Effects of β-adrenoreceptor–blocking drugs in patients with Raynaud’s phenomenon

JAY D. COFFMAN, M.D., AND HELEN M. RASMUSSEN, R.D.M.S.

ABSTRACT  Digital vasospastic phenomena have been reported to result from use of nonselective and cardioselective β-adrenoreceptor–blocking drugs. The effects of 80 mg/day propranolol and 100 mg/day metoprolol on finger hemodynamics and clinical responses were compared with those of placebo in 16 patients with Raynaud’s phenomenon. A double-blind, 2 week crossover study design was used with a 2 week washout placebo period between drugs. Total fingertip blood flow (FBF) as determined by venous occlusion plethysmography, fingertip capillary flow (FCF) as determined by radioisotope disappearance rate, and finger systolic blood pressure (FSP) were measured in a 28.3° and a 20°C room at the end of each period. Subjects kept diaries to record vasospastic attacks. There were no significant changes in FBF, FCF, or FSP in the warm or cool environment during drug treatment as compared with during the placebo period. A decrease in pulse rate occurred with both drugs and there was a decrease in blood pressure with metoprolol. There were no significant changes in the number of vasospastic attacks or in the patients’ overall evaluation of their conditions while they were receiving the drugs. It is concluded that the presence of Raynaud’s phenomenon is not a contraindication to the use of β-adrenoreceptor–blocking drugs in the normotensive population.


USE OF β-adrenoreceptor–blocking drugs has been associated with the development of Raynaud’s phenomenon, cold extremities, and intermittent claudication. The mechanism of action is unknown. Unopposed stimulation of vascular α-adrenoreceptors, decreased cardiac output and blood pressure resulting in lower perfusion pressure and blood flow, a decreased blood volume, or increased reflex sympathetic vasoconstriction by the central cardiovascular depressant effects of β-blockade have been suggested.1–4 β-Adrenoreceptors have been shown to be present in the arteriovenous anastomoses of the fingers. They are only responsive to humoral agents and not to neurogenic stimulation, but could be involved in the development of Raynaud’s phenomenon.5 Vasospastic phenomenon have been described with use of both nonselective and cardioselective agents2,6 and cardioselective agents have been shown to affect the peripheral circulation.7 Since these agents must sometimes be used in patients with Raynaud’s phenomenon and coronary artery disease, we investigated the effect of a cardioselective and a nonselective β-blocking drug in equivalent doses on fingertip hemodynamics and clinical symptoms in patients with Raynaud’s phenomenon.

Methods

Subjects gave informed consent and the institutional committee on human research approved the study protocol. Sixteen women who had had Raynaud’s phenomenon for 3 to 29 years were studied. Their average age was 35 years (range 24 to 59). Raynaud’s phenomenon was diagnosed in the presence of episodic attacks of well-demarcated color changes (white or blue) of the fingers on both hands on exposure to cold. Fourteen patients were classified as having idiopathic disease because of negative history, normal physical examination, and laboratory results; two subjects were classified as having collagen vascular disease on the basis of positive antinuclear antibodies.

Total fingertip blood flow (FBF) was measured by venous occlusion plethysmography and fingertip capillary flow (FCF) was measured by the disappearance rate of a radioisotope after a fingertip injection. The hand and arm were elevated slightly above heart level. The plethysmograph was attached by a finger cup sealed to the fingertip beyond the distal interphalangeal joint with caulking compound. A 2.5 cm pneumatic cuff was applied proximal to the finger cup. The lowest venous occlusion pressure required to obtain the maximal rate of increase in fingertip volume was determined at the beginning of each experiment and averaged 57 mm Hg. Changes in fingertip blood volume were detected by a Validyne low-pressure transducer (MP 45-14) connected by stiff plastic tubing to the outlet of the finger cup and recorded by a Hewlett-Packard 8805B preampli-
fier and recorder. The recording system was calibrated after equilibration for 1 hr at 28.3°C and 20°C room temperature by introducing known quantities of air into the system. Fingertip blood volume within the finger cup was determined by water displacement to express blood flow in milliliters per min per 100 ml of tissue. Arm blood pressure was determined by the sphygmonanometric method. The mean blood pressure was calculated by adding one-third of the pulse pressure to the diastolic pressure. Finger vascular resistance was calculated by dividing the mean arm blood pressure by total FBF and was expressed as millimeters mercury per minute per 100 ml of tissue. This is only an estimate of the finger vascular resistance because the finger blood pressure may be smaller than the brachial artery pressure in the warm environment. Finger systolic pressure (FSP) was measured by inflating the finger pneumatic cuff to suprasystolic pressure and then slowly releasing the pressure. The cuff pressure at which the first increase in fingertip volume occurred was recorded as the systolic pressure.

The disappearance rate of a radioactive isotope from a local injection in an adjacent fingertip was used as a measure of FCF. Approximately 0.01 ml Na131I in saline solution (0.9%) was injected with a 27-gauge needle into the skin of the pad of one fingertip. Disappearance rate was monitored by a scintillation probe, rate meter (time constant set at 5 sec), and linear recorder. The scintillation probe contained a thallium-activated sodium iodide crystal. Dose of the isotope used was about 2 µCi. Disappearance rates were plotted on semilogarithmic paper after subtraction of the background counts and were expressed as half-times. Disappearance rates were also converted into an estimated blood flow in milliliters per minute per 100 ml of tissue by dividing the natural logarithm of 2 by the half-time and multiplying by the tissue-to-blood coefficient (0.5) times 100.

The randomized, double-blind, crossover design consisted of a 2 week placebo run-in period, a 2 week drug period, a 2 week washout placebo period, and a 2 week alternate drug period. Finger hemodynamic studies were performed at the end of the placebo run-in and after each drug period. Measurements at each session were obtained after 1 hr in a warm (28.3°C) room and after 1 hr in a cool (20°C) room. Subjects took their medication at the beginning of the experiment. In the warm room, subjects were covered with a blanket, while in the cool room they wore only a hospital gown. The setting of the 20°C room with the patient in a short gown was chosen since previous experience has shown that lower temperatures may induce shivering. FBF and isotope disappearance rates were followed for 8 min in each environment. Arm blood pressure and FSP were also determined in the warm and cool rooms.

Metoprolol (50 mg), propranolol (40 mg), and placebo in identical tablets were supplied by Ciba-Geigy Pharmaceuticals Division and pills were taken two times a day. Blood samples for determination of chemical profiles and complete blood count and urine samples were collected at the beginning of the study and on each of the measurement days. Antinuclear antibodies and sedimentation rates were measured on the first visit. Subjects kept daily diaries of the frequency of their vasospastic attacks. They also gave an overall evaluation of their condition at the end of each period, rating their response as worse, unchanged, or as 25% to 50%, 50% to 75%, or 75% to 100% improved. The daily mean temperature in the Boston area was also recorded.

Hemodynamic data from the first placebo period and the two drug periods were analyzed and compared. Similar evaluations were performed for the diaries and overall evaluations for all four periods. Since there was a large variation in the FBFs and the number of vasospastic attacks between patients, log10-transformed data were also analyzed. A Latin square analysis was used to determine the effect of the order of administration of drugs.9 An analysis of variance for a crossover design with repeated measures was then used (Program SPSS-X). Where appropriate the Newman-Keuls test was applied to determine significance at the p < .05 level. Data were expressed as mean ± SE.

**Results**

There were no significant differences in the finger hemodynamic measurements between drug and placebo periods or between the two drug periods in the warm or cool rooms (table 1). In the cool room, the mean FBF tended to be smaller with both drugs than with placebo, but three patients had large blood flows in this environment (figure 1). One other patient had a large blood flow only while on metoprolol. When the values in these three patients were excluded, average FBF was very similar during the three periods: 2.1 ± 0.4 ml/100 ml tissue/min for placebo, 2.0 ± 0.3 ml/100 ml tissue/min for metoprolol, and 2.1 ± 0.4 ml/100 ml tissue/min for propranolol. With the exception of FSP, differences in parameter values recorded in the warm and cool rooms from patients on both

| TABLE 1 | Hemodynamic measurements in the finger during drug and placebo periods |
|---------|------------------------|------------------------|------------------------|------------------------|
|         | FBF (ml/100 ml tissue/min) | FVR (mm Hg/100 ml tissue/min) | FCF (ml/100 ml tissue/min) | FSP (mm Hg) |
| **Warm room (28.3°C)** | | | | |
| Placebo | 50.1 ± 9.2 | 4.8 ± 2.1 | 6.3 ± 0.4 | 94.0 ± 3.0 |
| Metoprolol | 44.0 ± 7.8 | 6.1 ± 2.9 | 6.3 ± 0.6 | 90.5 ± 3.8 |
| Propranolol | 46.4 ± 7.4 | 3.2 ± 0.8 | 6.5 ± 0.7 | 95.0 ± 4.8 |
| **Cool room (20°C)** | | | | |
| Placebo | 9.1 ± 3.8 | 38.0 ± 6.6 | 2.5 ± 0.4 | 104.8 ± 5.0 |
| Metoprolol | 6.4 ± 2.5 | 38.3 ± 7.2 | 3.2 ± 0.5 | 98.9 ± 4.9 |
| Propranolol | 3.8 ± 1.4 | 53.3 ± 12.3 | 2.3 ± 0.3 | 105.6 ± 4.4 |

Data are mean ± SE. There were no significant differences between drug and placebo periods for any of the variables.

FVR = fingertip vascular resistance.
drugs and placebo were significantly different. The FSP did not increase significantly in the cool room during either drug period (metoprolol p < .1; propranolol p < .06).

No significant differences were found with respect to number of vasospastic attacks per 2 week period or to the patients' overall evaluations of their symptoms between the two drug periods or between drug and placebo periods (tables 2 and 3).

After both metoprolol and propranolol there was a significant decrease in pulse rate compared with after placebo in both the warm and cool rooms (table 4). Pulse rate was not significantly different during the two drug periods in either environment. Mean blood pressure after metoprolol in both the warm and cool rooms was significantly lower than that during the placebo period. In the cool room blood pressure was significantly lower with metoprolol than propranolol (p = .01).

Average daily temperature in the Boston area was 5.9 ± 1.2° C during the first placebo period, 6.9 ± 2.0° C during the metoprolol period, 8.1 ± 1.6° C during the second placebo period, and 8.6 ± 2.2° C during the propranolol period; these were not significantly different.

Side effects with the medications were few and did not cause any patient to discontinue or decrease dosage of medication. Two patients on placebo reported lethargy and a third had depression. Two patients had lightheadedness, one had lethargy, one had nausea, and one had diarrhea while taking metoprolol. Two patients reported nausea, one lightheadedness, and one headaches while on propranolol. No abnormal blood test results or urinalyses were obtained during placebo or drug periods.

**Discussion**

In this study, 80 mg/day propranolol or 100 mg/day metoprolol for 2 weeks did not significantly alter FBF, FCF, or FSP in a warm or cool environment when compared with placebo. There were no significant

**TABLE 3**

<table>
<thead>
<tr>
<th>Period</th>
<th>Score&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>2.0 ± 0.1</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>2.4 ± 0.3</td>
</tr>
<tr>
<td>Placebo</td>
<td>2.1 ± 0.3</td>
</tr>
<tr>
<td>Propranolol</td>
<td>2.4 ± 0.2</td>
</tr>
</tbody>
</table>

Data are mean ± SE. There were no significant differences between the four 2 week periods.

<sup>1</sup>i = worse; 2 = unchanged; 3 = 25% to 50% improved; 4 = 50% to 75% improved; 5 = 75% to 100% improved.

**TABLE 4**

<table>
<thead>
<tr>
<th></th>
<th>Pulse rate (beats/min)</th>
<th>Mean blood pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Warm room (28.3° C)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>69.0 ± 3.4</td>
<td>78.8 ± 2.2</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>61.9 ± 3.1&lt;sup&gt;1&lt;/sup&gt;</td>
<td>72.7 ± 2.5&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Propranolol</td>
<td>61.8 ± 3.0&lt;sup&gt;1&lt;/sup&gt;</td>
<td>75.9 ± 2.0</td>
</tr>
<tr>
<td><strong>Cool room (20° C)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>65.4 ± 2.8</td>
<td>83.8 ± 2.9</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>56.9 ± 3.4&lt;sup&gt;1&lt;/sup&gt;</td>
<td>78.3 ± 2.3&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Propranolol</td>
<td>55.9 ± 2.4&lt;sup&gt;1&lt;/sup&gt;</td>
<td>83.0 ± 2.9</td>
</tr>
</tbody>
</table>

Data are mean ± SE.

<sup>1</sup>p = .01 for differences between drug and placebo.
changes in the number of vasospastic attacks recorded by diary or in the patients’ overall evaluations of their conditions while they were receiving the drugs. The decrease in pulse rate with both drugs and the decrease in blood pressure with metoprolol indicate a degree of β-adrenoreceptor blockade was produced. A greater decrease in blood pressure in normal subjects has previously been reported with metoprolol compared with propranolol and placebo. We were therefore unable to demonstrate a significant change in the digital circulation or an aggravation of Raynaud’s phenomenon in patients taking a nonselective or a cardioselective β-blocking agent with objective tests or subjective evaluations. It is possible that higher doses of the drugs may have produced different results, but Marshall et al. found no association between vasospastic symptoms and dose.

In a previous study, we have shown that patients with Raynaud’s phenomenon had significantly smaller FBFs and FCFs than normal subjects in a warm or cool environment. However, the overlap in flow values did not distinguish between patients and normal subjects on an individual basis. The average total flow measured in the warm room in this study was larger than that in our previous report, but the patients were not covered with blankets in the latter study. The cool room total and capillary flows are comparable; in the previous study they were significantly less than those in the normal subjects. In studying patients with primary or secondary Raynaud’s phenomenon, we usually find a few patients with large FBFs in the cool room. The three patients with large values in this study represented patients with primary and secondary disease and numbers of vasospastic attacks ranging from one to 53 per week. Furthermore, number of attacks did not increase during drug treatment in these patients. Apparently, they do not represent a special subset of the disease. Although the study group of 16 patients is rather small to allow generalization of results to the population at large, these patients represented a broad spectrum of the disease.

McSorley and Warren reported a decrease in skin temperature and skin and muscle blood flow in normal subjects on 80 mg propranolol daily, and 100 mg metoprolol daily also decreased skin flow in hypertensive patients. Nielsen and Nielsen, using a technique of finger cooling during ischemia, found increased digital arterial tone at low temperatures after administration of 120 to 240 mg propranolol daily but not after metoprolol (100 to 150 mg daily) in hypertensive patients. However, they also reported the development of vasospastic attacks in one patient on a cardioselective drug. Holti presents some evidence that patients with long-standing Raynaud’s disease and hypertension fared worse on 160 mg of long-acting propranolol than on 400 mg acebutolol. However, Steiner et al. reported no difference in finger temperature or symptoms in 14 hypertensive patients with Raynaud’s phenomenon during propranolol or labetalol treatment.

Almost all studies reporting the development of Raynaud’s phenomenon or cold extremities with β-blocking drugs concern patients with hypertension. Nielsen et al. have demonstrated that digital arterial tone during cooling is significantly greater among hypertensive subjects than among normotensive controls. Feleke et al. have commented that hypertension may predispose to vasospastic reactions.

It is unclear why there is such a marked variation in results of studies of the incidence of Raynaud’s phenomenon, cold extremities, or even intermittent claudication in patients on β-blockers or in the reported effects of these agents on skin and muscle blood flow in normal individuals or hypertensive patients. The incidence of this side effect varies from as low as 4.1% to as high as 41% in studies of patients with hypertension; both cardioselective and nonselective agents have been implicated. None of the patients in our study were hypertensive. In fact, patients with Raynaud’s disease tend to have a significantly lower blood pressure than normal subjects; average mean blood pressure was only 79 mm Hg in our group. Therefore, our results cannot be applied to hypertensive patients. Vasospastic phenomena do occur in nonhypertensive patients treated with β-blockers; eight of the 21 patients reported by Eliasson et al. did not have high blood pressure.

From our study and evidence in the literature, it may be concluded that the presence of Raynaud’s phenomenon is not a contraindication to the use of β-adrenoceptor–blocking drugs. Zacharias reported that only 3% of their hypertensive patients required withdrawal of the drug or reduction of the dose due to severe Raynaud’s phenomenon. This is especially important for the patient with coronary artery disease and Raynaud’s phenomenon for whom therapy with β-blocking agents may be a necessity. It is probably prudent to avoid use of β-blocking drugs in patients with hypertension and Raynaud’s phenomenon.

References
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J D Coffman and H M Rasmussen

Circulation. 1985;72:466-470
doi: 10.1161/01.CIR.72.3.466
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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