

Improved Hepatic Perfusion After Iloprost Infusion in Patients with HCV Chronic Infection: A Pilot Study with Possible Therapeutic Implications

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ABSTRACT

We performed a pilot study to evaluate whether portal flow volume (PFV) changed in subjects with chronic hepatitis C virus (HCV) infection with respect to control patients after infusion of iloprost, a prostacyclin analog. Six subjects with chronic HCV infection and arteriopathy of the lower limbs (CHCVIA) and 4 control patients affected only by HCV infection (CHCV) were studied with color Doppler sonography. CHCVIA patients were examined before and after 3 days of iloprost infusion, and CHCV patients were examined before and after 3 days with no treatment. In each patient, PFV was obtained after calculating portal flow velocity (PV), portal diameter, and portal vein cross-sectional area. The mean difference between basal and final values of the PFV of CHCVIA patients was significant ($p = 0.03$), as was the difference in the PFV (final values expressed as percent of basal values) in CHCVIA patients compared with those obtained in the CHCV patients ($p = 0.01$). We have observed significant improvement in hepatic perfusion in CHCVIA patients compared with CHCV patients after iloprost infusion. In light of these results, we suggest some possible therapeutic implications in patients with HCV infection. Further studies are necessary to confirm this hypothesis.

INTRODUCTION

IN HEALTHY SUBJECTS, THE HEMODYNAMICS of portal microcirculation is maintained by a correct balance between vasodilators (mainly, prostacyclin) and vasoconstrictors (endothelin) that regulate contraction and relaxation of the hepatic stellate cells.^(1,2) An imbalance of these vasoregulators, with vasoconstrictors prevailing over vasodilators, and an increase in hepatic fibrosis are causes of portal hypertension in patients with viral liver cirrhosis.⁽³⁻⁷⁾

To prevent the development of hepatic fibrosis, patients with chronic hepatitis C or B are treated with interferon (IFN) plus ribavirin or lamivudine, respectively.⁽⁸⁻¹¹⁾ However, treatments able to reduce the imbalance between vasoconstrictors and vasodilators and then to ameliorate portal microcirculation perfusion in patients with advanced viral chronic hepatitis do not yet exist. Treatment with iloprost, a prostacyclin analog, has been shown to improve hepatic perfusion in patients with arteriopathy of the lower limbs.⁽¹²⁾ To determine if this vascular effect

on portal circulation occurs also in patients with chronic viral hepatitis, we performed a pilot study in which we evaluated, with color Doppler sonography, the portal flow volume (PFV) in 10 patients affected by chronic hepatitis C virus (HCV) infection. We tested 6 of them basally and 3 days after iloprost treatment and the other 4 basally and after 3 days with no treatment.

PATIENTS AND METHODS

We studied, with color Doppler sonography, 6 subjects affected by chronic HCV infection (CHCVIA) (4 men and 2 women, mean age 55 ± 3.6 years), receiving iloprost at a dosage of 2 ng/kg/min (16 h/day) for 3 days as treatment for lower limb arteriopathy, and 4 control patients (CHCV) (3 men and 1 woman, mean age 53.7 ± 5.1 years) without iloprost treatment. All patients showed biochemical (raised serum alanine aminotransferase [ALT] levels), viral (HCV infection), and his-

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tologic (liver biopsy) evidence of chronic liver disease, with a histologic activity index ranging from 10 to 12 (Knodell score). In CHCVIA and CHCV, portal color Doppler sonography was performed by a single operator using General Electric 500 equipment and a convex 3.5-MHz probe. All patients were examined in the supine position after an 8-h fast. In each patient, PFV was obtained using the formula:

$$\text{PFV} = \text{Portal vein cross-sectional area (CSA)} \times \text{portal flow velocity (PV)}$$

CSA was determined after measuring the portal diameter and using the formula:

$$\text{CSA} = r^2 \times \pi$$

and PV was calculated by the Doppler system after positioning the electronic caliper at the crossing point of the portal vein with the hepatic artery. The final value of PV was the mean of three Doppler sonography evaluations performed at an angle lying between 56° and 60°, in accordance with other authors.⁽¹³⁾

During the infusion of iloprost, we did not observe significant side effects.

Statistical analysis

The mean difference between basal and final values of the PFV was analyzed, within the same groups of patients (CHCVIA and CHCV) by the Wilcoxon matched-pairs test.

The values of PFV after 3 days were expressed as a percent of basal values, and the differences observed in patients treated

with iloprost (CHCVIA) were compared with those observed in patients not treated (CHCV) (Mann Whitney U-test). A *p* value < 0.05 was considered sufficient to demonstrate statistical significance.

RESULTS

Ten patients with chronic HCV infection were studied with portal color Doppler sonography. In 6 patients, we measured the values of PFV before and after 3 days of iloprost treatment (CHCVIA), and in the other 4, we measured the PFV before and after 3 days without any treatment (CHCV). The rationale for iloprost treatment was the presence of lower limb arteriopathy.

Before iloprost infusion, the basal PFV mean value of CHCVIA patients was 1822.6 ± 543 ml/min, and after 3 days of treatment, it showed a 16.4% increase to 2158.4 ± 491 ml/min (Fig. 1). This difference was significant (*p* = 0.03), whereas in CHCV patients, there was no difference in the PFV mean value (2160.9 ± 328 ml/min vs. 2161.8 ± 312 ml/min) between basal and 3 days without treatment values. The difference in PFV (final values expressed as percent of basal values) in CHCVIA patients compared with CHCV patients was significant (*p* = 0.01).

DISCUSSION

Recently, we demonstrated that i.v. administration of the powerful arterial vasodilator, iloprost, caused a significant in-

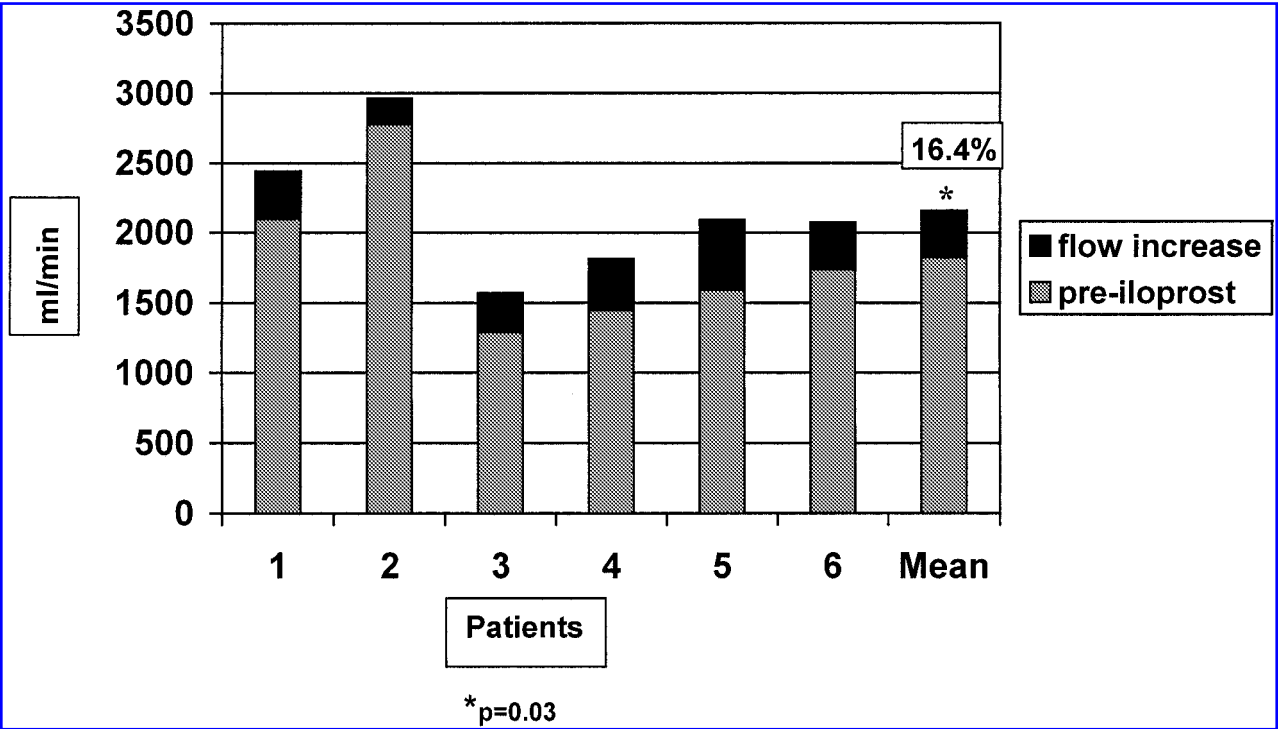


FIG. 1. Portal flow volume (PFV) before and after iloprost infusion in 6 CHCVIA patients.

crease in PFV in subjects affected by arteriopathy of the lower limbs.⁽¹²⁾ To confirm these data, we conducted this pilot study to evaluate the portal hemodynamic effects of iloprost in patients with chronic HCV infection.

The results were that the difference between basal and final PFV mean values was significant ($p = 0.03$) and the PFV mean values showed a 16.4% increase in CHCVIA patients after 3 days of iloprost treatment (Fig. 1). Also, the differences in PFV values in CHCVIA patients compared with those of CHCV patients were statistically significant ($p = 0.01$).

These first results suggest the possibility of regulating the homeostasis of the portal circulation. Being able to increase the hepatic perfusion so that an anti-ischemic effect is obtained certainly makes this possibility more attractive. In fact, better hepatic perfusion in situations such as precirrhotic chronic hepatitis suggests interesting clinical possibilities.

Increasing evidence indicates that the altered homeostasis of the portal microcirculation because of exaggerated vasoconstrictive activation of the hepatic stellate cells mediated by the opening of calcium channels⁽¹⁴⁾ plays an important role in generating portal hypertension. In this context, stable activation of hepatic stellate cells is responsible for maintaining long-term

sinusoidal resistance, and this causes portal hypertension⁽¹⁵⁾ and favors progressive development of hepatic fibrosis.⁽¹⁴⁾

In this pilot study performed in patients with chronic viral hepatitis, we demonstrate that iloprost increases the portal blood flow and improves hepatic perfusion. Iloprost could act directly on the hepatic stellate cells or compete with vasoconstrictor agents, inducing indirect relaxation effects on the hepatic microcirculation (Fig. 2). Because stable activation of stellate cells through the production of transforming growth factor- β (TGF- β) is the principal mechanism leading to hepatic fibrosis,^(16,17) the capability of iloprost to counteract their stable activation might also prevent the hepatic fibrotic response to this proinflammatory mediator.

Given these portal hemodynamic consequences of iloprost infusion, however, we can only speculate about possible therapeutic implications in patients with chronic hepatitis. Based on these preliminary results on the effects of iloprost infusion on portal hemodynamics in patients with viral chronic hepatitis, we plan more accurate and extensive research. In particular, we will study the long-term efficacy of iloprost (plus IFN and ribavirin or lamivudine) in patients with chronic hepatitis, and we will also monitor the development of fibrosis and cirrhosis.

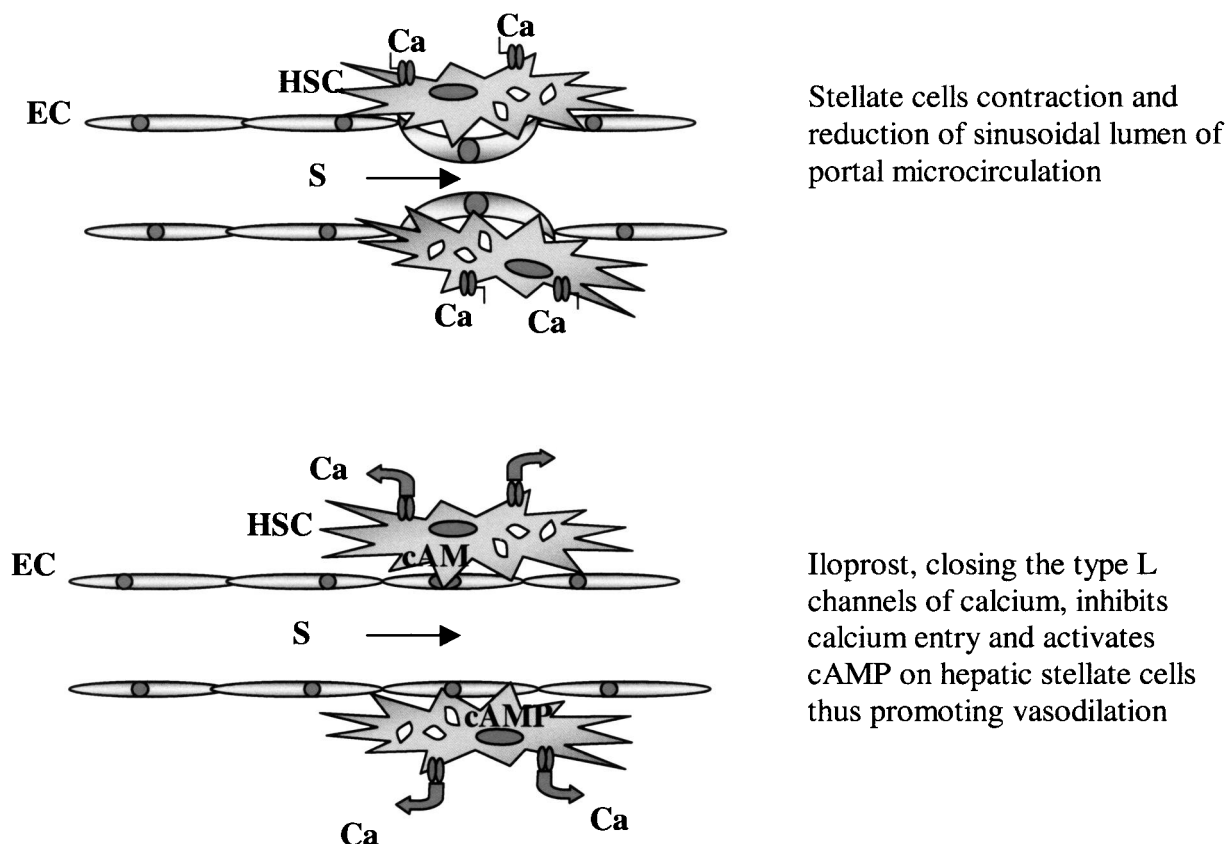


FIG. 2. Possible activity of iloprost on hepatic stellate cells of portal blood flow. HSC, hepatic stellate cells; EC, endothelial cells; S, sinusoid.

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