Medicinska istaživanja 2023; 56(1):21-29 | DOI: 10.5937/medi55-41696

OPEN ACCESS

Medical Research | Published by Faculty of Medicine University of Belgrade

ORIGINAL ARTICLE

Doppler assessment of splanchnic arterial flow in patients with liver cirrhosis: correlation with nitric oxide

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Recived: 10 December 2022
Revised: 02 January 2023
Accepted: 20 February 2023

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Funding information:
The authors received support from the Ministry of Education and Science of the Republic of Serbia (grant number 200110) and the Science Fund of the Republic of Serbia.

Competing interests:
The authors have declared that no competing interests exist

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Summary

Introduction/aim: Nitric oxide (NO) is a key mediator which, paradoxically, regulates sinusoidal (intrahepatic) and systemic/splanchnic circulation. The main goal of this study was to measure NO and compare serum values of NO with flow data in visceral blood vessels of the liver, spleen, kidney and intestine in patients with cirrhosis.

Material and methods: This prospective study included 80 patients with cirrhosis of the liver. Doppler ultrasonography was used to assess flow velocity and resistive index (RI) in the hepatic (HA), right (RRA), and left renal (LRA), splenic (SA) and superior mesenteric artery (SMA). NO concentration was determined using the DetectX® Nitric Oxide colorimetric detection kit.

Results: We found a statistically significant difference in the mean NO value in the group of patients without ascites compared to the ascites group, as well as in the group of patients with A stage in relation to C stage of cirrhosis ($p < 0.05$). There is statistically significant negative correlation between NO and diameter, and maximal and minimal velocity in LRA. There is significant positive correlation between NO and minimal velocity in SMA.

Conclusions: In this study, we found that patients with cirrhosis of the liver were exposed to significantly higher RI LRA, RRA, SA and HA. In patients with cirrhosis complicated by ascites and in those with end stage liver disease, the NO level was significantly higher. The concentration of NO had an effect on the diameter and flow rate in the LRA and flow rate in SMA.

Keywords: liver cirrhosis, nitric oxide, Doppler ultrasonography

Cite this article as: Glišić T, Đ. Popović D, Stojković-Lalošević M, Martinov J, Stojanović M, Jurišić V. Doppler assessment of splanchnic arterial flow in patients with liver cirrhosis: correlation with nitric oxide Medicinska istraživanja 2023; 56(1):21-29 10.5937/medi55-41696

INTRODUCTION

Hyperdynamic splanchnic and systemic blood flow is typical for patients with cirrhosis of the liver. The combination of arterial vasodilation and increased intravascular volume is necessary for full expression of hyperdynamic circulatory condition. Cirrhosis is associated with peripheral vasodilatation resulting from the effects of systemic vasodilator substances. Many vasoactive substances are involved in the development of portal hypertension. Among them, nitric oxide (NO) is a key mediator which, paradoxically, regulates sinusoidal (intrahepatic) and systemic / splanchnic circulation.

Doppler ultrasound has been in use for the assessment of arterial blood flow in patients with cirrhosis of the liver. Intrarenal vasoconstriction, caused by complex interactions between portal and systemic hemodynamics, occurs early in the non-ascitic phase of cirrhosis and before the occurrence of hepatorenal syndrome [1-3]. Arterial resistance index (RI) is the most widely used Doppler variable for the estimation of intrarenal vascular resistance in clinical studies. Available data suggest 0.70 as the upper limit for normal intrarenal RI [4].

NO has significant effects on renal blood vessels. Nitric oxide synthase (NOS) inhibition leads to an increased renal vascular resistance, during the stimulation of endothelial nitric oxide synthase (eNOS), and after the application of L-arginine, and it causes a reduction of the same resistance. Endothelial nitric oxide synthase and inducible nitro-oxide synthase (eNOS and iNOS) may be closely related to the pathophysiology of cirrhosis of the liver and kidney damage due to the fact that iNOS is expressed as an important part of the kidney tissue.

Nitric oxide is likely the most potent vasodilator molecule known today. In cirrhotic livers, NO production/bioavailability is significantly diminished, which contributes to increased intrahepatic vascular resistance [5,6-9]. Decreased NO production is explained by at least two mechanisms. Firstly, the NO synthesizing enzyme eNOS is inhibited by negative regulators (such as caveolin-1), which are up-regulated during cirrhosis; as a result, NO production is decreased [8]. Secondly, oxidative stress is increased in cirrhosis.

The role of NO in the modulation of intrahepatic vascular resistance (IHVR) has been well documented [10-12]. eNOS dysfunction in sinusoidal endothelial cells and consequent reduction in NO production (or bioavailability) plays an essential role [13]. This results in reduced vasodilation and a decreased capacity for antagonizing contractile factors such as endothelin-1, angiotensin II, norepinephrine, prostaglandin F2 and thromboxane A2 [14,15].

A hyperdynamic splanchnic circulatory state is a major accompaniment of portal hypertension (PHT). An increase in splanchnic blood flow and the subsequent increase in portal venous inflow aggravates and perpetuates PHT. The mechanisms underlying this phenomenon are not fully understood, but overproduction of endogenous vasodilators and decreased vascular reactivity to vasoconstrictors have been suggested [16].

NO plays a pivotal role in the pathogenesis of PHT. NO levels are differentially altered in cirrhosis, with a reduced production in the intrahepatic circulation and an increased NO production in the splanchnic bed. Ideally, a NO donor or drug delivery system that selectively targets liver cells without actions on systemic circulation is required to reduce PHT without adverse systemic effects.

Only few studies have examined renal blood flow in cirrhosis of the liver [17-20]. The clinical significance of these tests lies in the therapeutic approach to the phenomenon of arterial vasodilation, because of the changing views on the application of beta-blockers or beta-agonists in the treatment of portal hypertension. Once developed, portal hypertension affects extrahepatic vascular bed in splanchnic and systemic circulation, leading to arterial vasodilation and formation of collateral, which increases the flow of blood in the portal vein, and this is exacerbated by portal hypertension [5, 21].

We found no report of correlations between serum nitric-oxide (NO) level and visceral arteries resistive index in the available literature.

Therefore, the aim of the present study was to assess the relationship between NO levels, hepatic (HA), splenic (SA), right renal artery (RRA) and left renal artery (LRA) blood flow in patients with cirrhosis of the liver.

MATERIAL AND METHODS

Subjects

This prospective study included patients with cirrhosis of the liver in different clinical stages, diagnosed at the Clinic for Gastroenterohepatology, University Clinical center of Serbia, from June 2010 to September 2012. The criteria for exclusion from the study were hepatocellular carcinoma, cardiorespiratory diseases, hypertension, renal artery stenosis, acute and chronic kidney lesions, diabetes mellitus, recent alcohol abuse, vasoactive medication and diuretics use during the study, portal vein thrombosis, and patients under the age of 18. The diagnosis of cirrhosis of the liver was based on clinical and histologic findings. The etiology was alcoholic, viral, autoimmune, or metabolic. The liver function was assessed by Child-Pugh score. The control group included healthy subjects.

Methods

Nitric oxide concentration (reference values 11–76 μmol/L) was determined using the DetectX® Nitric Oxide colorimetrical detection kit which was designed to measure nitrate and nitrite that are present in different samples. Basically, the NO measured after the serum sample was incubated with a nitrate reductase and

Table 1. Descriptive characteristics of patients with cirrhosis of the liver

Variable	n (%)
Gender	
Male	58 (72.5%)
Female	22 (27.5%)
Etiology of cirrhosis	
Hepatitis B	7 (8.9%)
Hepatitis C	8 (10.13%)
Autoimmune	5 (6.33%)
Alcohol	52 (65.9%)
Other	8 (8.74%)
Clinical characteristics	
Esophageal varices	41 (51.25%)
Ascites	50 (62.5%)
Abdominal collateral pathways	9 (11.25%)
Hepatic encephalopathy	24 (30.0%)
Hypertension	26 (32.5%)

NADH. Reductase in combination with NADH reduces nitrate into nitrite. After 20 minutes of incubation at room temperature non-ferrous reagents A and B were added and incubated at room temperature for 5 minutes. The colored product was read and accounts subtracted the measured concentrations of nitrite from the total concentration of nitric oxide in the sample.

On the same day, together with biochemical analyses, the patients and controls underwent color-coded and pulsed wave Doppler measurements of blood flow velocity and RI in the right and left interlobar renal arteries, hepatic artery, splenic artery and superior mesenteric artery, using a Toshiba Xario SSA-660A or Toshiba Aplio SSA-790 ultrasonographic system (Toshiba, Tokyo, Japan), with a 2- to 6-MHz multifrequency convex probe. The RI was automatically calculated from the Doppler spectrum as (Vmax-Vmin)/Vmax, where Vmax was the maximum systolic blood flow velocity and Vmin was the maximum end-diastolic velocity.

Statistical analysis

Statistical analysis was performed by the SPSS 13.0 statistical package (IBM-SPSS, Armonk, NY). All results are expressed as mean±SD. Comparisons between subgroups were made using the Mann-Whitney U test and Kruskal Wallis test as appropriate. Correlations were evaluated using the appropriate Spearman's p coefficients. Values of $p<0.05$ were considered significant.

Ethical approval

This Manuscript is a part of the doctoral thesis''Noninvasive research of arterial splanchnic circulation in liver cirrhosis: correlation with serum nitric oxide (NO) and ammonia" that has been completed and mentored by deceased Professor Mirjana Perisic, MD, PhD and co-mentored by Professor Vladimir Jurišić, MD, PhD.

The preparation of the doctoral thesis was approved by the University of Belgrade, Decision No. 020-1883/33, 27.05.2010.

RESULTS

The study included 80 cirrhotic patients. The average age was 56.26±10.5 years in men and 48.86±14.5 years in women. The control group consisted of 11 men, 46.76±14.6 years old, and 9 women, 40.66±14.6 years old. Patient characteristics are presented in **Table 1** and Doppler variables are presented in **Table 2**.

RRA Vmax is similar in patients with cirrhosis of the liver and in controls, whereas LRA Vmax is higher in patients with cirrhosis then in healthy controls **(Figure 1)**. HA and SA Vmax are higher in patients with liver cirrhosis than in controls **(Figure 1)**.

RRA Vmin is lower in patients with cirrhosis of the liver than in controls, as Vmin in LRA. SA Vmin is similar in patients and in controls **(Figure 2)**. RRA, LRA, SA, and HA RI are higher in patients with cirrhosis than in controls **(Table 1)**.

Table 2. Doppler variables in patients with cirrhosis of the liver and in healthy controls

Blood vessel	Variable	Patients with liver cirrhosis (n = 80)	Healthy controls (n = 20)	p
Right renal artery	Vmax (cm/s)	88.9 ± 31.6	83.3 ± 16.7	0.286
	Vmin (cm/s)	24.3 ± 8.9	29.3 ± 70	0.022
	RI	0.72 ± 0.08	0.65 ± 0.04	<0.001
Left renal artery	Vmax (cm/s)	99.4 ± 30.5	80.0 ± 17.1	<0.001
	Vmin (cm/s)	27.4 ± 9.2	31.2 ± 7.8	0.1
	RI	0.71 ± 0.09	0.61 ± 0.05	<0.001
Hepatic artery	Vmax (cm/s)	125.7 ± 67.7	79.3 ± 20.3	0.001
	Vmin (cm/s)	35.5 ± 25.6	28.9 ± 10.4	0.766
	RI	0.72 ± 0.09	0.64 ± 0.07	<0.001
Splenic artery	Vmax (cm/s)	144.5 ± 54.9	94.5 ± 20.6	0.001
	Vmin (cm/s)	44.8 ± 19.0	38.1 ± 9.5	0.278
	RI	0.68 ± 0.09	0.59 ± 0.06	<0.001

RI - resistance index; Vmax - maximum systolic blood flow velocity; Vmin - maximum tele diastolic blood flow velocity

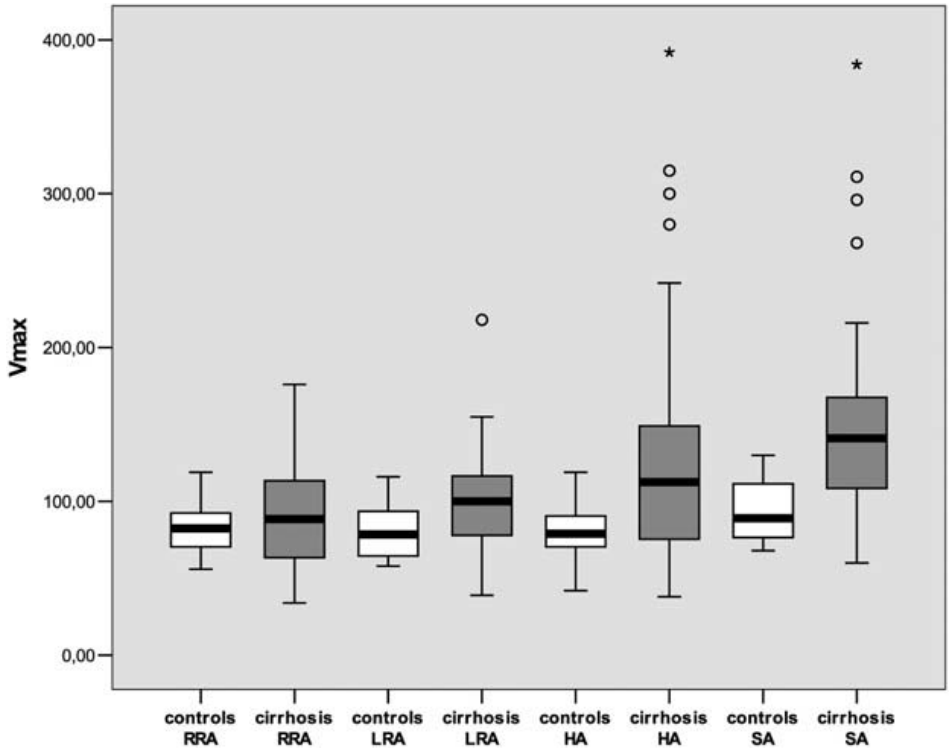

Figure 1. Box-and-whiskers plot showing maximum systolic blood flow velocity (Vmax) in patients with liver cirrhosis and in healthy controls
Vmax-maximum systolic blood flow velocity (cm/s), RRA- Right renal artery, LRA-Left renal artery, HA- Hepatic artery, SA- Splenic artery
The bottom and the top of the box are the first and third quartiles, respectively, while the horizontal band dividing the box is the median. The whiskers represent the lowest and highest data within 1.5 interquartile range, while outlying data are shown as small circles.
* Extreme values, which in the non-parametric analyzes have not changed the significance to a great extent

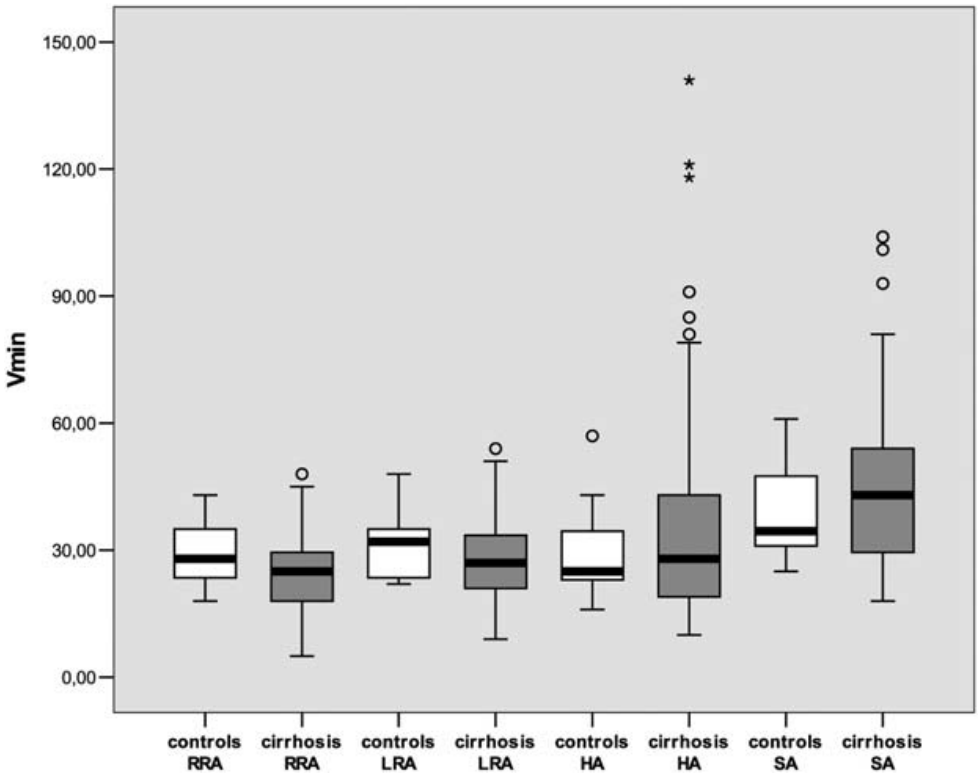

Figure 2. Box-and-whiskers plot showing maximum end-diastolic blood flow velocity (Vmin) in patients with cirrhosis and in healthy controls
Vmin-maximum end-diastolic blood flow velocity (cm/s), RRA- Right renal artery, LRA-Left renal artery, HA- Hepatic artery, SA- Splenic artery
The bottom and the top of the box are the first and third quartiles, respectively, while the horizontal band dividing the box is the median. The whiskers represent the lowest and highest datum within 1.5 interquartile range, while outlying data are shown as small circles

* Extreme values, which in the non-parametric analyzes have not changed the significance to a great extent

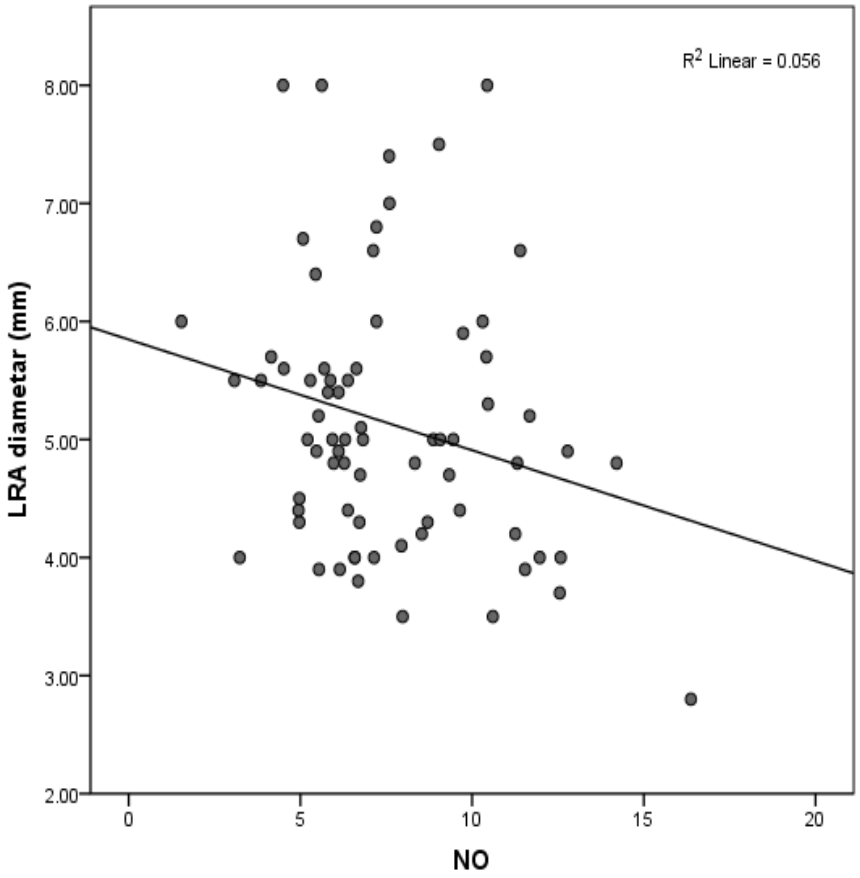

Figure 3. Correlation between nitric-oxide serum level and left renal artery diameter

LRA – left renal artery, NO – nitric-oxide

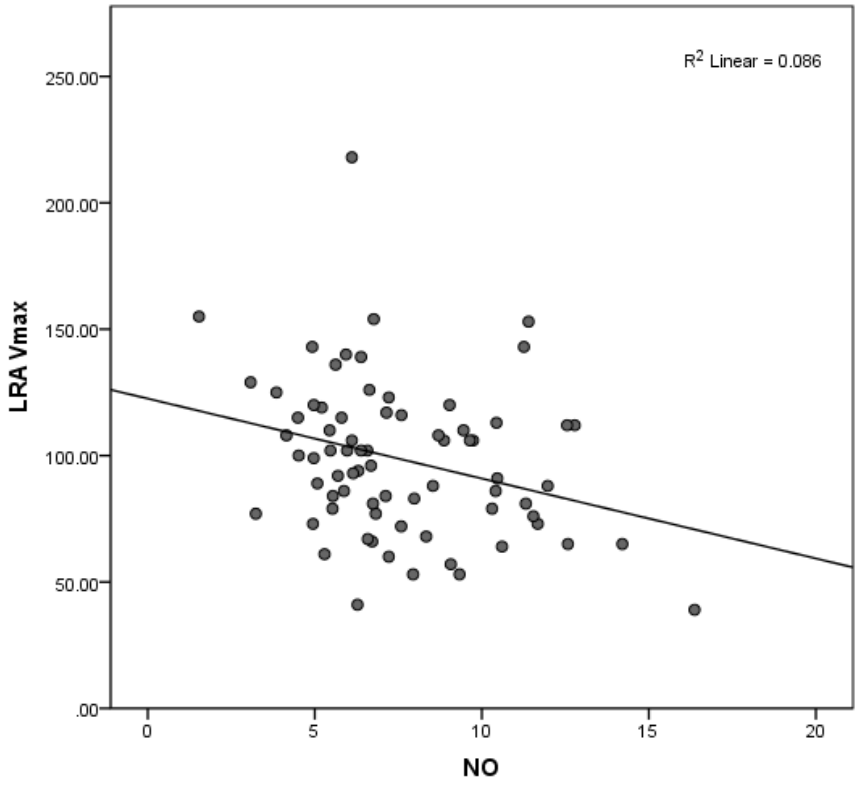

Figure 4. Correlation between nitric-oxide serum level and systolic blood flow velocity in left renal artery in patients with liver cirrhosis

Vmax – systolic blood flow veleocity, LRA – left renal artery, NO – nitric-oxide

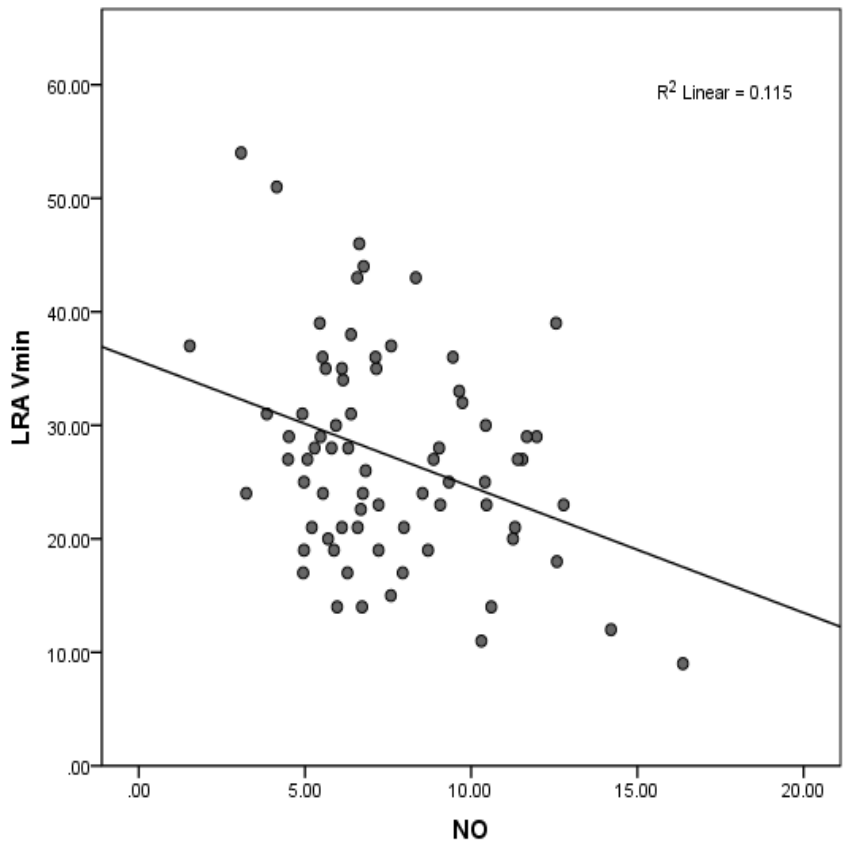

Figure 5. Correlation between nitric-oxide serum level and diastolic blood flow velocity in left renal artery in patients with liver cirrhosis

Vmin – dyastolic blood flow veleocity, LRA – left renal artery, NO – nitric-oxide

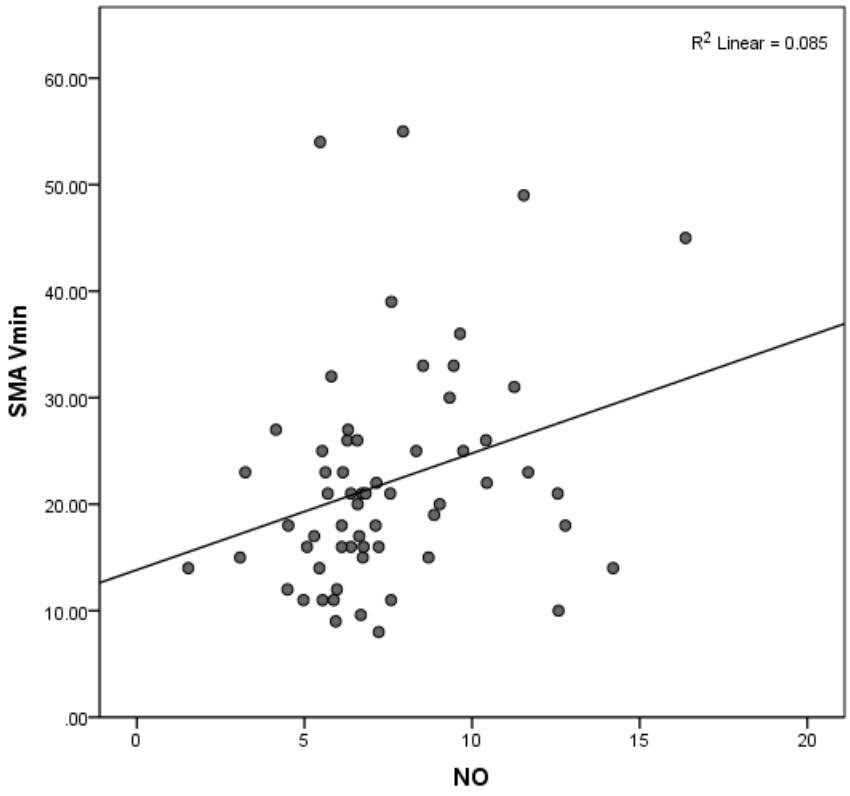

Figure 6. Correlation between nitric-oxide level and diastolic blood flow velocity in superior mesenteric artery in patients with cirrhosis of the liver

Vmin – diastolic blood flow velocity, SMA – superior mesenteric artery, NO – nitric-oxide

The average plasma level of NO in patients with cirrhosis is 7.7± 3.2 μmol/L. There is a statistically significant difference in median values for NO in the group of patients without ascites (Med=6.7 μmol/L) and in the group of patients with ascites (mild ascites Med=7.2 μmol/L; moderate/large ascites Med=8.3 μmol/L) ($p < 0.05$). Given the stage of cirrhosis according to the Child-Pugh classification there is a significant difference in median values for NO in the group of patients with stage A (Med=6.9 μmol/L) and stage C (Med=8.0 μmol/L) cirrhosis of the liver ($p < 0.05$).

There is a significant negative correlation between NO level and diameter of LRA **(Figure 3)**. There is a significant negative correlation between NO level and Vmax **(Figure 4)** and Vmin in LRA **(Figure 5)**. There is a significant positive correlation between NO level and Vmin in SMA **(Figure 6)**. There are no significant correlations between other variables.

DISCUSSION

Renal hemodynamic changes are commonly developed during the course of cirrhosis of the liver [22]. Duplex Doppler sonography can detect renal vasoconstriction in patients with cirrhosis [23].

In our study, the majority of patients with cirrhosis of the liver had normal levels of plasma nitric oxide, while NO value increased with the presence of cirrhosis and ascites, which is explained by the fact that the ascites result from hemodynamic changes. That matches with the results of other authors [24-26]. The Child-Pugh score is used to assess the prognosis of chronic liver disease, mainly cirrhosis. It consists of total bilirubin, serum albumin, prothrombin time, ascites and hepatic encephalopathy. We found that patients with stage C of liver cirrhosis had higher serum NO level, which means that in the advanced stages of cirrhosis there is an increased level of NO.

Arterial circulation in the kidneys is specific in patients with cirrhosis of the liver compared to other tested splanchnic artery and compared the left renal artery to the right.

There was a statistically significant negative correlation in median values of NO and the diameter of left renal artery (LRA). There was no correlation with the right renal artery. Increasing levels of NO lead to a decrease in LRA diameter. This intrarenal vasoconstriction is explained as a consequence of the complex impact of the portal and systemic circulation and with a fact that this nitrogen molecule has vasoconstrictive action in cirrhosis of the liver. These changes are described in the early pre-ascites phase of cirrhosis, and they precede the occurrence of hepatorenal syndrome [27, 28]. NO is vasodilator in visceral arteries. However, NO is vasoconstrictor in renal arteries. The phenomenon of renal vasoconstriction is very important in the study of hemodynamics in portal hypertension. In hepatorenal syndrome, renal vasoconstriction progresses, and the value of NO in serum grows.

We found statistically significant negative correlation between systolic and diastolic blood flow velocity and NO plasma levels in patients with cirrhosis. However, a specific flow only in the left renal artery can be the result of specific spleno-renal reflex, specific neural connections between the spleen and the left kidney, which participate in normal regulation of blood pressure and renal blood flow. They also participate in portal hypertension in renal and cardiovascular dysfunction. Study Jacobs-Kaufmann, Hamza et al, from 2003-2012, showed that NO, with other mediators, increases the release of fluid from the spleen vascular tree, increasing intrasplenic micro-vascular pressure, and the operation of the mediators in the afferent and efferent blood vessels of the spleen [29]. Changes in intrasplenic flow and the action of NO activate splenic afferent and efferent renal nerve fibers [29].

There was a statistically significant positive correlation between NO level and diastolic blood velocity flow in SMA that can be explained by vasodilator effect on this artery, like on the other splanchnic arteries. In addition to this explanation, increased release of NO by the SMA endothelium occurs before the development of hyperdynamic splanchnic circulation. Increased splanchnic iNOS occurs and persists in residual macrophages SMA. Elevated levels of NO and diastolic slower speed in SMA could open the way to the development of splanchnic hyperdynamic circulation and development of advanced liver disease.

CONCLUSION

In conclusion, patients with cirrhosis of the liver complicated with ascites and those with end-stage liver disease have greater NO levels. Specific blood velocity flow only in the LRA may be the result of specific spleno-renal reflex, and NO as a potent vasoactive molecule can have an influence on diameter of LRA, as well as on blood flow velocity in this artery. On the other hand, this nitric molecule has an opposite effect on the SMA leading to slower diastolic flow, but can be predictive data for the onset of splanchnic hyperdynamic circulation.

Acknowledgments

None

Conflict of interest

None to declare.

Author Contributions

Glisic T, design of the work, collecting data, analysis, interpretation of data, preparing the draft of the manuscript, manuscript revision; Popovic D, collecting data,

interpretation of data, manuscript revision; Stojkovic-Lalosevic M, collecting data, interpretation of data, Martinov J, collecting data, interpretation of data; Stojanovic M, collecting data, interpretation of data; Jurisic V, conception and design of the work, collecting data, analysis.

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PROCENA SPLANHNIČNOG ARTERIJSKOG PROTOKA DOPPLER ULTRASONOGRAFIJOM KOD PACIJENATA SA CIROZOM JETRE: KORELACIJA SA NIVOOM AZOT OKSIDA

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Sažetak

Uvod/cilj: Azot oksid (NO) je ključni medijator koji, paradoksalno, reguliše intrahepatičku i sistemsku/splanhničnu cirkulaciju. Glavni cilj ove studije bilo je merenje nivoa azot oksida, poređenje vrednosti serumskih vrednosti NO sa podacima o brzinama protoka krvi u visceralnim krvnim sudovima jetre, slezine, bubrega i creva kod pacijenata sa cirozom jetre.

Materijal i metode: U ovu prospektivnu studiju bilo je uključeno 80 pacijenata sa cirozom jetre. Doppler ultrasonografija je korišćena radi procene brzine protoka i rezistivnih indeksa (RI) u hepatičkoj (HA), desnoj (DRA) i levoj renalnoj (LRA), slezinskoj (SA) arteriji i gornjoj mezenteričnoj arteriji (SMA). Koncentracija NO je određivana primenom DetectX® Nitric Oxide kolorimetrijskog detekcionog kita.

Rezultati: Utvrđena je statistički značajna razlika u srednjoj vrednosti NO u grupi bolesnika bez ascitesa u odnosu na grupu sa ascitesom, kao i u grupi pacijenata sa A stadijumom u odnosu na C stadijum ciroze jetre ($p < 0,05$). Postoji statistički značajna negativna korelacija između vrednosti NO i dijametra i maksimalne i minimalne brzine u LRA. Prisutna je statistički značajna pozitivna korelacija između vrednosti NO i minimalne brzine u SMA.

Zaključak: Pacijenti sa cirozom jetre imaju signifikantno više RI u LRA, DRA, SA i HA. Kod pacijenata sa cirozom komplikovanom ascitesom i onima sa završnom fazom bolesti jetre, nivo NO je signifikantno viši. Koncentracija NO ima uticaja na dijametar i brzinu protoka u LRA, kao i na minimalnu brzinu protoka u SMA.

Ključne reči: ciroza jetre, azot oksid, Dopler ultrasonografija

Primljen: 10.12.2022. I **Revizija:** 02.01.2023. I **Objavljen:** 20.02. 2023

Medicinska istaživanja 2023; 56(1):21-29