# *Effects of Autonomic Neuropathy on Renal Blood Flow in Patients with Liver Cirrhosis*

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**ABSTRACT**

***Aim**: We evaluated the effect of autonomic neuropathy on renal blood flow in patients with cirrhosis.*

***Method**: Fifty-nine patients with liver cirrhosis and 45 healthy controls were enrolled in the study. The size and parenchymal thickness of both kidneys were measured in all patients and controls. Renal vascular resistance indices(RI) of the kidneys were evaluated by Doppler ultrasonography and autonomic neuropathy tests defined by Ewing and Clarke were administered on all patients included in the study.*

***Result**: While there was no difference in parenchymal thickness or the size of either kidney between cirrhotic patients and the control group, the renal vascular RI of the renal artery (right kidney 0,70±0,06 vs. 0.61±0.03 and left kidney 0.69±0.06 vs. 0.61±0.03) and interlobar artery (right kidney 0.65±0.06 vs. 0.57±0.04 and left kidney 0.66±0.06 vs. 0.56±0.03) showed significant difference (p< 0.005). The renal artery RI of advanced stage cirrhosis (Child-Pugh B and C) was higher than that of early stage cirrhosis (Child-Pugh A) and the difference was statistically significant (p= 0.04). The frequency of autonomic neuropathy increased with Child-Pugh stage (p< 0.05); the comparison for all parameters (kidney size, parenchymal thickness and RI) between patients with and without autonomic neuropathy showed no statistically significant difference between groups (p> 0.05). Similarly, there was no statistically significant difference in any parameter between patients with or without ascites (p> 0.05).*

***Conclusion**: Renal artery and interlobar artery RI increased in cirrhotic patients compared to controls but no effect of autonomic neuropathy was established on renal hemodynamics.*

***Key words**: Liver cirrhosis, resistance indices, autonomic neuropathy*

### *Sirozlu Hastalarda Otonom Nöropatinin Renal Kan Akımı Üzerine Etkisi*

***Amaç:*** *Sirozlu hastalarda otonom nöropatinin renal kan akımı üzerine etkilerini araştırmayı amaçladık.*
***Metod:*** *Çalışmaya 59 karaciğer sirozlu hasta ve 45 sağlıklı kontrol alındı. Tüm hastaların ve kontrol grubunun her iki böbrek boyutları ve parankim kalınlıkları ölçüldü. Renal vasküler rezistans indeksleri (Rİ) sağ ve sol böbrekten doppler ultrasonografi ile değerlendirildi ve çalışmaya alınan tüm hastalara Ewing ve Clarke tarafından tanımlanan otonom nöropati testleri yapıldı.*
***Bulgular:*** *Sirotik hastalar ile kontrol grubu karşılaştırıldığında, sırası ile her iki böbrek boyutlarında ve parankim kalınlığında fark yok iken, her iki böbrekten ölçülen renal arter (sağ böbrekten 0,70±0,06 karşılık 0,61±0,03 ve sol böbrekten 0,69±0,06 karşılık 0,61±0,03) ve interlober arter Rİ (sağ böbrekten 0,65±0,06 karşılık 0,57±0,04 ve sol böbrekten 0,66±0,06 karşılık 0,56±0,03) arasında anlamlı fark vardı (p<0.005). Erken evre siroz (Child-Pugh A) ve ileri siroz (Child-Pugh B ve C) karşılaştırıldığında renal arter Rİ ileri evre siroz grubunda istatistiksel olarak anlamlı derecede daha yüksek bulundu (p=0,04). Child-Pugh evresi arttıkça otonom nöropati sıklığıda artmaktaydı (p< 0.05). Ayrıca otonom nöropatisi olan ve olmayan sirotik hastalarda, bütün parametrelerde (böbrek boyutu, parankim kalınlığı ve RI) fark yoktu (p> 0.05). Benzer olarak, asiti olan ve olmayan hastalar arasında da bu parametrelerde bir fark yoktu. (p> 0.05).*
***Sonuç:*** *Renal arter ve interlobar arter Rİ kontrol grubuna göre sirotik hastalarda armıştı ama otonom nöropati varlığının renal hemodinamikler üzerine herhangi bir etkisi tesbit edilmedi.*

***Anahtar kelimeler:*** *Karaciğer sirozu, rezistans indeks, otonom nöropati*

## INTRODUCTION

In cirrhosis related portal hypertension, circulation is hyperdynamic, that is, characterized by an increased cardiac output, low systemic arterial resistance and decreased arterial pressure (1,2).

Renal vasoconstriction and sodium retention exist in patients with hepatorenal syndrome due to the activated autonomic nervous system (ANS) and particularly sympathetic nervous system (3). Several studies have reported an increase in catecholamine secretion in the renal and splanchnic vascular bed (4). The importance of hepatorenal innervation is apparent by the increase in afferent renal sympathoadrenergic activity related with increased intrahepatic pressure (5). Vasoconstriction of afferent arterioles in the kidney causes a decrease in renal blood flow and glomerular filtration rate (GFR), and an increase in tubular sodium and water reabsorption. Renal sympathectomy increases GFR in cirrhotic rats and patients with hepatorenal syndrome; it has instigated transient improvements in renal blood flow and renal function (6).

Autonomic neuropathy prevalent in liver patients has been associated with high mortality rates (7). The incidence of autonomic neuropathy in cirrhotic patients ranges from 45% to 80%. Increased mortality in patients with autonomic neuropathy, representing a patient group with poor prognosis, has been reported (8). Autonomic neuropathy may be a factor in the pathogenesis of patients with hyperdynamic circulatory syndrome. Some studies have indicated that liver cirrhosis patients with autonomic neuropathy may not display an appropriate or inadequate response to conditions with high mortality such as sepsis or variceal bleeding (7-9). Individuals with chronic alcohol consumption may demonstrate peripheral neuropathy. While the cause of neuropathy in these patients is not known, it is attributed to the direct toxic effect of alcohol on the nervous system (10).

While the cause of stomach motility disorders in patients with cirrhosis is not known, autonomic neuropathy is considered to be responsible. Studies (10-12) have shown a correlation between delayed stomach voiding and autonomic neuropathy in patients with cirrhosis. In view of current knowledge, the presence of autonomic neuropathy in patients with cirrhosis may have an effect on renal hemodynamics and kidney complications of cirrhosis. Accordingly, we aimed to establish the differences in renal blood flow between patients with or without cirrhotic autonomic neuropathy by renal Doppler, and the effects of autonomic neuropathy on renal blood flow.

The incidence of autonomic neuropathy in cirrhotic patients changes between 45% to 80%. Patients with autonomic neuropathy are reported to represent a patient group with high mortality and a poor prognosis (13,14). The incidence of autonomic neuropathy is also reported to be increased in conditions other than cirrhosis that cause portal hypertension such as extrahepatic portal vein obstruction and non-cirrhotic portal fibrosis and liver transplantation in patients with terminal liver cirrhosis show improvements of up to 70% following transplantation (15).





***Table 1****. Demographic features of patients enrolled in the study*

| | *Controls* | *Patients* |
|---|---|---|
| *Total number* | *45* | *59* |
| *Child-Pugh A* | | *30* |
| *Child-Pugh B* | | *17* |
| *Child-Pugh C* | | *12* |
| *Sex (F/M)* | *26/19* | *25/34* |
| *Age (years)* | *55.8 ± 12.3* | *57.4± 10.3* |
| *Etiology of cirrhosis* | | |
| *Hepatitis B* | | *22* |
| *Hepatitis C* | | *22* |
| *Cryptogenic* | | *9* |
| *Alcohol* | | *4* |
| *Autoimmune* | | *2* |

## MATERIALS AND METHODS

This study was conducted on 104 subjects: 59 patients diagnosed with liver cirrhosis and the remaining 45 were healthy individuals. Twenty-five of the cirrhotic patients were female and 34 male, while 26 of the control group were female and 19 male. The median age of cirrhotic patients was 57.4 years (range: 31-87), and that of the control group was 55.8 years (range: 21-74). The Child-Pugh classes and etiology of the patients' cirrhosis and demographics are given in Table 1.

The study was approved by the Başkent University Medical School Research and Ethics Board. The diagnosis of liver cirrhosis was made by histological examination of liver biopsy materials or clinical, biochemical or direct and indirect ultrasonography findings (signs of portal hypertension such as coarsened parenchymal echo of the liver, irregular liver margin, caudate lobe/right lobe ratio above 0.65, splenomegaly, increases in portal vein diameter, ascites) (16).

Exclusion criteria were patients with a history of use of medications that could cause autonomic neuropathy, a diagnosis of diabetes mellitus, ischemic cardiac disease, hypertension, nephrectomy, renal cyst, renal artery stenosis, renal function disorder, history of stenting of abdominal vascular structures, portal vein thrombosis, lack of healthy measurements due to obesity, pregnancy or suspicion of pregnancy, previous abdominal surgery, history of diseases and medications that could affect kidney blood flow were excluded.

All patients with cirrhosis were stratified according to the Child-Pugh classification (17). The age, gender, etiology, right and left kidney size, parenchymal thickness, major renal artery and interlobar artery resistance indices of patients with liver cirrhosis were evaluated. The same measurements were performed on the control group.

### Autonomic neuropathy tests

Autonomic neuropathy tests as described by Ewing and Clarke (18) were performed on all patients. Three standard tests were used in order to assess cardiac parasympathetic functions (heart rate response to Valsalva maneuver, heart rate changes during deep breathing, and heart rate response to standing) and two standard tests to evaluate sympathetic functions (blood pressure responses to standing and blood pressure response to sustained handshake). The Ewing and Clarke tests (Table 2) were used to stratify patients into four groups: normal; early parasympathetic damage: one test out of three abnormal; definite parasympathetic damage: at least two tests out of three abnormal; combined sympathetic and parasympathetic damage: in addition to definite parasympathetic damage, one or two sympathetic test abnormal.

***Table 2****. Assessment of autonomic neuropathy tests (18).*

| | *Normal* | *Borderline* | *Abnormal* |
|---|---|---|---|
| *Tests reflecting parasympathetic functions* | | | |
| *Heart rate response to Valsalva maneuver* | *≥ 1.21* | *1.11-1.20* | *1.10* |
| *Change in heart rate with deep inspiration (beat/min) (maximum/minimum heart rate)* | *≥15* | *11-14* | *≤10* |
| *Heart rate response to standing up (30:15 ratio)* | *≥1.04* | *1.01-1.03* | *≤1.00* |
| *Tests reflecting sympathetic functions* | | | |
| *Blood pressure response to standing up (decrease in systolic BP* | *≤10* | *11-29* | *≥30* |
| *Blood pressure response to sustained handshake (increase in diastolic BP)* | *≥16* | *11-15* | *≤10* |

*BP = blood pressure (mmHg)*

***Table 3**. Bilateral mean kidney size, parenchymal thickness, major renal artery and interlobar artery RI values in cirrhotic patients and the control group*

| | Cirrhotic patients | Control group | p |
|---|---|---|---|
| Right kidney size, mm | 104.32±12.28 | 107.80±9.02 | 0.099 |
| Left kidney size, mm | 109.34±12.01 | 107.27±8.77 | 0.312 |
| Right kidney parenchymal thickness, mm | 13.3±2.4 | 12.7±1.4 | 0.168 |
| Left kidney parenchymal thickness | 12.7±2.l | 12.0±1.8 | 0.073 |
| Right renal artery RI | 0.70±0.06 | 0.61±0.03 | <0.001 |
| Left renal artery RI | 0.69±0.06 | 0.61±0.03 | <0.001 |
| Right interlobar artery RI | 0.65±0.06 | 0.57±0.04 | <0.001 |
| Left interlobar artery RI | 0.66±0.06 | 0.56±0.03 | <0.001 |

*mm: millimeter, RI: resistance indices .*

**Evaluation of renal blood flow by Doppler ultrasonography**

All patients were evaluated by using renal color Doppler ultrasonography following an 8-hour fast during the preceding night. A Siemens 5000 device with 3.5 MHz convex probes was used to determine major and interlobar artery resistance indices. Patients were placed in the contralateral decubitis position (right decubitis for the left kidney) or the supine position, and the Doppler angle was held at 30-60 degrees. In all cases, measurements were taken from both kidneys at the top, middle and bottom poles, and averages were calculated. All recordings were made with patients holding their breath, and thus major and intrarenal arterial vascularization were revealed while minimizing respiratory artifacts. Sampling was made at the level of the major and interlobar artery in order to measure blood flow rates. Resistance indices values were expressed as the average of 3 measurements for each kidney, using software already existing in the system (RI= S-D/S; S: peak systolic rate, D: end-diastolic rate).

**Statistical analysis**

The SPSS 9.0 computer program was used for statistical calculations. Tests used for statistical analysis were the Student t test (the Mann-Whitney U test when needed), chi-square and Kruskall-Wallis tests. A p value of < 0.05 was considered statistically significant.

**RESULTS**

Right and left average kidney size, parenchymal thickness, major renal artery and interlobar artery resistance indices values are given in Table 3. There was no difference between cirrhotic patients and the control group regarding bilateral kidney size and parenchymal thickness while renal artery and interlobar artery resistance indices measurements showed statistically significant results (p< 0.001). Regarding cirrhotic patients, only right kidney parenchymal thickness showed a significant difference (p< 0.05) (Table 4). Of the 59 patients with cirrhosis, 37 patients had autonomic neuropathy. Of the 37 patients with documented neuropathy, 12 had early parasympathetic damage, 18 definite parasympathetic damage, and 7 combined sympathetic and parasympathetic damage.

***Table 4**. Bilateral mean kidney size, parenchymal thickness, major renal artery and interlobar artery RI values in patients with early and advanced cirrhosis*

| | Early stage cirrhosis (Child-Pugh A (n:30) | Advanced cirrhosis (Child-Pugh B and C (n:29) | p value |
|---|---|---|---|
| Right kidney size, mm | 100.60±8.72 | 108±14.26 | 0.018 |
| Left kidney size, mm | 107.50±9.80 | 112.4±13.84 | 0.238 |
| Right kidney parenchymal thickness, mm | 12.20±2.04 | 14.45±2.26 | 0.001 |
| Left kidney parenchymal thickness, mm | 12.43±2.11 | 13.14±2.20 | 0.215 |
| Right renal artery RI | 0.68 ± 0.07 | 0.72 ± 0.05 | 0.041 |
| Left renal artery RI | 0.68 ± 0.06 | 0.70 ± 0.07 | 0.158 |
| Right interlobar artery RI | 0.64 ± 0.06 | 0.66 ± 0.06 | 0.135 |
| Left interlobar artery RI | 0.65 ± 0.05 | 0.66 ± 0.06 | 0.348 |

*mm: millimeter, RI: resistance indices*

***Table 5**. Renal color doppler ultrasonography results in cirrhotic patients with or without autonomic neuropathy*

| | autonomic neuropathy (+)(n:37) | autonomic neuropathy (-)(n:22) | p value |
|---|---|---|---|
| Right kidney size, mm | 104.3±13.7 | 104.2±9.6 | >0.05 |
| Left kidney size, mm | 109.3±12 | 109.2±12.2 | >0.05 |
| Right kidney parenchymal thickness, mm | 13.6±2.4 | 12.7±2.2 | >0.05 |
| Left kidney parenchymal thickness, mm | 12.8±2.1 | 12.6±2.2 | >0.05 |
| Right renal artery RI | 0.70 ± 0.06 | 0.70 ± 0.07 | >0.05 |
| Left renal artery RI | 0.69 ± 0.07 | 0.68 ± 0.06 | >0.05 |
| Right interlobar artery RI | 0.66 ± 0.06 | 0.64 ± 0.06 | >0.05 |
| Left interlobar artery RI | 0.66 ± 0.06 | 0.65 ± 0.05 | >0.05 |

*mm: millimeter; RI: resistance indices*

As shown in table 5, there was no statistically significant difference between the values of kidney size, parenchymal thickness, major renal and interlobar artery resistance indices as obtained with renal color Doppler ultrasonography for the 37 cirrhotic patients with autonomic neuropathy and the 22 without (table 5). Also as shown in table 6, in the 37 cirrhotic patients with neuropathy, there was no significant difference in renal color Doppler ultrasonography measurements between patients with early parasympathetic, marked parasympathetic, combined sympathetic and parasympathetic damage (p> 0.05).

Ascites was present in 17 (28.8%) of the 59 cirrhotic patients. The renal color Doppler ultrasonography findings of cirrhotic patients with or without ascites showed no difference (p> 0.05). Furthermore, there was no difference between the group with autonomic neuropathy and with ascites and the group with autonomic neuropathy but without ascites (p> 0.05).

**DISCUSSION**

Liver cirrhosis is a disease that can affect several organs besides the liver. One of such organs is the kidneys. Renal color Doppler ultrasonography enables rapid and non-invasive imaging of the interlobar, interlobular and arcuate arteries, moreover making perceiving increases in resistance indices values long before the development of apparent renal failure (19). The results of our study on patients with cirrhosis on increased renal artery resistance indices were similar to those of previous studies (19,20) in patients with differentiated acute tubular necrosis and acute prerenal failure (19) and patients with decompensated cirrhosis; cases compared with compensated cirrhosis without ascites and healthy controls (20). Furthermore, upon comparison of patients with early (Child A) and advanced (Child

***Table 6**. Renal color Doppler ultrasonography results in cirrhotic patients with autonomic neuropathy according to type of autonomic neuropathy*

| | Early PI (n:12) | Marked PI (n:18) | Combined sympathetic and PI (n:7) | p |
|---|---|---|---|---|
| Right renal artery RI | 0.71±0.007 | 0.70±0.06 | 0.68±0.03 | >0.05 |
| Left renal artery RI | 0.70±0.05 | 0.68±0.08 | 0.70±0.06 | >0.05 |
| Right interlobar artery RI | 0.64±0.05 | 0.67±0.07 | 0.66±0.03 | >0.05 |
| Left interlobar artery RI | 0.66±0.06 | 0.66±0.07 | 0.66±0.05 | >0.05 |

*RI: resistance indices , PI: parasympathetic injury*

B, C) cirrhosis, advanced cirrhotic patients had higher resistance indices values. There was no difference in the comparison of patients with or without ascites. Our study also showed a correlation between increases in the Child score and increases in renal artery resistance indices and interlobar artery resistance indices values. (21-24).

Autonomic nervous system dysfunction is a complication that may present in diabetes mellitus and with alcohol consumption. However, it is common in patients with cirrhosis. Autonomic neuropathy seen often in terminal liver patients, is associated with high mortality rates (7). Autonomic neuropathy may have a role in the pathogenesis of patients with hyperdynamic circulatory syndrome. Some studies (9,10) have demonstrated that patients with liver cirrhosis who have autonomic neuropathy show inappropriate or inadequate response to conditions with high mortality such as sepsis or variceal bleeding. The frequency of autonomic neuropathy in cirrhotic patients of our study is similar to the ones of previous studies (9,10). Renal artery and interlobar artery resistance indices, increased in cirrhotic patients compared with controls. But no different between cirrhotic patients with or without autonomic neuropathy of renal artery and interlobar artery resistance indices. This indicates a lack of effect of the presence of autonomic neuropathy on renal hemodynamics. On the other hand the importance of hepatorenal innervation is made apparent through the increase in afferent renal sympathoadrenergic activity due to increased intrahepatic pressure (5). Renal sympathectomy increased glomerular filtration rate in cirrhotic rats, and moreover, lumbar sympathetic blockade caused transient improvements in renal blood flow and renal functions in patients with Hepatorenal syndrome (HRS) (6). We did not observe a distinct relationship in our study, in which we investigated the role of autonomic neuropathy on the prognosis of cirrhotic patients and the effects of autonomic neuropathy on renal blood flow. Similar studies that include patients with HRS may more clearly demonstrate the effect of autonomic neuropathy in this patient group.

In conclusion, renal artery and interlobar artery resistance indices increased in cirrhotic patients compared to controls but no effect of autonomic neuropathy was established on renal hemodynamics.

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