Arch Gynecol Obstet (2006) 274:303–309
DOI 10.1007/s00404-006-0175-6

ORIGINAL ARTICLE

Prediction of HELLP syndrome with assessment of maternal dual hepatic blood supply by using Doppler ultrasound

Ikuno Kawabata · Akihito Nakai · Toshiyuki Takeshita

Received: 30 March 2006 / Accepted: 17 April 2006 / Published online: 6 May 2006

Abstract *Objective*: Early structural and functional changes in the systemic vasculature have been proposed to play a major pathogenetic role in HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome. Our objective was to assess whether the evaluation of maternal hepatic blood supply is instructive to the prediction of onset of HELLP syndrome. *Design*: Prospective observation study. *Population*: Fifty-eight women with severe preeclampsia and 60 healthy pregnant controls at 25–36 weeks gestation. *Methods*: Angle-corrected time-averaged flow velocity and the cross-sectional area of common hepatic artery and portal vein were measured by using Doppler ultrasonography in 58 women with severe preeclampsia and in 60 healthy pregnant controls at 25–36 weeks gestation. Intravascular flow volumes were calculated from the product of the time-averaged velocity and the cross-sectional area. The total liver blood flow was taken as the sum of flow volumes in the hepatic artery and portal vein. *Results*: The total liver blood flow decreased significantly to about 40% of control in 9 women with severe preeclampsia who developed HELLP syndrome within 4 days after the examination, but not in 49 women with severe preeclampsia without HELLP syndrome. *Conclusion*: The results indicated that the decrease in dual hepatic blood supply preceded the onset of HELLP syndrome.

I. Kawabata · A. Nakai (✉) · T. Takeshita
Department of Obstetrics and Gynecology,
Tama Nagayama Hospital, Nippon Medical School,
1-7-1 Nagayama, Tama-City,
Tokyo 206-8512, Japan
e-mail: nakai-3@nms.ac.jp

Keywords Hepatic artery · Portal vein · HELLP syndrome · Doppler ultrasound

Introduction

HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome is a variant of preeclampsia associated with a high maternal mortality and morbidity. Improved outcome is based on early recognition of onset of this syndrome to allow intensive care and treatment, including the aggressive monitoring of the status of both mother and fetus [1]. Although recent studies suggest that endothelial damage in the maternal hepatic circulation is important in the pathogenesis of this syndrome [2–5], there is no study that has examined the maternal hepatic blood supply for the prediction of onset of this syndrome.

It is well known that Doppler ultrasonography provides a noninvasive method of monitoring and characterizing the physiology of the dual hepatic blood supply in several conditions and disease states [6–14] with high reproducibility [15]. Several investigators [10, 16–22] have demonstrated the reciprocal relationship between hepatic arterial and portal venous blood flows. This effect would tend to maintain constant the volume of blood flowing through the liver [10, 16, 17, 19].

However, control of liver blood flow by reciprocal changes in the dual hepatic blood supply is an incomplete explanation [22–24]. In fact, our preliminary results [25] demonstrated that the hepatic perfusion in healthy pregnant women increased during third trimester compared to nonpregnant level. Because the hepatic arterial blood flow remained unchanged during

pregnancy, major determinant of the increase in the hepatic perfusion was the portal venous return. However, the effect of preeclampsia and HELLP syndrome on the interaction between hepatic arterial and portal venous blood flow is still unknown.

In this prospective study, we applied this tool to assess whether the evaluation of maternal hepatic blood supply is instructive to the prediction of onset of HELLP syndrome.

Materials and methods

Between November 2000 and August 2002, at the Tama Nagayama Hospital of Nippon Medical School, we studied 68 women with severe preeclampsia at 25–36 weeks gestation. The Doppler ultrasound examination was performed within 24 h after severe preeclampsia was diagnosed in each patient. None of the patients had begun antihypertensive treatment at the time of the Doppler ultrasound study. Of these, nine patients developed HELLP syndrome within 4 days after the examination. After the Doppler ultrasound examination, appropriate management for each patient with severe preeclampsia were performed (i.e., antihypertensive treatment, administration of magnesium sulfate, and/or immediate delivery). We compared these women with 64 healthy pregnant controls, who were matched by age and gestational age at the examination. The controls were randomly chosen from the outpatients who visited our hospital. All of these subjects provided written informed consent for participation in this study, which was approved by the institutional review board. These women denied having a history of liver disease, diabetes, or essential hypertension and had singleton pregnancy.

Inadequate Doppler waveforms were obtained in 14 of 132 women (11%) because of adiposis and inability to visualize the target vessels or the inability of some women to hold their breaths long enough; these were not included for further analysis. Four cases belonged to the control group and ten to the severe preeclampsia group without HELLP syndrome.

Severe preeclampsia was defined as an elevated blood pressure of >140/90 mmHg in both systole and diastole, or a rise in systolic (more than 30 mmHg) or diastolic (more than 15 mmHg) values over the baseline blood pressure obtained before 16 weeks gestation on at least two measurements 6 h apart, and proteinuria >300 mg per 24 h or >100 mg/dl in at least two random urine specimens collected 6 or more hours apart. The HELLP syndrome requires the presence of at least three of the four following clinical and laboratory findings: (1) upper abdominal pain; (2) hemolysis, defined by an increased lactate dehydrogenase level (>600 U/l); (3) elevated liver enzymes, defined as increased aspartate aminotransferase (>70 U/l); and (4) low platelets, defined as a platelet count $< 100 \times 10^9$/l.

All subjects were fasted for 12 h prior to Doppler ultrasound examination. All measurements were obtained with the subject lying in Fowler's position. The subjects were instructed to suspend respiration during the measurements. All of the women were examined by means of Doppler ultrasound with a 3.5-MHz convex type transducer (Hitachi-Medico EUB-515A, Hitachi, Tokyo, Japan). The sample volume of the Doppler system was set at 3 mm, the smallest velocity scale was used in all cases, and a low wall-filter setting was used. Pulsed Doppler US waveforms were displayed at sweep speeds of 40–80 mm/s. The velocity scale was adjusted so each Doppler waveform filled as much of the scale as possible.

A transverse scan was made at the epigastrium to locate the common hepatic artery in its longitudinal axis. The Doppler cursor was placed over the lumen of the artery segment as near to the origin as possible, at the point where it first became horizontally straight. Angle-corrected velocity waveform measurements were obtained in each artery; the insonation angles were less than 60°. The time-averaged mean velocity was calculated with machine software (Hitachi-Medico EUB-515A, Hitachi, Tokyo, Japan) by placing electronic calipers on Doppler tracing displayed on the image monitor. At least three similar, sequential Doppler waveforms were recorded and the single best tracing obtained in each artery was selected for analysis. On the duplex image, which showed both the longitudinal two-dimensional image of the common hepatic artery and the Doppler waveform, the cross-sectional area of the artery was measured at the same point by mapping the perimeter of the vessel lumen with ''traker ball'' at right angles to the vessel (Fig. 1a).

For the portal vein, the angle-corrected time-averaged mean velocity was measured while viewing the vessel on its longitudinal axis with a right lateral intercostal approach to achieve a more acute angle for Doppler measurement. Care was taken to ensure that the velocity was measured at the point where the portal vein becomes intrahepatic and before it branches into the left and right portal trunks. The cross-sectional area of the portal vein was measured similarly at the same point at right angles to the vessel. The cross-sectional area was calculated automatically by mapping the perimeter of the vessel lumen (Fig. 1b).

Hepatic arterial and portal venous blood flows were calculated from the product of the measured

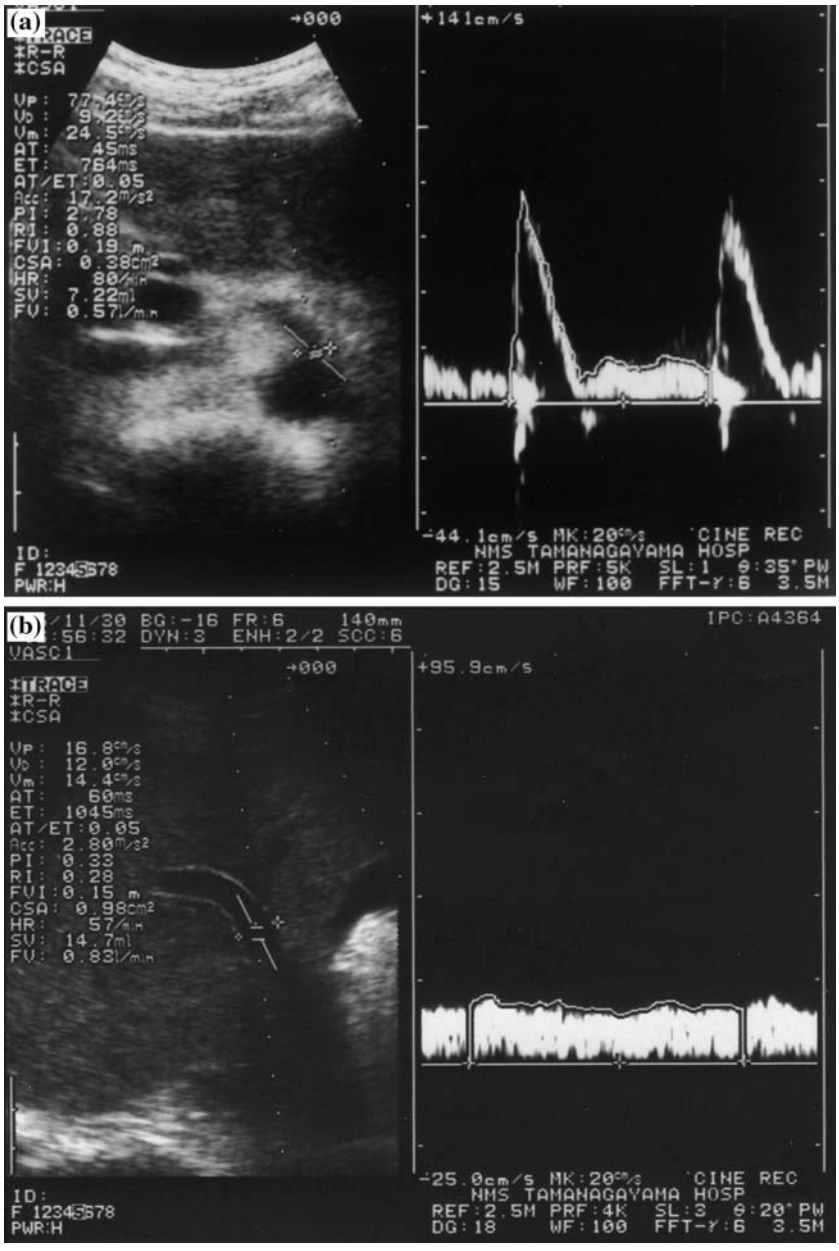

Fig. 1 Typical Doppler trace image of **a** hepatic artery and **b** portal vein in healthy pregnant women at 31 weeks gestation

time-averaged velocity of blood in the vessel and the cross-sectional area of the lumen of the vessel. The total liver blood flow was taken as the sum of the hepatic arterial and portal venous blood flow [12, 15]. Hepatic arterial resistive index (RI) was determined with the following equation: RI = (peak systolic velocity - end diastolic velocity)/peak systolic velocity.

All data were expressed as the mean and standard deviation. One-way analysis of variance followed by Scheffé *F*-test was used to compare the values within each study group. Differences with *P* value of less than 0.05 were considered to be statistically significant.

Because all of the examinations were performed by one of two operators (A.N. and I.S.), the interobserver reproducibility and intraobserver reproducibility of Doppler ultrasound measurements were assessed in a separate series of studies. By using Doppler sonography, the two investigators performed the measurements as mentioned above in the hepatic artery and portal vein of ten healthy pregnant women aged 28–32 years at 30–35 weeks gestation. For each patient in this group, the Doppler waveform was measured three times in succession by each investigator, and the variability between observers or measurements was analyzed.

Interobserver reproducibility and intraobserver reproducibility were quantified by using the intraclass correlation coefficient R_i [15, 26–28]. The following criteria for clinically relevant agreement were used: poor, R_i less than 0.40; fair, R_i greater than or equal to 0.40 but less than or equal to 0.59; good, R_i greater than or equal to 0.60 but less than or equal to 0.74; and excellent, R_i greater than or equal to 0.75 [27]. The agreement was only considered acceptable from a clinical point of view when the R_i value was ≥ 0.60, which has been described by biostatisticians [27, 29] as either ''good to excellent'' [27] or ''substantial to almost perfect'' [29]: the agreement was considered not acceptable from poor to fair ($R_i < 0.60$), regardless of the level of statistical significance. The R_i was derived from two-way analysis of variance in which the repeated measurements and subjects were factors. The formula used to calculate the R_i was (MSS - MSE)/((MSS + (k - 1)MSE) + k(MSO - MSE)/n), where MSS is the mean squared variation between subjects; MSO, the mean squared variation between repeated measurements; MSE, the residual mean squared; k, the number of repeated measurements; and n, the number of subjects.

Results

All of the subjects recruited, 58 and 60 subjects finally completed the study in severe preeclampsia and the control group, respectively. In the women with preeclampsia, nine subjects developed HELLP syndrome between 2 and 4 days after the ultrasound examination. Of these, seven subjects were diagnosed before delivery while two developed postpartum.

The characteristics of the subjects at the ultrasound examination are reported in Table 1. There was no substantial difference in the mean age, parity, and gestational age of subjects among the three groups. In the mean values of the arterial pressures and the urine protein, there were significant difference between the control group and the other two groups. In the women with severe preeclampsia who developed HELLP syndrome, the both aminotransferase increased significantly compared to the control group, but the individual values did not reach the criteria for the HELLP syndrome. There were no significant differences in the other laboratory data for the diagnosis of HELLP syndrome (i.e., platelet count and lactate dehydrogenase) among the three groups.

The time-averaged mean velocity, cross-sectional area, blood flow, and insonation angle of the hepatic artery and the portal vein, and the total liver blood flow in the three groups are shown in Table 2. In the severe preeclampsia without HELLP syndrome, portal venous blood flow decreased significantly to about 70% of control, but hepatic arterial blood flow appeared to be slightly elevated to about 130% of control (not significant). Therefore, there was no significant difference in the total liver blood flow between the severe preeclampsia without HELLP syndrome and control. In contrast to this, in the HELLP syndrome, both the portal venous blood flow and the hepatic arterial blood flow decreased significantly to about 30 and 70% of control, respectively; as a result, the total liver blood flow markedly decreased to about 40% of control (Table 2).

Table 3 shows interobserver reproducibility and intraobserver reproducibility of Doppler ultrasound measurements in the separate studies. The level of interobserver reproducibility in the blood flow measurements was good for the portal vein and excellent for the hepatic artery. The level of intraobserver reproducibility in the blood flow measurements was excellent for both the hepatic artery and portal vein in observer 1. In observer 2, the level of intraobserver reproducibility in the blood flow measurements was excellent for the portal vein and good for the hepatic artery. Thus, both the interobserver reproducibility and the intraobserver reproducibility of blood flow measurements were clinically acceptable in this study.

Discussion

This prospective study indicates that the total liver blood flow was reduced in women with severe preeclampsia who developed HELLP syndrome within 4 days after the examination, but not in women with severe preeclampsia without HELLP syndrome. Because changes in the portal venous blood flow were similar in severe preeclampsia with or without HELLP syndrome, albeit more pronounced in the HELLP syndrome, the major determinant of the difference was the hepatic arterial blood flow. Furthermore, the most important result of this study was that the decrease in dual hepatic blood supply preceded the onset of HELLP syndrome.

Our results in the control group confirmed the previous study [25] which reported an increase in the portal venous flow and the total liver blood flow of healthy pregnant women to about 150 and 160% of nonpregnant levels during third trimester, respectively. These findings are contrary to conventional results

Table 1 Characteristics of subjects

	Controls	Preeclampsia without HELLP	Preeclampsia with HELLP	*P* value
No. of participants	60	49	9	
Age (years)	31 (4)	33 (4)	30 (4)	0.07
Nulliparous, no. (%)	43 (72)	34 (69)	6 (67)	0.94
Gestational age at examination (weeks)	31 (4)	31 (3)	32 (2)	0.69
Systolic blood pressure (mmHg)	103 (12)	140 (21)[a]	152 (12)[a]	< 0.001
Diastolic blood pressure (mmHg)	59 (11)	84 (13)[a]	80 (15)[a]	< 0.001
Urine protein (g/24 h)	0 (0)	3.6 (0.7)[a]	3.7 (0.4)[a]	< 0.001
Body mass index (kg/m^2)	23 (3)	24 (5)	25 (4)	0.21
Aspartate aminotransferase (U/l)	14 (7)	17 (10)	24 (9)[b]	0.003
Alanine aminotransferase (U/l)	10 (6)	12 (6)	22 (11)[b]	< 0.001
Lactate dehydrogenase (U/l)	235 (75)	271 (81)	257 (63)	0.34
Platelet count ($\times 10^9$/l)	226 (51)	210 (49)	202 (63)	0.18

Continuous data represent mean values and standard deviation unless otherwise indicated

[a]Significant difference against controls (one-way ANOVA followed by the Scheffé *F*-test)

Table 2 Blood flow parameters of hepatic artery and portal vein in controls and preeclampsia with or without HELLP syndrome

	Controls	Preeclampsia without HELLP	Preeclampsia with HELLP	*P* value
No. of participants	60	49	9	
Hepatic artery				
Cross-sectional area (cm^2)	0.7 (0.3)	0.8 (0.3)	0.5 (0.2)†	0.01
Time-averaged mean velocity(cm/s)	24.5 (4.6)	25.8 (4.9)	22.3 (4.5)	0.09
Blood flow (l/min)	0.9 (0.4)	1.2 (0.4)*	0.6 (0.2)†	< 0.001
Resistive index	0.76 (0.06)	0.78 (0.06)	0.81 (0.07)	0.13
Beam angle (deg.)	50 (10)	53 (6)	51 (5)	0.46
Portal vein				
Cross-sectional area (cm^2)	1.7 (0.4)	1.5 (0.4)	0.5 (0.2)*†	< 0.001
Time-averaged mean velocity (cm/s)	18.8 (4.1)	15.3 (3.8)*	13.8 (2.1)*	< 0.001
Blood flow (l/min)	1.9 (0.5)	1.3 (0.4)*	0.5 (0.2)*†	< 0.001
Beam angle (deg.)	29 (19)	26 (24)	22 (19)	0.615
Total liver blood flow (l/min)	2.8 (0.7)	2.5 (0.6)	1.1 (0.3)*†	< 0.001

All data represent mean values and standard deviation

*$P < 0.05$ against control, $^\dagger P < 0.05$ against the preeclampsia without HELLP syndrome (one-way ANOVA followed by the Scheffé *F*-test)

Table 3 Intraobserver reproducibility for Doppler measurements ($n = 10$)

	Interobserver R_i	Intraobserver R_i	
		Observer 1	Observer 2
Hepatic artery			
Cross-sectional area (cm^2)	0.72	0.8	0.65
Time-averaged mean velocity (cm/s)	0.69	0.74	0.71
Blood flow (l/min)	0.86	0.85	0.71
Resistive index	0.14	0.32	0.35
Portal vein			
Cross-sectional area (cm^2)	0.67	0.87	0.75
Time-averaged mean velocity (cm/s)	0.76	0.78	0.79
Blood flow (l/min)	0.71	0.95	0.95
Total liver blood flow (l/min)	0.72	0.94	0.92

Poor $R_i < 0.40$, *fair* $0.40 \le R_i < 0.59$, *good* $0.60 \le R_i \le 0.74$, *excellent* $R_i \ge 0.75$

[30], which suggested that despite a marked increase in cardiac output, there were no significant changes in hepatic blood flow during pregnancy. The author applied the technique of hepatic vein catheterization to evaluate maternal hepatic blood flow. This technique may involve varying degree of surgical manipulation which influences maternal cardiac function and hemodynamics. In contrast, Doppler ultrasound measurement, which was used in this study, is not known to result in any harmful effects to the mother and fetus and is routinely used in obstetric care. Therefore, our results could be regarded to reflect more physiological conditions than the previous study.

The present results in preeclampsia without HELLP syndrome showed a reciprocal change between hepatic arterial blood flow and portal venous blood flow. We speculate that these changes tend to preserve the volume of hepatic blood flow and may act an important role to maintain maternal liver functions in the women with preeclampsia. The liver is supplied by two blood flow systems, the hepatic artery and the portal vein. The hepatic arterial blood flow normally supplies approximately 25–35% of the total blood flow to the liver [12, 15, 31], and most anatomical evidence suggests that it mixes completely with portal venous blood flow in or before the hepatic sinusoids, after which it leaves the liver through the hepatic veins [31]. This mixing of the hepatic arterial and the portal venous blood provides the hepatic circulation with the unique phenomenon of interaction between blood streams. Findings from previous investigations [10, 16–22] have demonstrated that an increase in the inflow volume of one circulation evokes a response in the other vessel consisting of reciprocal increase in vascular resistance. This effect would tend to maintain constant the volume of blood flow through the liver and supports our findings in preeclampsia without HELLP syndrome. Ming et al. [32] suggested that nitric oxide is the major endogenous mediator involved in the hepatic vascular escape, characterized by the recovery of the initial decreased blood flow and vascular conductance toward the control level during continued vasoconstrictive stimulation.

However, control of liver blood flow by reciprocal changes in vascular resistance is an incomplete explanation [22–24]. Lautt et al. [24] demonstrated that hepatic arterial blood flow increased when portal venous flow was decreased, but there was no compensatory increase in portal blood flow when hepatic arterial flow was decreased. Indeed, the present results from HELLP syndrome showed no reciprocal increase in the hepatic arterial blood flow, suggesting that the hepatic arterial and portal venous vascular territories have regulatory mechanisms that allow for independent changes. The results of experimental studies [33–35] in rats and primates have shown that inhibition of nitric oxide synthesis during normal pregnancy results in a clinical picture that is similar to that of HELLP syndrome. Furthermore, in a case report, the beneficial effect of a nitric oxide donor in the treatment of HELLP syndrome was documented [3]. Although the exact mechanisms are not clear, these clinical and experimental findings allowed us to postulate that ability of nitric oxide production or vascular reactivity for nitric oxide may be implicated in the differences between the preeclampsia with and without HELLP syndrome.

We believe that if these data can be validated in a larger population of patients, the Doppler ultrasound parameter of maternal dual hepatic blood supply could become a relevant marker for the prediction of onset of HELLP syndrome.

References

1. Sibai BM, Ramadan MK, Usta I et al (1993) Maternal morbidity and mortality in 442 pregnancies with hemolysis, elevated liver enzyme levels, and low platelet count (HELLP syndrome). Am J Obstet Gynecol 169:1000–1006
2. Oosterhof H, Voorhoeve PG, Aarnoudse JG (1994) Enhancement of hepatic artery resistance to blood flow in preeclampsia in presence or absence of HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets). Am J Obstet Gynecol 171:526–530
3. De Belder AJ, Lees C, Martin J, Moncada S, Cambell S (1995) Treatment of HELLP syndrome with nitric oxide donor. Lancet 345:124–125
4. Kurzel RB, Au AH, Rooholamini SA (1996) Doppler velocimetry of hepatic blood flow in postpartum patients with HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet). Am J Obstet Gynecol 175:1677–1678
5. Fischer T, Schneider MP, Schobel HP et al (2000) Vascular reactivity in patients with preeclampsia and HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome. Am J Obstet Gynecol 183:1489–1494
6. Gaiani S, Bolondi L, Bassi AL et al (1989) Effect of meal on portal hemodynamics in healthy humans and in patients with chronic liver disease. Hepatology 9:815–819
7. Goldberg REA, Rade C, Knelson M, Haaga J, Minkin S (1990) The response of the portal vein to an oral glucose load. JCU 18:691–695
8. Sabba C, Weltin G, Cicchetti DV et al (1990) Observer variability in echo-Doppler measurements of portal flow in cirrhotic patients and normal volunteers. Gastroenterology 98:1603–1611
9. Tincani E, Cioni G, Cristani A (1993) Duplex Doppler ultrasonographic comparison of the effects of propranolol and isosorbide-5-mononitrate on portal hemodynamics. J Ultrasound Med 12:525–529
10. Platt JF, Rubin JM, Ellis JH (1995) Hepatic artery resistance changes in portal vein thrombosis. Radiology 196:95–98

11. Platt JF, Yutzy GG, Bude RO, Ellis JH, Rubin JM (1997) Use of Doppler sonography for revealing hepatic artery stenosis in liver transplant recipients. AJR 168:473–476
12. Leen E, Angerson WG, Cooke TG, Mcardle CS (1996) Prognostic power of Doppler perfusion index in colorectal cancer, correlation with survival. Ann Surg 223:199–203
13. Iwao T, Toyonaga A, Oho K et al (1997) Value of Doppler ultrasound parameters of portal vein and hepatic artery in the diagnosis of cirrhosis and portal hypertension. Am J Gastroenterol 92:1012–1017
14. Fisher AJ, Paulson EK, Kliewer MK, Delong DM, Nelson RC (1998) Doppler sonography of the portal vein and hepatic artery: measurement of a prandial effect in healthy subjects. Radiology 207:711–715
15. Oppo K, Leen E, Anderson WJ, Cook TG, Mcardle CS (1998) Doppler perfusion index: an interobserver and intraobserver reproducibility study. Radiology 208:453–457
16. Greenway CV, Oshiro G (1972) Intrahepatic distribution of portal and hepatic arterial blood flows in unanesthetized cats and dogs and the effects of portal occlusion. J Physiol 227:473–485
17. Kock NG, Hahnloser P, Roding B, Schenk WGJ (1972) Interaction between portal venous and hepatic arterial blood flow: an experimental study in the dog. Surgery 72:414–419
18. Mathie RT, Lam PHM, Harper AM, Blumgart LH (1980) The hepatic arterial blood flow response to portal vein occlusion in the dog, the effect of hepatic denevation. Pflugers Arch 386:77–83
19. Richardson PDI, Withrington PG (1981) Liver blood flow. 1. Intrinsic and nervous control of liver blood flow. Gastroenterology 81:159–173
20. Mathie RT, Blumgart LH (1983) The hepatic haemodynamic response to acute portal venous blood flow reductions in the dog. Pflugers Arch 399:223–227
21. Mathie RT, Alexander B (1990) The role of adenosine in the hyperaemic response of the hepatic artery to portal vain occlusion (the ''buffer response''). Br J Pharmacol 100:626–630
22. Kawasaki T, Carmichael FJ, Saldiva V, Boldan L, Orrego H (1990) Relationship between portal venous and hepatic arterial blood flows: spectrum of response. Am J Physiol 259:G1010–G1018
23. Condon RE, Nyhus LM, Chapman ND, Harkings HN (1962) Portal vein and hepatic artery interactions: studies in the isolated, perfused liver. Gastroenterology 43:547–556
24. Lautt WW, D'almeida MS, Mcquaker J, D'aleo LD (1988) Impact of the arterial buffer response on splanchnic vascular responses to intravenous adenosine, isoproterenol, and glucagon. Can J Physiol Pharmacol 66:807–813
25. Nakai A, Sekiya I, Oya A, Koshino T, Araki T (2002) Assessment of the hepatic arterial and portal venous blood flows during pregnancy with Doppler ultrasonography. Arch Gynecol Obstet 266:25–29
26. Bartko JJ, Carpenter WT Jr (1976) On the methods and theory of reliability. J Nerv Ment Dis 163:307–317
27. Cicchetti DV, Sparrow SA (1981) Developing criteria for establishing interrater reliability of specific items: applications to assessment of adaptive behavior. Am J Ment Defic 86:127–137
28. Nakai A, Asakura H, Oya A et al (1999) Pulsed Doppler US findings of renal interlobar arteries in pregnancy-induced hypertension. Radiology 213:423–428
29. Landis JR, Koch GG (1977) The measurement of observer agreement for clinical data. Biometrics 33:159–174
30. Mannell EW, Taylor HC (1947) Liver blood flow in pregnancy: hepatic vein catheterization. J Clin Invest 26:952–956
31. Greenway CV, Stark RD (1971) Hepatic vascular bed. Physiol Rev 51:23–65
32. Ming Z, Han C, Lautt W (1999) Nitric oxide mediates hepatic arterial vascular escape from norepinephrine-induced constriction. Am J Physiol 277:G1200–G1206
33. Baylis C, Engels K (1992) Adverse interaction between pregnancy and a new model of systemic hypertension produced by chronic blockade of endothelial derived relaxing factor (EDRF) in the rat. Clin Exp Hypertens Pregnancy 11:117–129
34. Kanayama N, She L, Maehara K, Kajiwara Y, Terao T (1996) Induction of HELLP syndrome-like biochemical parameters by stimulation of the celiac ganglion in rats. J Hypertens 14:453–459
35. Podjarny E, Ben-Chetrit S, Rathaus M et al (1997) Pregnancy-induced hypertension in rats with adriamycin nephropathy is associated with an inadequate production of nitric oxide. Hypertension 29:986–991