Non-Invasive Assessment and Evaluation of Portal Hypertension in Patients with Liver Cirrhosis

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ABSTRACT

Ultrasonography examination is an one of examination that can be used to see the abnormality of portal vein system.

The technology of ultrasonography examination has further developed especially after using of Doppler ultrasonography which could portray haemodynamic changes from portal vein in liver cirrhosis patient. From this examination we also could predict bleeding.

Key words: Liver cirrhosis, portal hypertension, doppler ultrasonography.

INTRODUCTION

Liver cirrhosis is a chronic liver disease signified by the presence of fibrosis and nodules. This disorder usually begins with inflammation, widespread liver necrosis, formation of connective tissues and regeneration nodules. Changes in the structure of the liver result in changes in the circulation. Functional liver cirrhosis is classified into two stadiums, compensation (early/latent cirrhosis) and decompensation (followed by liver failure and portal hypertension).^{1,2}

Portal hypertension occurs due to an increase in the pressure of the portal vein system due to increased resistance of the blood vessels and/or increased portal vein blood flow.^{1,3,4}

Liver cirrhosis accompanied with portal hypertension can cause bleeding of the upper gastrointestinal tract due to rupture of the esophageal varices. Seventy percent of patients with liver cirrhosis will eventually suffer from portal hypertension and esophageal varices. Djojoningrat reported a prevalence of gastrointestinal bleeding due to esophageal varices of 70.2% in RSCM in the year 1988. Soemarno, et al reported 93% prevalence of upper gastrointestinal bleeding due to esophageal varices and gastropathy.⁷ The prevalence on initial bleeding is 36%, and 70% on repeated bleeding.⁸

Sonography is a diagnostic tool that can be utilized to diagnose abnormalities of the portal vein system.

Sonographic technology has further developed with the invention of Doppler combined analysis and standard color ultrasonography, which can portray haemodynamic changes in the portal vein in patients with liver cirrhosis and is currently the most un-invasive technique to evaluate the portal vein blood flow. The sensitivity and specificity of Doppler ultrasonography is 83% and 93% respectively.^{11,12}

HEMODYNAMIC CHANGES OF THE PORTAL SYSTEM

Portal hypertension is mostly due to liver cirrhosis. In Indonesia, cirrhosis is most frequently caused by a virus, while cases abroad are more commonly due to alcohol. Other causes of portal hypertension include thrombosis, tumor, etc.^{1,2,3,4}

The portal vein system consists of a venous network that begins at the superior mesenteric vein, goes through the portal vein and end at the hepatic vein. Before the portal vein enters the liver, it branches in two to supply the right and left hepatic lobe.

As we know, the portal pressure is attained from changes in the hepatic vein. It ranges between 5-10 mmHg measured using catheterization.^{1,5,6} Portal hypertension occurs due to an increase of pressure in the portal vein system due to an increase in blood vessel resistance and/or a pathologic increase in portal vein blood flow.



Figure 1. Portal vein system and collateral pathways of portal hypertension. Portohepatic to SVC: Peripancreatic (a), portosystemic: Gastroesophageal varices (b), paraesophageal vein (c),. Portosystemic to IVC: Gastrorenal (d), paraumbilical (e), splenorenal (f), splenoretroperitoneal (g), mesentericocaval (h), paracolic (j), pelvic (k). CV coronary vein; GEV gastroepiploic vein; IMV inferior mesenteric vein; IVC inferior vena cava; PV portal vein; SMV superior mesenteric vein; SV splenic vein.

Changes that occur:^{1,2,3,4}

1. Increased blood vessel resistance

Due to liver fibrosis because of the formation of collagen tissues due to liver sinusoid that hardens and causes mechanic obstruction

2. Increased portal vein blood flow

Due to vasodilatation of the splanchnic artery because of humoral factors (glucagons, NO synthase), neurogenic factors, and local mechanisms

3. Portosystemic collateral formation

Due to the mechanism of compensation because of pathologic portal blood flow to the heart and its resistance; This occurs as a mechanism to reduce the pressure of the portal system

4. Hyperdynamic condition

Due to an increase in the level of endogen vasodilators which causes vasodilatation and an eventual increase in plasma volume

5. Splenomegaly

PRINCIPLE OF MEASUREMENT USING THE DOP-PLER ULTRASOUND DEVICE

As we know, increase in the portal pressure occurs due to increased blood flow to the portal vein. Thus, we could indirectly measure pressure in the portal vein by measuring the portal vein blood flow using the Doppler echo.

Similar to the blood vessel system in general, changes in venous system pressure is a result of blood flow and blood vessel resistance, stated by Ohm's Laws through

$$\mathbf{P} = \mathbf{Q} \mathbf{x} \mathbf{R}$$

the formula:4,7

P = Pressure changes

- Q = Blood flow
- R = Blood vessel resistance



Figure 2. Scheme of the formation of portal hypertension

Thus, the pressure will increase if there is an increase in blood vessel resistance and/or portal vein blood flow. On the other hand, the portal pressure will drop if there is a reduction in blood vessel resistance and/or portal vein blood flow.

Increased blood vessel resistance is caused by liver fibrosis that creates an obstruction/constriction, thus increasing the speed of blood flow, as stated in Pouseuille's theorem, with the formula:^{4,7}

R = resistance N = coefficient of viscosity L = blood vessel length r = blood vessel radius



Laminary flow

Figure 3. Doppler echo ultrasonography. Portrays increased blood flow through a narrowing tube

N = coefficient of viscosityL = blood vessel length

r = blood vessel radius

Using Doppler echo ultrasonography portrays not only the liver and the portal vein diameter, but also the characteristics of the blood vessel and blood flow, by mea-



	C Fdmax	
Portal vein velocity =	$\frac{1}{2}$ Fo. Cos α	Cm/sec

Figure 4. The formula to obtain the rate of portal vein blood flow

suring the speed of the portal vein flow using a certain technique. After the portal vein diameter is attained, we could obtain the rate of portal vein blood flow using a certain formula.

Note:

C = ultrasound wave velocity (1.5 x 10^5 Cm/sec) Fdmax = maximum Doppler frequency shift

- Fo = ultrasound wave frequency (3.5 Mhz)
- α = angle between Doppler beam and the direction of portal vein flow

Important notes:

- 1. α has to be less than 60°
- 2. The state of the following blood flows:
 - Hepatopetal: flow towards the liver, must be normal. For example: blood flow from the portal vein to the liver.
 - Hepatofugal: flow away from the liver, reverse flow, often found in portal hypertension.
- 3. No or minimal ascites.

DOPPLER ULTRASOUND MEASUREMENT IN PA-TIENTS WITH PORTAL HYPERTENSION

- 1. Measurement technique and requirements:^{9,13,14,15,16}
 - a. The patient must have fasted prior to the examination.
 - b. The patient is not allowed to drink medication that would reduce the pressure of the portal vein, obstruct the H pump, or H_2 receptor antagonist.
 - c. Supine position. The examination is carried out with the patient in supine position.
 - d. The patient must rest for at least 15-30 minutes prior to the examination.
 - e. The transducer is placed at a less than 60° angle to the portal vein before it branches to the right and left lobe, exactly below the hepatic artery¹⁷ or above the inferior vena cava.¹⁸
 - f. Measurements are taken while holding the breath for 4 seconds.
 - g. A minimum of 3 measurements are taken and the values averaged.
- 2. Measurement of the portal vein system

Measurement of the diameter:

Lafortune et al conducted the following experiment in which the portal vein pressure of 64 patients with cirrhosis was measured using angiography, while the diameter was measured using ultrasonography.

From this experiment they found no relationship between increased portal pressure and the diameter of the portal, superior mesenteric or splenic veins, but a change was noticed in the diameter of the coronary vein.

A coronary vein with diameter of more than 0.7 Cm could signify severe portal hypertension

Measurement of the direction of the flow:²⁰

Gaiani et al studied 15 patients with hepatofetal flow and 29 patients with hepatofugal flow based on examination using Doppler ultrasound. These patients were followed for an average of 13 months, to discover the relationship between the direction of blood flow and survival rate and risk of bleeding.

After follow up, they found that there was no relationship in the survival rate of the two groups, but the risk of bleeding was very high in patients with hepatofetal blood flow.

3. Evaluation of bleeding ⁷

Soemarno et al measured the flow and the velocity of portal vein blood flow in 115 men and 39 women with upper gastrointestinal bleeding from the Emergency Unit of St. Carolus Hospital.

They found that the velocity of flow in 32 pa-

Patient Group (n)	n	Portohepatic Pressure (mmHg)	Portal Vein Diameter (Cm)	Diameter of The Superior Mesenteric Vein (Cm)	Diameter of The Splenic Vein (Cm)	Diameter of The Coronary Vein (Cm)
1	4	2,6 ± 1,5 (0-6)	2,1 ± 0,3 (1,6-2,4)	1,9 ± 0,2 (1,8-2,2)	1,5 ± 0,5 (1-2,2)	0,47 ± 0,21 (0,2-0,7)
2	15	8,9 ± 1,1 (>6-10)	1,9 ± 0,2 (1,4-2,3)	1,7 ± 0,2 (1-2)	1,3 ± 0,3 (0,8-1,7)	0,8 ± 0,13 (0,3-0,7)
3	15	13,5 ± 1,5 (>10-15)	$1,8 \pm 0,3$ (1,2-2,3)	$1,6 \pm 0,2$ (1,2-1,9)	1,3 ± 0,3 (0,6-1,8)	0,72 ± 0,21 (0,4-1,2)
4	15	18,5 ± 1,3 (>15-20)	$1,9 \pm 0,2$ (1,4-2,3)	1,7 ± 0,2 (1,3-2)	1,3 ± 0,2 (1-1,8)	0,79 ± 0,3 (0,3-1,7)
5	15	22,6 ± 1,3 (>20-25)	1,6 ± 0,3 (1,1-2)	1,6±0,3 (1-2)	1,3 ± 0,3 (0,8-1,8)	0,7 ± 0,23 (0,2-1)
Control	32	-	1,8 ± 0,3 (1-2,2)	1,5 ± 0,3 (1-2)	1,1 ± 0,3 (0,8-1,5)	

Table 1.	Measurement of the por	al vein s	system in	five	groups	of	cirrhosis	patients	and	one
	control group ¹⁹									

Table 2. Systemic parameter and portal hemodynamic in 12 patients with cirrhosis²¹

Parameters	24 hrs Observation									
	0800	1200	1600	2000	2400	0400				
Pulse rate (pulse/minute)	77 ± 4	77 ± 4	78 ± 4	79 ± 4	78 ± 4	78 ± 4				
Mean arterial pressure (mmHg	90 ± 12	90 ± 11	88 ± 12	89 ± 12	89 ± 13	90 ± 10				
Cardiac output (I/minute)	$\textbf{6,2} \pm \textbf{0,6}$	$\textbf{6,2} \pm \textbf{0,8}$	$\textbf{6,3} \pm \textbf{0,8}$	$\textbf{6,3} \pm \textbf{0,7}$	$\textbf{6,8} \pm \textbf{0,7}$	$6,6\pm0,9$				
Peripheral blood vessel resistance (dyne sec cm ⁻⁵)	1170 ± 230	1165 ± 200	1110 ± 221	1145 ± 224	1050 ± 228	1080 ± 197				
Portal vein blood flow (mm/mnt)	603 ± 110	680 ± 79	632 ± 179	631 ± 169	917 ± 248	697 ± 178				

tients who suffered from bleeding of the esophageal varices and portal hypertension gastropathy was 14-18 Cm/sec. The velocity of flow in 14 patients with gastric bleeding was above 19 Cm/sec.

They concluded that a portal vein velocity above 8 Cm/sec signifies portal hypertension. A portal vein velocity above 9 Cm/sec signifies high risk of upper gastrointestinal bleeding. A portal vein velocity above 14 Cm/sec means upper gastrointestinal bleeding could result from esophageal varices or portal hypertension gastropathy. Thus, we could predict bleeding.

4. Diurnal variation²¹

Alvarez et al conducted an experiment on diurnal fluctuation in 12 patients with liver cirrhosis, 10 men and 2 women ages 30-71 years. The patients were admitted to the hospital and the hemodynamic condition and blood flow was evaluated using Doppler ultrasound every 4 hours for 24 hours, and taken at least 2 hours after meals and after 30 minutes of rest in supine position. They found that the cardiac output and portal vein blood flow increased at midnight.

The mechanism of such increase in portal vein blood flow is still unknown. It is possible that this variation is due to humoral and neurogenic factors, which are an increase in the vasodilator component rhythm VIP (vasoactive intestinal peptide), a strong endogenous vasodilator which peaks at midnight, or a reduction in sympathetic activity due to reduced secretion of cathecolamine at midnight.

The variation of portal vein blood flow especially at midnight explains why the incident of varicose bleeding is highest at night.

	Prior to meals	After meals	% of icrease
NS(n = 12)	$16\pm4,1$	$19,7\pm4,8$	24
CAH (n = 11)	$\textbf{17,3} \pm \textbf{4,1}$	$\textbf{20,4} \pm \textbf{4,9}$	18,2
LC (n = 11)	$12,4\pm2,3$	$12,7\pm3,1$	3,2

Table 5. The effect of a standard mean on portal vehi blood now velocity	Table 3.	The effect of	a standard m	eal on portal	vein blood	d flow velocity ²²
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NS = Normal patients; CAH = Chronic Active Hepatitis; LC = Liver Cirrhosis

tients with liver cirrhosis. Measurements were taken using Doppler ultrasonography first during fasting and the second time 60 minutes after taking a standard Italian meal (1100 calories = 18% protein, 39% fat, 43% carbohydrate)

This experiment showed an increase in portal vein blood flow in normal patients, patients with chronic hepatitis and those with cirrhosis, but the increase in cirrhosis patients was not very large.

Increase of blood flow, influenced by meals was due to both intrinsic mechanisms, which are increased transmural arteriole pressure and increased vasodilator agents, extrinsic mechanisms, such as the autonomic nervous system, as well as the influence of the gastrointestinal hormones gastrin and glucagon.

From this study, we conclude that meals can cause increased portal vein blood flow, consequently increasing portal pressure.

6. Evaluation of therapy

1. Experiment using pitressin and ranitidine:¹⁴

Ohnishi et al studied 15 men and 4 women with portal hypertension. Measurements were taken using both angiography and Doppler ultrasound. The portal vein blood flow was measured before and after therapy. Several patients received intravenous pitressin 0.3 U/minute for 15 minutes, and the others received intravenous ranitidine 50 mg/30 minutes.

They found that there was a reduction in portal vein blood flow after administration of both pitressin and ranitidine. Similar results were obtained using angiography and Doppler ultrasound using the formula Y = 0.6 X - 1.723 (Y = angiography and X = Doppler ultrasound).

Doppler ultrasonography is sufficiently accu-

		Portal	Vein Ve	locity (cn	n/sec)	Portal Vein Flow				
Patient Number	Therapy	Cinean phy Me	giogra ethod	USG Do Meth	oppler nod					
		before	after	before	after	ml/minute	ml/minute/kg	ml/minute	ml/minute/kg	
1	Pitresin	9,9	3,3	19,5	7,7	499	8,6	156	2,7	
2	Pitresin	9,3	5,4	18,2	12,5	859	12,1	484	6,8	
3	Pitresin	3,8	3,0	9,8	6,4	216	3,7	153	2,6	
4	Pitresin	12,2	4,9	21,9	12,1	622	9,3	232	3,5	
5	Pitresin	8,2	2,4	16,2	5,0	556	8,7	153	2,4	
6	Pitresin	9,2	3,1	17,9	8,4	469	7,2	134	2,1	
7	Pitresin	8,1	2,8	15,2	6,2	705	10,8	203	3,1	
8	Ranitidine	6,2	6,4	14,3	14,6	442	6,2	449	6,3	
9	Ranitidine	9,6	10,3	16,1	17,6	742	9,5	791	10,1	
10	Ranitidine	11	11,0	19,9	20,9	743	14,6	743	14,6	
11	Ranitidine	10,4	10,3	20,4	19,8	705	12,4	698	12,2	
12	Ranitidine	5,1	4,1	13,2	12,5	407	6,6	327	5,3	

Table 4. Portal vein velocity in 12 patients with portal hypertension, before and after administration of pitresin and ranitidine¹⁴

Measurement	n	Base Value	After Propanolol	р	Change
MAP (mmHg)	15	95 ± 10	91 ± 12	<0,02	-3,6 ± 5,1
HR (bpm)	15	68 ± 7	61 ± 7	<0,001	$-12,6 \pm 4,6$
CO (l/mnt)	10	6,03 ± 1,18	$4,48 \pm 0,88$	<0,005	$-24,5 \pm 11,5$
PVP (mmHg)	9	$20,1 \pm 6,3$	$17,6 \pm 6,2$	<0,001	$-13,3 \pm 6,7$
WHVP (mmHg)	6	$20,4 \pm 4,6$	$18,5 \pm 4,6$	0,025	$-9,6 \pm 5,6$
FHVP (mmHg)	6	8,0 ± 2,9	8,3 ± 2,3	NS	+10,0 ± 23,3
PVP-FHVP (mmHg)	6	$11,5 \pm 3,7$	9,0 ± 4,4	<0,02	-24,8 ±14,2
WHVP-FHVP (mmHg)	6	12,3 ± 2,5	$10,2 \pm 2,6$	<0,001	$-18,2 \pm 5,9$
EHBF (I/mnt)	6	$0,934 \pm 0,303$	$0,633 \pm 0,115$	NS	$-27,3 \pm 17,1$
PVF (l/mnt)	10	$0,740 \pm 0,227$	$0,558 \pm 0,160$	<0,005	$-22,3 \pm 14,4$

Table 5. The effect of propanolol on the systemic and splancnic hemodynamic condition¹⁵

rate to measure portal vein flow and could also be utilized to observe hemodynamic changes of the portal pressure.

2. Experiment using propanolol:¹⁵

Ohnishi et al studied 12 men and 3 women, aged 31-71 years, 13 with liver cirrhosis and 1 with hepatoma. Measurements were taken simultaneously using catheterization and Doppler ultrasound. Measurements were taken before and after administration of 5 mg of propanolol intravenously for 35 minutes. There was a decrease in pulse rate (-12.6%), reduced cardiac output (-24.5%) and reduced hepatic blood flow (-27.3%).

Propanolol reduces the portal vein pressure by reducing portal vein blood flow. This is due to decreased cardiac output caused by a blockage of the B1 adrenergic receptor.

CONCLUSION

- 1. The Doppler ultrasound was used as a method to evaluate the presence of portal hypertension.
- 2. The Doppler ultrasound is currently the most un-invasive technique to assess portal vein blood flow.
- 3. The Doppler ultrasound could be used as a non-invasive method to evaluate changes in the hemodynamic condition of the portal vein due to medication or other causes.
- 4. Using Doppler ultrasound, we can predict bleeding.

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