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Iloprost Enhances Portal Flow Velocity and Volume in Patients with Systemic Sclerosis

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Abstract. *Background: Iloprost, a prostacyclin analog, reduces hepatic microcirculatory damage after ischemia-reperfusion injury in animal liver models. The objective of this study was to evaluate whether the portal flow velocity changes after Iloprost infusion in patients with systemic sclerosis and Raynaud's phenomenon, who usually have increased risk of microvascular thrombosis and transient liver disturbances. Patients and Methods: Fifteen patients (3 males and 12 females, median age 58 years, range 47-66 years), with systemic sclerosis and Raynaud's phenomenon, were exclusively treated with an infusion of Iloprost (2 ng/kg/min, 6 h/day) for 5 days. In each subject, the portal flow velocity (PV, cm/sec) and portal flow volume (PFV, mL/min) were obtained by using portal color Doppler ultrasonography equipment. Results: Iloprost administration significantly ($p<0.001$) increased both the PV (23.6±3.4 cm/sec vs. 29.1±3.9 cm/sec) and PFV (1748.8±310.7 mL/min vs. 2254.9±404.1 mL/min) values. Conclusion: Hepatic perfusion significantly improved after Iloprost administration, suggesting that such treatment might be useful in preventing vascular complications in patients with systemic sclerosis. Iloprost improves the portal hemodynamics, favoring local microvascular patency, and its effectiveness may be safely monitored by using portal color Doppler ultrasonography.*

Iloprost (or PGI2), discovered in 1976, is an analog of prostaglandin I, a prostacyclin physiologically produced by humans (1). It has vasodilator and platelet aggregation inhibitor properties, and has been successfully used in the treatment of primary pulmonary hypertension, Raynaud's phenomenon, systemic sclerosis, severe chronic ischemia of the lower limbs and Buerger's disease (2, 3). It has been reported that Iloprost has hepatic cytoprotective effects (4). Furthermore, it has been demonstrated that Iloprost improved the hepatic bioenergetic integrity of animal donor livers if added to the organ preservation solutions, and attenuated the hepatic microcirculatory damage after ischemia-reperfusion injury in animal liver models (5, 6). In addition, it has recently been demonstrated that Iloprost significantly increased the portal vein flow and also seemed to improve the renal circulation, without any effect on the hepatic and mesenteric arteries, in subjects with arteriopathy of the lower limbs (7).

The aim of this study was to evaluate the efficacy of Iloprost on hepatic microcirculation in patients with systemic sclerosis and secondary Raynaud's phenomenon. These patients have an increased risk of microvascular thrombosis and transient liver disturbances in comparison to a population with arteriopathy of the lower limbs, resembling patients with viral chronic hepatitis (8, 9).

Patients and Methods

Study population. Fifteen consecutive patients, with systemic sclerosis and secondary Raynaud's phenomenon, were enrolled in the study. There were three men and twelve women, with a median age of 58 years (range 47-66 years). The diagnosis of systemic sclerosis was made according to the conventional criteria of the American College of Rheumatology, whereas Raynaud's phenomenon was diagnosed on the basis of a history of episodic digital pallor and cyanosis (10). Patients previously treated with prostacyclin analogs or affected by arterial hypertension and treated with anti-hypertensive agents were excluded from the study. Other exclusion criteria were liver cirrhosis, malignancies, platelet disorders and a history of stroke or myocardial infarction, as well as advanced systemic sclerosis, characterized by dyspnea at rest, because the prognosis of these patients was particularly poor. Each patient underwent pre-study

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Table I. *Skin, esophageal and pulmonary involvement in enrolled patients with systemic sclerosis and Raynaud's phenomenon.*

Patient	Skin involvement	pH monitoring and manometry	Endoscopy	Spirometry	Blood gas analysis	Chest X-ray	Chest CT-scan	Antinucleus antibodies
1	Digital ulcers	Normal	Normal	Normal	Normal	Some hilar calcifications	Ground glass pattern	Positive
2	Negative	Normal	Normal	Normal	Normal	Normal	Normal	Positive
3	Morphea	Normal	Esophageal reflux	Normal	Normal	Normal	Normal	Positive
4	None	Normal	Normal	Restrictive abnormalities	Normal	Normal	Ground glass pattern	Positive
5	None	Esophageal immobility	Normal	Normal	Normal	Normal	Normal	Negative
6	None	Normal	Normal	Restrictive abnormalities	Normal	Normal	Ground glass pattern	Positive
7	Digital ulcers	Esophageal immobility	Normal	Restrictive abnormalities	Normal	Normal	Honeycomb pattern	Positive
8	None	Normal	Normal	Restrictive abnormalities	Normal	Normal	Ground glass pattern	Positive
9	None	Normal	Normal	Normal	Mild hypoxia	Normal	Honeycomb pattern	Positive
10	Digital ulcers	Esophageal immobility	Esophageal reflux	Restrictive abnormalities	Hypoxia	Normal	Honeycomb pattern	Positive
11	Digital ulcers	Esophageal immobility	Normal	Normal	Normal	Normal	Normal	Negative
12	None	Normal	Normal	Normal	Mild hypoxia	Normal	Ground glass pattern	Positive
13	None	Normal	Normal	Restrictive abnormalities	Normal	Normal	Ground glass pattern	Positive
14	Digital ulcers	Esophageal immobility	Normal	Restrictive abnormalities	Normal	Normal	Ground glass pattern	Negative
15	Digital ulcers	Esophageal immobility	Esophageal reflux	Restrictive abnormalities	Hypoxia	Normal	Honeycomb pattern	Positive

evaluation: (i) general clinical examination, including systolic and diastolic blood pressure and heart rate measurements, (ii) routine laboratory evaluation (red and white blood cell counts, renal function, liver enzymes, total protein and albumin, serum lactate dehydrogenase, electrolytes), (iii) immunological assays (auto-antibodies), (iv) molecular markers for occult cancer (carcinoembryonic antigen [CEA], alpha feto-protein [AFP], CA 15-3, CA 125, CA 19-9), (v) standard urinalysis (dipstick analysis for blood, glucose and proteins), (vi) electrocardiogram and echocardiography, (vii) abdominal and pelvic ultrasonography, (viii) endoscopy, (ix) chest X-ray, and (x) thoracic CT-scan. Only patients affected by systemic sclerosis and secondary Raynaud's phenomenon without complications, such as rest dyspnea, pulmonary arterial hypertension and renal insufficiency, were included in the study. Some patients suffered from gastroesophageal reflux disease or esophageal dysmotility, while others had limited skin involvement, with or without digital ulcers, and showed signs of pulmonary functional abnormalities (Table I). The frequency of Raynaud's attacks in the enrolled patients was quite similar, varying from five to eight episodes per month. The standard medical treatment for each patient was optimized before inclusion into the study.

All the enrolled patients were treated with Iloprost infusion at 2 ng/kg/min (6 h/day) for 5 days.

Informed consent was obtained from all participants in accordance with institutional review board approval. The study protocol was approved by the Ethical Committee of the University of Campus Bio-Medico, Rome, Italy.

Portal color Doppler examination. All the patients underwent an initial color Doppler ultrasonography (US) examination of their portal vein before and after treatment with Iloprost. The patients, examined in a supine position, were studied by the same operator, using General Electric 500 equipment and a convex 3.5 MHz probe, after an 8-hour fast. Portal flow velocity measurements (PV) were obtained, after positioning the electronic caliper at the crossing point of the portal vein with the hepatic artery. To minimize casual variability of flow velocity along the course of the portal vein, the results were expressed as a mean of three Doppler US evaluations, performed with an angle of insonation lying between 50° and 60°. Furthermore, after measurement of the portal diameter (mm), the portal vein cross sectional area (CSA) (mm^2) was calculated basing on the formula "$r^2 \times \pi$". Finally, the portal flow volume (PFV) (mL/min) was obtained applying the formula "CSA x PV". In no case did complications require the Iloprost treatment to be discontinued.

Statistical analysis. The reported data were expressed as mean±standard deviation (SD), and differences between means were tested by the unpaired Student's *t*-test . A value of $p<0.01$ was considered to be statistically significant.

Results

Overall, the pre- and post-Iloprost infusion PV values were 23.6±3.4 and 29.1± 3.9 cm/sec, respectively ($p<0.001$). The

baseline PFV value was 1748.8±310.7 mL/min and, after Iloprost infusion, it was 2254.9±404.1 mL/min ($p<0.001$). After 5 days of Iloprost infusion, the mean PFV of all patients increased by 22.4%. Figure 1 shows the PV and PFV values for each patient before and after Iloprost infusion. The increase of portal perfusion was not uniform in all the subjects, however no patient showed a decrease in PV or PFV. During the treatment, no patient suffered from Raynaud's phenomenon. Only mild side-effects, such as transient nausea, headache and flushing, were observed. One patient developed an episode of vomiting on the first day of treatment, without further complications, thus not requiring the suspension of Iloprost infusion.

Discussion

We have already demonstrated a significant increase of PV and PFV after Iloprost treatment in patients without abnormalities of the liver microcirculation (7). Iloprost treatment is not yet used in patients with chronic liver hepatitis. However, patients with systemic sclerosis and secondary Raynaud's phenomenon present similar clinical features and hepatic hemodynamics, since they are at a greater risk of developing transient liver disturbances and microvascular thrombosis (8, 9).

Both PV and PFV significantly ($p<0.001$) increased after Iloprost infusion, and no patient showed a decreased portal perfusion, the lowest hepatic perfusion increase being 8.5% after treatment. These results suggest that Iloprost may provide a better hepatic flow and a potentially better liver function, independently of the population treated.

In healthy subjects, several vasoactive substances (vasoconstrictors and vasodilators) regulate the homeostasis of liver function, and contribute to the regulation of the portal microcircle patency in the various segments of the afferent portal venules and hepatic arterioles, particularly in the sinusoids (11-15). In particular, prostacyclin (PGI2) is thought to have a powerful local vasodilatory effect on portal microcirculation acting on hepatic stellate cells of the hepatic microcirculation through a calcium-dependent mechanism, opposing to vasoconstrictors such as endothelin (16). Moreover, PGI2 counteracts the vasoconstrictive and pro-aggregatory actions of thromboxane A_2 (17). Because of its properties and because it displays an antitumor-necrosis-factor-alpha (TNF) action, PGI2 probably contributes to prevent ischemia/reperfusion injury in transplanted liver patients (18-21). In fact, after liver transplantation, there is an imbalance of hepatic microcirculation commonly called the "non-reflow" phenomenon, which seems to be due to an increase of thromboxane A_2 together with the decreased generation or activities of PGI2 and nitric oxide (22-24). Moreover, an increased microvascular hepatic local production of endothelin-1 (ET-1) also occurs (25), thus causing enhanced portal resistance and inducing hepatic microcirculation impairment (25, 26). Therefore, PGI2, by counteracting the activities of these molecules, is able to reduce ischemia/reperfusion injury, and to improve the oxygen delivery index and hepatic venous oxygen saturation after liver transplantation (19-21, 27). Iloprost may also improve hepatic perfusion by antagonizing endothelin-induced vasoconstriction, or through other mechanisms (28).

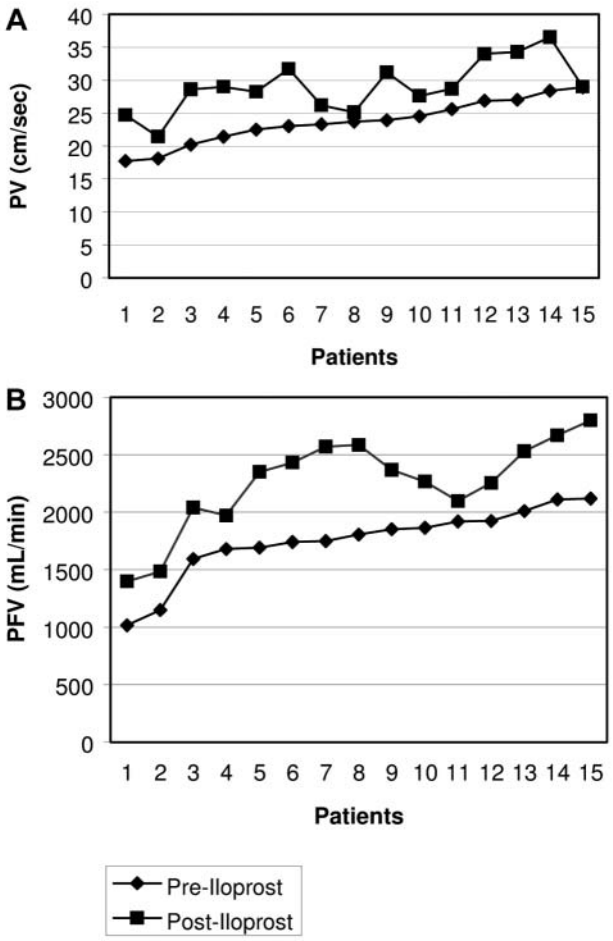

Figure 1. *Portal flow velocity (A) and portal flow velocity volume (B) before and after Iloprost infusion.*

Additional studies are necessary to establish the exact interrelationship between Iloprost and portal circulation, in order to define possible strategies for the correct use of these hemodynamic effects on liver diseases. It has also been demonstrated that portal color Doppler US is a useful tool to investigate changes in hepatic hemodynamics in transplanted liver patients (29). Therefore, the real efficacy of Iloprost treatment on portal microcirculation, for example to prevent ischemia/reperfusion injury after liver transplantation, might be monitored by observing the changes of hepatic perfusion using color Doppler US.

Conclusion

Iloprost improves the portal hemodynamics, favoring local microvascular patency, and its effectiveness may be safely monitored by using portal color Doppler US.

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