Double-Blind, Placebo-Controlled Study of Intravenous Prostacyclin on Hemodynamics in Severe Raynaud’s Phenomenon: The Acute Vasodilatory Effect Is Not Sustained

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Summary: In 12 patients with severe Raynaud’s phenomenon (RP: ischemic ulcers or intractable pain despite use of narcotic analgetics), we studied the acute and long-term hemodynamic effects of epoprostenol on systemic and finger skin circulation. Epoprostenol was infused intravenously (i.v., initial infusion rate of 2 ng/kg/min, with a subsequent increase of 2 ng/kg/min every 30 min to the individually tolerated maximal dose of 8 ng/kg/min) in a triple, 5-h, double-blind, placebo-controlled cross-over study. During epoprostenol infusion, systolic blood pressure (SBP) remained stable, while diastolic BP (DBP) decreased (−8 mm Hg, p < 0.02), with a simultaneous increase in heart rate (HR *f 14 beats/min, p < 0.001). Forearm blood flow (FBF) increased and forearm vascular resistance (FVR) decreased during epoprostenol as compared with placebo infusion (p < 0.01). Epoprostenol caused a significant increase in fingertip skin temperature (p < 0.01) as well as in laser Doppler flux (p < 0.02) before and after a standardized cooling test of the hand as compared with placebo. The increase in transcutaneous oxygen tension reached significant difference only during recovery (p < 0.02). No long-term improvement was noted during two additional cooling tests performed 1 and 6 weeks after the completed epoprostenol or placebo triple-infusion cycle. Repeated long-lasting epoprostenol infusion immediately improves the microcirculation, but these effects are not sustained after 1 week. Key Words: Epoprostenol—Raynaud’s phenomenon—Cooling test—Finger skin temperature—Laser Doppler flux.

Although the incidence of Raynaud’s phenomenon (RP) is ~10–15% of the general population in the colder regions of the United States and northern Europe (1), relatively little is known about its underlying pathophysiology (2), as is reflected by most experimental treatment protocols, resulting in some individual relief, but no major general improvement (2).

Prostacyclin [prostaglandin I₂ (PGI₂) or epoprostenol] is a potent vasodilator and platelet aggregation inhibitor (3), produced by intact blood vessel wall endothelium. Its mechanism of action depends on increase in cyclic AMP (4) through activated adenylyl cyclase (5). Depletion of prostacyclin might lead to vasospasm. Although this had never been shown to cause primary RP, endothelial dysfunc-

PATIENTS AND METHODS

Twelve nonsmoking patients with severe RP (i.e. either trophic skin lesions or pain that could not be sufficiently treated by morphinomimetics) were included in this ran-
domized, double-blind, placebo-controlled cross-over study. Exclusion criteria were the current use of drugs that may affect RP or a myocardial infarction or ischemic stroke ≤3 months before the start of the study. All patients gave written informed consent to the trial protocol, which was approved by the Ethical Committee, University Hospital Nijmegen. According to the criteria of Allen and Brown (9) 2 patients were classified as having primary RP. The remaining 10 were diagnosed as having secondary RP due to connective tissue diseases according to American Rheumatism Association (ARA) criteria (10,11).

The study design consisted of an initial cycle with either three epoprostenol or placebo infusions with an interval of 1 week between infusions, followed by an 8-week washout period and the subsequent cross-over cycle (again with three infusion periods). Each infusion lasted 5 h, during which either the drug or placebo was administered through a catheter positioned in an antecubital vein.

The initial dosage of epoprostenol was 2 ng/kg/min, with increments of 2 ng/kg/min every 30 min to 8 ng/kg/min or to the individually maximal tolerated dose. All tests were performed in a climate-controlled room (25°C) after a 30-min acclimatization period. The patients were asked not to consume alcohol for the 2 h before the tests and not to drink caffeine-containing beverages or to smoke for 24 h before the start of the experiment.

On the distal volar surface of the second, third, and fourth fingertip of the right hand, respectively, we measured Finger Skin Temperature (FST) in degrees centigrade by a thermocouple (Ellab Instruments), laser Doppler-estimated finger blood flux (LDF) in perfusion units (PU) by a periflux (Perimed) and transcutaneous oxygen tension (TcPO₂) in mm Hg by a Tacomette with the probe heated to ≤45°C (Novametrix). LDF and TcPO₂ measurements were performed after calibration. After the infusion a 5-min occlusion period enabled us to register the first three epoprostenol or placebo infusions with an in-

The clinical characteristics of the 12 RP patients are shown in Table 1. The acute effect of intravenous epoprostenol on BP, HR, FBF, and FVR are shown in Fig. 1. There were no significant differences in baseline values between epoprostenol and placebo.

During epoprostenol infusion, SBP decreased from 134 ± 7 to 127 ± 5 mm Hg (NS). DBP decreased from 77 ± 4 to 69 ± 3 mm Hg (p < 0.02). As a consequence, MAP decreased 8 mm Hg from 96 ± 5 to 88 ± 3 mm Hg (p < 0.05). HR increased from

<table>
<thead>
<tr>
<th>Patient/age/sex</th>
<th>Body mass index</th>
<th>Diagnosis</th>
<th>Duration of RP</th>
<th>Nutritional skin lesions</th>
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<tr>
<td>1/45/F</td>
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<td>6</td>
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<td>SRP/PSS</td>
<td>16</td>
<td>+</td>
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<tr>
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<td>9</td>
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<tr>
<td>12/36/M</td>
<td>20.3</td>
<td>PRP</td>
<td>19</td>
<td>+</td>
</tr>
</tbody>
</table>

a Age and duration in years.

b Body weight (kg)/height² (m).

c PRP, primary Raynaud’s phenomenon; SRP, secondary Raynaud’s phenomenon; PSS, progressive systemic sclerosis; VOD, vascular occlusive disease; UCTD, undifferentiated connective tissue disease.

d No trophic skin lesions (−); minor lesions (+); ulcers or gangrene (+).
Epoprostenol did not affect FBF or FVR, although these differed significantly (p < 0.01) as compared with values in placebo-treated patients (+2 ml/100 ml/min and -9 AU, respectively).

The effects of epoprostenol infusion on the microcirculation (FST, LDF, and TcPO₂) are shown in Fig 2. Baseline microcirculatory values between epoprostenol and placebo did not differ significantly.

Before the FCT, epoprostenol increased FST from 29.4° ± 1.2° to 32.1° ± 0.9°C (p < 0.02), with a significant final difference of 2.6°C as compared with placebo (p < 0.01). In contrast to placebo, epoprostenol caused an increase in LDF from 14 ± 3 to 23 ± 5 PU (p < 0.01), which was significantly greater than the value in placebo condition (p < 0.01). No effect on TcPO₂ was observed.

During cooling, the decrease in all microcirculatory parameters was not significantly different in epoprostenol and placebo. During recovery, epoprostenol resulted in a complete microcirculatory recovery of FST from 20.6° ± 0.5° to 31.4° to 0.8°C (p < 0.01) and LDF from 11 ± 4 to 24 ± 5 PU (p < 0.01). During placebo, the increase was less for both (p < 0.01). The differences in TcPO₂ between epoprostenol and placebo reached significance only late during recovery (p < 0.02). As compared with

FIG. 1. The effect of epoprostenol (solid line) and placebo infusion (dashed line) on systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), mean arterial pressure (MAP), forearm blood flow (FBF), and forearm vascular resistance (FVR) in time. All values are mean ± SE.
placebo, epoprostenol improved neither the macro- nor the microhemodynamics, as determined by an additional FCT performed 1 and 6 weeks after the triple epoprostenol or placebo infusion cycle.

Side effects were reported during 88% of the epoprostenol infusions and in 5% of the placebo infusions. Most frequent were flushing (75%), headache (56%), and palpitations (47%). Other complaints were nausea, vomiting, dizziness, abdominal cramps, and retrosternal pain (without changes in ECG). In 9 of the 36 epoprostenol infusions, the infusion rate had to be reduced; the experiment had to be discontinued prematurely in 3. Patient 3 experienced temporary blurred vision, although ophthalmic examination showed no abnormalities. Patient 12 complained of retrosternal pain during all three epoprostenol infusions.

**DISCUSSION**

Theoretically, epoprostenol is expected to improve the impaired microcirculation in patients with RP since it is a powerful vasodilator and platelet inhibitor. Indeed, our findings showed a pronounced acute hemodynamic effect on the systemic circulation (increased FBF and HR, decreased BP and PVR) as well as on the microcirculation (increased FST, LDF, and TcPO₂) during epoprostenol infusion; an effect that was also observed previously in normal healthy volunteers (12). However, 1 week after the completed triple-infusion cycle, all of the cited signs of vasodilation and improvements in microcirculatory hemodynamics had already disappeared. This short-term effectiveness of epoprostenol is in agreement with its short t½ of 2-3 min. The lack of long-term effects is in contradiction to results of several studies, although some studies report minor effectiveness (13). Belch and colleagues (7) reported that hand temperature increased significantly 1 week after a triple 5-h epoprostenol infusion cycle (7.5 ng/kg/min) as compared with placebo; for ≤6 weeks, they noted a decrease in number and duration of attacks as well as healing of trophic skin lesions in the epoprostenol-treated group. Dowd and associates (8) performed an uncontrolled 72-h epoprostenol infusion (5-7 ng/kg/min) in patients who all had secondary RP (SRP) due to systemic sclerosis. For ≤2 weeks after the infusion period, FST was significantly increased. The mean duration of the subjective response, as assessed by a diary, was 9 weeks. Rademaker and co-workers (14) reported a long-term benefit of the more stable prostacyclin analogue iloprost in SRP due to systemic sclerosis and suggested that iloprost might heal endothelial lesions in systemic sclerosis, subsequently leading to de novo synthesis of epoprostenol. Fiessinger and colleagues (15) showed that iloprost was more effective than aspirin for relief of rest pain due to leg ischemia and healing of trophic lesions in patients with thromboangiitis obliterans.

During epoprostenol infusions, total skin blood flow as well as oxygen delivery to the skin improved. TcPO₂ was measured to indicate skin oxygen tension (16), thus representing capillary nutritional skin flow (17). The LDF measurements are supposed to represent total skin blood flow, as well as that through part of arteriovenous shunts and the capillary loops (18,19). The laser Doppler technique...
measures the frequency shift of back-scattered laser light by moving erythrocytes in the outermost layers of the skin (19). Monitoring of LDF has proven to be of value in intervention studies (20,21). Its major disadvantage is the enormous inter- and intraindividual variation (22) caused by rapid sympathetic reflex activity in thermoregulatory arteriovenous shunt flow (23). To reduce this variation, we averaged the three infusion series with either epoprostenol or placebo. Nevertheless, an obvious interindivdual variation in LDF remained, shown by the SE. Many different measurement techniques (skin temperature, laser Doppler, finger BP, finger-tip plethysmography, dynamic nailfold capillary microscopy) and provocation tests (local cold, contralateral cooling, whole body cooling, postischemia hyperemia) are used to objectify vasospasm.

A standardized finger cooling test (24) was used as a model to mimic a Raynaud’s attack. Although obtaining the specific discolorations during local cold challenge of the hand is rarely possible, this FCT has been used successfully in several placebo-controlled therapeutic studies (20,21). In contrast to the cooling test used in the present study, most tests are not carefully standardized and their reproducibility and diagnostic values have not been outlined. Yet other tests or measurement techniques could have yielded different results. Although all patients had severe RP, the heterogeneity of our patient population (2 primary RP and 10 secondary RP, 7 of whom had systemic sclerosis, and 2 of whom had unclassifiable autoimmune disease and 1 of whom had vascular occlusive disease) could have biased our study. The effects of intravenously administered epoprostenol in one of these specific subgroups could not be analyzed.

In general, the side effects were dose dependent. Flush and headache occurred with 4 ng/kg/min, whereas palpitations, nausea and vomiting were noted in the 6–8-ng/kg/min range. The infusion rate had to be reduced in 9 patients; complaints usually disappeared after reduction. The total dosage used during all epoprostenol infusions in this study appears to be sufficient to obtain clinical effects if one considers the low (0.5 mg/kg/min for 6 h) dose that was effective in another study (25).

The term double-blind is a questionable one in studies like the present study. Because of the frequent visible side effects (flushing) that occurred during epoprostenol infusion, both the physician and the patient were often aware of the identity of the drug used.

Although the patients were asked to keep a diary during and after the trial to note the number, severity, and duration of attacks, only 4 of them were able to record them reliably and fully during the 3-month study period. Two patients obviously misunderstood the meaning of the diary, and in 2 the number times duration of attacks often exceeded the 24-h daily period. Therefore, the diary results were not analyzed. Epoprostenol benefits skin microcirculatory flow during the infusion period, but these effects disappear soon after discontinuation of the infusion. Whether comparable agents with a longer t½, such as iloprost, have a more prolonged circulatory and also subjective effect remains to be established. The development of oral analogues in the near future will be a major advance.

REFERENCES

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