Selective and Nonselective Beta-adrenoceptor Blockade in Hypertension: Responses to Changes in Posture, Cold and Exercise


SUMMARY The hypertensive response to the infusion of epinephrine is exaggerated in subjects treated with non-cardioselective beta-adrenergic antagonists, but not in subjects given cardioselective agents. In this study, we sought to determine whether the same holds true when hypertensive patients treated with these drugs are subjected to acute physiologic stress. According to a randomized crossover protocol, 13 hypertensive men received oral metoprolol and propranolol for 5 weeks each. The dosage was adjusted to maintain diastolic resting blood pressure at 80–90 mm Hg. During the last week of each treatment period, measurements were made of responses to a change in posture (lying to erect), isometric hand grip, hand immersion in cold water and progressive incremental and steady-state exercise on a cycle ergometer. In addition to within-patient comparison of the two drugs, the responses were also compared with those in six healthy untreated controls.

The increases in blood pressure associated with the pressor tests were similar during treatment with the two drugs. The heart rate increased less in controls and was similar in the two treatments. During incremental exercise, ventilation was significantly lower during propranolol treatment than during metoprolol. This effect was not found during steady-state exercise, probably owing to a reduced rate of adaptation to exercise with propranolol. During steady-state exercise, cardiac output was similar with the two treatments.

The extent of pressor responses to cold stimulus and to isometric and dynamic exercise were similar during selective and nonselective beta blockades, so we conclude that such increases in blood pressure are largely mediated by neural sympathetic pathways rather than by circulating epinephrine. In hypertensive patients, selective beta antagonists confer no benefits over nonselective antagonists in the presence of blood pressure surges associated with hand immersion in cold water and isometric and dynamic activity.

WE STUDIED the hypothesis that surges in blood pressure (BP) in response to various activities are smaller in hypertensive patients treated with the selective beta antagonist metoprolol than in those treated with the nonselective beta blocker propranolol. Nonselective beta-adrenoceptor blockade during certain forms of endogenous sympathetic stimulation may paradoxically increase BP,1,2 because of the blockade of vascular (vasodilator) beta receptors, thereby unmasking alpha-receptor-mediated vasoconstriction.3 During epinephrine infusion in normal subjects4 and in hypertensive patients,5 BP and peripheral resistance increase acutely in those pretreated with propranolol, but not in those pretreated with metoprolol. However, it is not known whether control of such transient BP fluctuations is clinically beneficial in terms of preventing life-threatening events such as subarachnoid hemorrhage. Nevertheless, on first principles, treatment with selective agents would be preferable if acute increases in BP associated with everyday sympathetic activation are also less pronounced.

In the present study, we addressed the following questions: In doses that are equally effective in the treatment of hypertension, is metoprolol more effective than propranolol in suppressing the BP surges that follow common forms of cardiovascular stress? If so, is this effectiveness gained at the expense of increased liability to postural hypotension? Finally, is treatment of hypertensive patients with either drug associated with larger or smaller hypertensive surges than those in untreated normal subjects?

Materials and Methods
The study was approved by the institution's ethics committee.

Patients
Thirteen male patients with mild hypertension requiring treatment gave informed written consent to participate in the investigation. All had a diastolic BP greater than 100 mm Hg on two or more measurements before treatment. No patient had asthma or cardiac failure; two patients had diabetes mellitus requiring insulin. According to a randomized, crossover design, each patient received metoprolol for 5 weeks, followed by propranolol for 5 weeks, or vice versa. During each course of treatment, the patients were followed by one of the investigators to ensure that they were receiving adequate doses of medication to maintain a sitting diastolic BP (DBP) less than 90 mm Hg. All other antihypertensive medications except diuretics were discontinued, and the dosage of diuretic was kept constant throughout the study. During the last week of each treatment phase, the patients came to the laboratory at 9:30 a.m.; the last dose of medication was at 7:30 a.m. A venous blood sample was drawn into heparinized tubes, and the plasma freshly separated and frozen for later determination of plasma propranolol or metoprolol concentrations by established techniques.6,7

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the provocative tests did not know which drug each patient was taking, and the patients were asked not to divulge this information.

Six normotensive male volunteers who received no medication also underwent provocative testing on one morning. The protocol for their tests differed from that of the hypertensive patients in that the effect of posture was not examined, and steady-state exercise test was not conducted.

Protocol for Provocative Testing
In all of the maneuvers, heart rate (HR) was determined from an electrocardiographic tracing on a Mingograf 81 multichannel recorder and BP was measured in the left arm using a random-zero mercury sphygmomanometer (Hawksley). DBP was read at the disappearance of Korotkoff sounds (phase V). The following maneuvers were performed sequentially.

Change in Posture
HR and BP were measured after 5 and 10 minutes in the supine position. The subject then stood and measurements were repeated at 30 seconds and 1, 3 and 5 minutes.

Isometric Hand Grip (IHG)
The subject was seated comfortably beside a table. The right forearm rested on the table with the wrist pronated and the elbow in approximately 90° flexion. A spring dynamometer (Stoelting Co.) was adjusted to fit the subject's hand comfortably. With the dynamometer dial covered, the subject was asked to sustain maximal hand contraction for 1–2 seconds; the force (kg) was recorded, and the best of three attempts was taken as the maximal voluntary contraction (MVC). Thirty percent of MVC was used as a target for sustained IHG because this degree of effort induces significant changes in HR and BP in normal subjects. In each patient, receiving either treatment, the same size and target settings were used.

After measuring resting HR and BP, the subject was asked to sustain IHG at the target level for four minutes, during which HR and BP were measured. The subject was carefully instructed to avoid glottic closure during the maneuver and was continuously observed to ensure that the target force was maintained. This procedure was repeated 20 minutes later.

Cold Pressor Test
Resting HR and BP were measured before the cold pressor test. Then, the subject immersed his right hand up to the wrist in a basin of iced water (0–4°C). HR and BP were measured at 1-minute intervals for 5 minutes.

Dynamic Exercise Tests
A progressive exercise test (stage I) was performed. The subject was seated on a calibrated, electrically braked cycle ergometer (Elema EM-370), pedalling at 60 rpm. Power output was increased by 100 kpm/min each minute until the subject could not continue. HR, BP and inspired ventilation (\(V_i\)) were measured at rest and during the last 15 seconds of each minute throughout exercise. The maximal power output achieved was also recorded. \(V_i\) was measured by a dry gas meter (Parkinson-Cowan CD4) fitted with a potentiometer connected to the recorder.

Steady-state Exercise Test
After a 30-minute rest period, a steady-state exercise test (stage II) was performed, using a power output of 400 kpm/min in all subjects, irrespective of performance during the stage I test. When a steady state was achieved, HR, BP, \(V_i\) and the tidal carbon dioxide concentration and mixed expired carbon dioxide and oxygen concentrations were measured.

Mixed venous \(P_{CO_2}\) was measured by the carbon dioxide equilibration rebreathing method corrected for the alveolar-arterial \(P_{CO_2}\) difference. Mixed expired gas was sampled distal to a mixing chamber, and oxygen and carbon dioxide concentrations were measured with paramagnetic (Godart Rapox) and infrared (Godart Capnograph) analyzers, respectively. End-tidal carbon dioxide concentration was obtained by sampling gas at the mouthpiece. The gas analyzers were calibrated using reference gases whose values had been checked by the Lloyd-Haldane method.

Arterial \(P_{CO_2}\) was estimated from the end-tidal carbon dioxide concentration using the correction of Jones et al. Oxygen uptake, carbon dioxide output, the respiratory exchange ratio and cardiac output (CO) were calculated according to standard formulas.

Statistical Analysis
Correlations between dosages and drug concentrations were determined by linear regression and the correlation coefficient was referred to a two-tailed \(t\) distribution for significance testing. Statistical comparison of the results from provocative testing with the two agents was performed by two-tailed paired \(t\) tests. Analysis of variance for repeated measurements was used to compare variables in the stage I exercise test. Differences between drugs were judged statistically significant if the likelihood of a false-positive result was less than 0.05.

Results
The subjects' physical characteristics, drug dosages and plasma concentrations are listed in table 1. BP control was adequate in each patient. Propranolol and metoprolol dosage ranges were 140–160 and 50–300 mg/day, respectively. The respective ranges of plasma drug concentrations were 8–102 and 18–296 \(\mu\)g/l.

There were significant positive correlations between propranolol doses and plasma concentrations \((r = 0.64, p = 0.019)\), metoprolol doses and plasma concentrations \((r = 0.79, p = 0.001)\), propranolol and metoprolol doses \((r = 0.81, p = 0.001)\) and propranolol and metoprolol plasma concentrations \((r = 0.75, p = 0.003)\).

Resting (basal) BP and HR were consistently similar on both drugs. Resting HR in the normal sub-
subjects differed little from that of hypertensive subjects who received β blockade, but resting BP was lower in the normal subjects.

Change in Posture
On assuming the upright position after 10 minutes of recumbency, there was a mean reduction in systolic BP (SBP) of 16 mm Hg during propranolol treatment and 12 mm Hg during metoprolol treatment ($p = 0.152$) (fig. 1). The corresponding increase in HR was also greater with propranolol than with metoprolol; the difference, although small, was significant ($p = 0.011$). No differences in SBP and HR were evident after 5 minutes in the standing position. There were no significant differences between the treatments with respect to DBP.

Cold Pressor Test
After hand immersion in cold water, no statistically significant differences were evident between measurements during the two drug treatment periods. In the control subjects, resting BP was lower during hand immersion; the change in BP was of the same order as in the treated patients, but the HR response was initially greater (fig. 1).

Isometric Hand Grip
BP and HR increased during IHG, with no significant difference between results with different treatments (fig. 2A). Although BP was lower at rest in control subjects than in patients, the increase during IHG was similar and the HR response greater. Repeating the IHG maneuver yielded similar results (fig. 2).

Progressive Dynamic Exercise
The mean HR response in the treated subjects diverged increasingly from that of the controls as exercise progressed (fig. 3). HR during propranolol treatment was consistently about 2 beats/min less than during metoprolol, but neither individual nor cumulative differences were statistically significant. Ventilation was less with propranolol at all power outputs (fig. 4); the difference was statistically significant at 500 and 600 kpm/min ($p = 0.025$ and 0.012, respectively), but was greater in controls than in the patients with either treatment. Both in the controls and in the treated patients, SBP increased with increasing levels of exercise, and was generally about 4 mm Hg higher with metoprolol than with propranolol (fig. 5), but neither individual nor cumulative differences were statistically significant. There were no significant differences in DBP between the two treatments. In the control subjects, SBP and DBP remained approximately 15 mm Hg below values in the patients.

Maximal HR and ventilation were significantly greater with metoprolol than with propranolol ($p = 0.01$).

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### Table 1. Patient Characteristics and Plasma Drug Levels

<table>
<thead>
<tr>
<th></th>
<th>Propranolol</th>
<th>Metoprolol</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Age (years)</td>
<td>Weight (kg)</td>
</tr>
<tr>
<td>Hypertensive patients (n = 13)</td>
<td>45.0 ± 0.15</td>
<td>87.3 ± 10.1</td>
</tr>
<tr>
<td>Untreated normal controls (n = 6)</td>
<td>37.2 ± 8.7</td>
<td>76.8 ± 21.6</td>
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</table>

Values are mean ± SD.

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**Figure 1.** Effects of change in posture (left) and cold pressor test (right) on blood pressure and heart rate during treatment with propranolol (triangles) and metoprolol (squares). Filled circles indicate controls. Asterisk indicates a significant difference between treatments for change in posture ($p = 0.011$). Mean values are shown; bars indicate so.
Effects of isometric hand grip for 4 minutes on blood pressure and heart rate with propranolol (triangles) and metoprolol (squares) treatments and in controls (circles). Two studies were carried out (left and right panels) 20 minutes apart. None of the differences were significant.

0.032 and 0.024, respectively (table 2). The maximal power output was also higher with metoprolol ($p = 0.069$). There were no significant differences in maximal BP in any of the subject groups. Maximal power output, HR and ventilation were all significantly greater in the controls than in either treatment group.

Steady-state Exercise

During steady-state exercise at 400 kpm/min, SBP was significantly greater with metoprolol than with propranolol (table 3) ($p = 0.037$), but no other significant differences were demonstrated. With both treatments, CO was within the predicted normal range.

Discussion

The wide interindividual variation in plasma propranolol and metoprolol concentrations reflected by the large standard deviations on either drug (table 1) can be ascribed to interindividual variation in dosage; variable patient compliance with prescribed treatment; variable time of sampling relative to the time of the last dose; and to pharmacokinetic variation.

Examination of the effects of three pressor stimuli showed no major hemodynamic differences between metoprolol and propranolol in dosages that controlled resting BP comparably. Thus, it seems unlikely that
under these conditions nonselective β blockade would give rise to excessive surges in BP because of unopposed α-receptor activation. The drugs appeared equally effective in controlling BP in the situations studied, and presumably, this is true for everyday stresses associated with acute BP fluctuations.

The provoked BP increases in our treated hypertensive patients were similar to those in the control subjects, but it does not follow that the increases would also have been of the same order in untreated patients. For ethical reasons we did not subject hypertensive patients to a 5-week placebo treatment.17,18 Our treated patients and untreated healthy controls were not well matched; the patients were older, shorter, heavier and probably less physically fit. Nevertheless, important differences in exercise variables did not occur, except with respect to maximal power output and the HR response.

Exercise has been used as a pressor stimulus in studies of selective and nonselective β blockers given intravenously4,19 and orally.20-22 No significant hemodynamic differences between the drugs was found. However, only Leenen et al.22 and Pearson et al.21 examined the effect of progressive incremental exercise of the type we used. Waal-Manning,23 used steady-state exercise and found that atenolol, a selective β blocker, allowed SBP to increase to a higher level than did the nonselective drugs studied, without affecting HR or DBP. Spence and Paterson,24 comparing oral metoprol with propranolol, found a greater HR response to IHG with metoprolol, but this difference was not evident on dynamic exercise. Moreover, during neither IHG nor dynamic exercise was there any difference in BP, although CO during exercise was significantly lower with propranolol. Our finding of a significantly higher (8 mm Hg) SBP during steady-state exercise with metoprolol is thus in keeping with these studies and others.25 Although the small but per-

<table>
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<th>Table 2. Results at Maximal Power Output During Stage I Exercise Test</th>
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<tr>
<td>Power output (kpm/min)</td>
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<td>------------------------</td>
</tr>
<tr>
<td>Untreated normal controls</td>
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<tr>
<td>Hypertensive patients</td>
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<tr>
<td>Propranolol</td>
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<tr>
<td>Metoprolol</td>
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<td>*p &lt; 0.05.</td>
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Values are mean ± SD.

*p < 0.05.

Abbreviation: BP = blood pressure.

<table>
<thead>
<tr>
<th>Table 3. Results of Steady-state Exercise at 400 kpm/min</th>
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<tr>
<td>Predicted†</td>
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<td>------------</td>
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<tr>
<td>Systolic BP (mm Hg)</td>
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<tr>
<td>Diastolic BP (mm Hg)</td>
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<tr>
<td>Heart rate (beats/min)</td>
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<td>Ventilation (l/min)</td>
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<td>Oxygen uptake (l/min)</td>
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<td>Carbon dioxide output (l/min)</td>
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<td>Respiratory exchange ratio</td>
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<tr>
<td>End-tidal PCO2 (mm Hg)</td>
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<td>Estimated arterial PCO2 (mm Hg)</td>
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<td>Mixed expired PCO2 (mm Hg)</td>
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<td>Mixed venous PCO2 (mm Hg)</td>
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<tr>
<td>Venous-arterial CO2 difference (ml/100 ml)</td>
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<td>Cardiac output (l/min)</td>
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* p < 0.05.
† Values predicted from Jones et al.12
Abbreviations: BP = blood pressure; PCO2 = carbon dioxide tension.
sistent HR differences in the incremental and steady-state exercise tests in our patients were not statistically significant, they may indicate slightly more potent β blockade with propranolol in the dosage used. This could account for the small hemodynamic differences between the drugs. The HR response to pressor stimuli in the treated patients appeared attenuated, but the BP response was similar to that in the controls.

Two studies4–6 that examined the role of β blockers in opposing the hemodynamic consequences of epinephrine infusion showed markedly exaggerated increases in BP in subjects who received propranolol, but normal responses in those who received metoprolol. This difference contrasts with the minimal effect seen in our own and other clinical studies not using epinephrine infusion, suggesting that the cardiovascular response to pressor stimuli during exercise is mediated by adrenergic neural mechanisms rather than by the humoral effects of circulating epinephrine. Thus, neurally released norepinephrine (predominantly an α-receptor agonist) will have relatively little influence on β receptors in blood vessels. Consequently, whether or not coexistent β blockade is selective has little bearing on peripheral resistance. In contrast, in the presence of circulating epinephrine (a powerful α- and β-receptor agonist), which generally produces a net reduction in peripheral resistance, the extent of vasodilatation will be antagonized less with selective than with nonselective β blockade. Hence, nonselective β blockade, which blocks β-receptor-mediated vasodilatation more than does selective blockade, allows epinephrine to have a greater pressor effect.

Progressive incremental exercise is associated with a fivefold increase in epinephrine (and norepinephrine) concentrations in plasma.29 Moreover, propranolol is associated with even larger increases in circulating epinephrine (but not norepinephrine) during exercise.27 Nevertheless, as the exercise pressor responses we obtained were equivalent with selective and nonselective β blockade, we conclude that the hemodynamic responses are more dependent on neural sympathetic discharges than on circulating epinephrine.

Patients who received propranolol had a lesser ventilatory response to progressive exercise. Absence of the effect on steady-state exercise suggests that this finding was related to the rate of adaptation to the changing metabolic demand inherent in the incremental test rather than to the magnitude of the ultimate adaptation. This speculation is supported by the small lag in HR response to exercise with propranolol (fig. 3), and also by the apparent delay in adaptation to postural change with propranolol (fig. 1). Thus, CO may be slower to adapt to the increasing work load, flow of carbon dioxide from the working muscles may be delayed, and the ventilation, which during exercise is largely a response to carbon dioxide flux,28 may be similarly delayed. A less likely explanation is that β blockade, or perhaps only β1 blockade,29 inhibits the central or peripheral chemoreceptors and thus depresses the ventilatory response to carbon dioxide. Such an effect of propranolol was found in cats by Llados and Zapata,30 and in man by Mustchin et al.,31 but not by Patrick and Pearson29 or Folgering and Braakhkeke.33 The increased ventilatory response to isoprenaline or norepinephrine infusion is effectively inhibited by β blockers,34–36 but a reduction in CO may be the explanation for this.36,37 Twentyman and Tattersfield26 reported that propranolol reduced ventilation, carbon dioxide output and oxygen uptake early in exercise, but these variables became normal as exercise continued, which suggests slower adaptation rather than resetting of some physiologic threshold.

Our study has shown that in doses producing equivalent control of hypertension at rest, metoprolol and propranolol have approximately equal effects on the surges of BP resulting from the various provocative maneuvers. The extent of postural hypotension is similar with both drugs. The changes in BP induced by pressor stimuli are of the same order in hypertensive patients given β blockade as in untreated healthy control subjects. With respect to everyday activities that produce acute hypertension, we conclude that there are no hemodynamic advantages in treating hypertensive patients with one or other type of β-blocking drug.

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