Prediction of Variceal Haemorrhage in Patients with Alcohol-Induced Cirrhosis

ALKOLE BAĞLI SİROZ HASTALARINDA VARİS KANAMALARININ PREDİKSİYONU

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Summary

The aim of this study was to find the correlation between risk of gastroesophageal variceal bleeding and portal flow patterns in alcohol induced cirrhosis.

25 alcohol induced, histologically proved cirrhotic patients (9 females; mean age of 56 years) underwent real-time pulsed and colour Doppler ultrasound. Eight patients experienced variceal bleeding; three of them after the Doppler study. The cross sectional area and maximum velocity of flow in the main portal vein were calculated for each patient and sex and age matched control group of 25 subjects. All patients had upper gastrointestinal system endoscopy and liver function tests.

3 patients had stagnant or reversed, 6 had hypodynamia, 7 had normodynainic and 9 had hyperdynamic portal blood flow. Twenty percent of patients without varices at endoscopy had hyperdynamic portal blood flow. This percentage was 29 in patients with varices which did not bleed and 63 in patients with variceal bleeding.

Although the correlation between portal flow patterns and the risk of gastroesophageal variceal bleeding needs to be evaluated in larger series with long term follow-up, our results are promising and demonstrating that patients with hyperdynamic portal flow and/or collaterals directly feeding the gastroesophageal varices are more prone to variceal bleeding.

Key Words: Cirrhosis, Variceal haemorrhage, Doppler ultrasound

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Özet

Alkolizm bağlı olarak gelişen karaciğer sirozunda gastro-özofajeal varis kanama riski ile portal kan akımı arasındaki ilişkiyi bulmak.

Histolojik olarak alkole bağlı karaciğer sirozu tespit edilen 25 hasta (9 kadın, ortalama yaş 56) gerçek zaman "pulsed" ve renkli Doppler ultrasonografi ile incelendi. Portal venin kesit alanı ve içinden geçen kan akımının maksimum hızı, hem hastalarda, hem de cins ve yaş uyumlu 25 kişilik bir kontrol gurubunda ölçüldü. Tüm hastalara karaciğer fonksiyon testleri ve üst gastroentestinal sistem endoskopisi yapıldı.

3 hastada ters veya durağan, 6 hastada hipodinamik, 7 hastada normodinamik ve 9 hastada hiperdinamik portal ven akımı saptandı. Endoskopide, varisi olmayan hastaların %25'inde hiperdinamik portal ven akımı saptandı. Bu oran, varisi olan ve kanamayan hastalarda %29, kanayan hastalarda ise %63 idi.

Portal kan akımı tipleri ile gastroözofajeal kanama riski arasındaki bağlantının her ne kadar daha fazla hasta içeren ve uzun süreli takip edilen çalışmalarla ortaya konması gerekirse de, bu çalışma, hiperdinamik portal kan akımı ve/veya gastroözofajeal varisleri doğrudan besleyen koli at er ali eri olan hastalarda kanama riskinin, diğer hasta gruplarına göre daha yüksek olduğunu göstermiştir.

Anahtar Kelimeler: Siroz, Varis kanaması, Doppler ultrason

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Portal hypertension is the consequence of various conditions including the alcohol-induced cirrhosis (AIC). Altered hemodynamics in portal hypertension results in the development of an extensive network of portosystemic collateral vessels. Gastroesophageal varices, because of their tendency to cause massive gastrointestinal haemorrhage, are the more relevant clinical feature of the portosystemic collateral circulation (1). Kleber et al reported 29 % of bleeding and 46 % mortality rate during a mean follow-up period of 21 months in a study including 109 cirrhotic patients with endoscopically diagnosed oesophageal varices without previous bleeding (2). There is also a significant

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positive correlation between alcoholic aetiology and high bleeding incidence in cirrhotic patients (3). Furthermore, operative mortality rate may exceed 50% in the presence of alcoholic hepatitis during elective surgery for decompression shunts after the first variceal bleeding (1,4).

Prophylactic conventional portosystemic shunt surgery is not generally advised for patients who have not bled because only 30-40 % of these patients ultimately bleed from their varices, making 60-70 % of the procedures unnecessary (4). However, distal splenorenal shunts have been shown to improve the five year survival from variceal bleeding in 45% of AIC patients (5-7). Thus, the treatment of gastroesophageal varices before bleeding in cirrhotic patients with high risk, especially when the cirrhosis is secondary to chronic alcoholism, might improve the survival rates from variceal bleeding.

Although some positive correlation between endoscopic findings and high risk of bleeding has been demonstrated, overall application of clinical, laboratory or endoscopic parameters to guide prophylactic treatment can not accurately determine the target population (8-11).

Pulsed and colour Doppler sonography is a non invasive imaging method to analyse the portal system, portasystemic collaterals and their hemodynamics (12-15). Up to now there is no ultrasonographic criteria that determines the risk of variceal bleeding in patients with AIC (16-19). The aim of this study was to determine the correlation between the risk of variceal bleeding and portal flow patterns.

Subjects and Methods

Twenty five patients with histologically proved AIC underwent real-time pulsed and colour Doppler examinations. The population included 25 subjects (16 males) 42-65 years old (mean, 56 years). None of the patients had a surgical decompression for gastroesophageal varices. The study was conducted over a 11 months period.

All patients had upper gastrointestinal endoscopy for the diagnosis of gastroesophageal varices and endoscopies were performed a maximum of three days before ultrasound studies. In 15 patients, including those who had experienced variceal bleeding, endoscopy revealed gastroesophageal varices. All patients have been followed for gastrointestinal bleeding for a mean period of five months (range 2-10 months). Five of the patients had already experienced gastroesophageal variceal bleeding. Three patients had bleeding after the study. Bleeding occurred 27, 46 and 72 days after the ultrasound study in these three patients. For the patients who had already bled the ultrasound studies were done within two days after the bleeding (range 5 h to 2 days) and before any definitive treatment, such as sclerotheraphy, for variceal haemorrhage was done. Patients who had already received beta blockers were not included into the study.

All patients were examined by the same sonographer, who was blinded to endoscopic findings, in the supine position with a coimnercially available Acuson 128 within the brachat computed sonography unit (Mountain view, CA) which combines real time sonography with either pulsed or colour Doppler. Sector transducers operating at 2.5 and 3.5 MHz were used; 19 patients with 2.5 MHz sector transducer and seven patients with 3.5 MHz sector transducers. Patients were fasted for 7 to 12 h. The main portal vein and its branches, the collaterals, the inferior vena cava and hepatic artery and veins were examined with colour Doppler study. This examination was performed according to the protocol suggested by Patriquin et al. which consists of a systemic qualitative Doppler examination of the portal circulation and its potential portosystemic collaterals (20).

The maximum velocity of flow in the main portal vein was measured by positioning a 1-mm range gate within central part of the vessel lumen in its extrahepatic portion. The main portal vein was examined in a plane transverse to its longitudinal axis at the site of the velocity tracing and its cross sectional area was calculated by using the ellipse function of the unit. This function calculates automatically the cross sectional area of the vessel after determination of two perpendicular diameters of vessel by the operator using calliper markers. Both velocity and cross sectional area measurements were done after a deep inspiration.

Table 1. Doppler flowmetry results in different group of patients

	Group 1	Group 2	Group 3	Group 4
Main Portal Vein cross sectional area (cm^2)	1 ± 0.23 (0.71-1.43)	1.35 ±0.66 (0.39-2.27)	1.28 ±0.49 (0.50-2.01)	2.37 ±0.33 (2.01-2.84)
Velocity Max. (cm/min)	27.73 ± 1.58 (25-31)	14.27 ±15.05 (15-30)	24.67 ± 4.74 (15-29)	27.667 ±2.16, (25-31) *
Mean Portal Blood Flow (ml/min)	948.01 ± 195.94 (724.9-1321.4)	848.49 ± 779.29 (402.7-1813)	951.80 ±497.17 (96.5-1718.6)	2271.92 ±226.23* (2096.1-2714)
(ml/minxkg)	13.02 ±2.3 (9.75-16.94)	11.51 ± 10.84 (6.2-25.9)	14.51 ±5.17 (6.62-22.9)	28.47 ±2.17* (25.07-30.17)
Weight of patient (kg)	72.33 ± 8.63 (61-81)	71.67 ±6; 17 (65-85)	71.56±6.12 (64-80)	80 ±7.75 (69-90)

Data are expressed as mean ± SD, the numbers in parentheses show the range. * significant difference.

The mean portal blood flow (MPBF) in the main portal vein was calculated for each patient according to the following formula,
MPBF=Cross sectional area(cm2)x maximum velocity (cm/sec)x 0.57 x 60

(0.57 is a constant taken from an experimental study performed in order to determine MPBF using bovine blood and a silicon tube (21-24). MPBF is calculated as ml/min so multiplied by 60.)

The maximum velocity of flow in the main portal vein, in its extrahepatic portion, the cross sectional area at the point of velocity sampling and flow rate per kilogram of body weight were calculated for each subject. No attempt was made to test the change in diameter, velocity or flow changes during quite breathing or suspended respiration at different phases of respiratory cycle.

Twenty five patients, sex and age matched with the cirrhotic patients, without any physical or laboratory evidence or history of hepatic dysfunction also underwent a colour and pulsed Doppler ultrasound study to determine the normal range of main portal blood flow. They are selected among the patients who were referred to our department for urinary system sonography .

The twenty-five AIC patients were classified according to three categories of criteria.

1. The first classification was based on the absence or presence of gastroesophageal varices at endoscopy and whether the patient had a variceal bleeding or not. According to these two set of criteria patients were grouped into three. The first group was composed of the cirrhotic patients without gastroesophageal varices at endoscopy. The second group consisted of the patients with varices which did not bleed and the third group of those which bled (Table 1).

2. The second classification was performed according to Doppler flowmetry results: MPBF inferior to 10 ml/min/kg was considered as hypodynamia, MPBF between 10 and 17 ml/min/kg as normodynamic and finally MPBF superior to 17 ml/min/kg as hyperdynamic. In order to determine the normal limits, the MPBF of control group was accepted as normal range determinant (Table 2).

3. The third classification was based on the data gained from both Doppler flowmetry and colour Doppler examination, namely the type of flow (hypo, hyper, normo etc.) and type of collaterals.

The significance of difference of MPBF between different groups of patients were tested by the rank sum two sample test. P values < 0.05 were considered statistically significant.

No attempt was made to correlate the endoscopic staging of varices and portal blood flow. The flow was calculated in cubic centimetre per minute and weight of patient.

As sampling angle larger than 60 degrees can produce an overestimation of velocity calculation, pulsed Doppler angle was always less or equal to 60 degrees. Variceal bleeding in our study is defined as the presence of mclena or hematemcsis or both

Table 2. Distribution of 25 cirrhotic patients according to their portal blood flow dynamics.

	NO VARICES (n=10)	VARICES WITHOUT BLEEDING (n=7)	VARICES WITH BLEEDING (n=8)
STAGNANT OR REVERSE PBF (No detectable blood flow in main portal vein Doppler study with or hepatofugal flow)	2	1	i
HYPODYNAMIC PBF (<|0 ml/min/kg)	3	2	1
NORMODYNAMTC PBF (10-17 ml/min/kg)	3	2	2
HYPERDYNAMIC PBF (>|7 ml/min/kg)	2	2	5

PBF : Portal blood flow.

together with significant decrease of haemoglobin (>2g/dl) and confirmation of the active bleeding side from varices at endoscopy.

The tests used to evaluate the hepatic function included serum albumin, total bilirubin, alanine and aspartate aminotransferases levels.

For the statistical data analysis, the commercially available Statview program (Abacus Concepts, Inc. 1987) was used on a Macintosh IICX computer.

Results

Eight of the 25 AIC patients suffered bleeding. Three of them experienced variceal bleeding during the observation period. Bleeding has occurred 27, 46 and 72 days after the ultrasound study in these three patients. Of eight subjects who experienced bleeding either previously or during follow up period, two bleeded from varices, in the gastric fundus and six others from oesophageal varices.

Twenty-one collateral veins were detected in 19 patients. Six patients had paraumbilical collaterals with recanalised umbilical veins (> 5 mm) with uepatofugal flow. In two patients, recanalised umbilical veins were associated with enlarged tortuous Paraumbilical veins and superficial abdominal varices. Perisplenic/retroperitoneal collaterals were pe second most encountered type of shunt and seen five patients. One of these patients had also a Pontaneous splenorenal shunt. Three patients had Pcriparicreatic collaterals. In three patients with variceal bleeding, reversed blood flow was detected in the left gastric (coronary) vein. In two other patients spontaneous splenorenal shunts and in an other perisplenic collaterals were detected. In six patients no collateral venous circulation was detected at ultrasonography.

The maximum velocity of flow in the main portal vein, in its extrahepatic portion, the cross sectional area at the point of velocity sampling and flow rate per kilogram of body weight are displayed on the Table 1.

The MPBF rate in patients with variceal bleeding was 28.5±2.2 ml/minxkg and in patients without variceal haemorrhage but with known gastroesophageal varices, the MPBF rate was 14.5±5.2 ml/minxkg. The rank sum two sample test performed to determine the significance of difference of MPBF rate between the four groups of subjects showed that MPBF rates of subjects with variceal bleeding were significantly higher than rates of the other three groups ($p < 0.05$; the test results comparing the bleeders group with other three groups (group 1,2 and 3) were 0.028, 0.028, 0.028 respectively). No significant difference of MPBF rate is found between the first three groups (p was always less than 0.05; comparison between group 1 and 2; $p = 0.61$, group 1 and 3; $p = 0.21$, group 2 and 3; $p = 0.07$).

Of 25 cirrhotic patients 3 had stagnant or reversed, 6 had hypodynamic, 7 had normodynamic and 9 had hyperdynamic portal blood flow. 20%

Table 3. Correlation between hepatic blood tests and portal flow dynamics in 25 cirrhotic patients

	Albumin (g/dL) (R: 3.5-5.5)	Total Bilirubin (mg/dL) (R: 0.1-1.0)	ALT (U/L) (R: 8-20)	AST (U/L) (R: 8-20)
STAGNANT OR REVERSE PBF (No detectable blood flow in main portal vein with Doppler study or hepatofugal flow)	2.83±0.38	3.86±2.11	256±21	245±37
HYPODYNAMIC PBF (<9 ml/min/kg)	2.99±0.59	2.02±1.33	153±37	146±35
NORMODYNAMIC PBF (9-17 ml/min/kg)	3.48±0.66	1.I2±0.67	68±23	59±18
HYPERDYNAMIC PBF (>I7 ml/min/kg)	3.18±0.73	2.72±1.78	233±32	218±46

PBF : Portal blood flow, R : Reference range, ALT : Alanine aminotransferase, AST : Aspartate aminotransferase. Data are expressed as mean ± SD.

(2/10) of patients without varices at endoscopy had hyperdynamic portal blood flow. This percentage was 29 (2/7) in patients with varices who did not bleed and 63 (5/8) in bleeders.

Among the eight bleeders, hypodynamic blood flow was detected in one patient, hyperdynamic flow in five patients and two patients had portal flow in the normal range. Of seven patients with gastroesophageal varices and who did not bleed, two had hyperdynamic, three had hypodynamic portal blood flow and two subjects had portal flow in the normal range. In patients without detectable gastroesophageal varices at endoscopy, three subjects had hyperdynamic portal blood flow. Sensitivity and specificity of Doppler flowmetry for the prediction of variceal haemorrhage were found to be 62.5% and 70.6% respectively.

None of the six patients with recanalised umbilical vein had bleeding and only one of them had gastroesophageal varices at endoscopy.

Serum aminotransferase levels were highest in patients with stagnant or reversed portal blood flow, followed by patients with hyperdynamic blood flow. Patient with normodynamic portal blood flow had the least perturbed serum aminotransferase, albumin and biluribun levels. Patients with hypodynamic portal blood flow have better hepatic function than the patients with stagnant, reversed and hyperdynamic portal blood flow (Table 3).

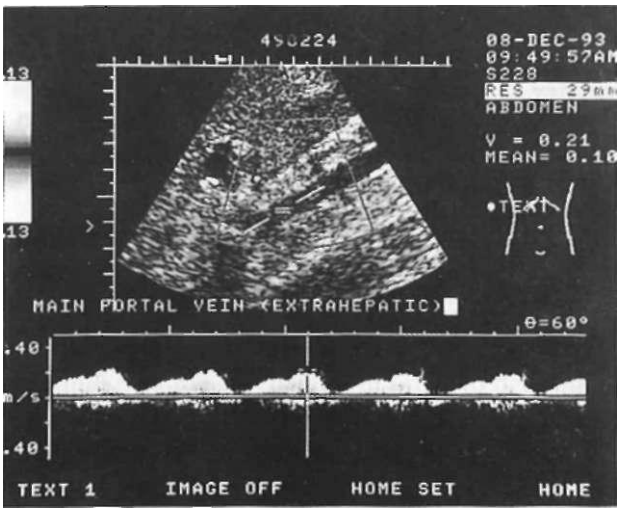

Figure 1.

Discussion

Patients with alcohol induced liver cirrhosis have a large portal flow spectrum varying between reversed and hepatopetal flow whereas some patients have values significantly higher than normal subjects. This wide spectrum of flow may be due to the development of collaterals and the different dynamics may result from the type of collaterals. For this reason, portal blood flow patterns classified as hypo, normo, hyperdynamic, reverse or stagnant must be correlated with colour Doppler ultrasound findings to understand better the flow dynamics, as

collaterals and direction of flow in them are easily demonstrated by colour Doppler ultrasound.

Most studies stated out that the portal pressure must increase at least 12 mm Hg beyond the inferior vena cava pressure for bleeding to occur (25-28). However, this is almost the same pressure gradient needed for the formation of varices (25,27).

Moreover, above this threshold gradient, there is no clear correlation between portal pressure and the risk of variceal bleeding (25-27).

Rigau et al. reported that variceal pressure is markedly and significantly higher in patients who have bleeded from varices than in those who have never bleed, in spite of a similar portal pressure in both groups (9).

In some other studies, significant differences in portal pressure between bleeders and non-bleeders have been demonstrated. However it is not an uniform finding as several large studies have failed to document any difference in portal pressure according to the previous occurrence of variceal bleeding (25,26,29,30).

The apparent contradiction in these reports may be explained by the presence of different type of collaterals or by the fact that the cause of bleeding is the sudden rise in the portal pressure rather than a stable but high one.

In order to explain the contradiction in those studies, we analysed and regrouped the patients according to data gained both from Doppler flowmetry and colour Doppler examination;

In the first group, there was no ultrasonographically detectable collateral vessels but a slight increase of portal flow. None of the patients in this group had varices at endoscopy.

The second group had portasystemic collateral formation with hepatopetal flow in the main portal vein. This group -was subdivided according to the type of collaterals. Assessment of umbilical shunt was of clinical importance in this group as drainage to systemic circulation through a recanalised umbilical vein reduce the pressure in portal system and consequently the formation or bleeding from oesophageal varices. In our study none of the six patients with repermeabilised paraumbilical veins with a diameter exceeding five mm and a hepatofugal flow in it has experienced a variceal bleeding and only one of them had gastroesophageal varices at endoscopy. In the second subgroup, portal flow was slightly or significantly decreased depending on the severity of portosystemic extrahepatic collaterals. Those patients had mostly dilated peripancreatic and/or perisplenic veins and/or spontaneous splenorenal shunts. They had a hypodynamic portal blood flow.

The third subgroup contained the patients with dilated coronary or short gastric veins. This patient subgroup had high risk of variceal bleeding relative to other subgroups with hypodynamic or normodynamic blood flow in the main portal vein as these veins drained directly to gastroesophageal varices. In the fourth and last subgroup, portal blood flow was significantly high (hyperdynamic blood flow). The risk of gastroesophageal variceal bleeding was the highest in this subgroup and they had worse hepatic function than the patients with normo and hypodynamic portal blood flow.

The last two groups of patients has stagnant or reversed blood flow in the main portal vein and highly disturbed hepatic function.

We concluded that although duplex Doppler flowmetry in clinical practice is operator, equipment or technique dependent, it supplies additional and important information for the analysis and understanding of the portal flow dynamics (24). A classification of different portal flow patterns and dynamics can be done on the basis of Doppler flowmetry and colour Doppler examination. Although the correlation between this kind of classification and hepatic function and or the risk of gastroesophageal variceal bleeding needs to be evaluated in larger series with long term follow-up, the results gained from this study are promising and demonstrating that patients with hyperdynamic portal flow and/or collaterals directly feeding the gastroesophageal varices arc more prone to variceal bleeding. The patients with hypo- or normodynamic portal blood flow have better hepatic function than the patients with stagnant, reverse or hyperdynamic portal blood flow.

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