



# Impact of Propranolol on Preventing Renal Dysfunction in Patients with Cirrhosis

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## ABSTRACT

### BACKGROUND

One of the earliest diagnostic signs of hepatorenal syndrome in patients suffering from liver cirrhosis is an increase in the renal vascular resistive index (RI). In this study, the impact of propranolol on decreasing this index and to postpone the probability of hepatorenal syndrome has been investigated.

### METHODS

In the current research, 30 patients with liver cirrhosis with different age and sexes have been enrolled. Demographic data and complete medical history have been collected using a specific questionnaire. At first, renal artery Doppler ultrasonography was performed to determine the RI. The patients were then treated with propranolol, and under supervision, the dose of the drug was increased gradually every 3 to 5 days to reach the target of 25% decrease in resting heart rate. One month after reaching the target dose of the medicine, Doppler ultrasonography was repeated for the patients and the second RI was compared with the pretreatment ones.

### RESULTS

According to our results after treatment with propranolol, a significant decrease of RI was observed ( $p < 0.01$ ). However, there was no significant difference in the glomerular filtration rate (GFR) before and after treatment with propranolol ( $p = 0.290$ ). In our study, we found that administering propranolol was associated with significant changes in RI and GFR between the patients with compensated and decompensated cirrhosis (mean change:  $-0.005 \pm 0.017$  vs.  $-0.058 \pm 0.045$ ;  $p < 0.01$  for RI and  $-4.226 \pm 17.440$  vs.  $13.486 \pm 12.047$ ;  $p < 0.01$  for GFR in patients with compensated and decompensated cirrhosis, respectively).

### CONCLUSION

Propranolol reduces renal vascular RI in patients with cirrhosis. The response rates in the patients with decompensating cirrhosis were significantly higher than the patients with compensating cirrhosis

### KEYWORDS:

Renal vascular resistive index, Cirrhosis, Color Doppler ultrasonography

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## INTRODUCTION

Advanced cirrhosis is associated with poor clinical outcome and is a leading cause of death.<sup>1</sup> Patients with liver cirrhosis regularly develop kidney dysfunction. In addition, kidney dysfunction, especially vasoconstriction of the renal arteries, plays an important role in the hepatorenal syndrome (HRS) and patients' prognosis.<sup>2</sup> The impairment of renal function caused by marked vasoconstriction of the renal arteries is caused by complex changes in systemic hemodynamics.<sup>2</sup>

Kidney failure caused by renal vascular constriction may persist weeks or even months before the development of clinical signs or before the rise in the

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level of serum urea and creatinine concentrations.<sup>3</sup> As the disease progresses, the hemodynamic disturbances expand into the splanchnic and systemic circulatory beds. At end-stage liver disease, systemic vascular resistance is markedly decreased due to arteriolar vasodilatation induced by the release of mediators.<sup>4</sup> In compensated phase, increases in plasma volume and cardiac output lead to the stability of the effective arterial volume and pressure.<sup>5</sup> In advanced cirrhosis, however, the splanchnic vasodilatation is so extreme, which overwhelms this compensatory mechanism.<sup>6</sup> Consequently, activation of endogenous vasoconstrictor mediators causes renal vasoconstriction and sodium and fluid retention. These events eventually lead to the evolution of ascites and renal dysfunction.<sup>7</sup>

Doppler renal ultrasonography is a simple and non-invasive diagnostic tool, which is widely used to study blood flow and arterial vascular resistance as parameters for vasoconstriction in liver cirrhosis.<sup>8</sup> This method enables the accurate study of renal vascular hemodynamics, which has been validated in several pathological conditions.<sup>9</sup> Doppler ultrasound measurement of the resistive index (RI) is used to quantify renovascular resistance in patients with cirrhosis before HRS development.<sup>10</sup> It has also been found that abnormal raised impedance values have prognostic value in the identification of patients who are at greater risk for subsequent development of complications such as refractory ascites, HRS, and death.<sup>11</sup>

In patients with cirrhosis, early kidney failure or renal arteries vasoconstriction can be predicted by renal arterial RI measurement.<sup>12</sup> Beta-blockers have been widely used for the prevention of variceal hemorrhage in patients with cirrhosis. But their efficacy has rarely been evaluated on renal hemodynamics of patients with cirrhosis.<sup>13</sup> Administering propranolol causes increased level of noradrenaline and, as a consequence, sodium and water retention. The other effect is reduction in plasma renin, angiotensin, and aldosterone levels ( $\beta$ 1 blockade), which increases salt and water excretion. On the other hand, renal vasoconstriction due to  $\beta$ 2 blockade has been proposed as a mechanism by which  $\beta$  blockers may impair renal blood flow (RBF) and glomerular filtration rate (GFR). However, the clinical significance of these changes and the impact on patients with cirrhosis remain to be elucidated.<sup>14</sup>

## MATERIALS AND METHODS

The study was approved by the medical Ethics Committee of Mashhad university of medical sciences and informed consent was obtained from all participants. The patients with liver tumors, having an infection or gastrointestinal bleeding during the course of admission, hepatorenal syndrome, therapy with vasoactive drugs (including beta blockers and diuretics), significant concomitant disease, and co-therapy, which might interfere Doppler ultrasound parameters, and renal function were excluded from the study.

Doppler ultrasound measurements of the right interlobar renal artery and the left interlobar renal artery were obtained by a single investigator according to standard protocol and the mean value was calculated. The RI was calculated using the formula  $RI = (\text{peak systolic velocity} - \text{end diastolic velocity}) / \text{peak systolic velocity}$ .

Laboratory results for liver and renal functions (serum bilirubin, albumin, prothrombin time, transaminases, cholinesterase, creatinine, urea nitrogen, and electrolytes) as well as a set of clinical parameters including arterial blood pressure, heart rate, age, sex, signs of hepatic encephalopathy, and finally the Child-Pugh score was collected to assess the severity of liver disease. The Model for End-Stage Liver Disease (MELD) score was calculated for all the patients according to the following formula:  $MELD \text{ score} = 9.57 \times \log_e [\text{serum creatinine (mg/dL)}] + 3.78 \times \log_e [\text{serum bilirubin (mg/dL)}] + 11.20 \times \log_e (INR) + 6.43$ .

The standard protocol of incremental dosing of beta blockers was used to achieve the target heart rate. Propranolol was started at a dose of 20 mg twice daily. The dose of propranolol was increased every 3 to 5 days as long as 25% of the resting heart rate was decreased or to the maximal dose of 320 mg/day if the medication was well tolerated and the systolic blood pressure remained  $\geq 90$  mmHg. The second Doppler study of renal vasculature was done to measure RI by the same operator one month after continuous administration of target dose of propranolol.

The diagnosis of liver cirrhosis was based on clinical, laboratory, and radiological findings. Besides the standard hematological and biochemical tests, we also tested GFR (mL/min), and correct GFR ( $GFR \times 1.73 / \text{body surface, mL/min}$ ).

**Table 1:** Clinical characteristics and parameters of renal and hepatic function in patients with cirrhosis

Variables	Values
Sex (male/female)	21/9
Age (years)	51.97 ± 11.56
Ascites (yes/no)	13/27
Time from diagnosis of liver cirrhosis to study (year)	6.09 ± 4.81
Serum Cr (mg/dL)	1.09 ± 0.24
<b>Etiology of liver cirrhosis, n (%)</b>	
HBV infection	13 (47.2%)
Cryptogenic	6 (16.7%)
HCV infection	5 (16.7%)
AIH	4 (11.1%)
Wilson disease	1 (5.6%)
PBC	1 (5.6%)

Abbreviations: Cr, creatinine; HBV, hepatitis B virus; HCV, hepatitis C virus; AIH, Auto-immune hepatitis; PBC, Primary biliary cirrhosis.

**Table 2:** Resistive index and glomerular filtration rate in patients with cirrhosis before and after administering propranolol

Variables	N	Before	After	p-value
<b>RI</b>				
Compensated	17	0.64 ± 0.03	0.64 ± 0.02	0.270
Decompensated	13	0.72 ± 0.02	0.66 ± 0.04	< 0.01
Total	30	0.67 ± 0.04	0.65 ± 0.03	< 0.01
<b>GFR</b>				
Compensated	17	72.80 ± 21.49	68.57 ± 9.41	0.333
Decompensated	13	60.53 ± 10.24	74.02 ± 10.10	< 0.01
Total	30	67.48 ± 18.34	70.93 ± 9.93	0.290

GFR: glomerular filtration rate, RI: resistive index

**Table 3:** Comparison of resistive index and glomerular filtration rate between patients with compensated and decompensated cirrhosis before and after administering propranolol

Variables	Compensated (n = 17)	Decompensated (n = 13)	p-value
<b>RI</b>			
Before	0.64 ± 0.03	0.72 ± 0.02	< 0.001
After	0.64 ± 0.02	0.66 ± 0.04	0.089
Δ (After-Before)	-0.005 ± 0.017	-0.058 ± 0.045	< 0.01
<b>GFR</b>			
Before	72.80 ± 21.49	60.53 ± 10.24	0.068
After	68.57 ± 9.41	74.02 ± 10.10	0.139
Δ (After-Before)	-4.226 ± 17.440	13.486 ± 12.047	< 0.01

GFR: glomerular filtration rate, RI: resistive index

Distribution of all continuous variables in this study was normal and they were reported as mean ± standard deviations. Differences between the two groups were tested by using independent sample t test for continuous data. The difference for GFR and RI variables before and after consumption of propranolol were tested by using paired sample t test. Relations between continuous data were tested by using Pearson. All the data were analyzed using SPSS software version 11 (SPSS Inc., Chicago, IL, USA).  $p < 0.05$  was considered as statistically significant.

RESULTS

Thirty patients (21 men, 9 women) with liver cirrhosis, with the mean age of  $51.97 \pm 11.56$  years (range 31 - 80 years) were included in this study. Of them, 17 patients had compensated cirrhosis and 13 patients had decompensated condition. The main characteristics of the patients with liver cirrhosis in this study are demonstrated in table 1. Hepatitis B virus infection (HBV) (n = 13) was the most frequent etiology of cirrhosis. Other etiologies consist of hepatitis C virus infection (HCV) (n = 5), cryptogenic (n = 6), Wilson disease (n = 1), and primary biliary cirrhosis (n = 1).

As shown in table 2, in patients with cirrhosis, after administering propranolol, a significant decrease of RI was observed (from  $0.67 \pm 0.04$  to  $0.65 \pm 0.03$ ;  $p < 0.01$ ). However, there was no significant difference in the GFR before and after administering propranolol (from  $67.48 \pm 18.34$  to  $70.93 \pm 9.93$ ;  $p = 0.290$ ). Pearson regression analysis showed no significant correlation between RI and GFR before ( $r = -0.084$ ,  $p = 0.659$ ) and after ( $r = 0.184$ ,  $p = 0.331$ ) administering propranolol among the patients with cirrhosis. Independent sample t test showed that RI of patients with decompensated cirrhosis was significantly higher than compensated ones (compensated:  $0.64 \pm 0.03$  vs.  $0.72 \pm 0.02$  in decompensated patients;  $p < 0.001$ ). However, there was no significant difference in the RI between the patients with compensated and decompensated cirrhosis after administering propranolol ( $0.64 \pm 0.02$  vs.  $0.66 \pm 0.04$  respectively;  $p = 0.089$ ).

As shown in table 3 there were not any significant differences between the GFR of the patients with compensated and decompensated cirrhosis before ( $72.80 \pm 21.49$  vs.  $60.53 \pm 10.24$  respectively;  $p = 0.068$ ) and after ( $68.57 \pm 9.41$  vs.  $74.02 \pm 10.10$  respectively;  $p = 0.139$ ) administering propranolol.

In our study, we found that administering propranolol was associated with marked significant changes in RI and GFR between the patients with compensated and decompensated cirrhosis (mean change:  $-0.005 \pm 0.017$  vs.  $-0.058 \pm 0.045$ ;  $p < 0.01$  for RI and  $-4.226 \pm 17.440$  vs.  $13.486 \pm 12.047$ ;  $p < 0.01$  for GFR in patients with compensated and decompensated cirrhosis, respectively).

## DISCUSSION

In this study, after analyzing the results, RI in patients with decompensated cirrhosis was significantly higher than compensated ones. In the next step, the effect of propranolol in reducing the RI was reviewed and approved. This effect in patients with decompensated cirrhosis was significant, but in patients with compensated cirrhosis was not significant despite the reduction in RI. Also, there were significant differences between the effects of propranolol on the RI changes of the two mentioned groups. Our data support the previous findings that RI in patients with decompensated cirrhosis was significantly higher than compensated ones. In a study of 50 adult patients, with compensated and decompensated liver cirrhosis, mean values of renal arterial RI for the patients was higher than the 15 healthy control individuals.<sup>15</sup> Furthermore, RI was higher in patients with decompensated cirrhosis than patients with compensated cirrhosis.

These results suggest that the degree of renal vasoconstriction alters with the severity of ascites.<sup>15</sup> At the various stages of hepatic cirrhosis, there may be different degrees of renal arterial vasoconstriction, which can elicit to a decrease in renal blood flow, resulting in oliguria and anuresis.<sup>16</sup> Ozkan and colleagues investigated 36 patients with decompensated cirrhosis, 39 patients with compensated cirrhosis, and 25 patients with normal kidney and liver functions. They found that RI was significantly higher in the decompensated group compared with the other groups.<sup>17</sup> In the literature, three other studies can be found that evaluated RI measurement in patients with cirrhosis with and without ascites. These studies also revealed higher RI values in patients with cirrhosis and ascites compared with the ones without ascites.<sup>9,18-19</sup>

Renal hemodynamic changes occur in early stages of cirrhosis before the development of ascites. However, as

the liver disease progresses, these changes lead ultimately to severe cortical hypoperfusion.<sup>20</sup> The development of portal hypertension is a probable promoter of increased renal vascular resistance, whereas liver function deterioration may be associated with the impaired tubular handling of sodium.<sup>21</sup> The peripheral arterial vasodilation appears to be correlated with these renal changes by activation of vasoconstrictor systems after the development of arteriolar vasodilatation.<sup>22</sup>

In the next step, the effect of propranolol in reducing the RI in patients with decompensated cirrhosis was significant, but in patients with compensated cirrhosis, despite the reduction in RI, was not significant. These results are in contradiction with the data that reported by Ozcan who showed after administering propranolol, RI decreased in the compensated patients but increased in the decompensated ones. There was a weak but statistically insignificant increase in the control individuals.<sup>17</sup>

Systemic and splanchnic hemodynamics, renal blood flow, and kidney function were evaluated in 13 patients with cirrhosis before and after oral acute and chronic administering 40 mg propranolol. Kidney blood flow and vascular resistance did not alter significantly after acute administering propranolol and kidney function did not alter significantly after acute or chronic administering propranolol. The researchers conclude that propranolol does not change kidney function in cirrhotic patients with good physical condition.<sup>23</sup> The renal effects of propranolol are complex based on their hemodynamic and neuro-humoral actions. Propranolol can increase the level of noradrenaline, which in turn leads to sodium and water retention. As mentioned above, another consequence of treatment with propranolol is reduction in the levels of renin, angiotensin, and aldosterone, which increase the excretion of salt and water.<sup>13</sup> In addition, kidney vasoconstriction caused by  $\beta_2$  blockade has been proposed as a mechanism by which  $\beta$  blockers may impair RBF and renal function.<sup>22</sup>

We did not find a significant correlation between RI values and GFR before and after administering propranolol among the patients with cirrhosis. The data about the relationship between RI and the renal function are controversial. Increased creatinine level is associated with concordance increase in RI.<sup>20</sup> Renal artery RI may be useful for identifying patients at increased



risk for developing kidney failure at an early stage. On the other hand, due to the paucity of available studies, there is no evidence that Doppler ultrasonography, by itself, can differentiate the patients with cirrhosis and impaired kidney function because of vasoconstriction, from the patients who have both vasoconstriction and intrinsic kidney damage.<sup>11</sup>

Renal vasoconstriction has been observed in several series of patients with cirrhosis due to increased RI.<sup>1</sup> In patients with cirrhosis and refractory ascites, including those with a normal serum creatinine, increased RI seems to be correlated with a higher risk of subsequent impairment of kidney function.<sup>24</sup> Similar results were observed when comparing cirrhosis patients with and without ascites and with the first signs of kidney failure.<sup>25</sup>

It has been hypothesized that peripheral arterial vasodilation is the main factor in the pathogenesis of functional kidney abnormalities in patients with cirrhosis.<sup>26</sup> This alteration in peripheral vascular tonicity is thought to be related to local or systemic excess of vasodilators such as vasoactive intestinal peptide, prostacyclin, substance P, and nitric oxide.<sup>27</sup> The localization of arterial vasodilation, as well as its link with renal sodium retention, is also debated.<sup>28</sup> According to recent clinical and experimental evidence, in patients with cirrhosis and ascites, reduction of arterial vascular resistance occurs mainly in the splanchnic area, whereas in the kidney vascular bed, arterial resistance is normal or even increased.<sup>8</sup>

# CONCLUSION

The results of the present study demonstrate that propranolol reduces renal vascular RI in patients with cirrhosis. The response rates in patients with decompensated cirrhosis were significantly higher than the compensated type. Thus, non-selective beta blocker is a good treatment option for improvement of the renal hemodynamics in patients with cirrhosis, particularly decompensated ones. The effects of beta blockers on long-term protection of cirrhotic patients with renal dysfunction need more investigations to become an accepted recommendation.

# CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

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