the ECG R wave signal and measured the beat-to-beat intervals and beat-to-beat systolic pressure. When present, artifacts were removed and corrected by means of linear interpolation with the previous and following beats. During controlled respiration, the subjects breathed at a rate of 16 breaths/min timed by a metronome. The passive head-up tilt test was performed by changing the body from a horizontally supine to an upright position (70°), which was maintained for 10 minutes. Spectral analyses of the heart rate and systolic arterial pressure variability signals were carried out on the time series using the autoregressive method.

The autoregressive analyses were made using the Levinson-Durbin recursive algorithm with the fixed order criterion (model order = 12). The power and frequency of every spectral component were computed and expressed in absolute values (ms² and Hz, respectively). The following components were considered: LF power, the power in the 0.04- to 0.15-Hz band; and HF power, the power in the 0.15- to 0.40-Hz band. The HF and LF values also were computed as normalized units (i.e., dividing the power of each component by total power after having subtracted the component < 0.04 Hz, and multiplied × 100), which were used to evaluate the LF/HF ratio.

The alpha index (α, the gain in the relationship between the RR period and systolic arterial pressure variabilities) was obtained by means of the simultaneous spectral analysis of RR and systolic blood pressure variabilities. This calculation was made using the square root of the ratio between RR and systolic blood pressure variability in the two major bands of LF (αLF) and HF (αHF). Coherence between the RR interval and either systolic pressure or respiratory signal variabilities were assessed by means of cross-spectral analysis. The α index was calculated only when the magnitude squared coherence (K²) between the RR and systolic blood pressure signals exceeded 0.5 (range 0–1) at LF and HF bands. Controlled respiration was considered if K² > 0.5 in a cross-correlation analysis of respiration and RR interval variabilities at the frequency of breathing.

**Statistical Analysis**

The data are expressed as mean ± SD. The absolute values of all of the frequency-domain pa-
Parameters were log transformed (ln) because of the skewed nature of their distribution. The effects of nadolol and metoprolol on each time- and frequency-domain parameter were evaluated in comparison with placebo, and the differences between the two drugs also were tested. When the data had a normal distribution of residuals, multiple between group comparisons of the mean values of each parameter were made using repeated measures analysis of variance associated with the Student-Newman-Keuls test. When the data did not have a normal distribution of residuals (i.e., LF/HF), Friedman's test associated with the Wilcoxon matched pairs test corrected for multiple comparisons was used. The differences between baseline and placebo values were tested by means of the paired data t-test (in the case of normal distribution) or the Wilcoxon matched pairs test.

A comparison was made between resting and controlled respiration or tilt values to evaluate the effect of the two conditions during the different drug administrations.

The statistical analyses were performed using the SPSS Statistical Package for Windows (1994, Version 6.0, SPSS Inc., Chicago, IL, USA). P < 0.05 was considered statistically significant.

**Results**

No statistically significant difference was found between baseline and placebo in any of the time- or frequency-domain parameters (Table I).

Both ß-blockers significantly reduced diastolic (P < 0.01) blood pressure (value during placebo 68 ± 9 mmHg; during nadolol 62 ± 12 mmHg; and during metoprolol 61 ± 99 mmHg), while neither significantly modified systolic blood pressure (value during placebo 122 ± 16 mmHg; during nadolol 109 ± 32 mmHg; and during metoprolol 111 ± 14 mmHg).

### Time-Domain Analysis

Statistical analysis showed that both nadolol and metoprolol significantly increased the values of NN and rMSSD evaluated over the 24-hour period. Neither of the drugs increased SDNN (Table II). During the daytime, both nadolol and metoprolol significantly modified NN and rMSSD, but only nadolol significantly modified SDNN (Table II). During the nighttime, only NN was significantly prolonged by the administration of nadolol. As a consequence, both ß-blockers tended to blunt the day/night difference in the values of NN and caused an inversion in the ratio of the daytime and nighttime values of SDNN and rMSSD.

### Frequency-Domain Analysis

The effects of the two ß-blockers and placebo on the frequency-domain parameters are shown in Table III.

As compared to placebo, HFnu was significantly increased by both ß-blockers under all of
P-BLOCKERS AND HEART RATE VARIABILITY

Table II.
Effect of Metoprolol and Nadolol on Time-Domain Heart Rate Variability Parameters in Comparison with Placebo

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Metoprolol</th>
<th>Nadolol</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-Hour Period</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NN (ms)</td>
<td>749.15 ± 63.44</td>
<td>902.1 ± 104.39*</td>
<td>941.85 ± 111.15*</td>
</tr>
<tr>
<td>SDNN (ms)</td>
<td>136.85 ± 33.21</td>
<td>132.95 ± 28.62</td>
<td>134.65 ± 36.07</td>
</tr>
<tr>
<td>rMSSD (ms)</td>
<td>32.1 ± 8.63</td>
<td>47.43 ± 13.06*</td>
<td>53.07 ± 17.12*</td>
</tr>
<tr>
<td>6 Hours Day Time</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NN (ms)</td>
<td>684.05 ± 57.24</td>
<td>882.65 ± 97.04*</td>
<td>902.25 ± 96.16*</td>
</tr>
<tr>
<td>SDNN (ms)</td>
<td>93.90 ± 29.87</td>
<td>122.90 ± 43.12</td>
<td>133.25 ± 66.17*</td>
</tr>
<tr>
<td>rMSSD (ms)</td>
<td>39.84 ± 14.51</td>
<td>90.18 ± 64.70*</td>
<td>115.75 ± 104.12*</td>
</tr>
<tr>
<td>6 Hours Night Time</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NN (ms)</td>
<td>920.75 ± 108.64</td>
<td>1002.25 ± 128.06</td>
<td>1060.25 ± 134.07*</td>
</tr>
<tr>
<td>SDNN (ms)</td>
<td>102.35 ± 33.26</td>
<td>114.40 ± 35.53</td>
<td>121.25 ± 36.90</td>
</tr>
<tr>
<td>rMSSD (ms)</td>
<td>62.46 ± 34.89</td>
<td>81.61 ± 40.66</td>
<td>102.03 ± 59.16</td>
</tr>
</tbody>
</table>

Values are means ± SD. NN = mean normal RR cycle length; SDNN = standard deviation of normal RR intervals; rMSSD = root mean square successive difference of normal RR intervals.

* P < 0.05 in comparison with placebo.

the studied conditions, whereas HFnu significantly increased only during tilt.

As compared to placebo, both metoprolol and nadolol significantly reduced the values of LFnu and LF/HF obtained during tilt test. The LFIn did not show any difference after either treatment.

The effects of controlled respiration and tilt on each parameter were evaluated during the administration of the two β-blockers and placebo (Table IV and Fig. 1).

There was a significant reduction in HFIn and HFnu during tilt when the subjects were administered placebo, which was blunted by the administration of either β-blocker.

During placebo administration, there also was a significant increase in LFnu and LF/HF (but not in LFIn) during tilt, a change that was once again blunted by the administration of either β-blocker.

Controlled respiration modified the various parameters studied, but its effects on controlled respiration were unaltered by the administration of either drug.

α Index

The α index was evaluated in 18 subjects, and the effects of the two β-blockers and placebo are shown in Table V. The α index was not calculated for two subjects because the K^2 between the RR and systolic pressure signals was < 0.5. In comparison with placebo, both β-blockers significantly increased the values of αHF under all of the studied conditions. There was no statistically significant change in αLF.

During placebo administration there was a significant reduction in αHF during tilt in comparison with the value observed at rest (P < 0.01). This reduction was blunted by the administration of either β-blocker.

On placebo, the values of αLF were significantly lower during tilt than during either controlled respiration or rest (P < 0.05). Both β-blockers again blunted this significant reduction.

Discussion

Time-Domain HRV

The results of the present study clearly show that both of the β-blockers tested are capable of lengthening cardiac cycles and modifying the time-domain parameters of HRV.

Neither of the drugs significantly modified 24-hour SDRR, possibly because β-blockers do not lengthen the RR cycles measured over a 24-hour period in the same way, as has already

PACE, Vol. 21 March 1998 563
shown by Cook et al.\(^2\) In particular, daytime cycles are prolonged more than nighttime cycles and, as a result, the SDRR intervals remain unchanged.\(^{20}\) This hypothesis is confirmed by our analysis of the effects of the \(\beta\)-blockers on SDRR during the daytime and nighttime hours: the daytime SDRR was prolonged by both drugs, but the difference was statistically significant only with nadolol.

**Frequency-Domain Parameters**

Although it is generally thought that \(\beta\)-blockers reduce LF power, the studies carried out so far have led to discordant results: one found that \(\beta\) blockers have no effect\(^{11}\); and the other found that they actually increase it.\(^2\) Both of these studies analyzed frequency-domain parameters over a 24-hour period but, when LF power is normalized, particularly over short-term recording,\(^3,12\) it has been shown that \(\beta\)-blockers do reduce LF. These discordancies might be due to the fact that any analysis of the absolute values of the 24-hour power of the LF component mainly depends on total variance.\(^12\) Moreover, information concerning the autonomic modulation of the heart period is lost when the frequency analysis is made over the entire 24-hour period.\(^1\)

In our study, the effects of nadolol, metoprolol, and placebo on the components of the power spectrum were analyzed over short-term recordings at rest, and then during controlled respiration and during a passive head-up tilt, the latter two being situations capable of changing the sympathovagal balance in opposite directions.\(^3,21\) Moreover, controlled respiration and tilt represent the conditions characterized by the highest repro-

### Table III.

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Metoprolol</th>
<th>Nadolol</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HFnu (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>34.1 ± 21.77</td>
<td>48.29 ± 22.83</td>
<td>44.72 ± 26.03</td>
</tr>
<tr>
<td>CR</td>
<td>59.38 ± 16.25</td>
<td>67.23 ± 15.76</td>
<td>69.12 ± 14.89*</td>
</tr>
<tr>
<td>Tilt</td>
<td>18.95 ± 12.95</td>
<td>41.69 ± 22.73*</td>
<td>38.44 ± 20.30*</td>
</tr>
<tr>
<td><strong>InHF (ms(^2))</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>5.92 ± 0.93</td>
<td>6.69 ± 1.2*</td>
<td>6.83 ± 1.11*</td>
</tr>
<tr>
<td>CR</td>
<td>6.32 ± 1.12</td>
<td>7.18 ± 1.20*</td>
<td>7.37 ± 1.08*</td>
</tr>
<tr>
<td>Tilt</td>
<td>4.87 ± 1.12</td>
<td>6.12 ± 1.40*</td>
<td>6.05 ± 1.32*</td>
</tr>
<tr>
<td><strong>LFnu (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>49.62 ± 22.52</td>
<td>35.42 ± 21.07</td>
<td>35.87 ± 22.47</td>
</tr>
<tr>
<td>CR</td>
<td>31.52 ± 16.45</td>
<td>21.31 ± 12.90*</td>
<td>18.61 ± 11.56*</td>
</tr>
<tr>
<td>Tilt</td>
<td>68.28 ± 15.72</td>
<td>48.36 ± 22.80*</td>
<td>44.12 ± 21.51*</td>
</tr>
<tr>
<td><strong>InLF (ms(^2))</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>6.49 ± 1.16</td>
<td>6.38 ± 1.09</td>
<td>6.62 ± 1.24</td>
</tr>
<tr>
<td>CR</td>
<td>5.57 ± 0.91</td>
<td>5.85 ± 1.18</td>
<td>5.9 ± 0.91</td>
</tr>
<tr>
<td>Tilt</td>
<td>6.50 ± 0.97</td>
<td>5.99 ± 2.32</td>
<td>6.17 ± 1.16</td>
</tr>
<tr>
<td><strong>LF/HF</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>3.86 ± 5.28</td>
<td>1.94 ± 3.53</td>
<td>1.92 ± 3</td>
</tr>
<tr>
<td>CR</td>
<td>0.66 ± 0.55</td>
<td>0.39 ± 0.37</td>
<td>0.31 ± 0.27*</td>
</tr>
<tr>
<td>Tilt</td>
<td>9.55 ± 11.56</td>
<td>2.13 ± 2.34*</td>
<td>1.85 ± 1.74*</td>
</tr>
</tbody>
</table>

Values are means ± SD. InHF = high frequency power computed as natural log value; HFnu = high frequency power computed as normalized units; InLF = low frequency power computed as natural log value; LFnu = low frequency power computed as normalized units; LF/HF = ratio of low to high frequency power; CR = controlled respiration; Tilt = head-up tilt test.

\(^*\) P < 0.05 in comparison with placebo.


**Table IV.**

Effects of Metoprolol, Nadolol, and Placebo on the Changes Occurring in Each Frequency-Domain Parameter During Both Controlled Respiration and Tilt

<table>
<thead>
<tr>
<th></th>
<th>InHF (ms²)</th>
<th>HF cf (Hz)</th>
<th>InLF (ms²)</th>
<th>LF cf (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Placebo</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>5.92 ± 0.93</td>
<td>0.26 ± 0.05</td>
<td>6.49 ± 1.16</td>
<td>0.10 ± 0.01</td>
</tr>
<tr>
<td>CR</td>
<td>6.32 ± 1.12</td>
<td>0.26 ± 0.01</td>
<td>5.57 ± 0.91*</td>
<td>0.10 ± 0.01</td>
</tr>
<tr>
<td>Tilt</td>
<td>4.87 ± 1.12*†</td>
<td>0.26 ± 0.04</td>
<td>6.50 ± 0.97†</td>
<td>0.09 ± 0.02</td>
</tr>
<tr>
<td><strong>Metoprolol</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>6.69 ± 1.2</td>
<td>0.27 ± 0.04</td>
<td>6.38 ± 1.09</td>
<td>0.10 ± 0.01</td>
</tr>
<tr>
<td>CR</td>
<td>7.18 ± 1.20</td>
<td>0.27 ± 0.01</td>
<td>5.85 ± 1.18</td>
<td>0.09 ± 0.02</td>
</tr>
<tr>
<td>Tilt</td>
<td>6.12 ± 1.40†</td>
<td>0.26 ± 0.04</td>
<td>5.99 ± 2.32</td>
<td>0.10 ± 0.01</td>
</tr>
<tr>
<td><strong>Nadolol</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>6.83 ± 1.11</td>
<td>0.24 ± 0.03</td>
<td>6.63 ± 1.24</td>
<td>0.10 ± 0.02</td>
</tr>
<tr>
<td>CR</td>
<td>7.37 ± 1.08</td>
<td>0.27 ± 0.01</td>
<td>5.9 ± 0.91</td>
<td>0.10 ± 0.01</td>
</tr>
<tr>
<td>Tilt</td>
<td>6.05 ± 1.32*†</td>
<td>0.25 ± 0.03</td>
<td>6.17 ± 1.16</td>
<td>0.10 ± 0.01</td>
</tr>
</tbody>
</table>

Values are means ± SD. InHF = high frequency power computed as natural log value; InLF = low frequency power computed as natural log value; HF cf = center frequency of the high frequency power; LF cf = center frequency of the low frequency power; CR = controlled respiration; Tilt = head-up tilt test.

* P < 0.05 in comparison with rest; † P < 0.05 in comparison with controlled respiration.

The results of the present study show that both nadolol and metoprolol significantly increased the HF component (evaluated as either HFln and HFnu) and reduced the LF component of the power spectrum (evaluated as LFnu), which is in line with previous results. No statistically significant difference was found between nadolol and metoprolol.

The net final effect of the two β-blockers is similar, being weak at rest and more evident in those conditions characterized by enhanced sympathetic or reduced vagal activity.

**Baroreflex Sensitivity**

A number of noninvasive methods for assessing baroreflex sensitivity have been described. In this study, we used the gain (or modulus) in the relationship between the spontaneous oscillations of the RR interval and those of systolic arterial pressure evaluated by means of spectral analysis (the α index). It has been demonstrated that this index closely correlates with baroreflex sensitivity, as measured by means of the standard phenylephrine test. We have measured blood pressure by means of the noninvasive finger-cuff method. However, it is known that the changes in arterial pressure evaluated by this method have been shown to accurately follow the changes in arterial pressure evaluated by mean invasive methods. Previous reports have suggested that β-blockers increase baroreflex sensitivity and, therefore, reduce efferent sympathetic activity directed to the heart. The hypothesis is that sympa-
PITZALIS, ET AL.

Figure 1. Plots of the changes, in comparison with resting conditions, in HFnu, LFnu, and LF/HF occurring during controlled respiration (C.R.) and head-up tilt when placebo, metoprolol, and nadolol were administered. HFnu = high frequency power computed as normalized units; LFnu = low frequency power computed as normalized units; LF/HF = ratio of low to high frequency power. *P < 0.05; tP < 0.01.

thetic stimulation (such as that occurring during tilt or active standing) reduces the sensitivity of the reflex and that the administration of a β-blocker increases it by blocking the β-adrenergic receptors and consequently reducing sympathetic afference and slowing heart rate.

The values of the α index obtained in this study are similar to those obtained by Steptoe and Vogele\textsuperscript{26} from the time-domain analyses of spontaneous systolic blood pressure and pulse interval sequences in 35 normal subjects whose age was similar to that of our population.

The trend of αHF we found is similar to that of the average index (the mean of the αLF + αHF) found by Lucini et al.\textsuperscript{30} In our study, there was a significant reduction in αHF during tilt when the subjects were on placebo, which was blunted by the administration of both metoprolol and nadolol.

Our findings demonstrate that only the αHF is modified by β-blocker administration under all of the considered conditions. The effect of both β-blockers on αHF and the lack of effect on αLF might be due to the fact that αHF explores the vagal arm of the baroreflex, which is better defined by the HF components. The baroreflex seems therefore to be characterized by two different responses (one faster and the other slower),\textsuperscript{31} and only the fast arm expressing vagal modulation is modified by β-blockers.

**Conclusion**

The results of the present study show that the effects of hydrophilic and lipophilic β-blockers on the time- and frequency-domain parameters of HRV are similar. In particular, their effect on 24-hour time-domain HRV is more evident during the day than the night, and their effect on frequency-domain parameters is mainly present during sympathetic stimulation, such as that induced by a head-up tilt (when both β blockers reduce the LF component of the power spectrum, prevent the reduction in the HF component, and maintain baroreflex sensitivity).

As far as the α index is concerned, these results suggest that its evaluation in the LF band differs from that in the HF band.

These results refer to patients with normal sympathovagal balance and cannot be extrapolated to patients with autonomic imbalance, such as those with essential hypertension or who have had a previous myocardial infarction. Further studies are needed to analyze the effects of β-blockers, particularly on baroreflex control in these subsets of patients.
References


This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.