SUMMARY Microelectrode recordings of multiunit sympathetic vasoconstrictor activity were made in muscle branches of the peroneal nerve in patients with essential hypertension before and during long-term treatment with the cardioselective beta-adrenergic receptor antagonist metoprolol. Nerve activity was quantified by counting the number of sympathetic bursts in the mean voltage neurogram. Metoprolol treatment lowered blood pressure and heart rate in all subjects. During long-term treatment, nerve activity was reduced both when compared to the level of activity after the first dose of the drug (p < 0.01) and when compared to the control level before treatment (p < 0.05). It is suggested that the reduction of sympathetic vasoconstrictor outflow to muscles contributed to the blood pressure reduction. (Hypertension 6: 557-562, 1984)

KEY WORDS • microelectrode recording • blood pressure • beta-adrenergic receptor antagonists

DESPITE widespread use of beta-adrenergic receptor antagonists in the treatment of arterial hypertension, we do not fully understand how they exert their antihypertensive effect. Acute intravenous administration of beta-adrenergic receptor antagonists devoid of intrinsic sympathomimetic activity reduces heart rate and cardiac output, while the blood pressure remains unchanged. Initially the peripheral vascular resistance increases, but with prolonged therapy it decreases and causes the blood pressure to fall, since the cardiac output remains reduced. 1 It is believed that the initial increase and the subsequent decrease in peripheral resistance is due to corresponding changes in sympathetic outflow, but no direct experimental evidence is available in humans because of the lack of adequate methods for measuring sympathetic nerve activity.

The development of the microneurographic technique 2 now makes possible the direct recording of sympathetic activity in human peripheral nerves. With this technique it has been found that sympathetic outflow to muscles is involved in blood pressure control. The sympathetic impulses are discharged in bursts in synchrony with cardiac rhythm, and their outflow is influenced by both arterial baroreceptors and intrathoracic low-pressure receptors. The activity can be quantified by counting the bursts and, although there are wide interindividual differences, in a given individual the level of sympathetic activity is remarkably constant over many months. 3 In the present study, we used this technique to investigate whether sympathetic outflow to muscles in patients with essential hypertension is influenced by long-term treatment with metoprolol, a cardioselective beta-adrenergic receptor antagonist without intrinsic sympathomimetic activity. The effect of acute intravenous administration of the drug has been presented in a previous report. 4

Methods

Patients

Eight patients who had been hospitalized for hypertension were recruited for the study, seven men and one woman aged 26 to 51 (mean 40) years. Hypertension was defined according to the World Health Organization (WHO) definition, namely, a level of 160/95 mm Hg or more on three different occasions, with an interval of a few weeks between each measurement. Our study criteria required no previous antihypertensive treatment, no finding suggestive of secondary hypertension on routine clinical investigation, no age greater than 59 years, and no contraindication to beta-blocking therapy. Furthermore, blood pressure could not repeatedly exceed 200/120 mm Hg, in order to make one-drug treatment possible for at least the duration of the study. Thus, except for the trial drug, all subjects were untreated during the investigation. No sedation or anesthesia was given during the record-
The protocol was approved by the Ethics Committee of the Medical Faculty of the University of Uppsala, and all subjects gave their informed consent.

Measurements

Nerve recordings were made with tungsten microelectrodes that had tips a few microns in diameter. The electrodes were inserted manually through intact skin into a muscle nerve fascicle in the peroneal nerve at the knee. Small electrode adjustments were made until an optimal position was found for recording sympathetic impulses. After amplification, the nerve signal was fed through an RC-integrating network (time constant, 0.1 seconds) to obtain a mean voltage display of the nerve activity. The analog signals of both original and mean voltage neurograms were stored together with other variables on an eight-channel FM tape recorder (Sabre VI, Sangamo, Sarasota, Florida). Neural activity was monitored on a storage oscilloscope (Model 549, Tektronix, Inc., Beaverton, Oregon) and a loudspeaker. Details about the technique and evidence for the sympathetic nature of the recorded impulses have been described previously.

Heart rate was measured from an ECG recorded by chest electrodes. Blood pressure was measured by a mercury sphygmomanometer on five visits to the outpatient clinic. All measurements were taken by the same physician after the patients had rested supine for 5 minutes. Pretreatment blood pressure was defined as the mean of three pretreatment measurements; long-term treatment pressure was the mean of measurements obtained at two visits after the patient had been on oral treatment for at least 3 weeks. Mean blood pressure was calculated by adding to the diastolic pressure one-third of the difference between the systolic and diastolic pressures.

Signal Analysis

The mean voltage neurogram was displayed from the tape on an ink jet recorder (Mingograph 800, Siemens-Elema Ltd., Solna, Sweden). Records were divided into 3-minute periods, and for each period all pulse synchronous bursts that could be identified by inspection of the mean voltage neurogram were marked and counted. For each 3-minute period, the strength of the sympathetic activity was expressed as the number of sympathetic bursts/100 heart beats and as the number of bursts/min. Separate mean values were calculated before treatment for all 3-minute control periods (C), after acute metoprolol administration (AM), and after long-term metoprolol treatment (LM); they are displayed in the tables and figures.

Biochemical Analysis

Plasma norepinephrine was analyzed by the radioenzymatic method described by Peuler and Johnson. Plasma renin activity (PRA) was determined according to the method of Fyhquist et al. Serum concentrations of metoprolol were analyzed by a gas liquid chromatographic method.

Experimental Procedure

Nerve recordings were made in all patients when the metoprolol treatment was initiated and after 6 to 29 weeks of oral treatment (mean 16 weeks). The same procedure was used in all recordings, with the patients lying in a comfortable supine position. Room temperature was 22° to 24° C.

After the electrode had been inserted and an optimal signal-to-noise ratio for sympathetic impulses had been obtained, spontaneous activity was recorded for 15 minutes. Blood samples for analyses of plasma norepinephrine and PRA were drawn. Then metoprolol (0.15 mg/kg body weight) was injected, and the recordings were continued for 20 to 30 minutes. Since all changes induced by metoprolol took place during the course of the injection (which took approximately 15 minutes), mean values after acute metoprolol were calculated from all 3-minute periods after the end of the injection. For oral treatment, metoprolol was given in a dose of 100 mg twice daily except in one subject (Subject 2 in Table 1) who was given 50 mg twice daily. At 4 to 6 hours prior to the second nerve recording, the patients took the regular morning dose except for Subject 1 (Table 1) who had not taken any tablets for the last 36 hours.

Statistics

Statistical significance of differences was evaluated by Student's t test on paired observations. Values are given as means ± sd.

Before metoprolol

After acute metoprolol

Long-term metoprolol

FIGURE 1. Segments of mean voltage neurograms (lower traces) from one patient recorded before and after intravenous injection of metoprolol and during long-term treatment. Upper two traces are respiratory movements (inspiration upward) and ECG, respectively.
TABLE 1. Effects of Metoprolol on Sympathetic Activity, Heart Rate, and Blood Pressure

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age, Sex</th>
<th>Symp. bursts/100 heart beats</th>
<th>Symp. bursts/min</th>
<th>Heart rate</th>
<th>BP Systolic (mean) diastolic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>C</td>
<td>AM</td>
<td>LM</td>
<td>C</td>
</tr>
<tr>
<td>1</td>
<td>26, M</td>
<td>55±4</td>
<td>70±6</td>
<td>55±2</td>
<td>34±2</td>
</tr>
<tr>
<td>2</td>
<td>36, F</td>
<td>57±4</td>
<td>82±3</td>
<td>60±5</td>
<td>47±4</td>
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<td>3</td>
<td>38, M</td>
<td>37±4</td>
<td>62±4</td>
<td>62±5</td>
<td>31±3</td>
</tr>
<tr>
<td>4</td>
<td>40, M</td>
<td>78±5</td>
<td>89±3</td>
<td>76±2</td>
<td>59±3</td>
</tr>
<tr>
<td>5</td>
<td>41, M</td>
<td>71±5</td>
<td>80±6</td>
<td>67±3</td>
<td>47±2</td>
</tr>
<tr>
<td>6</td>
<td>43, M</td>
<td>69±3</td>
<td>83±4</td>
<td>87±5</td>
<td>59±2</td>
</tr>
<tr>
<td>7</td>
<td>48, M</td>
<td>86±4</td>
<td>97±1</td>
<td>90±4</td>
<td>63±3</td>
</tr>
<tr>
<td>8</td>
<td>51, M</td>
<td>90±5</td>
<td>96±2</td>
<td>87±3</td>
<td>61±3</td>
</tr>
<tr>
<td>Mean ± sd</td>
<td>68±18</td>
<td>82±12</td>
<td>73±14</td>
<td>50±12</td>
<td>51±9</td>
</tr>
</tbody>
</table>

C = control; AM = after acute injection of metoprolol; LM = during long-term treatment with metoprolol; NS = not significant. All values are means ± SD.
*p < 0.01.
†p < 0.05.
‡Subject who did not take metoprolol for 36 hours prior to Recording 2.

Results

Effects of Metoprolol on Blood Pressure

As summarized in Table 1, long-term treatment with metoprolol lowered both systolic and diastolic blood pressure in all subjects. The reduction of mean blood pressure was 21 ± 7 mm Hg (mean ± SD).

Effects of Metoprolol on Sympathetic Activity and Heart Rate

During the control measurements, the sympathetic impulses were grouped in pulse synchronous bursts and did not change in general character after metoprolol was given. Figure 1 shows neurograms from one subject recorded before treatment, after acute injection of metoprolol, and after oral treatment. In a given subject there were only small variations in burst incidence between different 3-minute periods. If the variability in a given subject was expressed as the standard deviation of the subject’s mean burst incidence, the variability ranged between one to six bursts/100 heart beats, and there was no significant difference between variabilities before treatment, after acute injection of metoprolol, or on long-term treatment.

During the control period, the mean number of sympathetic bursts/min ranged between 31 and 63 (mean, 50). When patients were on long-term metoprolol treatment, the level decreased in most subjects (range, 34–55; mean, 41 bursts/min; p < 0.05). When compared to the level after the acute injection, the reduction was even more statistically significant (p < 0.01). Data from each subject are detailed in Figure 2 and Table 1. A change in the number of bursts/min could be due to a change in the number of bursts/100 heart beats and/or a change in heart rate. Compared to the control situation, the number of bursts/100 heart beats was unchanged when patients were on long-term treatment. Since the number of bursts/100 heart beats increased with the first injection of the drug, a significant decrease had taken place during oral treatment (p < 0.05). Heart rate decreased from a mean value of 75 bpm in the control situation to 57 bpm when patients were on long-term oral treatment (p < 0.01). After the acute injection, the mean level was 62 bpm, so that in most subjects there was either no change or a further decrease during oral treatment. The only exception was the subject who did not take the drug for 36 hours prior to the second recording; his heart rate was slightly higher at the second recording than at the first (Table 1, Figure 2).
Figure 2. Levels of sympathetic activity and heart rate in all subjects recorded before (C) and after acute injection of metoprolol (AM) and during long-term treatment (LM). Thick lines represent mean values. Dashed thin lines between AM and LM in center and right panels represent a subject who did not take metoprolol during the last 36 hours prior to the LM recording. Statistical significance of paired differences is indicated by the following symbols. NS = not significant; * = p < 0.05; ** = p < 0.01.

When, for each subject, the change of sympathetic activity during treatment (expressed as bursts/100 heart beats or bursts/min) was plotted against the changes of mean blood pressure or heart rate, there was no significant quantitative correlation. Nor was there a significant correlation between changes of nerve activity and duration of treatment.

Biochemical Measurements

There was no significant change of the plasma level of norepinephrine after long-term treatment with metoprolol (Table 2). Analysis of PRA in five subjects showed a decrease in all subjects after the acute administration of metoprolol and a further decrease after oral treatment. There were marked interindividual differ-

<table>
<thead>
<tr>
<th>Subject</th>
<th>Plasma norepinephrine (nmol/liter)</th>
<th>PRA (µg/1-hr⁻¹)</th>
<th>Plasma metoprolol (nmol/liter)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
<td>AM</td>
<td>LM</td>
</tr>
<tr>
<td>1</td>
<td>1.04</td>
<td>1.18</td>
<td>1.53</td>
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<tr>
<td>2</td>
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<td>3.42</td>
</tr>
<tr>
<td>8</td>
<td>1.44</td>
<td>2.05</td>
<td>1.66</td>
</tr>
</tbody>
</table>

Mean ± sd: 1.87 ± 0.79 1.91 ± 0.74 2.08 ± 0.80

*See Table 1 for explanation of abbreviations.
*p < 0.05.
ences in the serum concentration of metoprolol, but all subjects had measurable levels indicating that the drug had been taken (Table 2). There were no significant correlations between serum concentrations of metoprolol and the blood pressure reduction or changes of heart rate, sympathetic activity, plasma concentration of norepinephrine, or PRA.

Discussion

Although recordings were made only in the peroneal nerve, the results probably apply to other muscle nerves since muscle sympathetic activity at rest is similar in different extremity nerves. However, since sympathetic outflow to different effector organs is controlled differentially, the results cannot be generalized to sympathetic nerves innervating other vascular beds.

Effects of Metoprolol on Sympathetic Activity

The strength of neurally mediated responses of blood vessels probably depends on the number of impulses per unit time. Thus, in terms of peripheral vasoconstriction, it would be desirable to measure both the number of sympathetic bursts/min and the strength of the bursts. We found that during long-term oral treatment with metoprolol the number of bursts/min had diminished significantly when compared both to the situation after the first acute injection and to the control situation before metoprolol was given. Unfortunately, the strength of the bursts could not be compared between recordings made on different occasions since the strength is critically dependent on the position of the electrode tip in relation to the sympathetic fibers (and this cannot be adequately controlled). However, in previous recordings of muscle sympathetic activity when different segments of the tracings from a given recording site were compared, the strength of the bursts was found to vary in parallel with the number of bursts/100 heart beats. In the present study, the number of sympathetic bursts/100 heart beats on long-term treatment was lower than after the acute injection and unchanged compared to the control situation. Thus, in view of the parallelism between bursts/100 heart beats and burst amplitudes seen previously, there is reason to believe that the strength of the bursts was unchanged or decreased when patients were on long-term treatment with metoprolol. Consequently, a reasonable interpretation of the present data is that long-term treatment with the beta-adrenergic receptor antagonist metoprolol in patients with essential hypertension leads to a reduction of sympathetic vasoconstrictor outflow to muscles.

Since sympathetic impulses in muscle nerves are grouped in the cardiac rhythm, a change in the number of bursts/min can be due to a change of bursts/100 heart beats, a change of heart rate, or changes of both variables. This means that the heart-rate-lowering effect of the drug is of importance not only for changing central hemodynamics, but also for reducing the outflow of vasoconstrictor impulses to muscles (and possibly also to other vascular beds controlled by the arterial baroreflex). Our data give no information on why the number of bursts/100 heart beats (which increased in conjunction with the acute injection) returned toward control values during prolonged treatment; it could be either a direct effect on the central nervous system or an adaptation in some baroreflex loop. As discussed previously, the number of bursts/100 heart beats in human muscle nerves provides a measure of how often sympathetic outflow occurs in relation to available opportunities for outflow. In a given individual without drug treatment this measure is remarkably stable over many months.11 The present results suggest that long-term administration of a beta-adrenergic receptor antagonist that results in a moderate blood pressure reduction does not alter the pretreatment number of sympathetic bursts/100 heart beats, even though there was an initial transient change in conjunction with the first intravenous administration of the drug.

Functional Importance of the Reduced Sympathetic Outflow

Short-term hemodynamic effects of beta-adrenergic receptor antagonists devoid of intrinsic sympathomimetic activity are decreased heart rate and cardiac output, increased peripheral vascular resistance, and unchanged blood pressure. On prolonged therapy, cardiac output remains depressed up to at least 20 months while peripheral vascular resistance gradually returns toward the pretreatment level, and in parallel with this there is a fall in blood pressure.12-15 It seems likely that an initial increase of muscle sympathetic activity after the acute injection and a subsequent decrease during long-term treatment should contribute to these changes of total peripheral resistance. There are only a few studies on the changes in regional vascular resistance during long-term metoprolol treatment of essential hypertension. Using venous occlusion plethysmography, Svensson et al.16 found no change of vascular resistance in the forearm or calf after 6 weeks of treatment with metoprolol, but after 6 months, the forearm resistance was reduced whereas there was still no change in the calf. Such data must be interpreted with caution since they do not distinguish between contributions from skin and muscle or between neural effects and structural vascular changes, but the results are in reasonable agreement with our findings. In another study,17 renal blood flow (measured by single injection plasma clearance technique) was found to be unchanged after long-term metoprolol treatment, and since mean blood pressure fell, renal vascular resistance probably was reduced.

Although blood pressure and muscle sympathetic activity fell in all subjects during long-term treatment with metoprolol, there was no significant correlation between the changes in the two parameters. Blood pressure is a product of cardiac output and resistance to flow in many vascular beds. Since these target organs may be influenced by the drug to different degrees in different subjects, it is not surprising that in a small group there is no correlation between changes in blood pressure and sympathetic outflow to one particular vascular bed.
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