SUMMARY The effect of nadolol (N) on 24-hour blood pressure (BP) and heart rate (HR) values and on their variability was examined in ambulant patients with essential hypertension, using the Oxford method to obtain continuous intraarterial recording and a computer to have a beat-to-beat analysis of the data. The recording was carried out without treatment and after 10 days' administration of N once daily by mouth (dose range: 80-320 mg). After N, 24-hour BP and HR were reduced by 17 ± 3% and 27 ± 4% respectively as compared to before N, the effect being similar for both systolic and diastolic BP. The hypertension and bradycardia were significantly more marked during the day than during the night, neither showing any attenuation in the hours furthest from the administration of the drug. During N, there was a reduction in the 24-hour variation coefficient for HR but the reduction was limited to the longer term component of this phenomenon, the moment-to-moment variations remaining unaffected. The long- and short-term variation coefficients for BP were not modified under N. These findings suggest that N once a day can reduce BP for 24 hours in ambulant hypertensive patients. The lack of alteration in variability of BP and moment-to-moment HR suggests that the hypotension is achieved without interfering with the mechanisms involved in cardiovascular homeostasis. (Hypertension 5: 573-578, 1983)

KEY WORDS • ambulatory blood pressure monitoring • antihypertensive therapy • beta-blockers • blood pressure variability • nadolol • heart rate • heart rate variability • sleep • neural control of circulation

Several studies have suggested that nadolol, a new beta-blocking agent with a prolonged half-life in plasma, may be able to lower high blood pressure effectively when administered once a day. However, these studies have made use of isolated blood pressure measurements performed by the cuff method, a procedure open to errors. Blood pressure values that are obtained in this way represent no more than a tiny fraction of the many thousand values that occur during the day and night. Furthermore, these few values are usually obtained under conditions that do not reproduce patient's day-to-day life pattern.

In the present study we have investigated the antihypertensive effect of a daily administration of nadolol by directly recording arterial blood pressure for 24 hours in unrestrained patients. We have used the recording also to assess the effect of this drug on the variability of blood pressure and heart rate to uncover its influence on cardiovascular regulation.

Methods
Our study was performed in seven hospitalized hypertensive patients whose ages ranged from 37 to 64 years (mean, 47.9 ± 8.4 years). The patients (one man, six women) were selected for the study if they had no signs, symptoms, or history of cardiac failure, renal failure, coronary insufficiency, and a major disease other than hypertension. Selection was made if there had also been no treatment with antihypertensive drugs during the preceding 3 weeks, and no contraindication to the use of beta-blocking agents (cardiac failure, history or signs of bronchial asthma, sinus bradycardia, atrioventricular conduction defects). All subjects gave their written informed consent.

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Measurements

We used the Oxford method\textsuperscript{11-13} to obtain direct and continuous blood pressure recordings in our patients. In brief, a catheter was placed in a radial artery of the patient under local anesthesia with 2% lidocaine, and connected via a rigid-walled polyethylene tube to a plexiglas box bound to the patient's thorax at the level of the heart. The box contained a 40 ml saline reservoir connected through a short cable to a pressure transducer connected via a rigid-walled polyethylene tube to a battery-operated amplifier and to a tape recorder bound to the patient's waist on which the blood pressure signal was stored during the 24 hours. The method provided a faithful blood pressure recording, because of the long-term stability of the zero signal, the linearity of the transducer from 50 to 250 mm Hg, and the frequency-response of the whole tubing-transducer-amplifier system that was optimal up to 10 Hz. The small size and weight of the various parts of the system allowed patients to be normally dressed and ambulant during the recording period.

Protocol

The first 5 days of hospitalization were used to make the diagnosis of essential hypertension and to perform all the examinations (ECG, chest x-ray, fundus, electrolytes, renal function tests, etc.) necessary to evaluate the patients’ clinical status. A further 7-day period was allowed to elapse to obtain stabilization of the blood pressure values. After stabilization had been achieved for at least 3 days (cuff method pressure measurements performed twice a day in lying and standing position), a 24-hour direct and continuous blood pressure recording was obtained. Then nadolol was administered once a day, starting with 80 mg and doubling the dose at 2-day intervals until daily cuff measurements suggested that a hypotensive effect had been achieved. The effective dose was 160 mg in one patient, 240 mg in two patients, and 320 mg in the remaining four patients. After 10 days of nadolol treatment, a second 24-hour direct and continuous blood pressure recording was obtained. The daily dose of nadolol was always administered at 7 p.m., which was also the time at which the first and second 24-hour blood pressure recordings were started. During both recordings, the patient was allowed to move freely within the hospital area and to engage in social activities with others.

Data Analysis

The blood pressure recordings were analyzed by a computer (PDP-11/34, Digital Equipment, Marlboro, Massachusetts) as previously described.\textsuperscript{14} In brief, in each recording mean arterial pressure values were obtained by taking a large number of points (one every 50 msec) along the blood pressure signal and averaging them over periods of 3 seconds. This amounted to an integration of the blood pressure trace within these time intervals. Also, 3-second values were obtained for systolic blood pressure, diastolic blood pressure, and heart rate, and averages obtained for each half-hour, for periods of 2 and 8 hours, and for all 24 hours. In addition, each recording was evaluated in terms of variability of mean arterial pressure. Variability was assessed by calculating the standard deviation and the variation coefficient (standard deviation as a percentage of the mean value) of each half-hour and averaging them for the whole 24-hour period. In this way a measure was obtained of a relatively short-term variability, i.e., of variability within half-hours. A longer-term blood pressure variability, i.e., a variability among half-hours, was also obtained, by considering the standard deviation and the variation coefficient that resulted from the average of the mean blood pressure values of each half-hour. A similar assessment of variability was done for heart rate.

Group mean values were calculated from the individual patient’s means, the symbol ± indicating the standard error. Comparison of the data before and during treatment with nadolol was made by the \textit{t} test for paired observations, with \( p < 0.05 \) taken as the minimum level of statistical significance.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Hemodynamic effect of nadolol in seven subjects with essential hypertension. Data are shown as means ± standard errors for the whole group of subjects, the value in each subject representing the average of all 24-hour values. SBP = systolic blood pressure; DBP = diastolic blood pressure; MAP = mean arterial pressure; HR = heart rate; C = data during control; D = data during administration of nadolol.}
\end{figure}
Results

The average 24-hour arterial blood pressure values obtained in the recordings before and during nadolol administration are shown in figure 1, cumulatively for all seven patients. During nadolol administration, there was a significant and marked reduction in the 24-hour value of mean arterial pressure, and this reduction involved both the systolic and the diastolic blood pressure to a similar marked extent. There was also a significant and marked reduction in the 24-hour value for heart rate.

Figure 2 shows the mean arterial pressure and heart rate data for all seven patients before and during administration of nadolol, this time separately for the 48 half-hours of the 24-hour recorded periods. The blood pressure and heart rate values obtained during nadolol were invariably lower than those obtained before nadolol. There was no evidence for an attenuation of the effect on both blood pressure and heart rate during the half-hours that were furthest from the time of drug administration.

Our data provide three further sets of results. The recordings obtained before and after nadolol were analyzed for four different 2-hour periods: a morning period (approximately from 9 to 11 a.m.), an afternoon period (approximately from 3 to 5 p.m.), an evening period (approximately from 7 to 9 p.m.), and a night period when the patients were asleep (approximately within 0 to 4 a.m.). The reductions in mean arterial pressure and heart rate were 16.7 ± 2.9 mm Hg and 26.4 ± 3.3 bpm in the morning, 26.5 ± 3.0 mm Hg and 22.0 ± 3.3 bpm in the afternoon, and 19.2 ± 6.9 mm Hg, and 21.1 ± 5.0 bpm in the evening. Before nadolol, mean arterial pressure and heart rate were lower during sleep than during the day periods (−20.7

![Figure 2](image-url)
± 2.0 mm Hg for mean arterial pressure, and −12.4 ± 1.0 bpm for heart rate, \( p < 0.01 \). These lower values were further reduced by 16.9 ± 6.8 mm Hg and 13.6 ± 3.9 bpm, \( p < 0.01 \) during nadolol administration. Both effects were significantly less marked (\( p < 0.05 \)) than those observed during most of the day times.

Figure 3 shows the data on blood pressure and heart rate variability. Nadolol reduced the standard deviation for mean arterial pressure that was obtained within half-hours, but did not significantly affect the standard deviation among half-hours. The variation coefficients within and among half-hours were both not affected by the drug. For heart rate, nadolol also reduced the standard deviation but not the variation coefficient within half-hours, but, in contrast to arterial pressure, there was a very marked reduction in both standard deviation and variation coefficient among half-hours.

Finally, when the blood pressure tracing was examined at high speed, no hypotensive episode during exercise or change of posture was observed during treatment with nadolol, and the patients did not report any troublesome symptoms or untoward effects during this treatment.

Discussion

In our hypertensive patients, the 24-hour blood pressure recording performed during administration of nadolol, showed blood pressure values that were markedly lower than those observed when the recording was performed prior to the nadolol administration. Three possibilities may account for this finding. Because the recording performed during nadolol always followed that performed in absence of nadolol, the first possibility is that the hypotension resulted from a tendency of blood pressure to decline with time from a higher initial value. However, this is unlikely because the recording without nadolol was always performed after the patients had been hospitalized for a relatively long time.
time and after blood pressure values (whose decline is mainly seen within the first few days) had apparently stabilized. The second possibility is that the hypotension observed during nadolol was accounted for by a placebo effect. However, the fall in arterial pressure was accompanied by a marked bradycardia, which ensured that the pharmacological action of nadolol had indeed taken place. Furthermore, the decrease largely exceeded the modest reduction in blood pressure that can normally be seen during placebo. In this regard, it is important to emphasize that recent evidence questions whether any placebo-induced hypotension occurs when blood pressure is assessed, not through few isolated measurements, but via continuous 24 hour recordings.

The third possibility is, therefore, the most likely one: the lowering of blood pressure observed in our patients was at least in part the result of the pharmacological properties of nadolol. Our results demonstrate not only that the hypotension involves both the systolic and diastolic blood pressure, suggesting an action of nadolol on peripheral resistances as well as on the heart, but also that a single daily dose of this drug may reduce blood pressure for 24 hours with no waning of the hypotensive effect, even at the hours furthest from the drug administration. The value of these demonstrations is enhanced by the fact that the observations were made in ambulant patients.

Several further points of our study deserve to be discussed. The first concerns the effect of nadolol on heart rate. The marked and prolonged hypotension during nadolol administration was accompanied by a marked and prolonged bradycardia. In all patients the average 24-hour reduction in heart rate was 21 bpm, but during several periods of the day reductions close to 30 bpm were observed. This indicates that, whenever a marked lowering of blood pressure needs to be achieved by this drug, pronounced bradycardia is to be expected. Although undesirable in some instances, it may guarantee the protection beta-blocking agents offer in ischemic heart disease, which is so commonly associated with hypertension.

A second point concerns the effects of nadolol during sleep. In our patients, sleep was predictably associated with a significant reduction in blood pressure and heart rate. These values were further reduced by nadolol, but the reductions were less pronounced than those observed during the waking hours. This phenomenon differs from that displayed by an agent such as clonidine, which induces hypotension and bradycardia that is similar during sleep and wakefulness. It also differs from the effects of other beta-adrenergic agents, for example, oxprenolol and pindolol, with which sleep-induced hypotension is not further enhanced and the bradycardia may even be attenuated. This difference may be determined by the intrinsic sympathomimetic activity of the latter compounds. Under the reduced sympathetic tone of sleep, this activity may balance or prevail over the beta-blocking activity, preventing any further bradycardia and hypotension. This property could make these compounds inadequate to achieve optimal therapeutic effects during the night as well as during the day.

A third point refers to the variability of blood pressure. During nadolol, there was a significant reduction in the absolute short-term mean arterial pressure variation. However, this reduction was proportional to the reduction in blood pressure, so that the percent short-term variability remained unaffected. Also the percent long-term blood pressure variability was not significantly altered by nadolol. These findings suggest that spontaneous blood pressure oscillations are not modified by nadolol and, thus, that the mechanisms responsible for this phenomenon (to a large extent alterations in sympathetic cardiovascular drive) are unaffected by this type of drug. We have made similar findings during treatment with clonidine and labetolol.

The last point concerns the heart rate variability that was markedly reduced by nadolol. Two interesting observations are that the reduction in heart rate variability involved the long- but not the short-term alterations in heart rate and this was in striking contrast to the lack of reduction in blood pressure variability. These observations suggest that only the long-lasting changes in heart rate depend on cardiac sympathetic modulation, and that the short-lasting ones may be under a more prominent vagal control. They also allow speculaton that variability of cardiac functions does not bear a cause-effect relationship with blood pressure variability, which may therefore be determined by somatomotor phenomena.

References

Twenty-four-hour hemodynamic profile during treatment of essential hypertension by once-a-day nadolol.
G Mancia, A Ferrari, G Pomidossi, G Parati, G Bertinieri, G Grassi, L Gregorini and A Zanchetti

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