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# Evaluation of Cerebral Hemodynamics in Cirrhotic Patients by Transcranial Doppler Ultrasonography and its Relation to Hepatic Encephalopathy

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**Abstract**

The study aimed at Aim evaluation the cerebral hemodynamics in cirrhotic patients by transcranial Doppler ultrasonography and its relation to hepatic encephalopathy. This study is a prospective study , 50 subjects attended El Hussein university hospital, inpatient and outpatient clinic are classified into three groups, group I(10 subjects as a healthy control),group II (20 subjects with liver cirrhosis without hepatic encephalopathy) and group III(20 subjects with liver cirrhosis with hepatic encephalopathy). All patients included in the study underwent a full history taking,complete physical examination, liver functions tests,blood ammonia level,C.B.C,blood urea and serum creatinine and pelvi-abdominal ultarasonography. Transcranial Doppler done for all patients participated in the study using a 2 MHz transducer. The results showed that as regard Trans cranial Doppler ultrasound parameters, we found a statistical significant difference between the three groups as regard Pulsatility Index ($P < 0.001$), Breath-Holding Index ($P < 0.001$) ) , Maximum Flow Velocity($P < 0.001$) and Mean ($P < 0.001$), whereas Pulsatility Index, , Maximum Flow Velocity and Mean are higher in patient with Hepatic Encephalopathy, but Breath-holding index is low, there is no statistical significant difference ($P > 0.05$) between them as regard Minimum Flow Velocity. Conclusion: Transcranial doppler ultrasonography is easy, rapidly done not invasive method for evaluation of cerebral hemodynamic in cirrhotic patient and predection of hepatic encephalopathy.

**Keywords**: Transcranial doppler, Hepatic encephalopathy, Cirrhosis.

## 1. Introduction

Cirrhosis results from different mechanisms of liver injury that lead to necroinflammation and fibrogenesis; histologically it is characterized by diffuse nodular regeneration surrounded by dense fibrotic septa with subsequent parenchymal extinction and collapse of liver structures, together causing pronounced distortion of hepatic vascular architecture. This distortion results in increased resistance to portal blood flow and hence in portal hypertension and in hepatic synthetic dysfunction. [1,2] The risk of developing hepatic encephalopathy in cirrhotic patients is 20% per year, and at any time about 30–45% of people with cirrhosis exhibit evidence of overt encephalopathy.[3] Cerebral haemodynamics are altered in patients with cirrhosis, in relation to severity of disease and hepatic encephalopathy. Findings on impaired pulsatility index (PI) and breath-holding index (BHI) suggest that structural vascular damage and loss of vascular autoregulation are implicated in the pathophysiology of HE .[4,5] Patients with complications from portal hypertension such as ascites, hepatorenal syndrome, and hepatic encephalopathy (HE) present with distorted blood flow, and some studies in advanced stages of cirrhosis have shown reduced blood flow to skeletal muscle, brain and kidney, secondary to an increased vascular resistance.[6] Cerebral vascular resistance indices measured by using transcranial Doppler were increased in association with the severity of cirrhosis and encephalopathy, Cerebral pulsatility and resistive indices are real-time and useful parameters to assess and monitor cirrhotic patients.[7] Several studies have shown that patients with acute or chronic liver failure lose cerebral blood flow autoregulation, the abnormality being more pronounced in patients who have HE as well.[8] When autoregulation is lost, variations in mean arterial pressure cause a linear change in cerebral blood flow,In patients with hyperammonemia, the autoregulation curve shifts to the right meaning that these patients need a higher mean arterial pressure to maintain an adequate cerebral blood flow, This mechanism likely explains the disrupted cerebral hemodynamics observed in cirrhotic patients with hyperammonemia.[9] Transcranial Doppler ultrasonography (TCD) has emerged as a reliable tool for the study of cerebral autoregulation (CA) and some cerebral vascular disorders, This non-invasive test allows real-time recording of middle cerebral artery velocities, providing two functional indexes of cerebral hemodynamics: the pulsatility index (PI), which assesses arteriolar vascular integrity, and the breath-holding index (BHI), a measure of cerebrovascular reactivity(CVR)evaluating cerebral autoregulation .[10]

It is hypothesized that cirrhotic patients show cerebral vasoconstriction, which is more pronounced both in decompensated cirrhosis and in the presence of HE, Therefore the primary aim of this study was to evaluate cerebral hemodynamics by TCD in patients with compensated and decompensated cirrhosis, and patients with and without HE, compared to healthy subjects, Factors other than elevated levels of ammonia may be implicated in hepatic encephalopathy (HE) pathophysiology, including abnormal cerebral haemodynamics Transcranial Doppler ultrasonography (TCD) evaluates cerebrovascular structural integrity and reactivity, through pulsatility index (PI) and breath-holding index (BHI) respectively, The aim of this study was to evaluate cerebral haemodynamics by TCD in patients with compensated and decompensated cirrhosis, and patients with and without HE.[10]

**Patients and methods**

Aim of the work is to evaluate the cerebral hemodynamics in cirrhotic patients by transcranial Doppler ultrasonography and its relation to hepatic encephalopathy. Fifty subjects are included in the studies who were attended El Hussein University. The patient are classified into three groups, group I (10 subjects as a healthy control), group II (20 subjects with liver cirrhosis without hepatic encephalopathy) and group III(20 subjects with liver cirrhosis with hepatic encephalopathy). Patients with other causes of encephalopathy: e.g. uremic encephalopathy, hypertension, cardiovascular diseases, cerebral diseases, diabetes mellitus all have been excluded from the study. All patients included in the study underwent a full history taking( with stress on ascites , jaundice, lower limb edema , hematemesis ,and melena),complete physical examination liver functions tests : SGPT, SGOT, bilirubin (total and direct), serum albumin, PT, PC, INR, PTT, blood ammonia level, C.B.C, blood urea and serum creatinine and pelvi-abdominal ultarasonography. Transcranial Doppler done for all patients participated in the study using a 2 MHz transducer. The Doppler probe was held in the temporal region above the zygomatic arch, 1 to 5 cm anteriorly to the ear. The ultrasound window was located in each individual by searching the region where maximum amplitude of the Doppler signals was obtained, corresponding to the blood flow velocities (BFVs) of the middle cerebral artery (MCA). The PI and BHI of the middle cerebral artery were investigated. The PI is defined by the following equation: PI = SPV – EDV/MV
Where, SPV: systolic peak velocity; EDV: end-diastolic velocity; MV: mean velocity. Median value of the PI is 0.89 (IQR 0.8-1) in normal population.

The BHI consists of induction of hypercapnia during 30 seconds by apnea (breath-holding), with measurement of and pre- and post-flow velocities, as follows: BFVs are registered in MCA during 1 minute while on normal breathing (FV rest), and patient is then asked to perform the 30-second breath-holding after a normal inspiration (tapnea), continuously registering BFVs. Finally, BFVs are recorded during the 10 seconds after the end of the breath-holding period (BFVs apnea).The BHI is defined by the following equation: BHI = 100*(BFV apnea-BFV rest/ BFV rest * tapnea)( %/sec). Median value of BHI is 1.26 (IQR 0.94-1.54)%/sec in normal population .Values below this indicate loss of CVR.

**Statistical analysis**

Data were analyzed using Statistical Program for Social Science (SPSS) version 18.0.Quantitative data were expressed as mean± standard deviation (SD). Qualitative data were expressed as frequency and percentage. Independent-samples t-test of significance was used when comparing between two means.A one-way analysis of variance (ANOVA) when comparing between more than two means. Chi-square ($X^2$) test of significance was used in order to compare proportions between two qualitative parameters and Pearson's correlation coefficient (r) test was used for correlating data.

**RESULTS**

The study included 32 males (64%) and 18 females (36%), their mean age was 57.50 years ± 6.8, Weight (kg) 88.18± 12.01 and Length (cm) 170.42 ± 5.86 as shown in Table (1).

**Table (1):** Descriptive data of the study group.

| Descriptive Statistics | Min. | Max. | Mean | SD |
|---|---|---|---|---|
| Age | 45.00 | 73.00 | 57.50 | 6.86 |
| Wight (kg) | 60.00 | 110.00 | 88.18 | 12.01 |
| Length (cm) | 160.00 | 190.00 | 170.42 | 5.86 |

Comparing control and case groups as regard CBC parameter, it`s found a statistical significant difference between them as regard Hb ($P < 0.01$), but there is no statistical significant difference ($P > 0.05$) between both as regard WbCs as shown in Table (2).

**Table (5):** Comparison between diagnosis as regard CBC.

| CBC | Hepatic Encephalopathy | Liver cirrhosis | Normal | ANOVA test | p-value |
|---|---|---|---|---|---|
| **Hb.** | | | | | |
| Mean ± SD | 10.66±1.07 | 11.49±1.12 | 12.80±1.03 | 13.135 | **<0.001** |
| Range | 8.50-12.00 | 10.00-14.00 | 11.00-14.00 | | |
| $P_1$ | | **0.019** | **<0.001** | | |
| $P_2$ | | | **0.003** | | |
| **WbCs** | | | | | |
| Mean ± SD | 9.18±1.47 | 9.06±1.89 | 8.65±1.89 | 0.317 | 0.730 |
| Range | 6.00-11.00 | 4.50-12.00 | 5.00-11.00 | | |
| $P_1$ | | 0.821 | 0.434 | | |
| $P_2$ | | | 0.549 | | |

$P_1$: Comparison between hepatic encephalopathy and other group

$P_2$: Comparison between Liver cirrhosis and normal.

Comparing control and case groups as regard Liver function, there was a statistical significant difference between them as regard ALT ($P < 0.01$), AST ($P < 0.01$), Albumin ($P < 0.01$), Bilirubin ($P < 0.01$), PT ($P < 0.01$) and INR ($P < 0.05$)as shown in Table (3). When Comparing control with cases group as regard kidney function and ammonia, we found statistical significant difference between them as regard Urea ($P< 0.002$) and ammonia ($P< 0.001$)but there is no statistical significant difference ($P > 0.05$) between them as regard and s. creatinine shown in Table (4&5) . When Comparing control with patient groups as regard the transcranial Doppler ultrasound parameters, there was a statistical significant difference as the Pulsatility Index ($P < 0.001$), Breath-Holding Index ($P < 0.001$) ) , Maximum Flow Velocity($P < 0.001$) and Mean ($P < 0.001$), whereas Pulsatility Index, , Mean and Maximum Flow Velocity were higher in patients with Hepatic Encephalopathy than the other groups,however Breath-holding index is low, however there is no statistical significant differences ($P > 0.05$) between them as regard Minimum Flow Velocity Table (6) and fig(1).

Table(3): Comparing control and case groups as regard Liver function

| Liver function | Hepatic Encephalopathy | Liver cirrhosis | Normal | ANOVA test | p-value |
|---|---|---|---|---|---|
| **ALT** | | | | | |
| Mean ± SD | 77.55±21.57 | 85.60±51.41 | 14.60±2.80 | 66.161 | **<0.001** |
| Range | 35.00-120.00 | 98.00-301.00 | 10.00-20.00 | | |
| $P_1$ | | **<0.001** | **<0.001** | | |
| $P_2$ | | | **<0.001** | | |
| **AST** | | | | | |
| Mean ± SD | 86.30±20.62 | 110.20±51.31 | 14.60±2.17 | 68.146 | **<0.001** |
| Range | 54.00-115.00 | 95.00-290.00 | 12.00-19.00 | | |
| $P_1$ | | **<0.001** | **<0.001** | | |
| $P_2$ | | | **<0.001** | | |
| **Albumin** | | | | | |
| Mean ± SD | 2.64±0.66 | 2.68±0.45 | 3.82±0.43 | 18.645 | **<0.001** |
| Range | 1.20-3.70 | 1.70-3.50 | 3.40-4.50 | | |
| $P_1$ | | 0.838 | **<0.001** | | |
| $P_2$ | | | **<0.001** | | |
| **Bilirubin** | | | | | |
| Mean ± SD | 2.55±1.30 | 2.17±0.73 | 0.91±0.19 | 10.013 | **<0.001** |
| Range | 0.29-5.00 | 0.79-3.30 | 0.60-1.20 | | |
| $P_1$ | | 0.216 | **<0.001** | | |
| $P_2$ | | | **<0.001** | | |
| **PT** | | | | | |
| Mean ± SD | 15.75±1.39 | 16.72±1.54 | 13.60±0.74 | 17.562 | **<0.001** |
| Range | 14.00-18.30 | 14.00-20.00 | 12.00-14.50 | | |
| $P_1$ | | **0.029** | **<0.001** | | |
| $P_2$ | | | **<0.001** | | |
| **INR** | | | | | |
| Mean ± SD | 1.79±0.31 | 1.72±0.45 | 0.92±0.27 | 20.836 | **<0.001** |
| Range | 1.26-2.30 | 1.00-2.30 | 0.50-1.30 | | |
| $P_1$ | | 0.579 | **<0.001** | | |
| $P_2$ | | | **<0.001** | | |

**Table (4):** Comparison between diagnoses as regard kidney function.

| Kidney function | Hepatic Encephalopathy | Liver cirrhosis | Normal | ANOVA test | p-value |
|---|---|---|---|---|---|
| **Creat** | | | | | |
| Mean ± SD | 1.17±0.36 | 1.08±0.28 | 0.87±0.28 | 2.927 | 0.063 |
| Range | 0.60-1.70 | 0.50-1.70 | 0.50-1.30 | | |
| $P_1$ | | 0.371 | **0.020** | | |
| $P_2$ | | | 0.100 | | |
| **Urea** | | | | | |
| Mean ± SD | 27.60±6.72 | 31.05±4.99 | 22.60±4.33 | 7.532 | **0.002** |
| Range | 20.00-45.00 | 25.00-42.00 | 15.00-30.00 | | |
| $P_1$ | | 0.060 | **0.027** | | |
| $P_2$ | | | **<0.001** | | |

**Table (5):** Comparison between diagnosis as regard ammonia.

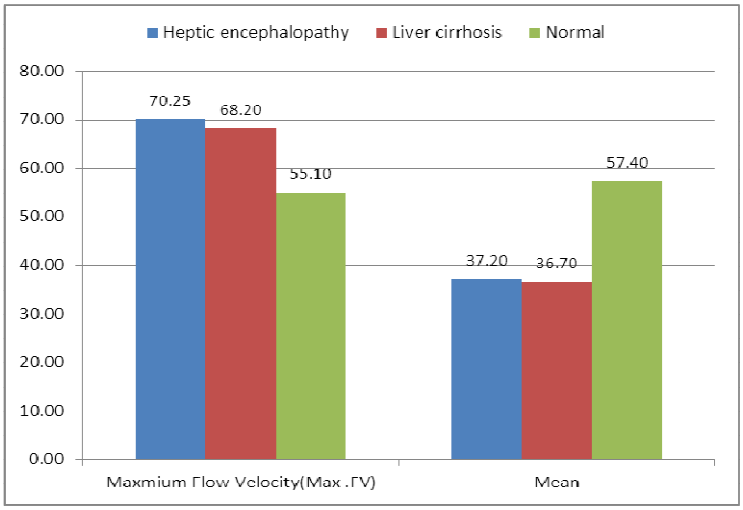
| Ammonia | Hepatic Encephalopathy | Liver cirrhosis | Normal | ANOVA test | p-value |
|---|---|---|---|---|---|
| Mean ± SD | 61.25±8.20 | 48.18±4.34 | 28.30±6.80 | 17.681 | **<0.001** |
| Range | 50.00-80.00 | 35.00-55.00 | 20.00-40.00 | | |
| $P_1$ | | **<0.001** | **<0.001** | | |
| $P_2$ | | | **<0.001** | | |

**Table (6):** Comparison between diagnoses as regard Transcranial Doppler ultrasound parameters.

| Transcranial doppler ultrasound parameters | Hepatic Encephalo-pathy | Liver cirrhosis | Normal | ANOVA test | p-value |
|---|---|---|---|---|---|
| **Pulsatility Index(PI)** | | | | | |
| Mean ± SD | 2.27±0.67 | 1.36±0.27 | 0.80±0.15 | 38.394 | **<0.001** |
| Range | 1.00-3.26 | 1.01-2.00 | 0.60-1.00 | | |
| $P_1$ | | **<0.001** | **<0.001** | | |
| $P_2$ | | | **0.003** | | |
| **Breath-Holding Index(BHI)** | | | | | |
| Mean ± SD/ | 0.84±0.40 | 0.97±0.12 | 1.34±0.09 | 11.598 | **<0.001** |
| Range | 0.01-1.30 | 0.55-1.10 | 1.26-1.50 | | |
| $P_1$ | | 0.158 | **<0.001** | | |
| $P_2$ | | | **<0.001** | | |
| **Maximum Flow Velocity(Max .FV)** | | | | | |
| Mean ± SD | 70.25±3.52 | 68.20±5.32 | 55.10±10.67 | 21.413 | **<0.001** |
| Range | 64.00-75.00 | 60.00-79.00 | 40.00-70.00 | | |
| $P_1$ | | 0.300 | **<0.001** | | |
| $P_2$ | | | **<0.001** | | |
| **Minimum Flow Velocity(Min FV)** | | | | | |
| Mean ± SD | 20.25±2.79 | 20.00±3.23 | 19.40±2.88 | 0.270 | 0.764 |
| Range | 16.00-25.00 | 15.00-29.00 | 15.00-25.00 | | |
| $P_1$ | | 0.793 | 0.467 | | |
| $P_2$ | | | 0.607 | | |
| **Mean** | | | | | |
| Mean ± SD | 37.20±5.40 | 36.70±5.44 | 57.40±2.37 | 67.491 | **<0.001** |
| Range | 29.00-45.00 | 30.00-47.00 | 55.00-62.00 | | |
| $P_1$ | | 0.752 | **<0.001** | | |
| $P_2$ | | | **<0.001** | | |

**Fig (1):** Comparison between diagnosis as regard Transcranial Doppler ultrasound parameters Pulsatility index and breath holding index in study groups.




Statistical correlations between Pulsatility Index and other laboratory and clinical parameters among the studied patients group, showing a significant positive correlation ($P < 0.05$) between Pulsatility Index and Wight, Hb, Albumin, Bilirubin, PT, INR and S. Creatinine as shown in Table (10) and Figure (24) (25), (26), (27), and (28), but there were no positive correlation ($P > 0.05$) between Pulsatility Index and Length, WBCs, ALT, AST, urea and ammonia. Also, statistical correlations between Breath-Holding Index and other laboratory and clinical parameters among the studied patients group, showing a significant positive correlation ($P < 0.05$) between Breath-Holding Index and ALT, AST, INR and S. Creatinine as shown in Table (10) and Figure (29) (30), (31) and (32), but there were no positive correlation ($P > 0.05$) between Breath-Holding Index and Age, Wight , Length, Hb, WBCs, urea, Albumin, Bilirubin, PT, and ammonia.

**Discussion**

Several studies have shown that patients with acute or chronic liver failure loss cerebral blood flow autoregulation, the abnormality being more pronounced in patients who have HE as well **(Hollingsworth, et al.**[8] In our study, when Comparing control with cases groups as regard Trans Cranial Doppler ultrasound parameters, we found statistical significant difference between them as regard Pulsatility Index ($P < 0.001$), whereas Pulsatility Index is more higher in cirrhotic patient with hepatic encephalopathy than cirrhotic patients without hepatic encephalopathy, and Breath-holding index ($P < 0.001$) is more low in cirrhotic patient with hepatic encephalopathy than cirrhotic patients without hepatic encephalopathy and this agreed with **Chavarria 2013**.[11] who found that Cirrhotic patients have altered cerebral hemodynamics when compared to healthy subjects, Abnormalities were more evident in patients presenting with decompensated disease, as well as in those with low grade HE (either minimal or overt). There was a progressive increase in PI and decrease in BHI, from healthy controls to patients with compensated cirrhosis, and from the latter to those with decompensated cirrhosis and or presence of HE, In patients with overt HE PI was higher compared with MHE, The gradient observed across the groups both in PI and BHI which suggests that patients with higher degree of HE have more alterations in cerebral hemodynamics, The increase in PI likely occurs a consequence of a higher vascular resistance secondary to microvascular structural deterioration (also known as arteriolosclerosis).

Our result are in agreement with **Macias Rodriguez 2015**.[12] who found that cerebral hemodynamics is altered in patients with cirrhosis, related to severity of the disease and HE, as evidenced by a high PI and impaired CVR. Thus, patients with decompensated cirrhosis or HE are at risk for cerebral hypoperfusion both in relation to microvascular damage and to a decreased ability for autoregulation, Loss of autoregulation would be particularly relevant during abrupt changes in systemic blood pressure, particularly hypotension, directly compromising cerebral blood flow and favoring HE.

Similar results obtained by **Kawakami 2001**.[13] who found that cerebral vascular resistance indices measured by using transcranial doppler were increased in association with the severity of cirrhosis and encephalopathy, Cerebral pulsatility and resistive indices are real-time and useful parameters to assess and monitor of cirrhotic patients

Also, our results are in agreement with **Alfonso Lag 1997**.[14] who found that cerebral autoregulation is often impaired in patients with cirrhosis and ascites. These patients can develop cerebral hypoperfusion if arterial pressure falls abruptly. Also, **Guevara 1998**.[15] found that in patients with cirrhosis and ascites there is a cerebral vasoconstriction which is probably related with the arterial hypotension and the over activity of vasoconstrictor systems.

**Table (7):** Correlation Study between transcranial Doppler ultrasound parameters and other parameters in the study groups.

| **Parameters** | | **Pulsatility Index(PI)** | **Breath-Holding Index (BHI)** |
|---|---|---|---|
| Age | r | -0.098 | 0.128 |
| | p | 0.499 | 0.374 |
| Wight (kg) | r | -0.348 | -0.108 |
| | p | **0.013** | 0.455 |
| Length (cm) | r | -0.171 | -0.045 |
| | p | 0.235 | 0.758 |
| Hb. | r | -0.504 | 0.183 |
| | p | **<0.001** | 0.203 |
| WbCs | r | 0.028 | -0.110 |
| | p | 0.848 | 0.447 |
| ALT | r | 0.041 | -0.274 |
| | p | 0.779 | **0.044** |
| AST | r | 0.049 | -0.314 |
| | p | 0.733 | **0.027** |
| Albumin | r | -0.421 | 0.193 |
| | p | **0.002** | 0.180 |
| Bilirubin | r | 0.560 | -0.262 |
| | p | **<0.001** | 0.066 |
| PT | r | 0.303 | -0.214 |
| | p | **0.032** | 0.136 |
| INR | r | 0.394 | -0.279 |
| | p | **0.005** | **0.050** |
| Creat | r | 0.311 | -0.280 |
| | p | **0.028** | **0.049** |
| Urea | r | 0.160 | -0.031 |
| | p | 0.267 | 0.832 |
| Ammonia | r | 0.758 | -0.459 |
| | p | **<0.001** | **<0.001** |

Cirrhosis, particularly in decompensated stages, is associated with hyponatremia and higher levels of some cytokines, these changes lead to endothelial and vascular smooth cell muscle dysfunction, with systemic hemodynamic derangement. Classically, the hemodynamic abnormalities of end-stage liver disease cause systemic hypotension, thus affecting systemic blood flow. Under certain circumstances there is further deterioration of flow affecting specific vascular beds, thus leading to tissue hypoperfusion and organ dysfunction, This is the case of hepatorenal and hepatoadrenal syndromes, The hemodynamic changes observed with TCD indexes in present study support the fact that cerebral vascular beds are affected in cirrhosis and decompensated cirrhosis, and bring further evidence to establish dysfunction of cerebral hemodynamics and hypoperfusion as part of the pathophysiology of HE **Jain, et al 2012**.[16]

Cerebral oxygen consumption and blood flow are reduced during HE, but subsequently returned to control values after recovery from HE episode. Of note, there was no association with cerebral metabolism of ammonia**. Dam, et al 2013** .[17]

Factors referred as HE precipitants such as dehydration, diuretics, acid-base disorders, infections, gastrointestinal hemorrhage, and TIPS-placement, alter systemic hemodynamics and could subsequently exert regional blood

flow abnormalities in cerebral circulation thus leading to HE. The improvement in mental status in patients with diuretic-induced HE after albumin infusion has been related to an increase in renal ammonia excretion and reduced oxidative stress **Jalan , 2004**.[18]

However, based on our findings it is possible that improving systemic and cerebral hemodynamics may also be implicated in resolution of HE, A recent study identified a subset of patients presenting decreased cerebral blood flow after TIPS placement, what was associated with development of HE **Zheng, 2012**.[19]

Thus, HE after TIPS may not only be caused by resulting hyperammonemia and direct neurotoxicity, but indirectly through disturbed cerebral hemodynamics. **Bosoi, 2009** .[20]

At our study we found Statistical correlations between Pulsatility Index and other laboratory among the studied patients group, showing a significant positive correlation ($P < 0.05$) between Pulsatility Index and Hb, Albumin, Bilirubin, PT, INR and S. Creatinine, but there were no positive correlation ($P > 0.05$) between Pulsatility Index and WBCs, ALT, AST, urea and ammonia and this concordance with **Kawakami 2001**.[13]

Also, we found statistical correlations between Breath-Holding Index and other laboratory parameters among the studied patients group, showing a significant positive correlation ($P < 0.05$) between Breath-Holding Index and ALT, AST, INR and S. Creatinine but there were no positive correlation ($P > 0.05$) between Breath-Holding Index and Hb, WBCs, urea, Albumin, Bilirubin, PT, and ammonia and this concordance with **Macias Rodriguez 2015**.[12]

Also, in our study we found that there is Negative correlation and significant between pulsatility index (PI) and breath-holding index (BHI) and this concordance with **Chavarria 2013**.[11]

Also, when we Compared control with cases groups as regard ammonia, we found statistical significant difference between them ($P< 0.001$) whereas ammonia is more higher in cirrhotic patient with hepatic encephalopathy than cirrhotic patients without hepatic encephalopathy and this concordance with **Dethloff 2008** .[9]

These results indicate that cerebral hemodynamics is altered in patients with cirrhosis, in relation to severity of disease and HE. Findings on impaired PI and BHI suggest that structural vascular damage and loss of vascular autoregulation are implicated in the pathophysiology of HE.

## References

1- Dooley J, Lok A, Burroughs AK, Heathcote E, eds. (2011)Sherlock's diseases of the liver and biliary system, 12th edn. Oxford: Wiley-Blackwell.

2- Lozano R, Naghavi M, Foreman K, et al. (2012) Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet; 380:2095–128.

3- Bajaj JS (March 2010). "Review article: the modern management of hepatic encephalopathy". Aliment. Pharmacol. Ther. 31 (5): 537–47.

4- Macías-Rodríguez RU, Duarte-Rojo A, Cantú-Brito C, Sauerbruch T, Ruiz-Margáin A, Trebicka J, Green-Gómez M, Díaz Ramírez JB, Sierra Beltrán M, Uribe-Esquivel M, Torre A (2014): Cerebral haemodynamics in cirrhotic patients with hepatic encephalopathy. Liver Int. Feb;35(2):344-52. doi: 10.1111/liv.12557. Epub 2014 Apr 29.

5- Iwakiri Y. Endothelial dysfunction in the regulation of cirrhosis and portal hypertension. Liver Int 2012; 32(2): 199-213.

6- Gines P, Schrier R W. Renal failure in cirrhosis. N Engl J Med 2009; 361(13): 1279-90.

7- Kawakami M, Koda M, Murawaki Y, Kawasaki H, Ikawa S. (2001) Cerebral vascular resistance assessed by transcranial color Doppler ultrasonography in patients with chronic liver diseases. J Gastroenterol Hepatol. Aug; 16(8):890-7.

8- Hollingsworth K G, Jones D E, Taylor R, Frith J, Blamire A M, Newton J L. Impaired cerebral autoregulation in primary biliary cirrhosis: implications for the pathogenesis of cognitive decline. Liver Int

2010; 30(6): 878-85.

**9-** Dethloff T J, Knudsen G M, Larsen F S. Cerebral blood flow autoregulation in experimental liver failure. J Cereb Blood Flow Metab 2008; 28(5): 916-26.

**10-** Yeo L L, Sharma V K. Role of transcranial Doppler ultrasonography in cerebrovascular disease. Recent Pat CNS Drug Discov 2010; 5(1): 1-13.

**11-** Chavarria L, Alonso J, Garcia-Martinez R, Simon-Talero M, Ventura-Cots M, Ramirez C, (2013): Brain magnetic resonance spectroscopy in episodic hepatic encephalopathy. J Cereb Blood Flow Metab . 33(2): 272-7.

**12-** Macías-Rodríguez RU, Duarte-Rojo A, Cantú-Brito C, Sauerbruch T, Ruiz-Margáin A, Trebicka J, Green-Gómez M, Díaz Ramírez JB, Sierra Beltrán M, Uribe-Esquivel M, Torre A (2015): Cerebral haemodynamics in cirrhotic patients with hepatic encephalopathy. Liver Int. Feb;35(2):344-52. doi: 10.1111/liv.12557.

**13-** Kawakami M, Koda M, Murawaki Y, Kawasaki H, Ikawa S (2001):Cerebral vascular resistance assessed by transcranial color Doppler ultrasonography in patients with chronic liver diseases.J Gastroenterol Hepatol;16(8):890-7.

**14-** Alfonso Lagi, Giorgio La Villa, Giuseppe Barletta, Simone Cencetti, Stefano Bacalli, Marcello Cipriani, Marco Foschi, Chiara Lazzeri, Riccarda Del Bene, Paolo Gentilini, Giacomo Laffi (1997): Cerebral autoregulation in patients with cirrhosis and ascites A transcranial Doppler study .journal-of-hepatology Volume 27, Issue 1, p1-250.

**15-** Guevara M, Bru C, Ginès P, Fernández-Esparrach G, Sort P, Bataller R, Jiménez W, Arroyo V, Rodés.(1998):Increased cerebrovascular resistance in cirrhotic patients with ascites.Hepatology;28(1):39-44.

**16-** Jain L, Sharma B C, Sharma P, Srivastava S, Agrawal A, Sarin S K.(2012): Serum endotoxin and inflammatory mediators in patients with cirrhosis and hepatic encephalopathy. Dig Liver Dis 44(12): 1027-31.

**17-** Dam G, Keiding S, Munk O L, Ott P, Vilstrup H, Bak L K, .(2013): Hepatic encephalopathy is associated with decreased cerebral oxygen metabolism and blood flow, not increased ammonia,uptake. Hepatology; 57(1): 258-65.

**18-** Jalan R, Pollok A, Shah SH, Madhavan K, Simpson KJ.(2002): Liver derived pro-inflammatory cytokines may be important in producing intracranial hypertension in acute liver failure. J Hepatol. ;37:536–538.

**19-** Zheng G, Zhang L J, Wang Z, Qi R F, Shi D, Wang L, (2012). Changes in cerebral blood flow after transjugular intrahepatic portosystemic shunt can help predict the development of hepatic encephalopathy: an arterial spin labeling MR study. Eur J Radiol ; 81(12): 3851-6.

**20-** Bosoi C R, Rose C F.(2009): Identifying the direct effects of ammonia on the brain. Metab Brain Dis . 24(1): 95-102.